

HEALTH SCIENCES

Theory, Current Researches
and New Trends

Prof. Dr. Nizami DURAN

Prof. Dr. Sıddık KESKİN

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HEALTH SCIENCES



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Editors

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PREFACE

The book 'Health Sciences: Current Researches and New Trends' is serving an academic forum for both academics and researchers working in such fields. Health sciences research is an interdisciplinary by nature. So it covers several fields such as medical, veterinary and pharmaceutical sciences. In this book, the academics working in different fields share their results with the scientific community. Thus more researchers will be aware of these studies and have some new ideas for their future studies. The selected articles have been reviewed and approved for publication by referees. It is hoped that the book will be of interest and of value to academics and researchers.

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CHAPTER I

AMINOGLYCOSIDE ANTIBIOTIC-INDUCED HEARING LOSS AND TRPM2 CATION CHANNELS

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1. Introduction

Hearing loss is a very common sensory impairment problem affecting approximately 466 million people (34 million children) worldwide (World Health Organization, WHO updated data March 1, 2020). According to scientific data, the number of people with hearing problems will be 900 million in 2050. Although the causes of hearing loss are mostly hereditary, due to ototoxins, it can also occur in advanced ages. Hearing loss also has an annual global cost of 750 billion USD. Sensory hair cells are special mechanically sensitive receptors in the cochlear system that generate vibrating and acoustic stimuli for hearing. Aging, ototoxic agents (some antibiotics, platinum-based chemotherapeutics, etc.), congenital complications, hereditary mutations, chronic ear infections and noise causes cochlear system degeneration, mechanical transduction dysfunction, and sensorineural hearing loss (Wong and Ryan 2015). The hearing impairment that follows this cochlear injury is directly related to the generation of reactive oxygen species (ROS). Aminoglycoside antibiotics, one of the autotoxic agents, are widely used in the treatment of infections, causing 25% hearing loss. Aminoglycoside ototoxicity is well characterized, it is relatively simple to apply in animal models (Michael et al., 2016). It is important to analyze the basic mechanisms underlying hearing problems and seek appropriate treatment protocols.

2. Cochlear system and molecular structure of hearing

The molecular mechanisms of mechanical conduction in hearing, which is one of our important sensory organs in maintaining our daily life, has not yet been fully understood in terms of its complex structures. Sensory connections in the auditory system are located inside the bone labyrinth of the inner ear. Environmental sounds are detected through

the hair cells in the corti organ in the spiral cochlear system. There are more than 16000 hair cells in the corti organ (Schwander et al., 2010). Cochlear hair cells can be classified into two different types with different properties and innervation: internal and external hair cells (Figure 1A, B). While inner hair cells are primary sound sensors, outer hair cells function as sound amplifiers (Ekdale, 2016). Sound waves following the ear canal are converted into mechanical movements with the miraculous design of the cochlear system. This event begins primarily with the vibration of the eardrum connected to the middle ear bones. The vibration of the middle ear bones is transmitted to the cochlea, which leads to the displacement of the cochlear fluid and the basilar membrane (Fig.1A). Displacement causes physical stimulation of hair cells in the basilar membrane, which converts mechanical movement into electrical reactions (Beurg et al., 2006; Ekdale 2016). Hair cells are arranged tonotopically throughout the cochlea: cells in the base of the cochlea are adjusted to higher frequency sounds, and cells in the cochlea apex are adjusted to lower frequency sounds. The perception of sounds in our ears, the conversion of mechanical signals into electrical signals are provided by Transmembrane channel-like proteins 1 and 2 (TMC1 and TMC2) structures localized in stereocilia. A small change in these conductors activated in the resting potential can make major changes in firing rates.

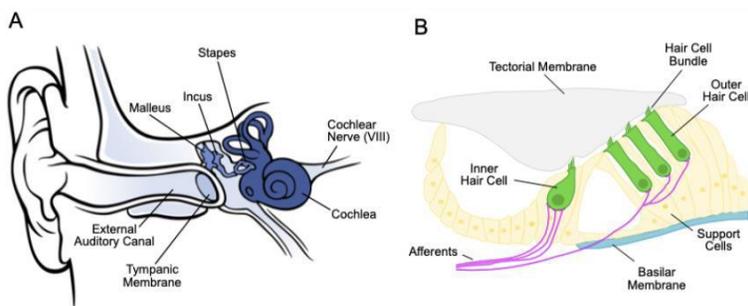


Fig.1 Cochlear system and hair cells (A) Scheme of the human ear. After the sound coming from the ear, vibrates the tympanic membrane,

it reaches the cochlea with malleus, incus and stapes bones. (B) Korti organ, internal and external hair cells. (Chittka and Brockmann 2005).

3. Aminoglycoside antibiotics and hearing loss

Hearing loss and deafness are serious problems that need to be addressed socially, as they cause social isolation and psychologically push people alone and increase the levels of depression and anxiety. Not only this size, but also expensive hearing aids, implant surgeries and their regular controls place a serious economic burden on people. Aminoglycoside antibiotics are highly preferred in terms of providing effective treatment options for gram-negative infections, bacterial infections in premature babies and tuberculosis. In addition to this treatment efficacy, irreversible damage to the hair cells in the inner ear known as mechanotransduction center and causing permanent hearing loss limits its use. Aminoglycosides enter the hair cells and cause oxidative damage by disrupting mitochondrial respiration. In addition to causing tinnitus, such antibiotics also cause hearing problems by affecting bilateral sensory neurons (Nadol et al., 1993). As can be seen, these damages cause irreparable results. To date, there is no FDA-approved drug to prevent the destructive consequences of these ototoxic agents. Therefore, it is imperative to develop new strategies against these permanent damages. Following events occur in hair cells due to the use of aminoglycoside antibiotics:

1. Aminoglycoside supports the formation of superoxide radicals such as hydroxyl
2. There is an excessive increase in intracellular calcium due to aminoglycoside
3. It causes mitochondrial membrane depolarization in hair cells, increases membrane permeability and triggers apoptotic cascades

4. Cochlear hair cells, hearing physiology and TRP channels

As it is known as the most basic subject in hearing physiology, the sound that travels through the ear canal and reaches the cochlea causes stereosliar movement in the hair cells. The submicron deviation that occurs in the stereosili beam within microseconds by the effect of the voice activates the ion channels and causes the flow of cations and this leads to a receptor potential. Although the mechanical transmission in hair cells is well known, the molecular identity of the channels responsible for this mechanotransduction remains unclear. These

physiological properties of hair cells suggest that the family of transient receptor potential (TRP) cationic channels, first discovered in the eye cells of the vinegar fly, may be good candidates to grasp the structure of the transduction channels. Understanding the true roles of these TRP channels in cochlear hair cells is essential for the development of alternative therapeutics against hearing problems.

The TRP cation channel family, which was first discovered in the eye cells of the *Drosophila melanogaster* type of vinegar fly, has six transmembrane domains (Ramsey et al., 2006). There are 6 families and 28 members classified according to the sequence homology of the amino acids contained in the structure of TRPs until now. These consist of ancrine, mucolipin, melastatin, canonical, vanilloid and polycysteine. TRP channel proteins tend to combine in the form of homo, hetero-tetramer to form individuals with functionally active constituents (Cheung & Miller, 2017). In this regard, TRPs, which are non-selective cationic channels of sensory signals, consisting of 7 subfamilies (Figure 2), are promising targets for the discovery of the molecular mechanisms underlying hearing loss problems associated with hair cell damage and important roles in cellular functions and signaling pathways in various physiological processes. (Ramsey et al., 2006). The wide range of expression levels in neuronal and non-neuronal cells and the search for solutions to persistent problems that do not respond to therapeutic approaches have increased the interest in these channels. It was found that 19 of the TRP superfamily were expressed in the Corti organ. In addition, TRPM2 mRNA levels are expressed 90 times higher in hair cells compared to other cells. The actual roles of the melastatin 2 subfamily (TRPM2), an ROS receptor in triggering the ROS and apoptotic cascades that occur in hearing loss in mice hair cells, remain unclear.

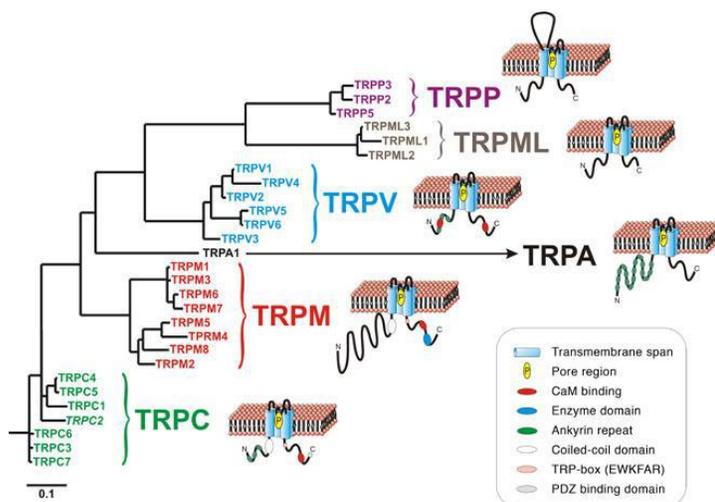


Fig.2 The phylogenetic tree and topology of TRP channels and important topological regions in these channels. CaM, calmodulin; Single letter amino acid code for the TRP box PDZ is the binding site for protein-protein interactions (Nilius et al., 2005).

5. TRPM2 cation channels as a ROS sensor

TRPM2 channel, one of the melastatin family, contains the N-, C-terminus and consists of 6 membrane-embedded transmembrane domains (S1-S6) in the cytosol. There is a 4-homologous structure at the N-terminus, which houses the calmodulin attachment point. Cation flow in the channel is carried out between the S5 and S6 segments. In the C terminal, there is the Nudix box activated by ADPR and this structure works like a ROS sensor in case of oxidative stress (Fig.3). Similar to the TRP channels, TRPM2 is a homo-tetrameric voltage-independent activated and nonselective cation channel. Reactive oxygen species (ROS) are produced by the electron transport chain during oxygenated respiration in mitochondria that function like power plants in cells. Activation of TRPM2 channels by oxidative stress has been shown to cause cell death with a sustained increase in cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) or increased cytokine production (Fig.4). As a result, inflammation and cell damage increase. Pharmacological inhibition of TRPM2 with 2-aminoethoxydiphenyl borate (2-APB) has been found to inhibit cell apoptosis (Gao et al., 2014). Increased intracellular ROS and excessive Ca^{2+} accumulation appear to coexist in

pathophysiological conditions, but their interaction with hearing loss due to damage to aminoglycoside-induced hair cells and their signaling mechanisms are not fully known. In this respect, we anticipate that TRPM2 channels will shed light on this uncertainty.

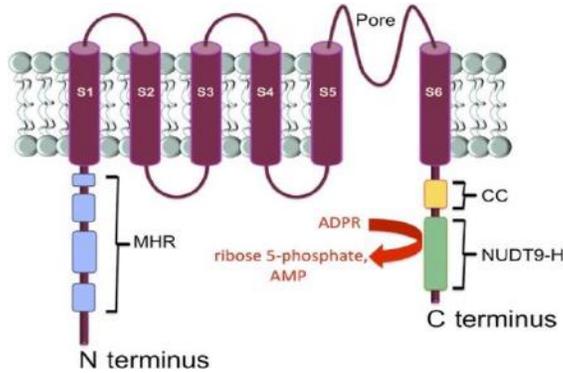


Fig.3 6-transmembrane structure, C and N end schematic representation of TRPM2 channel (Rosenbaum T, 2015).

The relationship between ROS and excessive intracellular calcium accumulation with the oxidative damage state in cochlear hair cells is well established. Therefore, apoptosis is an event in which coordinated fluctuations of ROS and Ca^{2+} are observed and examined very deeply (Giorgi et al., 2012). However, in addition to cell death, emerging evidence suggests that many different cellular signal events are regulated in accompanying and localized increases in ROS and Ca^{2+} transitions (Booth et al., 2016). The interaction between TRPM2 cationic channels and Ca^{2+} and reactive oxygen species (ROS) signaling pathways has been well established and mutual regulation has occurred in a number of subcellular locations. Along with TRPM2's localized in this cell membrane, many Ca^{2+} channels in intracellular organelles such as mitochondria are regulated by redox modifications. At this point, the common intersection point of TRPM2 activation mechanism and damage to hair cell damage is ROS. So, what are the roles of TRPM2 in the case of mitochondrial ROS caused by oxidative stress due to the use of ototoxic agents in hair cells? As we mentioned above, when we destroy the ROS accumulated in the environment, recovery in hair cells and hearing problems were detected. Will the hearing problems caused by ROS be reduced if the TRPM2 eliminates the channels by knockout? As we know, regulation of Ca^{2+} homeostasis is accomplished by a series of ion channels, pumps, and exchangers both at the cell surface

and in organelles that act as primary intracellular Ca^{2+} stores. ROS sensor cationic channels such as TRPM2 appeared in cellular hemostasis of cochlear mechanotransduction center hair cells in the auditory system.

These roles of TRPM2 in hearing loss due to oxidative damage in hair cells are important in the following headings:

1) **The role of TRPM2 in the maintenance of balance in the modulation of aminoglycoside-induced mitochondrial-ROS and Ca^{2+} fluctuations in hair cells.**

2) **The roles of these TRPM2s in the case of cellular hemostasis in cochlear hair cells in hearing loss**

3) **The effect of TRPM2-KO states on mitochondrial bioenergetics in TRPM2 mediated mitochondrial dysfunction due to damage to hair cells.**

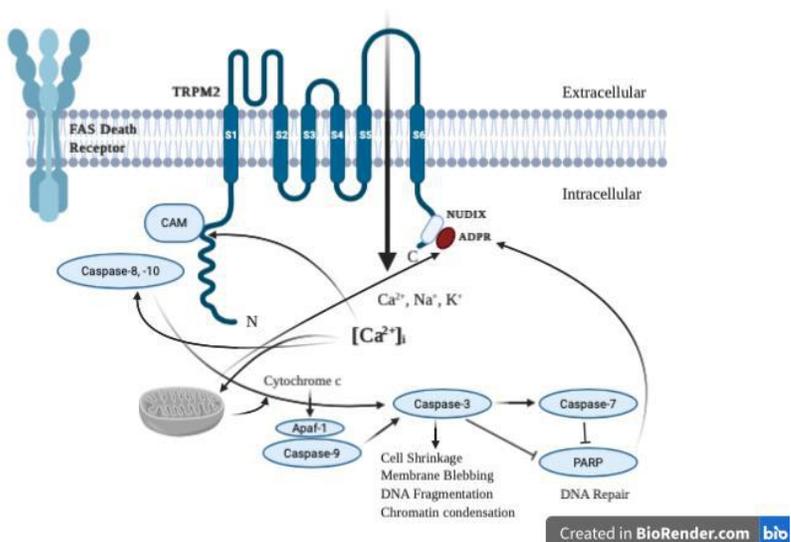


Fig.4 Activation of TRPM2 channels by acting as ROS sensor due to increase in mitochondrial ROS in cochlear hair Cells

Much more research is needed to gain a more holistic perspective on how to prevent hair cell damage due to the use of ototoxic drugs such as aminoglycoside antibiotics. There is currently no effective treatment

for sensorineural hearing loss due to exposure to ototoxic drugs in humans. In this context, the issue highlighted here is important for future treatment approaches. In this review, we aimed to evaluate the deafness of mice after treatment with aminoglycoside in terms of the mitochondrial ROS-activated TRPM2 cation channels developed in hair cells (Figure 5).

In this review, we focused on the interaction between Ca^{2+} and ROS. We have also discussed how redox regulation of Ca^{2+} transport mechanisms and Ca^{2+} signaling mediated by TRPM2 cation channels can regulate the cellular redox environment. The mitochondria of hair cells in which apoptotic pathways are activated produce reactive oxygen species (ROS) (Esterberg et al. 2016) and this situation can be tolerated by lowering ROS. This is possible through antioxidant treatment or synthesis of ROS neutralizing enzymes (Chen et al. 2013). It may also be possible by reducing the ROS in the environment by genetic deletion of TRPM2 channels or by pharmacological inhibition of these channels. ROS is a natural byproduct of oxidative phosphorylation produced at many positions along the electron transport chain in the mitochondria. ROS molecules react with DNA, proteins and lipids that cause mutations, and DNA chain breaks cause protein oxidation and lipid peroxidation. Aminoglycoside antibiotics and some chemotherapeutics cause this oxidative damage and consequently hearing loss in hair cells. Support for the ROS theory for hair cell loss comes from experiments where antioxidants have been found to improve the effects of aminoglycoside ototoxicity and noise-induced hearing loss (Quirk et al., 1994).

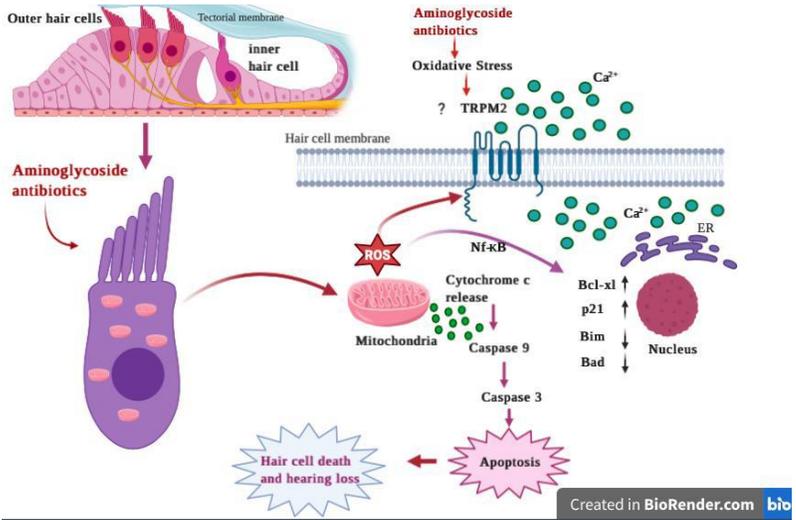


Fig.5 Relationship between mitochondrial ROS and apoptotic events occurring in hair cells of mice treated with aminoglycoside and TRPM2

6. Conclusion

It is understood that the origin of the aminoglycoside-induced ROS should be better understood and the focus should be on the development of therapies aimed at preventing this event. It is understood that aminoglycoside antibiotics, which are frequently used in effective treatment against bacterial infections, cause mitochondrial-ROS-induced hearing problems in hair cells and the necessity of molecular approaches to produce more radical and permanent solutions against this situation. In particular, understanding the roles of TRPM2 cation channels, known as ROS sensors, in this hearing loss is critical for therapeutic approaches. For this purpose, it is emphasized that it is important to reveal its true role in hearing using knockout-TRPM2 mice. In addition, the necessity of focusing on solutions that will make life easier for individuals with hearing problems and therefore exposed to social isolation is mentioned. Considering the serious costs of the hearing impaired, expensive hearing aids, cochlear implant surgeries and subsequent processes, it is understood that ROS sensitive TRPM2 cation channels will shed light on the dark areas in hearing problems that have not been understood until today.

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CHAPTER II

DIMENSIONALITY REDUCTION TECHNIQUE: PRINCIPAL COMPONENT ANALYSIS

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1. Introduction

Modern applications have gradually expanded the use of complex and high-dimensional data (Hadsell et al., 2006). Data mining algorithms are used to search for meaningful patterns in raw data sets (Maimon & Rokach, 2005). One of the main problems in machine learning and pattern recognition is making complex data available (Belkin & Niyogi, 2003). Multidimensional data pose a serious obstacle to the efficiency of most data mining algorithms. This obstacle is sometimes known as the "curse of dimensionality". Techniques that are highly effective in low dimensions cannot provide meaningful results when the number of variables increases (Hadsell et al., 2006; Maimon & Rokach, 2005). High-dimensional datasets created by biology, earth science, astronomy, robotics, modern manufacturing, and other science and industry fields allowed the development of new techniques for dimension reduction and visualization (Hadsell et al., 2006).

Dimension reduction aims to transform high dimensional data into a low dimensional representation (Hadsell et al., 2006). Ideally, the reduced representation should have a dimensionality that corresponds to the internal dimensionality of the data. The internal dimensionality of the data is the minimum number of variables required to take into account the observed properties of the data (Van Der Maaten et al., 2009). Reducing the dimensionality of data with minimal information loss is important for feature extraction, coding and computing efficiency. When the dimension of the data is reduced, constraints between variables can be defined and redundancy can be eliminated. Most algorithms decrease their performance as the number of variables increases, so minimizing even one dimension can result in computational savings (DeMers & Cottrell, 1993).

Dimension reduction methods are divided into two main groups as linear and nonlinear methods. Principal Component Analysis (PCA) and Linear Discriminant Analysis (LDA) are the leading linear methods. Both methods are the two most used algorithms because of their simplicity and efficiency (Yan et al., 2006). The main nonlinear dimension reduction methods can be shown as multidimensional scaling, Isomap, Maximum Variance Unfolding, Kernel PCA, diffusion maps, multilayer autoencoders, Locally Linear Embedding, Laplacian Eigenmaps, Hessian LLE, Local Tangent Space Analysis, Locally Linear Coordination and manifold charting (Van Der Maaten et al., 2009).

Linear techniques perform dimension reduction by embedding data in a linear subspace of lower dimensionality. Although there are various techniques for doing this, PCA is by far the most popular (unsupervised) linear technique (Van der Maaten et al., 2007).

Principal component analysis, which is used to determine linear relationships between variables, was first introduced by Karl Pearson in the early 1900s. Later, application areas were developed by Hotelling in 1933 and by Rao in 1964 (Timm, 2002). Principal component analysis, which is used to eliminate the dependency structure between variables or for dimension reduction, is used as a method of analysis used alone, as well as a data preparation technique for other analyzes. The interpretation of the statistical analysis results is very difficult if there is a dependency between the variables and therefore they are not independent. In such cases, principal component analysis is used. In principal component analysis, if the data matrix X consisting of n individuals (observations) and p variables are considered, the data matrix can be expressed as a collection of many points (each individual represents a point). In this matrix, if raw data is used, a variance-covariance matrix is used, if standardized data is used, the correlation matrix is used. The most important determinant of which of these two ways to choose, which can give different results, is the measurement units of the variables. If the measurement units of the variables are the same, it is recommended to use the variance-covariance matrix, if different, the correlation matrix is recommended (Özdamar, 2004). Principal Components Analysis; By making use of the linear relationship (correlation) between a large number of original variables containing continuous data; It is a multivariate analysis method that consists of linear combinations of original variables with minimal loss of information and includes the process of obtaining less number of new variables and interpreting the results. PCA, which is a quadratic method based on the covariance matrix of variables, is also known as singular

value decomposition (SVD), Karhunen-Loeve transform, Hotelling transform and empirical orthogonal function (EOF) method in various fields (Maimon & Rokach, 2005). The use of principal components analysis generally has three objectives;

1. Data reduction.
2. Estimation.
3. Putting the data set into a form that some methods can analyze

As a result of principal component analysis, principal components consisting of combinations of original variables provide the following three properties. These are:

1. There is no correlation between Principal Components.
2. First Principal Component is the variable that most explains the total variation.
3. As a result of principal component analysis, principal components are obtained as many as the original variables (Demir, 2010).

2. Literature Review

Destefanis et al. used PCA to analyze chemical, physical and sensory data on meat from different ethnic groups of young bulls. After analyzing the data matrix with 18 variables, 3 basic components were obtained. The first principal component explained 33.9% of the total variance, the second principal component 20.64% and the third principal component 7.94%. These three main components expressed 62.48% of the total variance explained by 18 variables. Thus, unlike classical correlation analysis, PCA allows defining which variables are associated with each other and in which direction at first glance (Destefanis et al., 2000).

Karamizadeh et al. emphasized the importance of PCA in determining and verifying facial features. Statistical information published in the field of face recognition technology reveals the success of PCA. They emphasized that PCA has two important disadvantages as well as its advantages such as size reduction, reducing complexity in a grouping of pictures, offering a smaller database and ignoring small changes in the background. First, they stated that it is difficult to interpret the covariance matrix correctly, the second is that it is not easy to understand small changes in PCA (Karamizadeh et al., 2013).

Reich et al. explained that Principal component analysis (PCA) is a useful tool for analyzing genetic data in human migration studies. In their studies that serve as a guide for scientists interested in using PCA

in genetic analysis; they underlined that it is possible to identify population infrastructure, correct stratification in disease studies, and make qualified inferences about human history with PCA (Reich et al., 2008).

Viana et al. drew attention to the increased particulate matter in the air due to their effects on human health. For this, they combined principal component analysis (PCA) with multiple linear regression (MLRA). Five independent factors were obtained by PCA. It has been determined that the first source contributing the most to the increase in the amount of particulate matter is industry and the second source is traffic (Viana et al., 2006).

Song et al. used principal component analysis (PCA) for feature selection. PCA is widely used in various fields such as image processing, pattern recognition, data compression, data mining, machine learning, and computer vision. PCA is a popular transformation method and superficially the transformation result is not directly related to the single featured component of the original samples. The proposed method clearly shows that the PCA has the potential to make feature selection and can select a number of key people from all feature components. Experimental results on face recognition show that the method can greatly reduce the dimensionality of original samples, as well as improve classification accuracy (Song et al., 2010).

Shlens showed how and why PCA is closely related to the mathematical technique of singular value decomposition (SVD). In his work, he led the researcher to a prescription and underlying assumptions about how to apply PCA in the real world. A comprehensive understanding of PCA is intended to provide a foundation for approaching the fields of machine learning and dimensional reduction. With minimal effort, PCA provides a roadmap on how to reduce a complex dataset to a lower dimension and sometimes reveals hidden, simplified structures (Shlens, 2014).

Borgognone et al. investigated which covariance matrix (cov-PCA) or correlation matrix (corr-PCA) should be used in PCA, both of which are derived from the data matrix. In a study in which PCA was used to analyze sensory descriptive data, it was stated that 22 out of 52 articles used corr-PCA, 7 used cov-PCA, and 23 were not known which PCA method they used. Since sensory scales are the same for all characteristics, it was emphasized that Cov-PCA should be used (Borgognone et al., 2001).

3. Results

Many approaches have been proposed for the size reduction task. Although the motivations of all these algorithms vary, their goals are similar, that is, to obtain a lower-dimensional representation and to facilitate the next classification task (Yan et al., 2006). As a result, dimension reduction makes it easier to classify, visualize, and compress high-dimensional data.

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CHAPTER III

ANALYZING DIAGNOSTIC VALUE OF C-REACTIVE PROTEIN/ALBUMIN RATIO WITH ROC CURVE IN NOVEL CORONAVIRUS DISEASE-19 (COVID-19)

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1. Introduction

Coronavirus disease 2019 (COVID-19), a global pandemic with catastrophic consequences for healthcare systems and populations around the world, causing serious respiratory illness such as pneumonia and lung failure was firstly reported in Wuhan city, Hubei Province, China (Z. Wu & McGoogan, 2020). It is important to predict the prognosis of patients to determine the direction of treatment. A simple, quick, and accessible parameter is needed to confirm treatment response and predict mortality in COVID-19.

Several classes of inflammation markers have been described: cytokines/chemokines, reactive oxygen and nitrogen species, prostaglandins and cyclooxygenase-related factors, and mediators such as transcription factors and growth factors. Among all these markers, the techniques currently available for C-reactive protein (CRP) is easy to perform and present low cost and high analytical sensitivity (Brenner et al., 2014). CRP is an acute-phase protein that circulates as a disc-shaped pentamer consisting of five identical subunits. It is produced following stimulation by various cytokines in response to inflammatory conditions. As the exact function of CRP is not fully understood yet, it is believed that it functions as part of the innate immune system (Bottazzi, Doni, Garlanda, & Mantovani, 2009). CRP levels have been studied in relation to prognosis and mortality in critically ill patients (Devran et al., 2012).

On the other hand, low serum albumin is known to be associated with poor prognosis and mortality (Artero et al., 2010). Based on this knowledge, we speculated that the ratio of CRP to albumin could be used as a diagnostic marker for COVID-19. In this retrospective study,

we aimed to evaluate the usability of CRP/albumin ratio in diagnosis and follow-up of patients with COVID-19.

2. Materials and methods

2.1. Patients and study design

This study was conducted at the Konya Education Research Hospital. The study was planned retrospectively in patients diagnosed with COVID-19 between 1 March 2020 and 29 June 2020. We excluded pediatric patients under 19 years and patients with clinical suspicion of COVID-19 but who PCR test negative. Patients without major data were excluded.

The laboratory results of the patients and the duration and location of the hospital stay were scanned and the data of the patients were obtained. CRP / Albumin ratios of intensive care unit and other clinics analyzed with roc curve. Other clinics defined as non-intensive care unit were Pulmonary medicine, Internal medicine, Infectious diseases and clinical microbiology.

2.2. Statistical analysis

Statistical analysis was performed using SPSS for Windows 21.0 (IBM Corp., Armonk, NY, USA). The statistical significance was calculated using Mann-Whitney Test. We evaluated the diagnostic value of CRP/albumin ratio, using roc analysis. $P < 0.05$ was considered statistically significant.

3. Results

57 patients admitted to the medical ICU and 1020 patients admitted to the other departments of the hospital (these patients were defined as non-survivors) from 1 March 2020 to 30 June 2020 were included in the study. One thousand seventy seven cases with the mean age of $47.3 \pm 17,65$ years were studied (0.54% male). 51.7 percent of the total 29 patients who died were male and 48.3 percent were female.

Figure 1 shows the ROC curve of CRP/albumin ratio. The cut-off point of CRP/albumin ratio was 1.895 and the sensitivity and specificity were 81% and 86%. Positive predictive value was 42% and negative predictive value was 97% (Fig.1).

Figure 2 shows the ROC curve of procalcitonin which is widely used in viral infections and has proven clinical value. The cut-off point of procalcitonin was 0.63 and the sensitivity and specificity were 44% and 85%. Positive predictive value was 16% and negative predictive value was 95% (Fig. 2).

Roc analysis results for all laboratory parameters are presented in Table 1. Area Under the Curve value (AUC) of the CRP / Albumin ratio, procalcitonin, CRP and albumin were 0.85, 0.64, 0.86 and 0.81, respectively (Table 1).

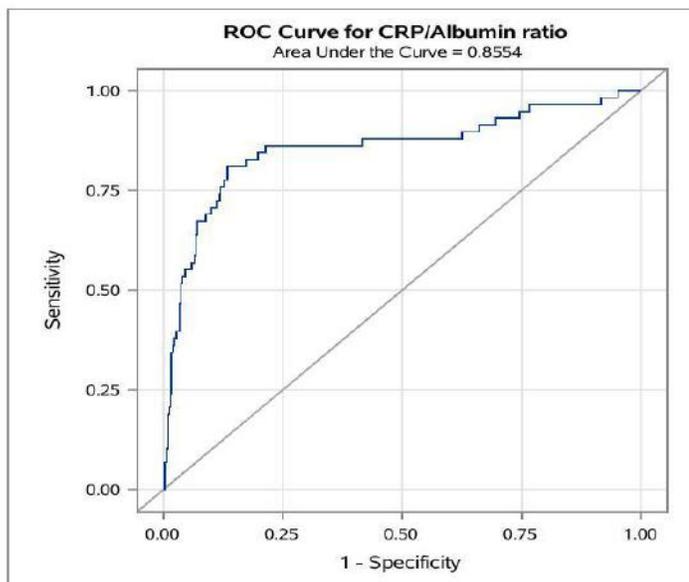


Fig. 1 ROC curves of CRP/albumin ratio in COVID-19 patients. The AUC of CRP/albumin ratio was 0.85. CRP, C-reactive protein; AUC, area under the curve.

Table 1 Roc analysis results of COVID-19 patients.

Variable	Cut-off point	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	AUC
CRP / Albumin ratio	1.89	81	86	42	97	0.85
Procalcitonin	0.63	44	85	16	95	0.64
Albumin	34.3	89	68	25	98	0.81
CRP	12	91	67	14	99	0.86

AUC, Area Under the Curve; CRP, C-Reactive Protein

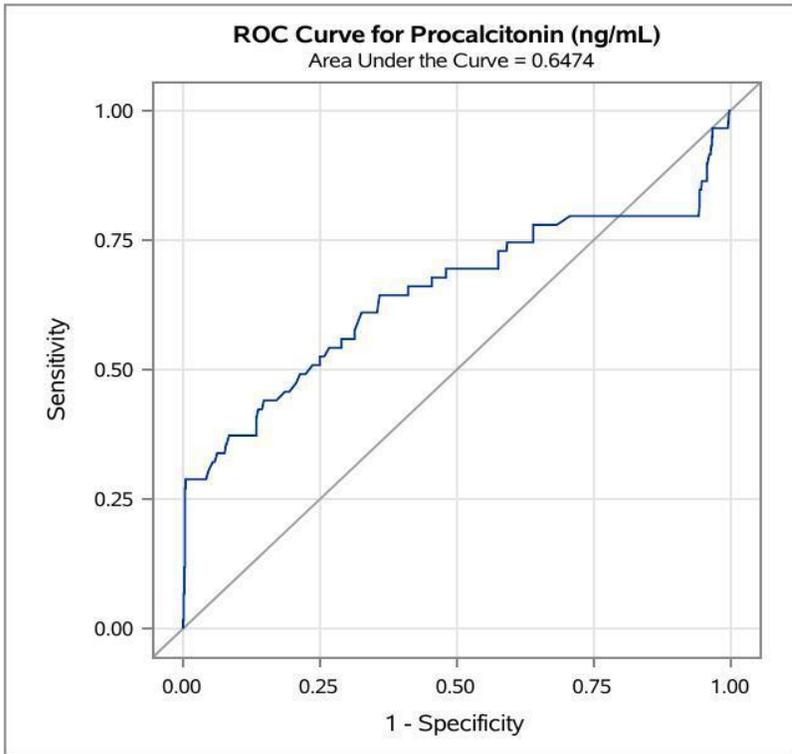


Fig. 2 ROC curves showing the diagnostic value of procalcitonin in COVID-19 patients. The AUC of procalcitonin was 0.65. The AUC value of procalcitonin is lower than that of the CRP / Albumin ratio. CRP, C-reactive protein; AUC, area under the curve.

4. Conclusions

CRP is a type of protein produced by the liver that is elevated in response to inflammation (Nehring & Patel, 2017). CRP levels have been shown to be associated with various conditions, including severe sepsis,

heart failure, and other inflammatory diseases (Ho, Lee, Dobb, & Webb, 2008; Villacorta, Masetto, & Mesquita, 2007). The inflammatory response also plays a serious role in COVID-19. Generally, CRP level is much higher in bacterial infections than in viral infections (Coster et al., 2019). In a study by Wang et al., many COVID-19 patients showed elevated CRP levels, which is in agreement with other studies. Moreover, aggravated cases in this study showed significantly higher levels of CRP than nonsevere patients, which suggested that CRP may be a serum marker of disease aggravation in

COVID-19 patients (Wang et al., 2020). Liu et al.'s study the serum levels of IL-6 and CRP had a significant correlation with the severity of COVID-19 and they suggested that these parameters can be used as independent factors to predict disease risk (Liu et al., 2020). Changes in the CRP levels have been previously reported in COVID-19 patients, but little is known about their correlation with disease severity. In a previous study, CRP in severe COVID-19 patients increased significantly at the initial stage, before CT findings and importantly, CRP, which was associated with disease development, predicted early severe COVID-19 (Tan et al., 2020). Luo et al. study results suggested that admission serum CRP level performed well in discriminating disease severity and predicting adverse outcome in patients with COVID-19 and patients with high CRP should be provided more attention and strengthened treatment (Luo et al., 2020). The most important finding of our study is to demonstrate the diagnostic value of CRP / Albumin Ratio in COVID - 19 patients.

Serum albumin is a negative acute phase maintenance protein that is rapidly downregulated by inflammatory processes, i.e., sepsis, trauma, and massive hemorrhage (Caironi & Gattinoni, 2009). A reduction of albumin concentration usually results in decreasing blood volume, which might even cause multiple organ dysfunction when serious. Furthermore, an essential function of albumin is to neutralize toxic compounds such as oxygen radicals and nitrite peroxides, decreased albumin can make infection control more difficult (Ma et al., 2017). Hypoalbuminemia is common in seriously ill patients, and serum albumin level has been associated with increased mortality in acutely ill patients in previous reports. Because of its value as an outcome predictor, serum albumin level has been added as one of the component parameters in the Acute Physiology and Chronic Health Evaluation III score (Niewiński, Starczewska, & Kański, 2014). In a meta-analysis of 90 cohort studies, hypoalbuminemia was a dose-dependent predictor of poor outcomes, such as mortality, morbidity, and prolonged intensive care unit and hospital stay. The association between hypoalbuminemia and poor clinical outcomes appeared to be independent of both nutritional status and inflammation in that study (Vincent, Dubois, Navickis, & Wilkes, 2003). Our study demonstrated that the diagnostic value of albumin and CRP is not as good as the CRP/albumin ratio in COVID-19 patients. Also, hypoalbuminemia can also be caused by previous diseases or general conditions, so it is difficult to use CRP or albumin as a biomarker alone (Simon, Gauvin, Amre, Saint-Louis, & Lacroix, 2004).

The CRP to albumin ratio is being used as a prognostic score to assess outcomes in patients with cancer, inflammation, and sepsis (Karayiannis et al., 2018). The combination of albumin and CRP into a single index has been suggested previously, and subsequent studies have shown that the CRP/albumin ratio is more consistent with prognosis than CRP or albumin alone (Ranzani, Zampieri, Forte, Azevedo, & Park, 2013). Kim et al. reported that the CRP/albumin ratio at admission was positively correlated with prognosis in patients with severe sepsis or septic shock treated with early goal directed therapy (Kim et al., 2015). In that study, the cut-off value for the CRP/albumin ratio as predictor of mortality was 5.09 in patients with severe sepsis or septic shock (Kim et al., 2015). In a study of elderly patients admitted via the emergency room, high-sensitivity-CRP/albumin ratio at admission to the emergency department was associated with all-cause in-hospital mortality among patients older than 65 years (Oh et al., 2017). The CRP/albumin ratio has been shown as a predictor of mortality in acute pancreatitis patients (Kaplan et al., 2017). Furthermore, the CRP/albumin ratio has predicted overall survival in various malignancies (Kinoshita et al., 2015; Mao et al., 2017; Saito et al., 2018; Wei et al., 2015; M. Wu, Guo, Guo, & Zuo, 2016). In our study, CRP / albumin ratio had greater accuracy than CRP in terms of diagnostik value in COVID-19 patients.

Viral infections do not usually affect the number of leukocytes, so the use of acute phase reactants, such as procalcitonin, as biomarkers may be of great help in reaching a diagnosis (Gilbert, 2010). Procalcitonin production depends on the presence of circulating tumor necrosis factor (TNF- α); in viral infections, macrophages produce interferon- α that can inhibit TNF- α , suppressing the elevation of procalcitonin, thus suggesting a viral origin (Johansson et al., 2014). We showed that the CRP / Albumin ratio has a much better sensitivity and specificity than procalcitonin in COVID-19 patients follow-up.

To our knowledge, this is the first article concerning the usability of CRP / Albumin ratios in patients with COVID-19. The findings from this single-center study need to be validated by multi-center research with larger samples.

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CHAPTER IV

SLEEP RESEARCH FROM PAST TO PRESENT

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The process of sleep has been a subject of interest for many years. The main reason for this interest is the fact that what happens during sleep and how it happens are not exactly known. At present, despite the increase in the number of research about sleep, the process of sleep is still not entirely clarified.

It is not exactly known to what date and period the researches conducted to clarify the process of sleep are based on. Until recently, sleep was regarded as a state between wakefulness and death. Wakefulness was considered as an active period whereas sleep was defined as a passive period close to death. With the researches after the 20th century, it was understood that sleep process is not a passive and near-death period.

Greek Philosopher and physiologist Alcmaeon, who lived around 500s BC, stated that sleep occurs when the blood moves away from the surface of the body into the larger blood vessels and when the blood moves back, the person awakens again. According to Democritus, who lived around 460-370s BC, famous for his atomic or indivisible matter theory, the soul is made up of slim, smooth and moving atoms and when some of the atoms come out, state of dormancy or unconsciousness

occurs. Aristotle, who lived in the 4th century BC, stated in his book “On Sleep and Sleeplessness” that sleep and awakening are opposites and that sleep occurs in the absence of wakefulness (Aristotle, 1849).

In the 2nd century AD, there were sleep rooms in Asclepeion which were believed to cure all diseases with sleep. One of the authors of that era, Aristides, described sleep and dream rooms (Steger, Brockmann, Melfi, & Parker, 2016). In early 13th century AD, at Gevher Nesibe Hospital and Medicine School, there were departments about the healing effects of music, plant extracts and sleep processes on psychological problems.

In his book which was published in 1834, Robert MacNish described the sleep process as a period between wakefulness and death (Macnish, 1834). In his book named “Sleep”, J. Allan Hobson, stated what has been found out about sleep in the last 60 years is more than what was found out in 6000 years (Hobson, 1989).

The statements of people who had to spend long periods in shelters during the World War and the complaints of submarine personnel led to studies on the effects of biological rhythms on humans. Aschoff and his followers among his students Honma and Czeisler have led the way for practices such as shift working pattern, flight times and summer time and established the standards (Czeisler & Brown, 1999).

In the 18th century, the field of chronobiology emerged which led to the idea that the 24 hour biological rhythm cycle in plants and animals is a direct result of the cycle of light and darkness (Richter vd., 2004). Researchers placed the heliotrope in a place where it could not receive any daylight and observed that the plant’s leaves were open when there was daylight outside and the leaves closed when it was dark outside (Monk & Welsh, 2003). This has been the foundation of the relationship between sleep process and chronobiology.

In the 19th century, number of research on sleep process increased and interest in sleep disorders started growing. In order to shed a light on sleep disorders, the researchers started analysing brain functions (W. C. Dement, 1990). Neuroanatomist Luigi Rolando dissected the brain hemisphere of birds and claimed that this action triggered a sleep-like period (Thorpy, 2011). Marie Jean Pierre Flourens repeated the same experiment on penguins. Studies on humans about the effects of

different times of the day and environmental factors on chronobiology had begun (Monk & Welsh, 2003).

Electrical activities in the brains of animals were first observed by Richard Caton in 1875. In the same century, 4 different sleep theories -vascular, chemical, neural and behavioural- were accepted (Kirsch, 2011).

The claim put forward by Philosopher Alcmaeon, that sleep starts as the brain is filled with blood is the basis of the vascular sleep theory. Albrecht Von Haller suggested the idea that blood flow makes the brain swell and inhibits its vitality. Robert MacNish suggested that there is a relationship between sleep and blood flow and that the brain is active during wakefulness and passive during sleep. Blumenbach claimed the opposite of Robert MacNish's idea and studied the sleep and wakefulness processes on a frozen brain by drilling a hole in the skull, suggesting that sleep can arise from slowed down blood flow (William C. Dement, 2005).

Neural sleep theory emerged when Camillo Golgi first demonstrated the neuron (Bentivoglio vd., 2019). The idea that sleep is triggered by the increase of lactic acid and decrease of oxygen in the body makes the basis of chemical sleep theory. Carbon dioxides and urotoxins are other chemicals that are thought to be responsible for the initiation of sleep.

Behavioural sleep theory is the theory which shows what type of an activity sleep is rather than the reason for sleep. Charles-Edouard Brown-Sequard claimed that sleep is an inhibitory effect. Marie de Manaceine claimed that sleep is a resting phase of unconsciousness. In late 19th century, this theory was abandoned when it was discovered that the brain stem plays a role on wakefulness and sleep processes. Important developments took place in this century regarding the pathology of sleep (Kirsch, 2011). The term narcolepsy was first defined by Jean Baptiste Edouard Gelineau in 1880. The term Narcolepsy derives from Greek words "narkosis" meaning drugs and "lepis" meaning suppression. Sleep apnoea syndrome was first defined by author Charles Dickens. In his book *Posthumous Papers of the Pickwick Club*, the character named Joe is a child who sleeps in his seat, is difficult to wake from sleep and snores, is depicted as suffering from sleep apnoea or obesity hypoventilation (William C. Dement, 2005).

In his experiments with dogs, Physiologist Ivan Pavlov showed that monotonous stimuli causes sleep and he emphasised that the physiology of the factors that lead to sleep cannot be sufficiently explained. In another study with dogs, Legendre and Pieron injected serum from sleep deprived dogs to awake dogs and the awake dogs became fatigued. With this study, researchers claimed the cause of the onset of sleep is a substance found in the blood (Shepard vd., 2005).

The first book which analysed the sleep process from a physiological perspective was written by Henri Pieron in 1913. The 1920 study of Nathaniel Kleitman on sleep deprivation in humans draws wide interest (William C. Dement, 2005). Kleitman observed that people who were sleep deprived the whole night were less sleepy in the morning compared to any moment of the sleep deprived night and claimed that it was incompatible with the idea that suggests the onset of sleep is affected by the increase of toxins in the brain or blood. Kleitman observed that individuals who were sleep deprived for 60 hours had the maximum level of fatigue and that this period had little effect on fatigue in cases of continuous sleep deprivation.

With the electrodes placed on the scalp by German psychologist Hans Berger in 1929, the electrical activity of the human brain was recorded for the first time and it was found that the brain waves differ during sleep and wakefulness (Blake & Gerard, 1937). Berger named the data electroencephalogram (EEG). In 1935, a group of researchers from Harvard University showed that the brain activities change during sleep. Therefore, they claimed that the electrical activity of the brain is different during the different stages of sleep (William C. Dement, 2005; Shepard vd., 2005). In 1937, researchers at University of Chicago observed that different brain waves were present during sleep and wakefulness in the EEG recordings they obtained from humans and they stated that they obtained high amplitude, short wavelength waves during sleep and low amplitude waves during wakefulness (William C. Dement, 2005). With this researched it came to light that the brain performs a slow and synchronised neural activity during sleep. Neurophysiologist Ferederic Bremer conducted studies on cats with the aim to examine the control neuronal mechanisms of sleep-wake regulation (Kerkhofs & Lavie, 2000). Bremer made accurate determinations about the brain`s activated areas and the neuronal

mechanisms during sleep but he claimed that the brain is in a passive state during sleep.

In 1937, Alfred Lee Loomis observed in EEG that there are five different stages during sleep and he named those stages as “A, B, C, D, and E”. The EEG recorded by Loomis is what we call NREM (non-rapid eye movement) sleep.

Nathaniel Kleitman and his student Eugene Aserinsky made electrooculography (EOG) recordings on children and then adults and they claimed the presence of slow and rapid eyeball movements in adults. Researchers described this situation with two different suggestions. The first suggestion leaned on the idea that rapid eyeball movements occurred when there are irregularities in the heart rhythm and respiration and that this is related to the superficial stage of sleep where the second suggestion associated rapid eyeball movements with dreaming. With the discovery of REM sleep, it became evident that the brain is in an active state during sleep contrary to what was previously thought that sleep was a passive state. With another study, Kleitman and Aserinsky unravelled that rapid eyeball movements occur during dreaming. Kleitman and Aserinsky recorded the whole night sleep of individuals and they claimed for the first time that the sleep consists of 90-120 minute stages and first it deepens and then becomes superficial, during the superficial stage rapid eyeball movement occurs and the sleep deepens again. In these studies, they also stated that during the first half of the night deep sleep is more intense and in the second half REM sleep is more intense (Gottesmann, 2009). After these developments in the field of sleep 1950s, researches on sleep, sleep disorders and treatments gained momentum.

Gerald Vogel observed that in narcoleptic individuals with excessive daytime sleepiness, REM sleep occurs right after the onset of sleep, not two hours after the onset of sleep as it normally should (Foulkes, Rechtschaffen, & Roth, 2012).

Richard Wurtman claimed that the melatonin hormone is synthesised in the pineal gland sensitive to light, which affects the circadian rhythm and is secreted between 23.00 and 05.00 in humans (Wurtman, 1967). With this study, Wurtman pointed at the relationship between the circadian rhythm and daylight which is important for the sleep-wake cycle.

Sleep apnoea, which was first mentioned by Charles Dickens, was unknowingly defined by two different research teams in France and Germany in 1966 (Karadağ & Ursavaş, 2007).

The term polysomnography was first used by Jerome Holland in 1974 (Attarian, 2006). Polysomnography is the simultaneous recording and analysis of different physiologic variants during sleep. Electroencephalography (EEG), electromyography (EMG) and electrooculography (EOG) are the main recording components of the polysomnography system. These main recording components are used in determining the sleep stages. In polysomnography, different components may be used for defining sleep physiology and sleep disorders. These are the components which enable the recording of respiratory parameters, muscle activity, snoring and body position (Öztura, 2010).

Before 2007, the sleep stages recorded with the polysomnography system were determined according to Rechtschaffen & Kales (R&K) scoring rules, nowadays they are determined according to the scoring rules of American Academy of Sleep Medicine (AASM) (Himanen & Hasan, 2000; Moser vd., 2009). In determining the stages of sleep, 30-second time windows are examined and each 30-second window is called a stage.

The sleep process consists of two main periods. These are NREM (Non Rapid Eye Movements, Non-REM) when there are no rapid eye movements and REM (Rapid Eye Movements) when there are rapid eye movements. NREM consists of three stages. These are N1, N2 and N3. N1 represents the most superficial sleep where N3 represents the deepest sleep. In literature, N1 and N2 are regarded as superficial sleep and N3 is regarded as deep sleep, delta sleep or slow sleep (Chokroverty, 2009).

NREM makes up almost 75-80% of total sleep duration. The stage present at the onset of sleep is N1. In other words, it is the stage of shifting from wakefulness to sleep and it makes up about 2-5% of total sleep duration. In this stage waking threshold is low and sleep may be easily interrupted. N2 makes up about 45-55% of total sleep duration. K-complex and sleep spindles are two N2 specific waveforms. N3 makes up about 15-25% of total sleep duration. REM sleep makes up about 20-25% of total sleep (Berry vd., 2017).

Sleep stages are determined according to the properties of the signals obtained from EEG, EOG and EMG recordings. In EEG recordings, electrodes are placed on the scalp in accordance with a specific placement rule. Jasper system, which is the international standard, is used for the placement of electrodes (Jasper, 1958; Klem, Lüders, Jasper, & Elger, 1999). In accordance with the developing technology, the number of electrodes has increased and different versions of the Jasper system have been developed (Jurcak, Tsuzuki, & Dan, 2007). In this system, the placement of electrodes is determined by letters and numbers. F stands for frontal area, C stands for central area, P stands for parietal area, O stands for occipital area and T stands for temporal area. Even numbers represent the electrodes on the right side and odd numbers represent the electrodes on the left side.

For determining the sleep stages with EEG recordings, F₄-A₁, C₄-A₁, O₂-A₁, F₃-A₂, C₃-A₂, O₁-A₂ electrode derivations are used and alternatively F_Z-C_Z, C_Z-O_Z, C₄-A₁ electrode derivations are used. The A₁ and A₂ electrodes in these derivations are reference electrodes. In EOG recordings, electrodes are placed 1cm below the left eye outer canthus and 1cm above right eye outer canthus and X₁-A₁, X₂-A₂ electrode derivations are used. Chin EMG is used in determining sleep stages. EMG electrodes are placed below and above the mandible.

In determining sleep stages, if alpha oscillations are observed during more than 50% of the 30-second sleep window, the time window is named wake. If alpha oscillations are not clearly observed, blinking at a frequency of 0.5-2 Hz in the time window, reading movements or rapid eye movements conjugated with normal muscle tone are present in EMG, the window is scored as wake. If alpha oscillation is observed in less than 50% of the time window, and there is low amplitude mixed frequency activity present in the time window, the window is scored N1. If there are no prominent alpha oscillations in the time window, and there is a 4-7 Hz oscillation and vertex sharp waves or slow eye movements are present, the time window is scored N1. If there is at least one K-complex or sleep spindle in the first half of the time window or the last half of the previous window, the time window is scored N2. If high amplitude slow oscillations at a frequency of 0.5-2 Hz are observed during at least 20% of the time window, the time window is scored N3. If mixed frequency and low amplitude EEG oscillations and

low jaw tonus and rapid eye movements are observed in the time window, the window is scored REM.

In recent years, interest in the study of information processing during sleep has increased. It is known that the sleep process is not a passive process and the brain continues to process during sleep and external stimuli are processed differently in sleep compared to wakefulness (Oniz, Inanc, Guducu, & Ozgoren, 2016; Yang & Wu, 2007).

In literature there are studies on the effects of sleep on learning and memory. Stickgold and his team researched the effects of sleep on memory and learning (Stickgold, Fosse, & Walker, 2002). Öñiz et al. researched the effects of sleep on learning and revising with the adapted word root completion test they developed. In the research, they made the participants memorise Turkish and Mongolian words before sleep and they divided the group into two. One group did not listen to any words during sleep and the other group listened to Turkish and Mongolian words, different from the words they had memorised before sleep. When the participants woke up they were repeated the roots of the Turkish and Mongolian words they had memorised before and the words they listened to in their sleep and they were asked to complete the words. With this design, the team which studied both explicit and implicit memory showed that learning during sleep is possible (Oniz, Inanc, Guducu, & Ozgoren, 2015). Among the studies on the effects of sleep on learning and memory, there are also studies which research the cognitive processes during sleep in case of the absence of some sleep stages or the presence of sleep deprivation (Gosselin, De Koninck, & Campbell, 2005; Stickgold vd., 2002).

Alongside studies on the effects of sleep on learning and memory, there are also studies which study the brain responses to external stimuli during sleep (Oniz vd., 2015, 2016; Özgören, Kocaaslan, & Öñiz, 2008). Sleep process is one of the most complex and difficult to measure states of the brain. It is known that the brain is not fully disconnected from the environment during sleep. The fact that many external stimuli can wake up the individuals with their physical as well as notional properties show that cognitive functions continue during sleep (Pratt, Berlad, & Lavie, 1999). However, it is still not fully known how information processing works during sleep. The biggest problem regarding this issue is that individuals cannot be ordered cognitive tasks

during sleep and they cannot make cognitive and/or behavioural responses. Therefore stimulation potential research designs are used in studies. Brain responses that occur as a result of external stimuli during its spontaneous activity are called stimulation potential. According to the purpose of the research stimuli such as aural, tactual, electrical stimuli may be used. Brain responses in studies where aural stimuli are applied are called aural stimulation potential and when tactual stimuli are applied the responses are called tactual stimulation potential. Stimulation potentials are widely used in literature as a method that sheds a light on the brain activities during sleep (Atienza, Cantero, & Escera, 2001; Campbell, 2000; Campbell & Colrain, 2002a, 2002b; Cote & Campbell, 1999; Karakaş vd., 2006; Karakaş, Bekçi, Çakmak, Erzen, & Aydın, 2007; Kocaaslan, Öviz, & Özgören, 2009; Oniz vd., 2016).

In studies where brain responses to the stimuli in sleep are examined, positive or negative response components were observed after the stimulant has been applied and these response components have been named based on the time they appeared. N100 response component refers to the negative response component which appears approximately 100ms after the stimulant has been applied whereas P200 refers to the positive response component which appears approximately 200ms after the stimulant has been applied.

In studies where Colrain et al. used aural stimuli in order to examine the brain responses during sleep they revealed that N100, P200, N300, P450, N550 and P900 response components occurred (Colrain, Di Parsia, & Gora, 2000). In another study which used aural stimuli P200, N300 and P900 response components occurred (Yang & Wu, 2007). Among studies where aural stimuli were used, N100, P200, N300, P450, N550 and P900 response components were observed in the study at which the amount of response components occurred (Kocaaslan, Öviz, & Özgören, 2010).

In the study which examined the brain responses to aural stimulation potential stimuli during sleep, depending on the deepening of sleep the amplitude of N100 response component decreased and amplitudes of N300 and P900 response components have increased. The results of the study show that this change observed in the response components imply that the information processing of the brain continues during different stages of sleep (Kocaaslan vd., 2010).

In majority of the studies which examined stimulation potentials during sleep, aural stimuli were used (Hull & Harsh, 2001; Kocaaslan vd., 2009, 2010; Özgören vd., 2008; Pratt vd., 1999). Öñiz et al. examined the brain responses to pain-free tactual stimuli during sleep in adults for the first time (İnanç, Özgören, & Öñiz, 2014; İnanç vd., 2014; Oniz vd., 2016). In a study which examined response components to tactual stimuli pre-sleep and during sleep, it was seen that P300 and N450 response components only occurred during pre-sleep wakefulness, P450 and N550 response components only occurred during sleep and P50, N100, P200, N300, P900 and Nlate response components occurred during pre-sleep and during sleep (Oniz vd., 2016). In addition it was seen in the study that the amplitudes of P50, N100 and P200 response components to sensory processing are greater during pre-sleep compared to sleep and N300, P450, P900 and Nlate response components have the greatest amplitude during sleep.

In a study where brain response components to pain-free tactual situation related potential stimuli during sleep were examined, constant pressure, pain-free tactual stimuli were applied on the index and middle fingers of the dominant hands (right) of individuals. In both superficial and deep sleep, the amplitudes of the response components to target and non-target stimuli were found to be similar. According to the study results, the brain response continues during sleep but the stimuli on the dominant hand are not distinguished (İnanç vd., 2014).

Due to the fact that the resolution of AASM, which is the classic scoring system used in determining the stages of sleep, is low, micro-processes cannot be observed during sleep and the use of new systems are advised (Himanen & Hasan, 2000; Nasibov, Özgören, Ulutagay, Oniz, & Kocaaslan, 2010; Nieuwenhuijs, 2006; Shirakawa vd., 2000). One of these new systems is Bispectral Index System (BIS) (Benini vd., 2005; Nieuwenhuijs, 2006; Özgören vd., 2008). BIS is a EEG based system used in the monitoring of the depth of anaesthesia. BIS values give constantly varying values between 0-100, 0 referring to the absence of brain activity and 100 referring to wakefulness (Keller, Crow, Foundas, Amunts, & Roberts, 2009).

It is known that high frequency, low amplitude activity is dominant in awake EEG recordings and there are many underlying desynchronised neuron group activities. With the onset of sleep, the frequency of brain activity decreases and oscillations with higher

amplitude than wakefulness are observed dominantly, which are known as alpha (8-16 Hz). It is known that with the deepening of sleep over time, the frequency of brain activity gradually decreases and its amplitude increases in EEG. This activity change in EEG is predominantly observed in theta (4-7 Hz) and delta (0.5-3 Hz) frequency bands. Classical sleep stages are defined using the reflection of the changes in neural activity of various brain structures in EEG frequency bands during sleep. From this perspective, with BIS system (or similar) accompanying classical staging method, the micro processes of individual's sleep processes can be examined. We can say that the BIS system can be used as a supportive system to the classical staging system.

Sleep is considered as a very critical process for mental as well as physical well-being. A healthy person spends approximately one third of their lifetime sleeping. Sleep is the prominent change in the brain function dynamics during the circadian rhythm. Researchers examined the change in the oxygen in the brain during sleep as well as how the brain responses are processed. They have reported that in daytime sleep the level of oxyhemoglobin increases with the onset of REM sleep (Kubota vd., 2011). In one of their studies, Öñiz et al. examined the change in oxygen levels in the prefrontal area of the brain at the beginning and the end of sleep and found that the oxygen level is significantly lower at the end of sleep (Oniz, Inanc, Taslica, Guducu, & Ozgoren, 2019). In light of this study, researchers claimed that the sleep process is essential for the regulation of metabolic capacity and rejuvenation.

With this article, we aimed to dig a little into the sleep process which is researched and studied with many methods and study designs. Many unknowns have come to light whereas many more unknowns still remain a mystery. It is obvious that gathering multi-method approach and multi-disciplines in this field is of utmost importance.

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CHAPTER V
**HEPATITIS A & B VIRUSES AND CHROMOSOME
DAMAGES**

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1. Introduction

Cytogenetic researches had put forward that besides the spontaneous changes in chromosomes: viruses, chemicals and radiation also do harm in genetic substance by preventing the replication of DNA. Hepatitis is literally liver inflammation and causes tissue and organ damage Hepatitis A virus (HAV) is part of the enterovirus group of the *Picornaviridae* family. Hepatitis A has a common distribution and consists of in both sporadic and epidemic forms. HAV is mainly contagious by person-to-person as infected via fecal-oral however, epidemics of widespread-source from contaminated water and food also take places.

Transmission is stimulated by crowding facilitate and poor sanitation Epidemics of HAV are widespread in institutions, prisons, under adverse soldierly and crowded housing projects situations. (Hunt., 2007)

Taxonomically, the Hepatitis B virus (HBV) is included in the Orthohepadnavirus genus and HBV is the prototype member of the family Hepadnaviridae with a partially circular DNA genome (Wassenaar, 2020; Ceejay et al., 2019)

Hepatitis B virus (HBV) is everywhere, but the distribution of infection chances across different areas of the world. In accordance with the World Health Organization, approximately two billion people have been in connection with HBV worldwide, with more than 240 million cases of chronic contagions. (Maléki et al., 2018) In 2015 researches, it was revealed that hepatitis B became chronically and caused cirrhosis and liver cancer. As a result of these complications, it was observed that 887.000 of the cases resulted in deaths each year owing to acute contagions cirrhosis of the liver, and hepatocellular carcinoma (Jue et al., 2019. Placidi L, et al., 2001)

Hepatitis B (HBV) is one of the major global health problem, of humanity worldwide (Wassenaar et al., 2019; Maléki et al., 2018)

Chronic Hepatitis B virus infection is the form in which the hepatitis B virus cannot enter the body and destroy for more than 6 months and may cause bad results such as liver damage (cirrhosis), hepatocellular carcinoma (HCC) and death. (Lopez. et al., (2002) It has also been suggested that it may increase the risk of pancreatic cancer. (Hassan. et al., (2008); Lopez. et al., (2002)) Chromosomal instability may also result from HBV infection. (Özkal P.et al. (2005)) In a less direct fashion, there may be liver cell damage mediated by cellular immune responses, lead to liver cancer by promoting cell death and proliferation.

Genetically mutations may amass in the context of necroinflammatory disease (Özkal P.et al., (2005); Levy L et al., (2002). Major progress has been produced in understanding the molecular formations of hepatocarcinogenesis. In chronic viral hepatitis as well as in different aetiologies of HCC (i.e. autoimmune or hereditary liver diseases, non-alcoholic fatty liver disease, alcoholic liver disease, and certain rare metabolic,) chronic inflammation, cell death and compensatory hepatocyte proliferation referred to as necro-inflammation is an important driver of liver fibrosis (Ringehan M., McKeating Jane A.& Protzer U.2017) Liver cirrhosis is the most important risk factor for HCC. Changes in crucial genes may be based on different types of genetic variances, aligning from subtle sequence changes of a slight nucleotides to cross chromosomal abnormalities, including, amplifications, translocations or deletions of major DNA components. (Özkal P.et al., (2005); Hepatocellular and pancreatic carcinomas might enhance the susceptibility of cells to genetic alterations (Levy L et al., 2002; Zimmermann U. et al., (1997) There are different protocols of mutation finding for deciding the genotoxic influences of chemical agents and physical condition on DNA. (Sarto F et al., 1990) Cytogenetic investigation of metaphase chromosome distribution can be used to define the genotoxic effects of an element, (Surralles J, & Natarajan AT. 1997; Celikler S. et al.,2009) Although classical studies on chromosomal aberrations have been carried on for HCC, there is a lack of cytogenetic information with regard to human hepatitis. (Huang SF 1999; Sarto F 1990; Surralles J. 1997; & Nasarek A1995) To the very of our knowledge, there are no published studies on the effects of viral hepatitis on chromosomes during acute and convalescent periods. In this study, we aimed to analyze the genotoxic effects of HAV and HBV on host DNA using a chromosome aberration (CA) assay in cases with viral hepatitis.

2. Materials and methods

Chromosomal lack of stability indecision may also outcome from HBV DNA integration combining

2.1 Study population

Data on forty cases among the ages of 20-80, obtained at their first presentation to Uludag University, Medicine Faculty. All analyses were carried out at the genetic laboratory in The Microbiology and Infectious Diseases Department. The cases were divided into two subgroups as 20 persons with HAV and 20 persons with HBV. Different serologic “markers” or compositions of markers are used to uncover, dissimilar states of HAV and HBV infection and to detect whether a patient has acute or convalescence, is immune to HBV as a result of preceding infection or vaccination is susceptible to infection laboratory parameters were evaluated for healthy and patient groups by Enzyme linked Immuno Sorbent Assay (ELISA) method (Abbott Laboratories, North Chicago, IL). All serum samples were screened for biochemical laboratory parameters (urine, bilirubinemia, AST and ALT levels) and HAV/HBV serological markers (HBs Ag; Anti HBs; Anti- HBc IgM; Hbe Ag, Anti Hbe and Anti HAV IgM) by commercial ELISA method. Each patient was sampled twice, first during the acute and then during the convalescence period. Ten academicians (age of 20-60) were chosen from the hospital at the Medical Faculty at Uludag University as control group. Individuals who had no genetic defects declared were included in the study unless they had the following conditions: 1) any infection during the previous month, 2) a history of recent X-ray procedures, 3) genetic illnesses, 4) any medical treatments. Also the individuals of all study groups were performed questionnaire including general information about age, alcohol intake, gender, and smoking. Knowledgeable permission was taken into account from every participant, and the working, a protocol was achieved, according to the Declaration of Helsinki

2.2 Preparation lymphocyte cultures and cell harvesting

Heparinised human peripheral blood was used in the essays and was taken from patients with viral hepatitis and control donors at two dissimilar time acute period and convalescence. Per person two cultures were provided by adding 0.3 ml of entire blood to RPMI 1640 medium (10X, Sigma), IU/ml penicillin-100 g/ml streptomycin (Biological Industries) and supplemented with 20% foetal calf serum (Biochrom AQ and 1, 6g/ml phytohaemagglutinin (PHA-L, Biochrom AG), 0.5 mg/ml L-glutamine and 6g/ml phytohaemagglutinin (PHA-L, Biochrom AG). Lymphocytes cultures were incubated at 37 C for 72 h. Metaphase cells were made by extra in extension colcemid (0.2 cml final concentration, Sigma) 2 h before harvesting. Chromosome slides were ready using standard procedure. (Celikler S. et al.2009; Moorhead.P.S.(1960))

2.3 Microscopic evaluation

Assays of cells with CAs was counted in 50 metaphase cells for every culture/person. The data from entire chromosomal aberrations set on, in two groups as pulverisations and gaps were both involved and excluded from entire chromosomal anomalies (TCA and TCA-(G+P), respectively). The most frequent chromosomal anomalies were chromatid breaks, isochromatid gaps, non-centric fragmentation and pulverization CAs were formed considering the recommendations of the EHC51 (Environmental Health Criteria) for Short-period experiment for Carcinogenic and Mutagenic Chemical materials. (Celikler S. et a.,2009; IPCS Guide World Health Organization, Geneva 1985.)

2.4 Statistical analysis

The importance levels of CAs in cultures from cases with viral hepatitis and volunteers in the control group were designated to use non-parametric statistics (Mann-Whitney U test). Unilateral tests were the most suitable when the hypothesis of the study was well-considered. The statistical importance level was determined $\alpha < 0.05$.

These investigations were performed with commercial software programs (SPSS 13.0)

3. Results

Table 1 demonstrates the properties of the patients and members of the control group. Age, current smoking habitudes and alcohol intake were resemblances among the subgroups (Table 1) The results of chromosome aberration test were summarized in Table 2 in term of study population. The results of total chromosomal and chromatid aberrations and all other investigated parameters demonstrated statistically significant differences between the two groups (Table 2, $p < 0.0001$). A chromosomal break is shown in figure 1. The translocation of the “p” arm of chromosome C to the “q” arm of chromosome A has been demonstrated in figure 2.

Table 1. General characteristics of the participants in the study.

	Controls	patients with HAV	patients with HBV
Number of subjects	10	20	20
Gender (male/female)	4/6	10/10	12/8
Age (years)(Mean \pm SD)	33.7 \pm 7.96	20.70 \pm 10.71	30.15 \pm 16.78

Smoking habits (n)			
Non-smokers	6	12	10
Smokers	4	8	10
Alcohol habits (n)			
Non-drinkers	10	20	20
Drinkers	0	0	0

Table 2. The frequencies of chromosome aberrations in cultured human lymphocytes from patients with hepatitis (HAV and HBV) patients and individuals in control group.

%	HAV patients ^a			HBV patients ^a	
	Controls	Acute period	Convalescence period	Acute period	Convalescence period
Gap	0.05 ± 0.06	0.76 ± 0.37***	0.07 ± 0.06	1.12 ± 0.25***	0.08 ± 0.06
Chromatid break	0.03 ± 0.04	0.98 ± 0.42***	0.03 ± 0.04	0.97 ± 0.26***	0.04 ± 0.05
Iso-chromatid break	0.03 ± 0.04	0.31 ± 0.10***	0.04 ± 0.04	0.34 ± 0.13***	0.05 ± 0.05
Pulverization	0.00 ± 0.00	0.01 ± 0.02	0.00 ± 0.00	0.01 ± 0.02	0.00 ± 0.00
Noncentric fragment	0.02 ± 0.03	0.03 ± 0.04	0.01 ± 0.02	0.03 ± 0.05	0.01 ± 0.02
TCA	0.12 ± 0.12	2.22 ± 0.75***	0.15 ± 0.12	2.57 ± 0.51***	0.19 ± 0.11
TCA-(G+P)	0.07 ± 0.08	1.41 ± 0.44***	0.08 ± 0.07	1.45 ± 0.30***	0.11 ± 0.07

TCA: total chromosome aberrations, TCA-(G+P): total chromosome aberrations excluding gaps ^{a:20} lymphocytes were counted per donor in each replicate for chromosome aberrations.

***: $p < 0.0001$; data are expressed as mean ± standard deviation.

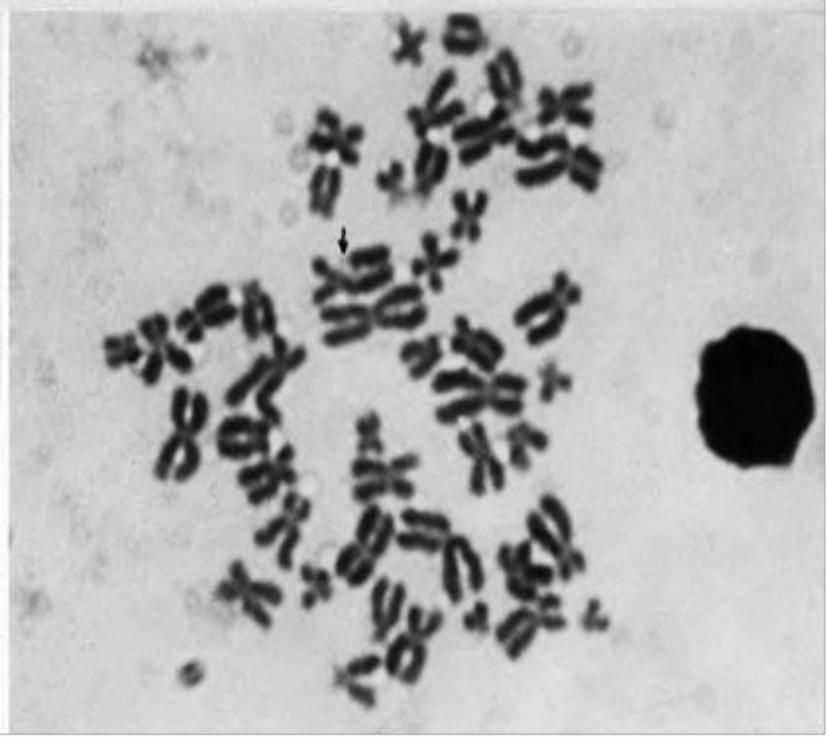


Fig 1. Chromatid break in a patient (x1000)
(Cytogenetics laboratory by Akçağlar S.)

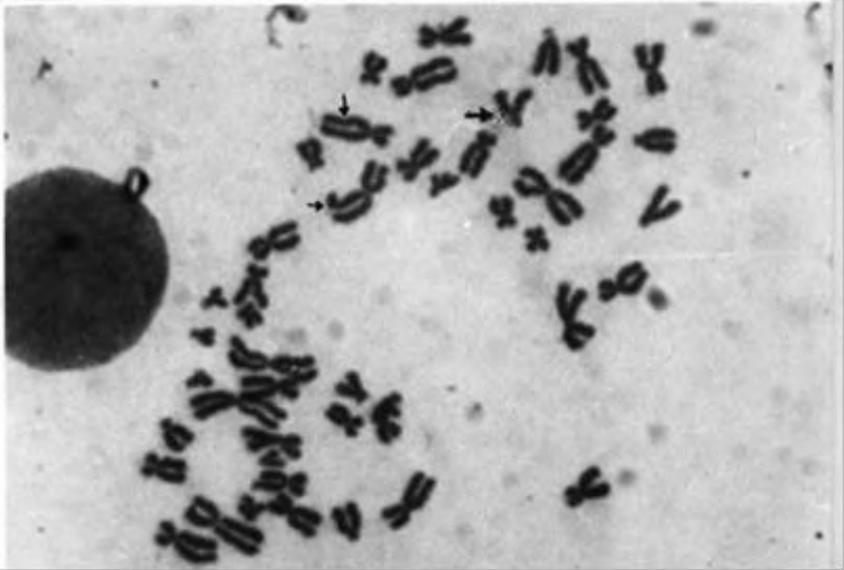


Fig 2. C/A Translocation and a gap in the metaphase in a hepatitis patient (x1000) (Cytogenetics laboratory by Akçağlar S)

4. Discussion

Many researchers have shown that some viruses can affect chromosome stability using *in vitro* and *in vivo* systems. Viruses disrupt the genetic structure by preventing DNA replication. Hepatitis B is liable for the deaths of 56,000 people annually. Hepatitis B is a contagious disease that invades the liver and to impact the lives of 15 million people in the WHO European zone. It is produced by the hepatitis B virus (HBV) and can cause acute and chronic contagion's causing to violent complications, including liver scarring and liver cancer in 20-30% of patients. Different research has demonstrated that HBV has mutagenic influences on somatic cells. (Hepatitis B in the WHO European Region (2017) (www.euro.who.int/hepatitis), www.who.int/hepatitis).

The HBV genome can associate into the human genome, and since these non-specific combining can occur within alternative areas, they may lead to chromosomal (Huang XH. et al.,2003). HBV DNA combining are fixed on not only to human hepatocyte genomes, but also to different cells known to transport HIV such as blood cells. Combininus cause the chromosomal Uncertainty, reason genetic recombinations (Chatterjee B& Ghosh PK,1989), and play a key role in hepatocellular carcinogenesis. (Zondervan PE. et al. 2000) Last research have demonstrated that HBV infection can origin genetic altering among hepatocytes and blood cells, as

confirmed by increased chromosomal breakage. (Huang XH. Et al.2003) We observed several types of chromosomal aberrations, with the most widespread ones being chromatid and iso-chromatid breaks, gaps. As observe in Table 2, we define that the frequency of total chromosomal abnormality was especially increased in both patient groups along the acute period ($p < 0,0001$, Table 2).

However, chromatid and iso-chromatid breaks, Gaps and the frequency of total chromosomal aberration did not differ between the control group and group of patients with HAV and HBV during the convalescence period (45-60 days) ($p > 0.05$). We conclude that viral integration into the host genome caused some abnormalitie s in chromosomes of patients during the acute phase of HAV and HBV infections, but thee abnormalities and breaks reversed during the convalescent period of infection. HBV DNA insertions are detected at casual location, in man cellular DNA, while some chromosomes are affected more often than other. (Kimbi G C. et al. 2005; Slagle BL et al.,1992. In their research with infectious hepatitis and serum hepatitis, Makino and Aya (1968) found that 24 patients with serum hepatitis had B/C reciprocal translocations. We were able to detect B/C translocations in patients, but we also detected events where the “p” arm belonging to the C chromosome had translocated to the q arm of chromosome A (Figure 2).

Makino and Aya (1968) showed the relationships between chromosomal breaks of the A, B, C, D and F groups and the rational lengths of chromosomes. In E and G group chromosomes, especially on the short arms of chromosomes Slagle BL et al. 1992; Makino&Aya (1968; Renda Y.,1968), certain breakage deficits were observed in HAV, A, C, D and F group breakages were proportional according to the length of the chromosomes, there were significantly increased numbers of breakages in the long (q)arm of B group chromosomes, and few breakages were observed in the E and G groups. In our study, we observed some chromosomal breaks in the A, B, C and D groups, but no anomalies among the E, F and G groups of patients with HBV and HAV. These data show that breakages were fixed on the long-length chromosomes according to the Denver karyotype breakage analysis.

In the study conducted by Renda (1968) the Gaps were found 1 2% in the group of patients and 4% in the control group, and the frequency of Gaps in infectious hepatitis cases was statistically different from other viral infections (for example; measles, mumps, chicken pox etc.). In our study, the map frequency of the patient group during the acute phase was also statistically different from that in the control group ($p < 0,0001$). This finding demonstrates that HAV and HBV created Gaps more effectively

than other viruses. We also observed chromosome breakage in a few cells from HAV and HBV patients during the acute period. We believe this occurs independent of the hepatitis type. According to our results obtained during convalescence, significant differences could not be detected between the control group and the infected group (Table 2). Chromosome breakage intensity is affected by, alcohol, cigarette smoking habits and age (Channarayappa JN & Ong T, 1990). In this research, age, alcohol and smoking habits were homogeneously distributed between the group of patients with HAV and HBV and the healthy group. Hepatitis virus synthesizes several viral proteins. These synthesized proteins are quite significant at their locations of effect and for the formation of chromosomal uncertainty. For example, HBV core proteins have been indicated to perform connect with histones, which may affect chromosomal structure and alter chromosomal structuring. In our study, frequency of breakage was remarkably varied, between the control group and the group of infected human with HBV and HAV ($p < 0.0001$).

This shows that hepatitis viruses increase chromosomal breakage and cause chromosomal uncertainty. It is notable that no difference was observed between the category of acute hepatitis patients.

4. Conclusion

The aim of the present study was to assess the chromosome aberrations induced by viral hepatitis, and the differences in the ratio of chromosomal breaks in acute viral hepatitis A and B during the acute and convalescence periods. If we summarize the results;

(1) HAV and HBV cases have increased ratios of chromosome breakage and lack of stability during the acute period of infection.

(2) Our findings propose that hepatitis viruses might possess genotoxic abilities, as determined by CA assay in patients with hepatitis.

(3) HAV and HBV can damage genetic material by preventing DNA replication during the acute phase, but these results can be reversible and do not cause permanent chromosomal damage.

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Footnote: The article on “Hepatitis A & B viruses and Chromosome Damages” which will be published as a book chapter, has been developed and studied part of the PhD thesis.

CHAPTER VI

POST-OPERATIVE INFECTIONS IN ENDOUROLOGICAL PROCEDURES AND PRE- PROCEDURAL PROPHYLAXIS

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Introduction

Endourology emerged as a minimally invasive treatment option in the 1980s for nephrolithiasis. Since then, it has also been used for the diagnosis and treatment of benign prostatic hyperplasia and urothelial carcinomas (1). Endourological surgeries are classified as clean-contaminated procedures because of colonization of the genitourinary tract (2). If the pre-operative urine sample is sterile the incidence risk of infection is low.

Conflicting reports have been shown in the literature regarding the rate of urinary tract infections (UTIs) after endourological procedures (2, 3). General risk factors for UTIs include high American Society of Anesthesiologists score (ASA), old age, diabetes mellitus (DM), obesity, smoking, hypoalbuminemia, and immune deficiency. Specifically, a history of previous UTIs and nephrolithiasis, presence of urinary tract obstruction, presence of bacteriuria and long-term urinary catheterization increase the likelihood of UTIs (3-5).

The use of antibiotic prophylaxis for endourological procedures remains an important matter of debate as there is no consensus (6, 7). Although mild post-operative infections can be simply treated with common antibiotic regimens, moderate and severe infections could lead to sepsis and cause major complications leading to death despite intense antibiotherapy (3).

We aim to review the infection rate in the post-operative period of the most common endourological procedures and the effectivity of pre-operative prophylaxis in preventing infection rates especially in the presence of asymptomatic bacteriuria (ABU).

Asymptomatic bacteriuria

According to IDSA (Infectious Disease Society of America) guidelines, asymptomatic bacteriuria is the presence of 1 or more species of bacteria growing in the urine at specified quantitative counts ($\geq 10^5$ colony-forming units [CFU]/mL or $\geq 10^8$ CFU/L), irrespective of the presence of pyuria, in the absence of signs or symptoms attributable to urinary tract infection (UTI). In catheterized patients, lower colony counts ($\geq 10^2$ to $< 10^5$ cfu/mL) are consistent with bacteriuria for both men and women in a single specimen (8).

Pre-operative bacteriuria is an important risk factor for the development of post-operative UTI (4). In the case of symptomatic patients with bacteriuria, it is recommended to treat them prior to surgery however in the case of ABU treatment is not always necessary. A pre-operative risk evaluation for bacteremia, sepsis, and UTI should be performed and the necessity of prophylaxis should be determined on an individual basis.

While routine pre-operative antibiotic prophylaxis is recommended in certain endourological procedures with high bacteremia and sepsis risk, it should not become a routine in procedures with low risk. The European Association of Urology (EAU) Urological Infections guideline recommends screening for ABU and to treat it preoperatively in cases where the urothelial mucosa will be violated during the procedure (3). However, Cai et al. have demonstrated that ABU has a protective impact in superficial infections in the urinary tract and pre-operative presence of ABU has not been found associated with a higher incidence of post-operative symptomatic UTI (9, 10).

Antimicrobial prophylaxis

There are several risk factors for the development of post-operative infections such as demographic features and comorbidities of patients, operation technique and duration, surgeon's skills and experience, and the amount of peri-operative bleeding (11). Besides these general factors, bacteriuria, pyuria, and urinary flow obstruction should be taken into consideration as specific risk factors for urinary tract infections (12). Pre-operative antimicrobial prophylaxis (AMP) (summarized in Table 1) aims to prevent infectious complications including bacteremia, UTI and sepsis following diagnostic and

therapeutic surgical procedures (3). While it is recommended for high-risk endourological procedures, there is no consensus on an approach for low-risk procedures (6).

Methods

For our literature review PubMed database was scanned for the following Medical Subject Headings (MeSH) terms: ‘infection’, ‘urinary tract infection’, ‘bacteriuria’, ‘endourology’, ‘urolithiasis’, ‘kidney stone’, ‘renal stone’, ‘urinary calculi’, ‘urinary stone’, ‘renal calculi’, ‘stricture’, ‘tumor’, ‘bladder’, ‘upper urinary tract’, ‘prostate’, ‘percutaneous nephrolithotomy’, ‘cystoscopy’, ‘ureterorenoscopy’, ‘transurethral resection’, ‘conservative’, ‘prophylaxis’, ‘mortality’, ‘life-threatening’ and ‘death’ for publications between January 2000 and July 2019. Boolean operators (AND, OR) were used to refine the search. Two authors (BES and IT) independently reviewed the title and abstract of citations. The full texts of potentially eligible publications were obtained and the reference lists of retrieved manuscripts were also screened for further potential publications.

1. Endourological lower urinary tract surgeries via transurethral access

The perineum, periurethral areas and the distal urethra are naturally colonized by bacteria. Bacterial colonization naturally increases with age, especially in females (5, 13). These bacteria can access the bladder by migration, via an indwelling catheter or during instrumentation for transurethral surgeries.

1.1. Diagnostic cystoscopy

Cystoscopy is a safe and well-tolerated procedure often performed in an outpatient setting. UTIs are generally caused by cystoscopic insertion of bacteria from the urethra. According to the most recent and largest meta-analysis, the UTI incidence rate is between 0.85 and 35%, where the septicemia rates vary between 6 to 10%, depending on risk factors and endourological techniques (14-16).

Looking at the recommendations from the major urological organizations on this topic; the American Urological Association (AUA) Best Practice Policy statement recommends consideration of ten host risk factors for infection after cystoscopy (11). The EAU guidelines do not recommend any routine AMP for cystoscopy in healthy patients. The routine use of prophylactic antibiotics before diagnostic cystoscopy cannot be justified based on the evidence from the most recent meta-analysis. the number needed to treat for preventing

one episode of symptomatic UTI is 32 ($p < 0.00001$; OR: 0.40, 95% CI: 0.29-0.54) and for preventing asymptomatic bacteriuria is 26 ($p < 0.00001$; OR: 0.34, 95% CI: 0.25-0.47) (14).

However, if the mucosal violation is expected or if the patient-related risk is high AMP should be considered in order to decrease post-operative UTI rates (3).

Major risk factors affecting host response are; older age, malnutrition, smoking, immunodeficiency, anatomic abnormalities of the urinary tract, presence of colonized foreign material such as an indwelling catheter, presence of bacteriuria, history of urogenital infection and neurogenic lower urinary tract dysfunction.

1.2. Transurethral surgeries for benign prostatic hyperplasia

Transurethral resection of the prostate (TURP) is the most common, and also the gold standard, method for the surgical treatment of lower urinary tract symptoms caused by benign prostatic hyperplasia (BPH) (17). Different techniques and energy sources, such as bipolar transurethral resection of the prostate (B-TURP), holmium, thulium and greenlight laser enucleation of the prostate (HoLEP/ThuLEP/ GreenLEP), bipolar plasma vaporization of the prostate (BPVP) and laser vaporization techniques, are popular alternatives among urologists for endourological treatment for BPH. In the most recent review, Cornu et al. reported UTI rates between 4 and 20% for TURP, 3 and 6% for B-TURP, 2 and 6% for BPVP, 0 and 10% for GreenLight PVP and 2 and 50% for HoLEP (18). In older series for TURP, the more serious complication, urosepsis, has been reported between 1% and 4%, with an associated mortality rate of 13%, which raises to 20% in men over 64 years old (19-21). Pre-operative AMP reduces the risk of UTI after endoscopic management (22) and is recommended by both AUA and EAU guidelines, where no specific recommendations are made for different techniques and technologies.

1.3. Transurethral resection of bladder tumor (TUR-B)

Transurethral resection of bladder tumor (TUR-B) is a common procedure in the daily urological practice for the diagnosis, staging, and treatment of bladder cancer. The incidence of post-operative UTI's following TUR-B has been reported between 1.7% and 6.3% in different studies, which recommended both AMP and no AMP (23, 24). There are few reports for the identification of risk factors for UTIs after TUR-B. Two recent studies showed that the history of pelvic radiotherapy, older age, longer pre-operative hospitalization, tumor size (>2 cm) and increased operative time are major risk factors for post-

operative UTIs (24, 25). There are conflicting recommendations by EAU and AUA guidelines. The AUA guidelines recommend AMP for all TUR-B cases (11). However, the EAU guidelines only recommend AMP in case of large tumors requiring a prolonged surgery time or in case of tumors with necrosis (3). More clarification on this subject is needed to define precise recommendations for AMP of TUR-B.

The efficacy of long versus short-course antibiotic treatment was compared in patients with ABU undergoing TUR-P, TUR-B. This study concludes that short-course therapy is adequate to prevent upper UTI and sepsis. Long course treatment should be given in case of resistant microorganisms (26). ABU increases the post-operative infection risk. Therefore, we recommend a prophylactic single-dose AMP pre-operatively in case of ABU.

2. Ureterorenoscopy

Ureterorenoscopy (URS) is a minimally invasive technique for diagnosis and treatment of ureterolithiasis and nephrolithiasis, upper urinary tract urothelial carcinoma and other obstructions of the upper urinary tract. Rigid, semi-rigid and flexible scopes are available for this purpose but with technological advancements flexible URS has become increasingly popular. Although the use of URS has been increased with expanding indications, the reported incidence of UTIs after URS did not change over time. The incidence has been reported with a wide range between 3.9% and 25% in the 90s and between 2.2% to 20% over the last decade (27-30).

2.1. Ureterorenoscopy for nephrolithiasis

Post-operative infections are one of the most common complications after URS. Up to 20% of patients are readmitted because of a post-operative UTI (31). Proposed predictive factors for symptomatic post-operative UTI include pre-operative infections, pre-operative stenting, and longer operation time for larger stones (≥ 2 cm) (32). The impact of pre-stenting can be explained by bacterial adherence to the stent.

In the case of an infected stone, there is a higher chance of post-operative UTIs compared to other stones (33, 34). In these cases, it is useful to use antibiotics targeting the bacteria found in stone or urine culture from the renal pelvis, as midstream urine culture may not reflect the main pathogen (18, 35).

Cindolo et al. emphasized the potential mortality following flexible URS due to urosepsis (36). In their multi-center experience, the placement of ureteral access sheath (UAS) has been considered among

the best measures to prevent the risk of endotoxin and bacterial dissemination after lithotripsy via URS (36). They recommend measuring serum pro-calcitonin levels in the early post-operative period, where 90 % of the lethal infectious complications occurred within 6 hours after the intervention (36).

Although according to the AUA guidelines AMP is not necessary prior to low-risk urological procedures, the EAU guidelines refer that bacteriuria is a definitive risk factor for endourological procedures. The two available meta-analyses on AMP for ureteroscopic nephrolithiasis treatment clearly showed that a single dose AMP has significantly reduced the incidence of pyuria and bacteriuria ($p < 0.001$ and $p = 0.001$, respectively). They both failed to show that a single-dose AMP reduces the risk of febrile UTIs in the post-operative period ($p = 0.59$) (37). Therefore, a single-dose AMP prior to surgery should be sufficient in patients without ABU.

2.2. Ureterorenoscopy for upper tract urothelial carcinoma (UTUC)

Ureteroscopic management of UTUC is indicated for low-risk tumors or in imperative cases. According to the EAU guidelines, low-risk tumor factors are; less than < 2 cm in size, unifocal involvement, non-invasive and low-grade histology (38).

Reports on post-operative infections in ureteroscopic procedures for UTUC are limited due to the low incidence of this disease (39). Only one study with a limited number of patients ($n=37$) reported the infectious complication rate (8,1% including fever, UTI, sepsis) following endoscopic treatment of UTUC (40).

3. Endourological upper urinary tract surgeries via percutaneous access

3.1. Percutaneous nephrolithotomy (PCNL)

Percutaneous nephrolithotomy (PCNL) is an endoscopic procedure for removal of large and complex stones in the upper urinary tract. (41). Fever in the post-operative period has been reported frequently with an overall incidence of 10.8% (42). Potentially life-threatening sepsis, which is typically due to bacteremia and endotoxemia, has been reported in 0.3–9.3% of patients after PCNL (43).

Diabetes and female gender were found to be associated with post-operative infection risk (OR: 14.6 and 7.8, respectively $p=.0001$) (44). A recent meta-analysis, which included 12 retrospective and 12 prospective studies, reported that presence of bacteria in the pre-

operative urine or peri-operative stone culture and the amount of trauma to the kidney (defined by the number of access tracts and necessity for blood transfusions), are significant factors for infections in the post-operative period (45).

Complex stone composition, which harbors a significant amount of endotoxin, is associated with infection, and stone manipulation causes the release of these endotoxins promoting sepsis (46). Despite appropriate antibiotic regimens based on pre-operative urine cultures, patients may still develop bacteremia or become septic. Microorganisms found from stone and renal pelvis urine cultures are often not found in cultures from voided urine samples. In a study it has been found that positive pre-operative urine and stone culture rates were 7% and 29%, respectively (47). Studies have documented that despite negative pre-operative urine cultures, 25–43% of pelvic urine or stone cultures may be positive, which puts these patients at great risk for post-operative urosepsis (48). Since post-operative leukocytosis and fever are quite common, procalcitonin levels in the early post-operative period may be useful for the recognition of the septic status (48). Pre-operative initiation of a proper antibiotic in case of bacteriuria, limiting operational time and ensuring a low-pressure irrigation setup, can help to decrease the number of infectious complications. However, the duration of peri-operative prophylaxis is unclear in the presence of ABU. Many studies that have included even the patients without ABU have shown that the duration up to 7 days had a significantly lower risk of fever compared to a single dose. Some authors recommended that intra-operative stone culture should be routinely obtained since it is more reliable than peri-operative urine culture (47).

3.2. Percutaneous access for upper tract urothelial carcinoma

As discussed above, upper urinary tract urothelial carcinoma (UTUC) can be successfully ablated with URS in a defined patient population. The antegrade percutaneous approach has limited indications for UTUC, where lesions are large or inaccessible via the retrograde route (39, 49). We could not identify any report for the incidence of infection in the postoperative period, which is in line with limited reports on this procedure.

PCNL is considered a high infection risk procedure and all patients are recommended to use pre-procedure single-dose AMP to prevent UTI and sepsis (3, 50). Cai et al., included a total of 2201 patients who have undergone endoscopic, laparoscopic and open surgery and evaluated the necessity of pre-operative assessment and treatment of ABU. All patients were given AMP in accordance with the EAU

guidelines and they found that pre-operative presence of ABU was not associated with a higher incidence of post-operative symptomatic UTI and urosepsis (9). Therefore, we recommend that pre-operative single dose AMP is adequate in the presence of ABU before percutaneous procedures. Choosing the right antibiotic for prophylaxis should be tailored according to the local resistant pattern, recent urine culture results, recent antibiotic exposure, potential side effects and drug allergy.

Conclusion

Although the success rate of endourological procedures is relatively high, post-operative infections are a common complication after these procedures. Patient's predispositions, perioperative factors, including duration and bleeding, and co-morbid illnesses are the main risk factors of infections after endourological procedures. The risk of bacteremia, sepsis, and symptomatic UTI should be identified and the necessity of prophylaxis should be determined by the individual case basis. While routine pre-procedure antibiotic prophylaxis is recommended in certain endourological procedures with high bacteremia and sepsis risk, it should not be used unwarranted with low-risk patients and unjustified ABU patients. Strict commitment to the guidelines helps reduce infectious complication risks.

Table 1: Antibiotic prophylaxis in various endourological procedures

	Is antibiotic prophylaxis recommended for cases without risk factors? ^a	Is antibiotic prophylaxis recommended for cases in presence of ABU?	Comment
Endourological lower urinary tract surgeries via transurethral access			
Diagnostic Cystoscopy	No	Yes- Single dose	If mucosal violation is expected and risk factors are present
TUR-P	Yes	Yes- Single dose	
TUR-B	Yes / No ^b	Yes- Single dose	
Ureterorenoscopy			
Diagnostic	Optional	Yes-single dose	If mucosal bleeding is expected (i.e. biopsy)

Stone surgery	Yes	Yes ^c	Need to be supported with further studies
Tumor surgery	Yes	Yes-Single dose	
Endourological lower urinary tract surgeries via percutaneous access			
PCNL	Yes	Yes- Short course (3 days)	Need to be supported with further studies
Upper tract tumor resection	Yes	Yes-single dose	Need to be supported with further studies

* Recommended antimicrobials; Trimethoprim, trimethoprim-sulphamethoxazole, cephalosporin 2 or 3, amino-penicillin plus beta-lactamase inhibitor

^a Recommendations of pre-operative antibiotic prophylaxis according to EAU and AUA guidelines

^b AUA guidelines recommend AMP for all TUR-B cases while EAU guidelines do not routinely recommend it except large tumors requiring a prolonged surgery time or tumors with necrosis

^c Although the single dose AMP decreases incidence of pyuria and bacteriuria, it does not decrease the postoperative febrile UTI

Author's Contribution

B Erturk Sengel: Data Collection, Manuscript writing

I Tinay: Data Collection, Manuscript writing

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Conflicts of Interest

The authors declare that they have no conflicts of interest

Human participants and/or Animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Not applicable

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CHAPTER VII

ANTIFUNFAL STEWARDSHIP

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Antimicrobial stewardship programs (ASP) are essential to combat antimicrobial resistance, minimize drug toxicity and medical costs in healthcare systems (1). By optimizing the antimicrobial therapy (dosing, duration, route of administration), less adverse effects, cost, antibiotic resistance, and better clinical outcomes are achieved (2). There are many studies and recommendations related to antibacterial stewardship. However, clinical experiences on antifungal stewardship (AFS) are very restricted.

Invasive fungal infections (IFI) are usually seen in intensive care units and in immunocompromised patients and they usually result in high mortality and morbidity. Currently, sensitivity and specificity of diagnostic tests for IFIs are not satisfactory. The development of new broad-spectrum antifungal agents and the positive impact of early treatment on mortality of IFIs lead to extended use of these new antifungals by physicians in both prophylaxis and treatment of IFIs. (3). In some situations, such as febrile neutropenia and severe sepsis, prophylaxis or empirical treatment may be inevitable. Prescribing prophylactic, empirical, pre-emptive, or targeted antifungal drugs may vary depending on wards or underlying diseases. Previous studies have shown that prophylaxis is mainly prescribed for hematological patients, and empirical or pre-emptive treatments are generally used in intensive care units (ICUs), while targeted therapy is used in medical and surgical wards (4). In a study, it was shown that 43% of antifungal prescriptions are made in medical wards, 25% in hematology-oncology units, and 17% in ICUs. The most common reason for prescribing antifungal agents was empirical treatment (42%). The main risk factor for IFI in these patients was immunosuppression. They found the rate of inappropriate antifungal prescription as 57% through a bedside audit (5). Lopez-Medrano et al. showed that most decisions of prescribing antifungals are not made by infectious diseases specialists but from other specialties (3). Furthermore, Valerio et al found that 33.3% of inappropriate prescriptions were made by infectious disease specialists

(5). These findings show us that the AFS program is necessary to ensure the appropriate usage of antifungals.

In Turkey, there is a nationwide antibiotic restriction program based on a computerized pre-authorization system, and approval is needed by infectious disease specialists, before prescribing an anti-infective agent. Inappropriate antimicrobial use is restricted by this system. Several studies demonstrated the positive impact of this restriction program on the health care system (6-8). However, it is not sufficient alone and it should be supported by other interventions such as prospective audits, feedback, and personal training.

A combination of the AFS program with a comprehensive care bundle is another intervention to achieve appropriate antifungal usage. Many studies showed that comprehensive care bundles improve candidemia management (9, 10). Murakami et al. showed that a candidemia care bundle, as an ASP without an infectious disease specialist, was found significantly effective on appropriate empirical antifungal therapy and treatment duration. However, they didn't find a significant difference in 30-day mortality (11). In a study evaluating the efficacy of a checklist bundle, a significant reduction in 14 and 30-day mortality rates was observed in patients with candidemia (12).

Immunocompromised and critically ill patients in ICU are at high risk for IFI. Empirical antifungal therapy should be started as soon as possible for these patients in the presence of high suspicion (13, 14). However, the proven IFI rates are quite low in the literature. The rate is only 29% among the patients who started empirical systemic antifungal therapy in a study (4). In another study, the rate was found as 35% (15). Valerio et al. found that 57.6% of patients receiving both empirical and pre-emptive antifungal treatment had a confirmed IFI (5). In some departments, experts may decide to start antifungal therapy because of the necessity of early treatment requirement. Therefore, the implementation of practical guidelines and training of the physicians is very important. However, universal guidelines cannot always be applied in daily practice. Each center should establish its own guidelines based on the epidemiologic and demographic characteristics of the community.

Antifungal use may be inappropriate in terms of indication, spectrum, dosage, duration and route of administration. ASP is crucial to minimize drug-related complications by optimizing the dose and duration of treatment and length of hospital stay. While studies generally determine the overall rate of inadequacy in any of the aspects considered, very few studies have evaluated these parameters

separately. In a study, an inadequate dosage rate was found in 3.8% of cases, and probable drug-related toxicity in 6.8% (4). Valerio et al. showed that the rates of inappropriate antifungal selection, duration, administration route, and dosage was 31%, 27%, 20%, 16%, respectively (5). Antworth et al. demonstrated that appropriate treatment duration increased by 30% when implementing AFS (9).

Studies in AFS are increasing day by day. Santiago-Garcia et al. demonstrated that inadequate prescribing of antifungals decreased from 15.2% to 5.3% by the development of guidelines and with training courses (16). Martin-Gutierrez et al. reported a significant reduction in antifungal consumption without increasing the incidence and mortality of hospital-acquired candidemia (17). In a systematic review including 14 interventional studies, it has been shown that the consumption of antifungals decreases while no impact on mortality and IFI incidence by applying AFS (18). The studies evaluating AFS on mortality have not yet shown any significant effect (3, 4, 19).

Because of inappropriate antifungal use, the emergence of resistance, and increased healthcare costs are other concerns. The emergence of resistance is not only limited to antibacterial agents. Antifungal resistance is also a major threat to patients. Just like antibacterial agents, inappropriate use of antifungals contributes to the emergence of resistance and higher cost (20). Prolonged exposure to broad-spectrum antibiotics is among the most important risk factors for fungal infections (13, 20). Therefore, the global reduction of antimicrobial exposure provides a reduction of hospital-acquired candidemia (21). Several studies showed a positive impact on the resistance rate of *Candida spp.* by implementing AFS (3, 22). Smart use of antifungals may result in changes in the susceptibility patterns of fungus.

Several studies also demonstrated the positive impact of AFS on healthcare costs. Given the prolonged hospital stay and adverse events relating to antifungal treatment, the cost increases. Lopez-Medrano et al. showed that antifungal expenditure may decrease by interventions of AFS (3). In another study, Swoboda et al. showed that a 50% decrease can be obtained by only implementing practice guidelines (23). Standiford et al. provided real-time monitoring of antimicrobial agents and determined a 45.8% decrease in antifungal costs (24).

After starting empirical or pre-emptive treatment, effective diagnosis of IFI is very important to continue or stop antifungal agents. Effective and accurate diagnostic tests are crucial to optimize antifungal therapy, controlling antifungal resistance, and better clinical outcome

in patients with IFIs (18). Non-culture based diagnostic methods may provide a more rapid diagnosis of IFI and be a part of the AFS program (20). Many studies recommend the usage of molecular diagnostics and/or serological biomarkers like galactomannan and 1-3 beta-D-glucan assay for early diagnosis (13, 14, 20). There are many studies which assess the positive and negative predictive values of these tests and the results are highly variable due to patient groups (25). In a study, it was shown that serial galactomannan and beta-D-glucan assays provided a significant reduction in the use of empirical antifungal treatment compared to standard diagnostic methods (26). In addition, there are some assays under development. One of these, the lateral flow device that detects a mannoprotein produced by actively growing *Aspergillus spp.*, appears promising (27). Another assay, T2 magnetic resonance-based method detects five different *Candida spp.* in whole blood within hours without the need for prior isolation (28). However, these assays require more studies to assess performance and effectivity.

The need for AFS programs increases every day despite the presence of infectious disease specialists. Given the high mortality and poor sensitivity of diagnostic tests, early empirical or pre-emptive therapy is significant, especially for immunosuppressive and critically ill patients. However, after excluding IFI, inadequate antifungal therapy should be withdrawn as soon as possible to avoid resistance, adverse events, and cost. AFS programs should target to improve clinical outcomes and prevent drug-related toxicity. Rapid-diagnostic tests may reduce the development of antifungal resistance, and cost. These programs should be encouraged by guidelines developed for IFIs.

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CHAPTER VIII

THE COVID-19 PANDEMIC IN LIGHT OF 10 FACTS ON WOMEN'S HEALTH

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Introduction

Novel coronavirus disease 2019 (COVID-19) announced as a pandemic by World Health Organization (WHO) on March 11, 2020 is a new strain of coronavirus first reported on 31 December 2019 (WHO, 2020a). With the first diagnosis of pneumonia of unknown etiology, patient accumulation occurred in hospitals.

Patients epidemiologically linked to a seafood and livestock wholesale market in Wuhan, China, Hubei Province (Bogoch, et al., 2020; Lu, et al., 2020). At the beginning of the new year, sporadic case reports were reported from Thailand (2 cases), Japan (1 case) and the Republic of Korea (1 case) (WHO, 2020b). Within the weeks, the infection has spread to all of China and other countries around the world (Phan et al., 2020; Holshue et al., 2020; Giovanetti et al., 2020). As of August 31, 2020 COVID-19 has been reported in 215 country/region resulting in more than 25,520,527 confirmed cases and more than 852000 deaths (Worldometer, 2020).

The attack rate was estimated between 1.4-2.5 and fatality rate was estimated at around 3.4 by WHO (WHO, 2020c). Symptoms of COVID-19 may appear in as few as 2 days or as long as 14 (estimated ranges vary from 2-10 days, 2-14 days, and 10-14 days), during which the virus is contagious but the patient does not display any symptom (asymptomatic transmission) or cause respiratory illness, ranging from the common cold to more severe disease that can result in death (CDC, 2020).

1. Epidemiology for Age and Sex

People in all ages may be infected by COVID-19. Older people, and people with comorbid medical conditions (such as asthma, diabetes, heart disease) appear to be more vulnerable to COVID-19 (China CDC, 2020). The median age of cases detected outside of China is 45 years, ranging from 2 to 74 years and 71% of cases were male (WHO, 2020d). In a study including 138 hospitalized patients it was found that the median age was 56 years and 54.3% were men. (Wang et al., 2020). Male sex and age were independent risk factors for COVID-19 death (Riccardo et al., 2020). Mortality rate was 0.2% between the ages 10-39 and was doubled in every 10 years of age starting from the age of 60. In confirmed cases, the mortality rate is 2.8% for women and 4.7% for men (China CDC, 2020; WHO, 2020d). The mean age of those who died was 81 years in Italy. Of those among died, 42.2% were aged 80–89 years, the male to female ratio is 80% to 20% with an older median age for women (Remuzzi & Remuzzi, 2020).

In Turkey, a total of 259,253 laboratory-confirmed cases and 6,370 deaths were reported due to COVID-19 by the Ministry of Health. Fatality rate was 2.36%. Among all reported cases, 49% were women and 51% were men. When the age distribution of the cases was examined, 7% were children aged under 16 years, 13.9% were between the ages 15-24, 49.4% were between the 25-49 age group, 18.6% were between the ages 50-64, 8.6% were in the 65-79 age group and 2.5% were 80 years old and above (T.C. Ministry of Health, Covid-19 Situation Report, 2020).

2. Risky groups

Epidemiological analyses by WHO and the Centers for Disease Control (CDC) showed that people who are at most risk death from COVID-19 belong to the vulnerable groups (CDC, 2020):

- People 65 years and older
- People who live in a nursing home or long-term care facility
- People of all ages with underlying medical conditions (asthma, severe heart conditions, diabetes, obesity, chronic kidney and liver disease)
- People who are immuno-compromised (cancer treatment, smoking, bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS, and prolonged use of corticosteroids and other immune weakening medications)

3. The COVID-19 Pandemic and 10 Facts on Women's Health

WHO reported 10 health hazards for women, including tobacco use, physical and sexual violence, reproductive problems, sexually-transmitted infections, HIV/AIDS, malaria and chronic obstructive pulmonary disease (WHO, 2011). Disease outbreaks affect women and men in different ways. Pandemics make existing gender inequalities for women and girls worse, and can impact how they receive treatment and care. Unequal access to information, care and basic health practices increase the health risks for women. Pandemics compound existing gender inequalities and vulnerabilities, increasing risks of abuse. In times of crisis such as an outbreak, women and girls may be at higher risk, for example, of intimate partner violence and other forms of domestic violence due to heightened tensions in the household. They also face increased risks of other forms of genderbased violence including sexual exploitation and abuse in these situations (UNPA, 2020).

3.1. Fact 1: Smoking

Smoking prevalence among men tend to be five times higher than women (The World Bank Data, 2016). However, due to recent aggressive tobacco markets chosed women as target group, tobacco use among younger females in developing countries is rising rapidly. Challenges for women are less success in quitting the habit, more relapses and less effective nicotine replacement therapy than men (WHO, 2011).

Smoking is already known to be a risk-factor for many other respiratory infections, including colds, influenza, pneumonia and tuberculosis (CDC, 2014.). Smoking is also associated with increased development of acute respiratory distress syndrome, a key complication for severe cases of COVID-19 (WHO, 2020f), among people with severe respiratory infections (Hsieh, et al., 2014; Calfee, et al., 2015). Any kind of tobacco smoking is harmful to bodily systems, including the cardiovascular and respiratory systems (World Heart Federation, 2012; World Health Organization, 2018).

Tobacco use may increase the risk of suffering from serious symptoms due to COVID-19 illness. Recent evidence indicates that, compared to non-smokers, having a history of smoking may substantially increase the chance of adverse health outcomes for COVID-19 patients, including being admitted to intensive care, requiring mechanical ventilation and suffering severe health consequences (Vardavas & Nikitara, 2020; Liu, et al., 2020).

3.2. Fact 2: HIV

Globally, it is estimated that there are 17.8 million women living with HIV (15 and older), constituting 52 per cent of all adults living with HIV. Women rates with HIV is a problem of all regions of WHO especially Africa and In Eastern Europe and Central Asia (UNAIDS, 2017). As with other chronic diseases, in two studies supported the probability of HIV/AIDS is a risk factor COVID 19 (Blanco et al., 2020; Guo et al., 2020).

3.3. Fact 3-4: Violence and abuse

Violence against women remains a major threat to global public health and emergency. Between 15% - 71% of women around the world have suffered physical or sexual violence committed by an intimate male partner at some point in their lives. The abuse cuts across all social and economic backgrounds. Violence has serious health consequences for women, from injuries to unwanted pregnancies, sexually transmitted infections, depression and chronic diseases (WHO, 2011). Intimate partner violence is the most common form of violence. Violence against women tends to increase epidemics. Older women and women with disabilities are likely to have additional risks and needs. Women who are displaced, refugees, and living in conflict-affected areas are particularly vulnerable (WHO, 2020g).

COVID-19 can exacerbate risks of violence and abuse for women

Many of women are now trapped in their homes with their abusers. In France, cases of domestic violence have increased by 30% since the lockdown on March 17 (Euronews.com, 2020). The number of domestic violence cases reported to a police station in Jingzhou, a city in Hubei Province, tripled in February 2020, compared with the same period the previous year. (Allen-Ebrahimian, 2020).

Reasons of exposed to violence due to COVID-19 (UN, 2020):

- Stress, the disruption of social and protective networks, and decreased access to services.
- “Stay at home” policy and measures
 - Spend more time with family members in close contact may bring additional stress and potential economic or job losses.
 - Less access to judicial, police services.

- Care work burdens may be overwhelming during this pandemic.
- Unpaid care work
- Limited access to vital sexual and reproductive health services.

3.4.

3.5.

3.6. Facts 5: Sexual health

Even though early marriage is on the decline, an estimated 100 million girls will marry before their 18th birthday over the next 10 years. This is one third of the adolescent girls in developing countries (excluding China). Young married girls often lack knowledge about sex and the risks of sexually transmitted infections and HIV/AIDS.

3.7. Facts 6-7: Reproductive health and neonatal mortality

About 14 million adolescent girls become mothers every year. More than 90% of these very young mothers live in developing countries. Every day, 1600 women and more than 10 000 newborns die from preventable complications during pregnancy and childbirth. Almost 99% of maternal and 90% of neonatal mortalities occur in the developing world (WHO, 2011).

In Latin America and the Caribbean it is estimated that an additional 18 million women will lose regular access to modern contraceptives, given the current context of COVID-19 pandemics (UN, 2020).

3.6. Fact 8: Malaria

The COVID-19 pandemic is characterized by a highly transmissible infectious process and there is a particularly elevated risk of severe disease among individuals with underlying health conditions. It is possible but currently unknown whether malaria and its consequences, especially severe anaemia, may increase severe COVID-19 disease risk (WHO, 2020h). Malaria-endemic countries in all WHO regions have reported cases of COVID-19. In the WHO African Region, which carries more than 90% of the global malaria burden, 45 countries had reported approximately 25 000 cases of the disease as of 30 April 2020 (WHO, 2020i). Insecticide treated nets (ITNs) reduce malaria cases in pregnant women and their children. When women earn an income, they are more likely than men to buy the nets for their households. However, use of the nets is often linked to sleeping patterns that sometimes preclude actual use by women (WHO, 2011).

3.7. Fact 9: COPD

In most countries women tend to be in charge of cooking. When they cook over open fires or traditional stoves, they breathe in a mix of hundreds of pollutants on a daily basis. This indoor smoke is responsible for half a million of the 1.3 million annual deaths due to chronic obstructive pulmonary disease (COPD) among women worldwide. During pregnancy, exposure harmful pollutants may cause low birth weight or even stillbirth (WHO, 2011).

Chronic Obstructive Pulmonary Disease is associated with increased risk of morbidity and mortality in community-acquired pneumonia (CAP) (Restrepo et al., 2006). Alterations in local/systemic inflammatory response, impaired host immunity, microbiome imbalance, persistent mucus production, structural damage, and use of inhaled corticosteroids have been hypothesized to contribute to such risk (Restrepo et al., 2018). With respect to COVID-19, levels of angiotensin converting enzyme 2 (ACE2), the reported host receptor of the virus responsible of COVID-19 (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2), have been observed to be increased in patients with COPD (Wan et al., 2020).

3.8. Fact 10: Chronic Disease

Burden of cardiovascular disease, cancers, diabetes, depression and other mental, neurological and substance abuse (MNS) disorders are increasingly among women globally. In fact, noncommunicable diseases (NCDs) account for 80% of deaths among adult women in high-income countries; 25% of deaths among adult women in low-income countries are attributable to NCD (WHO, 2011).

Among confirmed cases, fatality rate by comorbidity due to COVID-19 was 13.2% for cardiovascular disease, 9.2% for diabetes, 8.4% for hypertension, 8% for chronic respiratory disease and 7.6% for cancers (China CDC, 2020; WHO, 2020e).

4. What can be done for women during and after the COVID-19 pandemic?

Pandemic can further deepen gender inequalities in societies, shape the life of women and increase violence against women. It is vital to prepare public health action preparations by considering 10 Facts of women health and COVID-19 pandemic. It may be helpful to follow these steps in planning public health action preparations:

1. Ensuring women's access to public health messages related to COVID-19: Public health messages should be given in different

contexts to facilitate women's access to health care and to reduce their health risks. For this purpose, health literacy, which is at a low level, should be increased firstly.

2. Precautions should be taken to ensure continuity in standard health services: Particularly sensitive groups should be given importance in terms of pregnancy, delivery and postnatal services, emergency services, neonatal care, violence and abuse. Measures should be taken to monitor chronic diseases and control infection.

3. Socio-economic plans for COVID-19 should be designed on woman center and empowerment.

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CHAPTER IX

THE EFFECT OF GENOTYPE ON THE RISK OF PULMONARY HYPERTENSION IN PATIENTS WITH B-THALASSEMIA MAJOR: A CASE–CONTROL STUDY

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1.Introduction

Thalassemia is the most common hereditary genetic blood disorder characterized by abnormal and low hemoglobin production, leading to life-threatening anemia [1,2]. Depending on the clinical severity, two forms are distinguished: thalassemia major (TM) and thalassemia intermedia (TI) [1,2]. Heart complications are the leading cause of death in both forms of the disease [3]. Lung functional abnormalities and lung involvement have been identified within β -thalassemia since the early 1980s [4,5]. In their study on TM patients, Grisaru et al. reported that in addition to pulmonary functional impairment, they found symptoms of increased pulmonary pressure by evaluating Doppler pulmonary valve flow velocities [6]. In their study on a young and poorly treated Chinese TM population, Du et al. used the systolic transtricuspid gradient determined by Doppler and reported that increased pulmonary systolic pressure often occurred at an early stage of cardiac involvement [7]. In contrast, two subsequent studies on many well-treated Italian and Greek TM patients evaluated in the same method didn't confirm previous findings [8,9]. Derchi et al. reported the prevalence of pulmonary hypertension in Thalassemia major and thalassemia intermedia at 1.1% and 4.8%, respectively [10]. The underlying cause of pulmonary hypertension in thalassemia is multifactorial and includes causes such as hemolysis, chronic hypoxia, chronic iron deposition, high cardiac output, splenectomy, and oxidative stress [11,12]. Du et al. reported that pulmonary pressure is associated with the level of iron accumulation [8]. There are few studies on pulmonary hypertension and ferritin levels in thalassemia major patients, but it is not well known which thalassemia mutation causes more pulmonary hypertension. Therefore, in this study, we aimed to

evaluate pulmonary artery pressure with Doppler echocardiography in patients with different mutations with β -thalassemia major and to compare it with the control group to investigate the relationship between ferritin and pulmonary hypertension.

2.Methods and Materials

2.1. Field of study and ethical approval

This study was carried out between January 2013 and December 2014 at Adıyaman University Faculty of Medicine Research and Training Hospital. The study involved 7 β -thalassemia patients (4 boys and 3 girls) with transfusion-dependent different homozygous β -thalassemia mutation living in the Siirt province as group 1, 7 β -thalassemia patients with homozygous IVS-I-110 (G \rightarrow A) mutation (3 boys and 4 girls) as group 2, and 7 β -thalassemia patients (2 boys and 5 girls) with heterozygous compound mutation as group 3. A control group of eight children (4 boys and 4 girls) of the Siirt Maternity Hospital healthcare staff were included in the study. Each patient received a blood transfusion approximately every 3 weeks. All patients were using oral deferasirox (20-40 mg/kg/day) as iron chelation therapy. Only one patient in the group with heterozygous compound mutation used oral deferasirox and deferiprone together. The Adıyaman University Education and Research Hospital Ethics Committee approved the study protocol, and written informed consent was obtained from all the patients' parents.

2.2. Detection of beta-globin gene mutation

Venous blood samples were drawn from β -thal patients into EDTA-containing vacutainer tubes and transferred to the laboratory via cold chain. Blood samples were stored at -20°C until analyzed. DNA extraction from whole blood samples was performed using the QIA amp DNA blood mini QIAcube kit (Cat. #51104; Qiagen GmbH, Hilden, Germany) according to the manufacturer's protocol. DNA concentration and purity were determined spectrophotometrically using Qubit dsDNA Assay kit with Qubit 2,0 fluorometer (Invitrogen Life Technologies, Carlsbad, CA, USA). We designed primer sets on HBB DNA sequences [National Center for Biotechnology Information (NCBI)] (reference sequence: NG-000007.3). All the synthesized primers had a standard molecular biological quality (Protech Technology Enterprise Co., Ltd., Taipei, Taiwan). Table 1 shows primer sets for the detection of HBB gene mutations in exon 1, exon 2 and exon 3 (Table 1).

Table 1: Primary sets for detection of HBB gene mutations	
Detection for	Sequence (5' to 3')
Exon 1	P1 5'-GCCAGAAGAGCCAAGGACAGGTACGGC-3' (forward)
Exon 2	P2 5'-TCCTGAGACTTCCACACTGATGCAATC-3' (reverse)
Exon 3	P3 5'-TTGCACCATTCTAAAGAATAACAGTGA-3' (forward)
Exon 3	P4 5'-CAGGGGCTGTTGCCAATGTGCATTAGCTG-3' (reverse)

Primer P1 was used to detect mutations in exon 1, primer P2 was used to detect mutations in exon 2, and primers P3 and P4 were used to detect mutations in exon 3. Exon 1 and 2 were amplified together and exon 3 was amplified alone. Amplification was carried out in 25 µl reaction volume in a 0,2 mL polymerase chain reaction (PCR), tube using the GeneAmp PCR System 9700 thermocycler (Applied Biosystems, Foster City, CA, USA). The PCR mix contained 1,25 U Taq polymerase (Fermentas, Vilnius, Lithuania), 10 X buffer (with ammonium sulfate, pH 8,8; Fermentas), 1,5 mM MgCl₂ (Fermentas), 5pmol from each primer, 200µM and 100 ng sample DNA of each dNTP. The PCR program started with 40 denaturation cycles for 150seconds at 93°C. The process continued with 36 cycles including denaturation at 93°C for 30seconds, annealing at 58°C for 45seconds and primer extension at 72°C for 60seconds. It was completed with a last extension step at 5°C for 5min. The PCR products were then run on a 2.5% agarose gel containing ethidium bromide, and visualized under UV light using an imaging system (Biometra GmbH, Göttingen, Germany). The polymerase chain reaction products were purified using the QIAquick PCR Purification kit (Qiagen GmbH). The sequencing was performed using the BigDye Terminator v3.1 Loop Sequencing kit and an ABI PRISM V R 3130 Genetic Analyzer (Applied Biosystems). Genetic sequence analysis and alignment was performed using DNASTAR software (<https://www.dnastar.com>), and the identification of thalassemia mutation was performed using the Biotechnology Information Center database (<https://www.ncbi.nlm.nih.gov/guide/dnaran/>).

2.3. Biochemistry and Hemogram Analyses

Biochemical blood samples were centrifuged at 4 °C and 3500 rpm for 5 minutes and kept at -80 °C until the serum ferritin analysis. Serum ferritin levels were measured through the electrochemiluminescence immunoassay method using the (Hitachi High-Technologies Corporation, Tokyo, Japan) Roche Cobas E601 automatic electrochemiluminescence analyzer (Roche Diagnostics Co., Ltd., Mannheim, Germany). The average level of serum ferritin within three

months was measured. Complete blood count was made using a Cell-Dyn-Ruby hematology analyzer (Laboratoires Abbott, Rungis, Paris, France) from blood taken before transfusion. The average level of hemoglobin (Hb) was measured for three months.

2.4. Echocardiographic evaluation

Colored Doppler echocardiographic examination was performed using Hewlett Packard Sonos 1000 device and 7.5/5.0 mHz, 3.5/2.7mHz probes to all cases. According to the Teicholtz method, ejection fraction (EF) and shortening fraction (FS) were calculated digitally [13]. Tricuspid regurgitation velocity (TRV) color flow mapping and parasternal right ventricle access path were carefully detected in each subject using continuous-wave Doppler, apical four-chamber view, and a short-axis view at the aortic level. The average of at least three measurements for TRV was considered to be the result. Tricuspid insufficiency (TI) was found over TRV using Bernoulli's equation $TI = [4 \times (TRV)^2]$ [14]. Inferior vena cava diameter and respiratory variations were used to estimate right atrial pressure (RAP). Pulmonary artery systolic pressure (PASP) was calculated using the following equation: $TI + RAP$ [15].

2.5. Statistical analysis

For analysis, statistical packages for SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) were used. Mean and standard deviation values were calculated for continuous variables. The nonparametric Kruskal-Wallis H test was used to evaluate three cases and control groups since our sample size didn't meet the parametric analysis requirements. Non-parametric Mann-Whitney U test was used to evaluate the pair groups. The results were evaluated in the confidence interval of 95% and at the significance level of $p < 0.05$. The Spearman test was used for the correlation analysis between the measurement parameters we defined.

3.Results

In group 1 patients who participated in this study, 5 different [IVS-II-1 (G> A), Codon 15 (GG-GA), Codon 36/37 (-T), Codon 5 (-CT), IVS-I-1 (G> A)] homozygous mutations were detected (Table 2). In group 3 patients in our study, 7 different [IVS-I-110 (G>A)/IVS-II-1 (G> A), Codon 6 (A>T) HbS/ Codon 44 (-C)del, Codon 8/9 (+G)

/Codon 39 (C>T), Codon 44 (-C)del/ IVS-I-110 (G>A), Codon 44 (-C)del/ IVS-I-1 (G>A), -30 (T>A)/IVS-II-1 (G> A), -30 (T>A) / IVS-I-6 (T>C)] mutations were detected (Table 2).

Patients	Group 1	Group 2	Group 3
1	IVS-II-1 (G>A)	IVS-I-110 (G>A)	-30 (T>A)/IVS-I-6 (T>C)
2	Codon 15 (GG-GA)	IVS-I-110 (G>A)	Codon 44 (-C) del/ IVS-I-1 (G>A)
3	Codon 15 (GG-GA)	IVS-I-110 (G>A)	IVS-I-110 (G>A)/ IVS-II-1 (G>A)
4	Codon 36/37 (-T)	IVS-I-110 (G>A)	-30 (T>A)/ IVS-II-1 (G>A)
5	Codon 36/37 (-T)	IVS-I-110 (G>A)	Codon 6 (A>T)/ Codon 44 (-C) del
6	Codon 5 (-CT)	IVS-I-110 (G>A)	Codon 44 (-C) del/ IVS-I-110 (G>A)
7	IVS-I-1 (G>A)	IVS-I-110 (G>A)	Codon 8/9 (+G)/ Codon 39 (C>T)

Average values of age, Hb and serum ferritin values of children in group 1, group 2, group 3 and control group in our study were found as shown in table 3 (table 3).

Groups	Group 1 (mean±SD)	Group 2 (mean±SD)	Group 3 (mean±SD)	Control (mean±SD)	P value
Sociodemographic features					
Male	4	3	2	4	
Female	3	4	5	4	
Sum	7	7	7	8	
Biochemical tests					
Hb(g/dL)	10,60±1,1	11,34±1,3	10,8±1,8	13,1±1	p=0,008
Ferritin(ng/mL)	2704±1766	1156±764	1997±1429	86,8±27	P<0,001

In group 1, group 2, group 3 and control group children participating in this study, PASP, TRV, FS and EF averages were found as shown in table 4 (table 4).

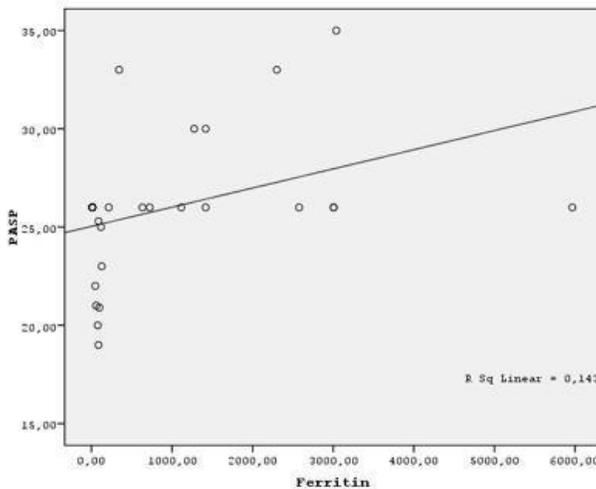
Table 4: Echocardiographic measurements in three cases and the control group					
	Group 1 (mean±SD)	Group 2 (mean±SD)	Group 3 (mean±SD)	Control (mean±SD)	P value
Systolic function					
EF (%)	0,72	0,76	0,73	0,7	p=0,236
FS (%)	35±3,4	45,6±15,4	36,3±6,2	35,5±1,6	p=0,130
Pulmonary flow					
TRV (m/s)	2,5±0,19	2,3±0,79	2,29	2,1±0,1	p<0,001
PASP (mmHg)	29,9±3,9	26,6±1,5	26	22±2,3	p<0,001

It was found that there was no statistically significant difference in EF, FS parameters of group 1, group 2, group 3, and the control group of children participating in this study ($p = 0.236$, $p = 0.130$, respectively). A statistically significant difference was detected in Hb, serum ferritin, TRV, PASP parameters of group 1, group 2, group 3, and the control group of children in our study ($p=0.008$, $p=0.000$, $p=0.000$, $p=0.000$, respectively). There was a statistically significant difference in Hb, serum ferritin, TRV, PASP parameters between group 1 and control group of children in our study ($p = 0.001$, $p = 0.000$, $p = 0.000$, $p = 0.000$, respectively). There was no significant difference between the other parameters we investigated. There was a statistically significant difference in Hb, serum ferritin, TRV, PASP parameters between group 2 and control group of children participating in this study ($p = 0.009$, $p = 0.000$, $p = 0.000$, $p = 0.000$, respectively). There was no significant difference between the other parameters we investigated. There was a statistically significant difference in Hb, serum ferritin, TRV, PASP parameters between group 3, and the control group children in our study ($p = 0.021$, $p = 0.000$, $p = 0.000$, $p = 0.000$, respectively). There was no significant difference between the other parameters we investigated. In our study, in group 1, in total 4 patients, one patient with homozygous Codon 15 (GG-GA), IVS-I-1 (G> A) mutations and two patients with Codon 36/37 (-T) mutations, Pulmonary hypertension was found in one patient who also carried the IVS-I-110 (G> A) mutation in group 2 (table 5).

Table 5: Mutations with pulmonary hypertension		
	Group 1 Patients Mutations	PASP (mm Hg)
1	Codon 15 (GG-GA) / Codon 15 (GG-GA)	33
2	Codon 36/37 (-T) / Codon 36/37 (-T)	35
3	Codon 36/37 (-T) / Codon 36/37 (-T)	33
4	IVS-I-1 (G>A) / IVS-I-1 (G>A)	30
	Group 2 Patients Mutations	
1	IVS-I-110 (G> A) / IVS-I-110 (G> A)	30

Moderate positive linear correlation was found between serum ferritin and PASP ($r = 0.671$, $p = 0.000$, figure 1).

Figure 1: Ferritin and PASP correlation



4. Discussion

Teawtrakul et al. detected the average level of serum ferritin at 2146.8 ± 1928 mg/dL in 139 β -thalassemia patients in Thailand [16]. In their study with 32 β -thalassemia major patients from Egypt, El-Beshlawy et al. detected serum ferritin level average at 2188.12 ± 1332.23 mg/dL in 21 patients with pulmonary hypertension, and serum ferritin level at 2325.52 ± 1285.93 mg /dL in 20 patients without pulmonary hypertension [17]. In their study with 36 β -thalassemia major patients, Hagar et al. detected the average level of serum ferritin at $(2696 \pm 2330$ mg/dL) in 16 patients with pulmonary hypertension and the average level of serum ferritin at $(3176 \pm 3701$ mg/dL) in 12 patients without pulmonary hypertension [18]. Serum ferritin levels we

detected in our group 1 thalassemia patients match the data of Hagar et al. in 16 β -thalassemia major patients with pulmonary hypertension in the USA. Serum ferritin levels we detected in our group 3 thalassemia patients match the data of serum ferritin levels detected by Teawtrakul et al. in Thailand and serum ferritin levels detected in β -thalassemia major patients in Egypt by El-Beshlawy et al. However, the serum ferritin levels we detected in our group 2 thalassemia patients are inconsistent with the lower levels of serum ferritin detected in Thailer patients by Teawtrakul et al., in Egyptian patients by El-Beshlawy et al., and in American patients by Hagar et al. This difference may be due to the difference in the amount of blood transfusion received by patients with thalassemia. As expected, it was found that there was a statistically significant difference in serum ferritin level parameters of group 1, group 2, group 3, and the control group children ($p = 0.000$). PASP levels of group 1, group 2, group 3, and the control group of children in our study were (29.9 ± 3.9 mmHg), (26.6 ± 1.5 mmHg), (26 mmHg), (22 ± 2.3 mmHg), respectively. In their study with 30 major Chinese patients with β -thalassemia major, Du et al. found the average PASP at 47mmHg [7]. In their study with 36 β -thalassemia major patients, El-Beshlawy et al. found the average PASP to be 33.96 ± 7.85 mmHg in 12 patients with pulmonary hypertension and 19.73 ± 4.26 mmHg in 12 patients without pulmonary hypertension [17]. In their study with 36 American β -thalassemia major patients, Hagar et al. found the average PASP level in 16 patients with pulmonary hypertension to be 30.5 ± 4 mmHg, and in 12 patients without pulmonary hypertension to be 19.9 ± 3 mmHg [18]. A statistically significant difference was found in the PASP level parameter of group 1, group 2, group 3, and the control group of children in our study ($p = 0.000$). Derchi et al. reported the prevalence of pulmonary hypertension in Thalassemia major and thalassemia intermedia to be 1.1% and 4.8%, respectively [10]. Du et al. analyzed 33 Chinese β -thalassemia major patients for PASP level and detected pulmonary hypertension in 30 patients (90.9%) [7]. Teawtrakul et al. analyzed 219 thalassemia patients in Thailand for PASP and detected pulmonary hypertension in 24 patients (10.9%) [16]. El-Beshlawy et al. analyzed 36 Egyptian patients with β -thalassemia major for PASP level and detected pulmonary hypertension in 12 patients (33.3%) [17]. Hagar et al. analyzed 36 American β -thalassemia major patients for PASP level and detected pulmonary hypertension in 16 patients (44.4%) [18]. In our study, we analyzed 21 β -thalassemia major patients

in the Siirt province of Turkey for PASP level and pulmonary hypertension was detected in 5 patients in total (23.8 %): 4 patients in group 1, 1 patient in group 2 (Table 5). The results of our study contradict the prevalence data of pulmonary hypertension in Thalassemia major and thalassemia intermedia patients by Derchi et al. Because in our study, in 4 patients carrying different homozygous β -thalassemia mutations (Codon 15 (GG-GA), IVS-I-1 (G> A Codon 36/37 (-T) Codon 36/37 (-T)) in group 1 found pulmonary hypertension (57.1%) , in group 3 carrying mild clinical heterozygous compound mutations [IVS-I-110 (G> A) / IVS-II-1 (G> A), Codon 6 (A> T) HbS / Codon 44 (-C) del, Codon 8/9 (+ G) / Codon 39 (C> T), Codon 44 (-C) del / IVS-I-110 (G> A), Codon 44 (-C) del / IVS -I-1 (G> A), -30 (T> A) / IVS-II-1 (G> A), -30 (T> A) / IVS-I-6 (T> C)] pulmonary hypertension was not found. According to the data of Derchi et al., Group 3 with a heterozygous compound mutation should have had more pulmonary hypertension. In our study, a moderate positive linear correlation was found between serum ferritin and PASP ($r = 0.671$, $p = 0.000$). This data confirm those of Du et al., which is pulmonary pressure being related to the level of iron accumulation. We identified the mutation types and PASP in 21 patients in Siirt province, and these findings will be able to be used in genetic counseling. However, there is a need for further researches on this subject which will be carried out with large study groups.

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CHAPTER X

AORTIC VALVE REPLACEMENT: CHOICE OF PROSTHESIS AND ANTITHROMBOTIC MANAGEMENT

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1. Choice of Prosthesis

Aortic valvular diseases are still an important group of cardiac diseases, in different countries with different etiologies. Thus; aortic valve operation is still one of the most commonly performed cardiac surgeries worldwide. The options available in treatment include aortic valve repair, aortic valve replacement with a mechanical or bioprosthetic valve. We have two options for replacing the diseased valve with a prosthesis mainly; mechanical or bioprosthesis. This choice is dependent on a multiplicity of factors, related to patient. The decision is determined mainly by estimating the risk of anticoagulation-related bleeding and thromboembolism versus the risk of valve degeneration and thus need for reoperation. Mechanical valves have longer durability for structural degeneration, but need for lifelong anticoagulation. Bioprosthetic valves are advantageous about no need for lifelong anticoagulation but have shorter time of durability. Mechanical valves are advised for younger patients who have life expectancy more than expected degeneration time of bioprosthesis. The aim of this choice is protecting the patient from the risks of cardiac reoperations. For older patients who have shorter life expectancy, bioprosthesis should be used with the aim of protection from the risks of anticoagulation related complications [1]. Birkmeyer and colleagues used a Markov state-transition model to simulate the happening of valve-related complications and life expectancy for patients undergoing AVR. Mechanical valves were found more favorable for patients at 50

years of age, tissue valves were favourable for the 60,70 and 80-year-old patients [2]. Although there is a wide consensus about the type of prosthesis for younger and older patients, aortic valve choice for the patient in between 50-70 years is very difficult. Stassano and colleagues published a clinical trial about the choice of prosthesis on this age group. Mechanical valve prosthesis seems to be better choice in aortic position for this age group [3]. Surgeon should make a decision by considering the patient's lifestyle and preferences. Choice of prosthesis is a subject of patient's own life, should be discussed in detail with the informed patient rather than setting exact age limits. (Table 1, Table 2, Table 3) [4,5].

Table 1: Choice of the aortic/mitral prosthesis in favour of a mechanical prosthesis; the decision is based on the integration of several of the following factors (2017 ESC/EACTS Guidelines for the management of valvular heart disease)

Recommendations	Class of recommendation	Level of evidence
A mechanical prosthesis is recommended according to the desire of the informed patient and there are no contraindications to the long-term anticoagulation. (Increased bleeding risk because of comorbidities, compliance concerns or geographic, lifestyle or occupational conditions.)	I	C
A mechanical prosthesis is recommended in patients at risk of accelerated structural valve deterioration. (Young age <40 years, hyperparathyroidism)	I	C
A mechanical prosthesis should be considered in patients already on anticoagulation because of a mechanical prosthesis in another valve position.	IIa	C
A mechanical prosthesis should be considered in patients <60 years of age for prostheses in the aortic position and <65 years of age for prostheses in the mitral position. (In patients 60-65 years of age who should receive an aortic prosthesis and those between 65-70 years of age in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of factors other than age.)	IIa	C
A mechanical prosthesis should be considered in patients with a reasonable life expectancy (>10 years according to age, sex, comorbidities and country-	IIa	C

specific life expectancy) for whom future redo valve surgery would be at high risk.		
A mechanical prosthesis may be considered in patients already on long-term anticoagulation due to the high risk for thromboembolism (atrial fibrillation, previous thromboembolism, hypercoagulable state and severe left ventricular systolic dysfunction.).	Ib	C

Table 2: Choice of the aortic/mitral prosthesis in favour of a bioprosthesis; the decision is based on the integration of several of the following factors (2017 ESC/EACTS Guidelines for the management of valvular heart disease)

Recommendations	Class of recommendation	Level of evidence
A bioprosthesis is recommended to the desire of the informed patient.	I	C
A bioprosthesis is recommended when good quality anticoagulation is unlikely (compliance problems, not readily available) or contraindicated because of high bleeding risk (previous major bleeding comorbidities, unwillingness, compliance problems, lifestyle, occupation).	I	C
A bioprosthesis is recommended for reoperation for mecial valve thrombosis despite good long term anticoagulant control.	I	C
A bioprosthesis should be considered in patients for whom there is a low likelihood and/or a low operative risk of future redo valve surgery.	IIa	C
A bioprosthesis should be considered in young women contemplating pregnancy.	IIa	
A bioprosthesis should be considered in patients >65 years of age for a prosthesis in the aortic position or >70 years of age in a mitral position or those with a life expectancy (should be estimated according to age, sex, comorbidities and country specific life expectancy.) lower than the presumed durability of the bioprosthesis. (In patients 60-65 years of age who should receive an aortic prosthesis and those between 65 and 70 years of age in the case of mitral prosthesis, both valve are acceptable and the choice requires careful analysis of factors other than age.)	IIa	C

Table 3: Factors used for decision making about type of valve prosthesis (AHA/ACC Valvular Heart Disease Guideline, Focused Update 2017)

Favor Mechanical Prosthesis	Favor Bioprosthesis
Age <50 y	Age >70 y
Increased incidence of structural deterioration with bioprosthesis (15-y risk: 30% for age 40 y, 50% for age 20 y)	Low incidence of structural deterioration (15-y risk: <10% for age >70 y)
Lower risk of anticoagulation complications	Higher risk of anticoagulation complications
Patient preference (avoid risk of reintervention)	Patient preference (avoid risk and inconvenience of anticoagulation and absence of valve sounds) ^j
Low risk of long-term anticoagulation	High risk of long-term anticoagulation
Compliant patient with either home monitoring or close access to INR monitoring	Limited access to medical care or inability to regulate VKA
Other indication to long-term anticoagulation (eg, AF)	Access to surgical centers with low reoperation mortality rate
High-risk reintervention (eg, porcelain aorta, prior radiation therapy)	
Small aortic root size for AVR (may preclude valve-in-valve procedure in future)	

2. Antithrombotic Management of Aortic Valve Prosthesis

Postoperative management of a patient in cardiac surgery department is as important as the surgical procedure itself. One of the most important issues in this patient population is prevention of thromboembolic events caused by the prosthesis [6,7]. Antithrombotic management should aim effective control of modifiable risk factors. Risk factors for thromboembolism are listed below in Table 4 [8]. Therapeutic INR levels are higher for these patients. Thus, INR should be individualized for each patient according to risk factors.

Table 4: Risk Factors for Thromboembolism

Atrial fibrillation	Cancer
Increased left ventricular cavity size	Systemic infection
Regional wall motion abnormality	Prior thromboembolic event
Increased age	Diabetes mellitus
Hypercoagulability	Hypertension
Decreased ejection fraction	Eosinophilia
	IgA against Chlamydia pneumoniae

3. Mechanical Prosthesis

Process of anticoagulation is one of the key factors sustains the durability and function of mechanical valves. When the levels of INR decrease, thromboembolic events become more common, at the opposite site; when it increases, bleeding complications become more common. Mechanical valve is not the only factor associated with thromboembolism in these patients, also most of them have secondary risk factors for thromboembolism. We have to control all modifiable risk factors. In case of anticoagulation with warfarin, as in our practise, drug-drug and food-drug interactions have to be taken into account. Because, the most important independent predictor of reduced survival is INR fluctuation due to anticoagulant variability. Especially in early postoperative period, anticoagulant levels are more likely to show fluctuations, frequent measurement of INR is obligatory. VKA is the only oral anticoagulation is recommended for mechanical valve prosthesis.

Anticoagulation with a VKA to achieve an INR of 2.5 is recommended in patients with a mechanical AVR and no risk factors for thromboembolism; if there are additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older generation mechanical AVR (such as ball-in-cage), anticoagulation to achieve an INR of 3.0 is recommended. These are the same recommendations for mechanical valve prosthesis both in 2014 AHA/ACC Valvular Heart Diseases Guideline and 2017 update. [5]

2017 ESC/EACTS Guidelines for the management of valvular heart disease has divided the patients into three groups according to prosthesis thrombogenicity for target INR levels, shown in Table 5. [4]

Table 5: Target INR for mechanical prosthesis

Prosthesis thrombogenicity	Patient related risk factors (Mitral or tricuspid valve replacement; previous thromboembolism; atrial fibrillation; mitral stenosis of any degree; LVEF <35%.)	
	None	1 or more risk factor
Low (Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St Jude Medical, On- X, Sorin Bicarbon)	2.5	3.0
Medium (Other bileaflet valves with insufficient data)	3.0	3.5
High (Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork-Shiley and other tilting-disc valves)	3.5	4.0

The INR levels proceed slowly increase to target levels while the patient under protection of subcutaneous Low Molecular Weight Heparin (100 IU/kg twice a day) or heparin (5000 U every 8 hours). Patients should be educated how to manage their anticoagulation. This an important part of the treatment. Patients should have knowledge about the influence of diet on anticoagulant levels. The importance of regular dosing, fluctuations in INR levels should be taught.[9]

The RE-ALIGN clinical trial, which the use of dabigatran for the mechanical valve prosthesis anticoagulation, was prematurely terminated because of an excess thromboembolic and bleeding events among patients in the dabigatran group. The use of NOACs is contraindicated for mechanical valves. [10] A brief summary for anticoagulation of mechanical prosthesis from 2017 EACTS/ESC Guideline for valvular heart disease is shown in Table 6.[4]

Table 6: Antithrombotic management of mechanical AVR (2017 ESC/EACTS Guidelines for the management of VHD)

Recommendations	Class of recommendation	Level of evidence
Oral anticoagulation using a VKA is recommended lifelong for all patients.	I	B
Bridging using therapeutic doses of UFH or LMWH is recommended when VKA treatment should be interrupted.	I	C
The addition of low-dose aspirin (75-100 mg/day) to VKA should be considered after thromboembolism despite an adequate INR.	IIa	C
The addition of low-dose aspirin (75-100 mg/day) to VKA should be considered in the case of concomitant atherosclerotic disease..	IIb	C
INR self-management is recommended provided appropriate training and quality are performed.	I	B
In patients treated with coronary stent implantation, triple therapy with aspirin (75 - 100 mg/day), clopidogrel (75 mg/day) and VKA should be considered for 1 month, irrespective of the type of stent used and the clinical presentation.	II	B
Triple therapy comprising aspirin (75–100 mg/day), clopidogrel (75 mg/day) and VKA for >1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics that outweighs the bleeding risk.	IIa	A
Dual therapy comprising VKA and clopidogrel (75 mg/day) should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.	IIa	B
In patients who have undergone PCI, discontinuation of antiplatelet treatment should be considered at 12 months.	IIa	B
In patients requiring aspirin and/or clopidogrel in addition to VKA, the dose intensity of VKA should be carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range >65 - 70%.	IIa	B

The use of NOACs is contraindicated.	III	B
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A new theory about the aortic valve prosthesis thromboprophylaxis is being debated nowadays. Platelet activation may be more important in aortic valve prosthesis protection against thrombosis. Thus aortic valve prosthesis might be managed with newer strong anti-platelet agents. Garcia-Rinaldi published the results of 178 patients followed out to 7,8 years treated with dual antiplatelet (aspirin and clopidogrel) only. Thromboprophylaxis in patients with mechanic AVR receiving clopidogrel and ASA seems to be effective with a low incidence of bleeding, TIA and ischemic stroke, and no valve thrombosis. A prospective randomised trial about warfarin versus antiplatelet-only treatment is necessary to prove effectiveness of this treatment exactly. [11]

4.Bioprostheses

Despite the overall lower thrombogenic state in patients with surgical aortic bioprosthesis, there is an increased risk of thromboembolic events especially first 3 postoperative months [7,12]. It is thought to be about the complete endothelialization of the sewing ring [13]. Early anticoagulation with oral vitamin-K antagonists (warfarin is most widely used) has been practised. The use of low dose aspirin is favoured nowadays as an alternative to warfarin which is related to increased bleeding complications [14]. 2017 ESC/EACTS Guidelines for the management of valvular heart disease have a brief summary about selection of antithrombotic prescription. Oral anticoagulation is recommended lifelong just for patients have other indications for anticoagulation. NOACs can be used in patients have AF three months after the operation, but there is lack of data from clinical trials. The use of low-dose aspirin for the first 3 months after a bioprosthetic AVR surgery instead of warfarin is an alternative management relies on low-level evidence (Table 7) [4].

2014 AHA/ACC Valvular Heart Disease Guideline has two recommendations about thromboprophylaxis after bioprosthetic AVR. Aspirin 75mg to 100mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve (Class IIa, Level of evidence B). In a prospective study of Whittlock and colleagues, incidence of thromboembolic events, bleeding and death were similar between the group of low-dose aspirin for the first 3 months after bioprosthetic AVR in sinus rhythm versus the group of VKAs. Anticoagulation, with a VKA, to achieve an INR of 2,5 may be reasonable for the first 3 months

after bioprosthetic AVR (Class IIb, Level of evidence B). According to supporting references; anticoagulation with an INR target of 2,5 (2-3) may be reasonable for at least 3 months and may be as long as 6 months, after AVR with a bioprosthesis [14,15]. Second recommendation has been updated in 2017 update of guideline, anticoagulation with a VKA to achieve an INR target 2,5 is reasonable for at least 3 months and for as long as 6 months after bioprosthetic AVR or MVR surgery in patients at low risk of bleeding. With this update; anticoagulation time was extended to 6 months and level of evidence updated from C to B-NR [16].

Table 7: Antithrombotic management of bioprosthetic AVR (2017 ESC/EACTS Guidelines for the management of valvular heart disease)

Recommendations	Class of recommendation	Level of evidence
Oral anticoagulation is recommended lifelong for patients with surgical or transcatheter implanted bioprosthesis who have other indications for anticoagulation. (Atrial fibrillation, venous thromboembolism, hypercoagulable state or, with a lesser degree of evidence, severely impaired LV dysfunction [EF<35%.])	I	C
Low-dose aspirin (75-100mg/day) should be considered for the first 3 months after surgical implantation of an aortic bioprosthesis or valve sparing surgery.	IIa	C
Oral anticoagulation may be considered for the first 3 months after surgical implantation of an aortic bioprosthesis.	IIb	C

ACTION (Anticoagulation Treatment Influence ON postoperative patients) registry is a study collected the data prospectively at 47 medical centers, between January 2006 and June 2009, 1118 patients bioprosthetic AVR was applied. Multiple variable analysis was performed to select the effective and safe method of thromboprophylaxis in between vitamin K antagonist and acetylsalicylic acid groups. At 180 days thromboembolism rates were 2,8% and 1,5% VKA and ASA groups respectively (p: 0,12); major bleeding was in VKA group 3,6% and in ASA group 1,3% (p:0,01). The 180-day survivals are estimated with Kaplan-Meier, freedom from major bleeding (p:0,01), re-operations (p:0,03) was significantly lower in the

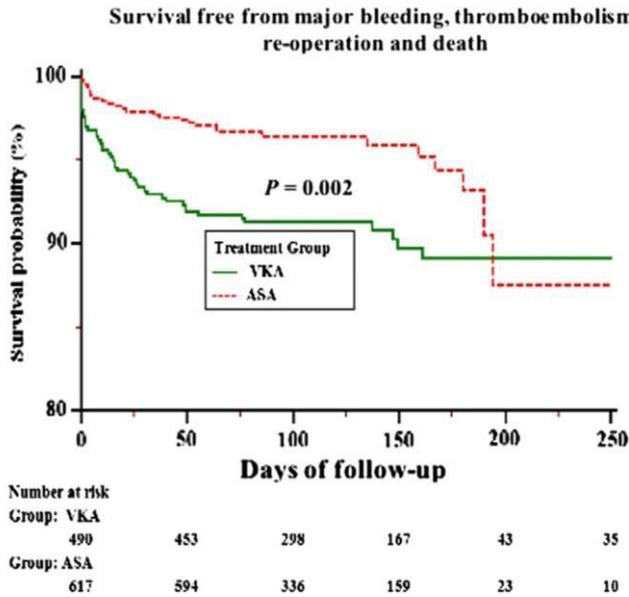


Figure 1: Kaplan–Meier cumulative estimates of survivals free from major bleeding, thromboembolism, repeat operation and death.

VKA than in the ASA treatment group. Freedom from major bleeding, thromboembolism, re-operation and death ($p:0,002$) were lower in the VKA than in the ASA treatment group (Figure 1) [17].

Sulman Rafiq and colleagues published an article of randomised controlled trial with similar results. 370 patients of bioprosthetic AVR were enrolled in trial, data from 328 patients were analysed. The results of this study did not demonstrate any statistically significant difference in thromboembolic events or major bleeding [18]. Opposite results came from a study cohort from Sweden, written by Christersson and colleagues. Comparison of warfarin versus antiplatelet therapy after bioprosthetic AVR was done on a group included all patients undergoing bioprosthetic AVR between 1 January 2008 and 31 December 2014, 9539 patients. Warfarin treatment up to 3 years after surgery was associated with lower incidence of ischemic stroke, compared with single antiplatelet treatment. Warfarin is associated with higher incidence of hemorrhagic stroke, but not with higher mortality

rates. Dual antiplatelet treatment has no superiority to single antiplatelet treatment group regarding the risk of thromboembolism or ischemic stroke [19].

The use of non-warfarin oral anticoagulants (NOACs) for anticoagulation after prosthetic valve surgery is a Class III recommendation and should not be used. VKAs are being advised when anticoagulation is needed lifelong for any other reason than the prosthesis itself. NOACs can also be used for atrial fibrillation in patients of bioprosthetic AVR except for the first three months, but there is a lack of data from clinical trials [20].

Some other small randomized controlled trials were documented on this issue, but the choice of antithrombotic management is still debatable. There are conflicting ideas and study results about the optimal thromboprophylaxis after biologic AVR surgery, including strategy, medication and duration of treatment. Dual antiplatelet treatment is not recommended if there is not any other indication. Choice of treatment should be made according to patient, compliance to treatment, access to health-care centers. New randomized controlled trials including large patient groups are necessary to decide exact treatment modality.

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CHAPTER XI

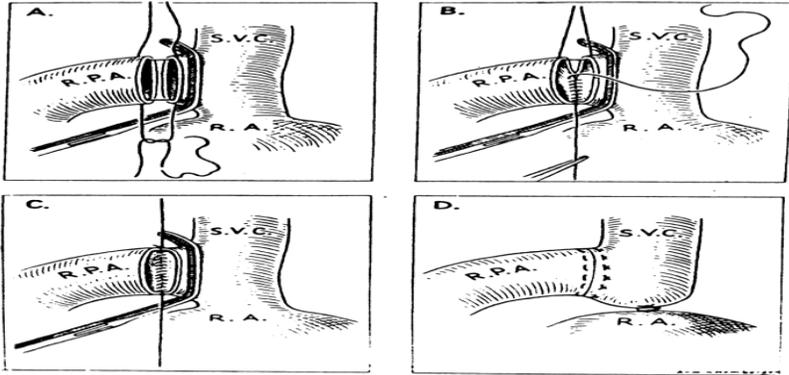
BIDIRECTIONAL GLENN SHUNT PROCEDURE WITHOUT CARDIOPULMONARY BYPASS

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1. History

Currently, cavopulmonary anastomosis is generally and widely referred to as Glenn shunt. Cavopulmonary anastomosis, which is one of the important milestones in the surgical treatment of congenital heart diseases (CHDs), has undergone various changes since the 1950s when it was first performed. In 1949, Rodbard and Wagner had experimentally anastomosed the right atrial appendage to the pulmonary artery (PA) and presented the first successful animal experimental study (1). In 1950, Carlon et al. (2) performed the cavopulmonary anastomosis in dogs for the first time in the literature. The first successful superior vena cava (SVC) to right PA shunt, also referred to as classic (unidirectional) Glenn shunt or unidirectional cavopulmonary anastomosis, was performed by Dr. William Glenn at Yale University in 1958 (3). Through a right thoracotomy, the SVC and right PA were transected and anastomosed end-to-side without cardiopulmonary bypass (CPB).



Glenn WW. Circulatory bypass of the right side of the heart. IV. Shunt between superior vena cava and distal right pulmonary artery; report of clinical application. N Engl J Med 1958;259:117-20



Glenn WW. N Engl J Med 1958;259:117-120.

Control angiography for Glenn procedure. (Glenn WW. Circulatory bypass of the right side of the heart. IV. Shunt between superior vena cava and distal right pulmonary artery; report of clinical application. N Engl J Med 1958; 259:117-20)

The classic Glenn shunt was shown to provide low-pressure pulmonary blood flow to patients with cyanotic CHD and to bring fewer volume loads to a single ventricle compared to systemic shunts (3). Over time, the classic Glenn shunt has evolved from unidirectional to bidirectional, which provided less distortion to the right PA and allowed low-pressure pulmonary flow to be delivered to both PAs. Bidirectional Glenn shunt (BDGS) is commonly performed as an intermediate stage

before the Fontan procedure in single ventricular cyanotic CHDs (4). It can be performed to reduce the volume load of the right ventricle in patients with Ebstein malformation, to ensure one and a half ventricular repair in patients with right-ventricular hypoplasia (4), and to train morphologic left ventricle by means of PA banding in patients with delayed transposition of the great arteries (5). Following the procedure, the ventricle volume overload decreases and oxygen saturation increases. Dogliotti et al. (6) performed BDGS for the first time in 1961.

Currently, BDGS is performed under CPB conventionally with aortic and bicaval venous cannulation or SVC and cannulation of the right atrium (RA). However, CPB is associated with inflammatory and mechanical risks. The use of CPB may result in increased lung damage and consequently, prolonged need for mechanical ventilation, hemolysis, increased cost, and systemic inflammatory reaction syndrome (7). Prolonged CPB duration has been found to be an independent predictor of poor clinical prognosis after BDGS (8). All these factors have led researchers to perform BDGS without CPB, also called off-pump BDGS. The most important problem here is the neurological complications caused by the increased pressure in the SVC under the clamp and the need for decompression in the SVC. The BDGS procedure can be performed easily without CPB in cases with bilateral vena cava. There are many techniques and approaches for performing BDGS without CPB. Lamberti et al. (9) defined BDGS without CPB for the first time in 1990. They used a temporary venoatrial shunt between SVC and RA.

2. Patient Selection

Patients should be evaluated carefully using echocardiography (Echo), angiography, and, if required, computed tomography (CT) to perform BDGS without CPB. If the following criteria are met and the surgical team has sufficient experience, BDGS can be performed without CPB (7,10-14).

- 1- Being older than three months of age
- 2- Having non-restrictive atrial septal defect
- 3- Having no advanced atrioventricular valve regurgitation
- 4- Having no other intracardiac disorder requiring correction
- 5- Having a preoperative mean PA pressure below 18 mmHg
- 6- Having a McGoon index of 1.5 and above
- 7- Having a pulmonary vascular resistance (PVR) less than 2 units/m²

Severe cardiac failure, renal and hepatic disorders, and thrombocytopenia have been reported among relative contradictions.

3. Preparing For Surgery and Anesthesia

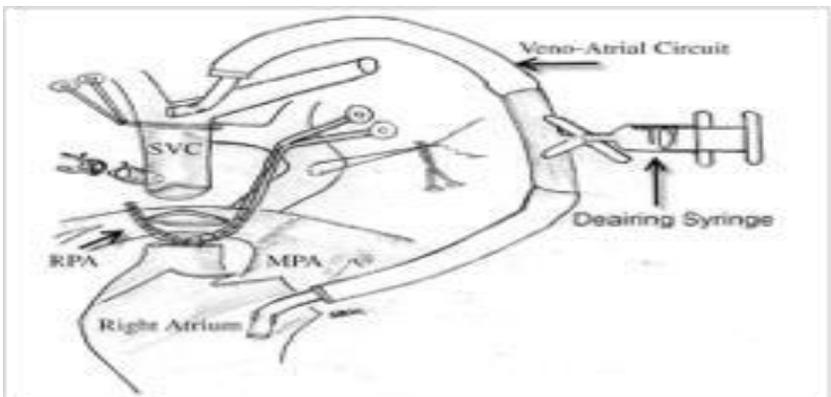
Cardiac catheterization and Echo were performed in all patients. Midazolam 0.1 mg/kg and ketamine 3 mg/kg were administered intramuscularly to the patients 15 minutes before anesthesia induction. All operations were performed under general anesthesia. All cases were monitored intraoperatively through five-lead electrocardiogram (ECG), pulse oximetry, capnography for end-tidal carbon dioxide (EtCO₂), jugular venous catheterization for venous pressure monitoring, radial or femoral artery cannulation for invasive artery monitoring, noninvasive arterial pressure monitoring, and near-infrared spectroscopy (NIRS). The BDGS procedure is performed under general anesthesia. Anesthesia was induced with fentanyl 5 µg/kg, and sevoflurane and rocuronium 0.9 mg/kg⁻ and maintained with sevoflurane and rocuronium 0.3 mg/kg/h, and fentanyl 5 µg/kg/h. Ventilation was adjusted to achieve an EtCO₂ of 30–35 mmHg, peak airway pressure of <20 mmHg, and positive end-expiratory pressure of 5 mmHg.

4. Operation Techniques

4.1. Glenn Shunt Performed Using Cavoatrial or Innominate Vein Right Atrial Shunt Without CPB

Although there are many methods in BDGS procedure performed without CPB, the method generally preferred by surgeons is temporary shunting established between the SVC or innominate vein and RA (7,9,13-16). Lamberti et al. (9) performed BDGS without CPB by shunting between the SVC and RA for the first time. Kandakure et al. (15) performed this procedure by shunting between the innominate vein and RA. Although there are some changes, this method is generally performed mainly via medium sternotomy under general anesthesia. Arterial blood gas pressure is measured before and after clamping the endotracheal tube. During the operation, PA diameter is evaluated, direct PA pressure is measured, and SVC and left innominate vein are completely dissected. During dissection, the lymphatic ducts are protected by staying closer to the cava. Similarly, the ipsilateral PA pressure is carefully dissected up to the hilar branches and encircled with a loop. If the patients have a history of nodal rhythm or blocked rhythm, pacing wires are electively placed before dissection at the beginning of the operation. Aortopulmonary shunts or patent ductus arteriosus (PDA) are identified if any, and they are, then, dissected. During this phase of the procedure, they are left undisturbed. Marker

stitches are placed on the anterior of the SVC at the place of possible division. The azygos vein is ligated and separated from the ligation site. Purse suture is placed on the innominate vein at the junction where it joins the SVC. The other purse suture is placed on the appendix of the right atrium. The PA branch is trial clamped for several minutes to control changes in arterial oxygenation. After systemic heparinization (3 mg/kg), the activated clotting time is tried to be kept above 200 seconds. The innominate vein-SVC junction and the right atrium are cannulated. They are connected through a three-way connector and carefully de-aired. The shunt is opened, and the head of the patients is elevated. The SVC is clamped at right atrial end and near the innominate insertion and is divided just below the marker stitch. The proximal end is closed with suture and the strings are used to retract it away from the PA branch. The PA branch is isolated within a Cooley clamp and opened between stay sutures. The SVC is anastomosed to the PA with continuous Prolene suture by determining the end of the divided azygos as a posterior landmark. The clamps are removed after the Glenn shunt is completed. Then, aortopulmonary shunt and PDA are ligated. Pulmonary artery banding (PAB) can be performed if antegrade pulmonary blood flow and Glenn pressure are high. After heparin is neutralized with protamine, bleeding is controlled, and cannulas are removed. The sternum is closed following the placement of chest drains. Shunting may not be required in the presence of bilateral SVC because decompression is provided from the other while the other is clamped.



Veno-venous shunt SVC: Superior vena cava, RPA: Right pulmonary artery, MPA: Main pulmonary artery. (Veno-venous shunt-assisted cavopulmonary anastomosis. Pramod Reddy Kandakure, Anil Kumar Dharmapuram, Suresh Babu Kale, Vivek Babu, Nagarajan

Ramadoss, Ramkinkar Shastri, Avinash Londhe, Ivatury Mrityunjaya Rao, Kona Samba Murthy. *Ann Pediatr Card* 2010 Vol 3 Issue 1.)

Lal and Mahant (17) reported a different technique using venoatrial shunt. They drained the blood into a reservoir through SVC cannula and pumped it to RA with the help of a roller pump (17). However, since this technique a kind of CPB application due to requiring a pump for draining the blood and a perfusionist for perfusion even though CPB is not used, whether it should be included in this classification is a matter of debate. Similarly, Chen et al. (10) described a similar method by modifying the SVC cannula used. Although technically the same method was used, the SVC cannula used was modified to allow both innominate vein drainage and to easily decompress SVC blood.



Figure 1. An oval open was created on the top of the external curvature in the standard right-angle venous cannula, resulting in a bidirectional right-angle venous cannula (Chen LW, Dai XF, Wu XJ, Wang QM. Placement of a modified cannula in the innominate vein for sufficient drainage during the bidirectional Glenn shunt procedure without cardiopulmonary bypass. *J Cardiothorac Surg.* 2015; 10:134. doi: 10.1186/s13019-015-0341-7.)



Figure 2. Conventional Medtronic (DLP venous cannula; Medtronic, Inc., Minneapolis, MN, USA) right angle venous canula.

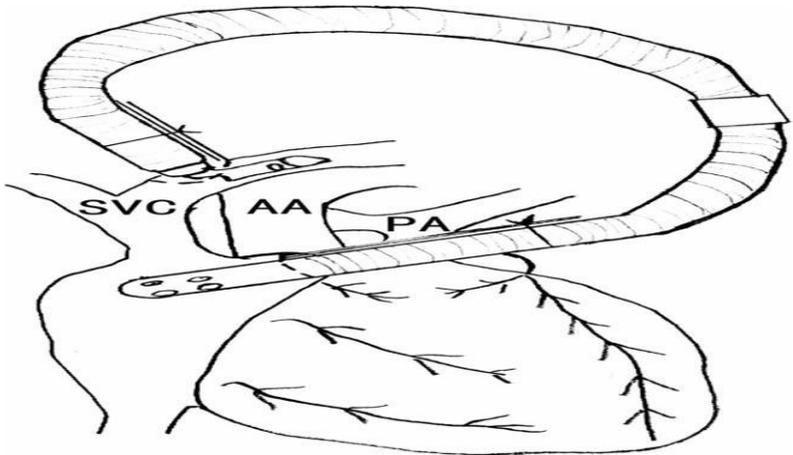
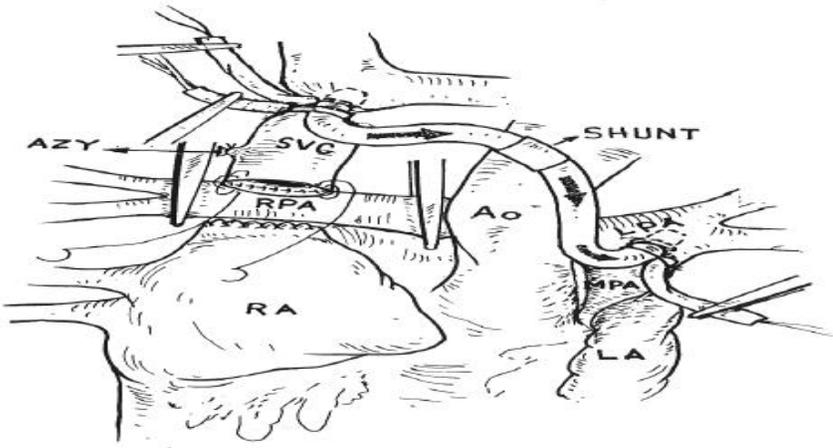


Figure 3: The bidirectional right-angle venous cannula was placed within the innominate vein for establishing the temporary veno-atrial bypass during the bidirectional Glenn shunt procedure in small infants. AA: ascending aorta; PA: pulmonary artery; SVC: superior vena cava; DVV: descending vertical vein (Chen LW, Dai XF, Wu XJ, Wang QM. Placement of a modified cannula in the innominate vein for sufficient drainage during the bidirectional Glenn shunt procedure without cardiopulmonary bypass. *J Cardiothorac Surg.* 2015; 10:134. doi: 10.1186/s13019-015-0341-7.)

4.2. Glenn Shunt Performed Using Cavopulmonary Shunt Without CPB

Murthy et al. (18) performed the off-pump BDGS procedure for the first time using cavopulmonary shunt and then, many surgeons have used this method (13,16,19). They defined this method as follows. Median sternotomy, pericardium was opened, and the SVC dissected. The azygos vein was ligated and divided. The right pulmonary artery (RPA) was dissected from the bifurcation to the hilar region. Purse-string sutures were placed longitudinally on the distal part of the SVC or innominate vein and main pulmonary artery (MPA). After systemic heparinization (2 mg/kg), a shunt was established between the SVC or innominate vein to the MPA with two standard right-angle cannulae. The pulmonary end of the right-angle cannula was directed towards the contralateral branch PA. The SVC was transiently occluded to fill up the circuit with blood to prevent air embolism. After establishing the

shunt, the cannulae were placed parallel to the patient for better drainage. The SVC was clamped and divided just above the cardiac end without damaging the sinus node. After clamping the SVC, there was a rise in venous pressure with improvement of oxygen saturation in all patients. The temporary shunt acts like a modified Glenn shunt. The cardiac end of the SVC was closed. The RPA was occluded at its proximal and distal ends with vascular clamps. It was opened at its superior aspect, and the distal end of the SVC was anastomosed to the RPA (end to side) using sutures. After shunt, the clamps were removed (Fig 1). The temporary shunt was disconnected in the middle and the blood in the cannulae was allowed to drain into the SVC and PA. Then, the cannulae were removed and the purse-string sutures were tied. During the all procedure, the patients' heads were elevated.



Murthy KS, Coelho R, Naik SK, Punnoose A, Thomas W, Cherian KM. Novel techniques of bidirectional Glenn shunt without cardiopulmonary bypass. *Ann Thorac Surg* 1999; 67:1771-4.

4.3. Glenn With Jugulo-femoral Venous Shunt Without CPB

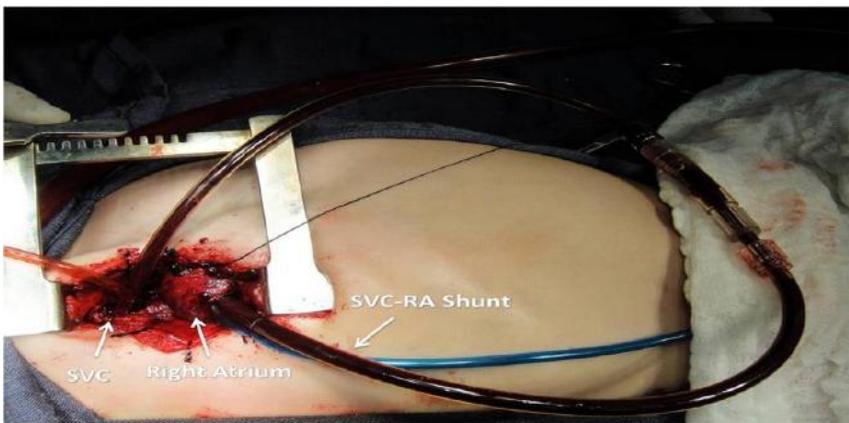
Abdelbaser and El Derie (20) performed the off-pump BDGS procedure for the first time using extrathoracic jugulo-femoral venous shunt. The technique is carried out as follows. After standard anesthetic technique extrathoracic jugulo femoral venous shunt was established by inserting a 16–18-gauge cannula into both right internal jugular and right femoral veins guided by ultrasound. Both cannulae were connected via a venous extension line after its filling with heparinised normal saline, with three-way stopcock in it close to the internal jugular cannula. This shunt was used after clamping of the SVC to drain the high-pressure venous blood from the internal jugular vein into the low-

pressure femoral vein. Active decompression of the SVC was used by applying negative pressure to the internal jugular cannula. Heparin 1–2 mg kg⁻¹ was administered via a central vein to achieve an activated clotting time of ≥ 200 s. The SVC was clamped, and the distal end of the SVC was anastomosed end-to-side to the right pulmonary artery. Blood from the right internal jugular vein was aspirated using a 20 ml syringe and re-injected into the right femoral vein under complete aseptic precautions with great care to avoid air injection. Syringe injection was repeated 10–20 times min aiming to maintain a CVP <20 mmHg. Methyl prednisolone 30 mg kg was given and the head of the operating table was elevated 30° upwards to allow better venous drainage by gravity through the collateral pathways and to minimise brain congestion. The CPB machine was available as standby for any significant haemodynamic disturbances that might occur, so we could complete the procedure on bypass safely. Dobutamine 5–10 µg/kg/min was infused before clamping of the SVC, and a volume load, 5 mL/kg, of colloid (fresh frozen plasma or blood, according to the haemoglobin level) was given to elevate the mean arterial pressure (MAP) to maintain for an adequate cerebral perfusion. Surgery was conducted through a standard median sternotomy. Mild systemic hypothermia was allowed by maintaining the nasopharyngeal temperature between 33°C and 35°C through the low operating room temperature to reduce brain metabolism. During the procedure, haemodynamic instability was managed by infusions of epinephrine up to 0.2 µg/kg/min norepinephrine up to 0.2 µg/kg/min and colloid infusion. After anastomosis, the right pulmonary artery and SVC clamps were released.

4.4. Glenn With Thoracotomy Using Cavoatrial Shunt Without CPB

Various surgeons have performed off-pump BDGS with thoracotomy using SVC-RA shunt (21, 22, 23). The procedure was performed under general anesthesia. Right anterior thoracotomy was performed in the 4th intercostal space. Circumferential control was gained around the entire length of the SVC, exposing this vessel completely by dissecting from the adjacent tissues. The azygous vein was divided and ligated, this was to ensure non steal phenomenon from the SVC to inferior vena cava through this vein. The right pulmonary artery was exposed, and circumferential control was gained around the right main pulmonary artery as well as the hilar branches. Intraoperative pressure of the right pulmonary artery (RPA) was measured for the feasibility of the procedure. Two purse-string-sutures with 5-0 polypropylene were performed, one at the proximal side of the SVC and

the other at the right atrial appendage. The patient was systemic heparinized with 300 units/kg to maintain activated coagulation time (ACT) above 250. A 12F right-angle cannula was placed high on the SVC and a 12F straight cannula was placed in the right atrium. These cannulas were de-aired and hooked together to create a venoatrial shunt and allow drainage of the upper body while the proximal SVC was occluded. The pulmonary artery was temporarily occluded using a partial clamp, to ensure acceptable oxygen saturations (maintained between 50-60%) and hemodynamic stability. The SVC was clamped and sectioned distally; the stump was oversewed using two layers of 6-0 polypropylene. The SVC was anastomosed to the RPA using continuous 6-0 polypropylene suture; the clamps were removed and hemostasis achieved. The shunt between the SVC and the right atrium was removed and the heparin reverted with protamine, finally the surgical incision was closed conventionally.



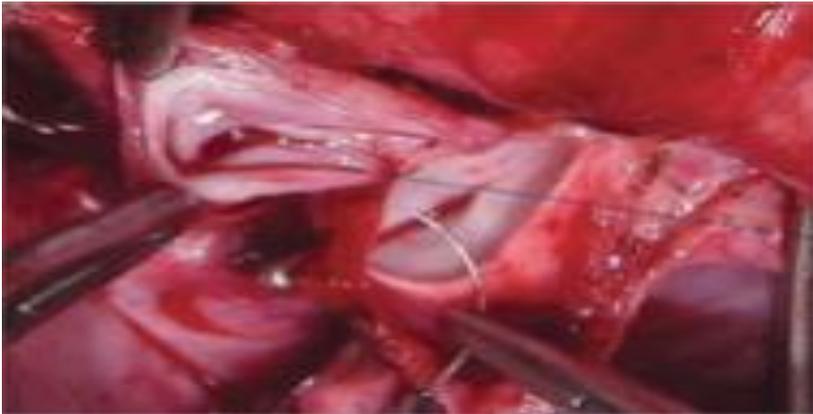
Guida, M., Cascio, A. L., Guida, G., Guida, G., Garate, E. D., Vasquez, M., Preto F, Pecchinenda, M. (2015). Off-pump bidirectional Glenn through right anterior thoracotomy. *Brazilian Journal of Cardiovascular Surgery*, 30(4), 497-500)

4.5. Glenn Without Shunt and

4.5.1. Via Sternotomy

In this method defined by Hussain et al. (4), Glenn was performed with the decompression of SVC through the azygos flow principle without using any shunt, and medical management. The details of the method are presented below. After median sternotomy, pericardium was opened and after assessing the cardiac anatomy, direct pulmonary artery (PA) pressure was taken in all patients. The SVC was dissected from the cardiac end to innominate vein junction. The azygos vein was

dissected but not ligated at this stage. After the main pulmonary artery (MPA) was dissected, the right pulmonary artery (RPA) was dissected up to branching. No manipulation of the BTS (if present) was done at this time. Heparin (1 mg/kg) was administered to achieve an activated clotting time (ACT) of 180 s or more. All patients received 30 mg/kg methyl-prednisolone before clamping. Attempt was made to clamp the SVC below the insertion of azygos vein so that it could provide some decompression of the proximal segment until the time the anastomosis was accomplished. At the same time, it was ensured that enough length of SVC was available for anastomosis. End to side anastomosis of SVC to RPA was performed using 6 '0' prolene 13 mm needle (Ethicon™, NW 8707). After ensuring adequate function of the Glenn shunt, the BT shunt was dissected and clipped or divided at this stage. The azygos vein was double clipped to ensure no steal occurred from the SVC to inferior vena cava (IVC) through the azygous vein. No drainage techniques were used to decompress the proximal SVC. We used Titanium clips (Ethicon Endosurgery™, LT400, Large) in place of vascular clamps to temporarily occlude the RPA/LPA when the working space was not adequate. A year after the study by Hussain et al. published in 2007, Anil Bhan, from the same team, published the manuscript titled "How I do it?" showing how they performed this technique (24).



Superior vena cava to right pulmonary artery anastomosis in progress Off-pump bi-directional Glenn shunt: How I do it? Anil Bhan, July 2008 Annals of Pediatric Cardiology 1(2):131-4. DOI: 10.4103/0974-2069.43879

In 2003, Maddali et al. (25) performed the off-pump BDGS procedure on two infants by decompressing SVC with manual aspiration without using any shunt. Similarly, Deebis et al. (14) and

Mostafa et al. (26) performed off-pump BDGS procedure without any shunt. The authors compared these cases with those who underwent BDGS with CPB and those who underwent off-pump BDGS assisted with shunts.

4.5.2. Via Thoracotomy.

Jahangiri et al. (27) performed off-pump BDGS via right thoracotomy without any decompression technique or shunt. This method is the first method performed without CPB and any decompression method. After standard anesthetic technique and monitorization, an internal jugular line was placed before the operation in all patients to measure the SVC pressure. The preoperative systolic blood pressure was calculated as the average of 3 different measurements before the SVC and right pulmonary artery were clamped. Right posterolateral thoracotomy was performed. After dissection of the SVC and right pulmonary artery, the azygos vein was ligated and divided. No shunt was used during the clamping of the SVC. The highest right internal jugular pressure reached during clamping of the SVC is median value of 26 mm Hg (range 19-65 mm Hg). The systolic blood pressure during clamping of the SVC was calculated as the mean of 3 different measurements during that period. The median clamp time was 11 minutes. The transcranial pressure during clamping was measured by calculating the difference between systolic blood pressure and the right internal jugular pressure (Transcranial pressure gradient). The median transcranial pressure was 71 mm Hg (range 15-91 mm Hg). In some cases the systemic blood pressure was raised by using dopamine and an α -agonist (metaraminol) with a view to maintain a gradient of more than 30 mm Hg. This gradient was chosen on empiric grounds to ensure cerebral perfusion. No active cooling of the patients was performed, but the temperature in the operating room was kept at 17°C. After the procedure, the patient was actively warmed with a hot air blanket.

5. Discussion

The bidirectional Glenn procedure (BGP) can be performed via median sternotomy or anterior right thoracotomy, furthermore the use of cardiopulmonary bypass or a temporary shunt between SVC and the right atrium or between SVC and pulmonary artery without CPB can also be considered. The decision about the approach and strategy is mainly based on the surgical team experience, patient's condition and the perioperative risk. Advancements in CPB and extracorporeal circulation techniques and equipment used have allowed all operations in pediatric cardiac surgery to be performed easily. Despite its

beneficial effects, CPB has many disadvantages. It may lead to hemolysis, air embolism, hemorrhage due to high dose heparin, and microembolism. Moreover, systemic inflammatory response syndrome may develop when blood comes into contact with the extravascular surface. There might be impairments in many systems, such as increased fluid in the lungs, reduced right ventricular compliance, and prolonged ventilatory support, with the activation of the systemic immune response. Furthermore, systemic inflammatory response may decrease flow in the early period in BDGS by temporarily increasing pulmonary vascular resistance (7,8,28). Advantages of avoiding CPB and aortic cross-clamping include earlier extubation, receiving fewer blood product transfusions, less inotropic support requirement, shorter length of hospital stay, and less chylothorax development. Increased pulmonary vascular resistance and hypoxia after CPB and possible development of aortopulmonary shunts may lead to prolonged pleural effusions (7,29-33). Nevertheless, it should not be forgotten that there are many factors affecting pulmonary vascular resistance in the postoperative period, including mechanical ventilation, pain, infection, and drug hypersensitivity (13). Avoiding CPB particularly in patients with lower weight can reduce its detrimental effects on vital systems and organs (4).

Many studies have shown that the shunt-assisted off-pump BDGS procedure is both economical and safe. It has been further reported to be associated with shorter length of stay in the hospital and intensive care unit (ICU), reduced time on the ventilator, lower pleural effusion rates, and less inotropic support requirement. Moreover, no major neurological problems were reported during the short-term follow-ups (13,19,34-36).

Similarly, in some studies supporting off-pump BDGS, no significant difference has been reported between on-pump and off-pump BDGS in terms of early postoperative complications (reexploration for bleeding, arrhythmia, congestive conditions, chylothorax, diaphragmatic paralysis, and neurological condition), operating time, post-BDGS oxygen saturation, BDGS pressure, inotropic support, length of stay in the ICU, and mortality rates. Off-pump BDGS has been reported to be a more economical method that can be preferred safely (4,7,9,14-18,37-40). Many different approaches have been defined for off-pump BDGS (7,9,13-23,29-38). A temporary venoatrial shunt was established between SVC and RA in 1990 by Lamberti et al. (9) and thus, surgery could be performed without using CPB for the first time. Lal and Mhant (17) performed a similar technique with the help of a reservoir and roller pump. As an alternative

to these methods, Murthy et al. (18) performed the off-pump BDGS procedure with SVC-PA shunt for the first time. In the study by Abdelbaser and El Derie (20) involving 40 patients published in 2020, the authors preferred to perform off-pump BDGS procedure by establishing an extrathoracic jugulo-femoral venous shunt between the jugular and femoral vein.

Good collaboration between anesthesiologist and surgeon is necessary for off-pump BDGS performed with venoatrial, cavopulmonary or jugulo-femoral shunt. In recent studies, it has been emphasized that 30 mg/kg methylprednisolone should be administered, and the head of the operating table should be at least 30 degrees elevated to reduce the edema formation and protect the brain (20). It is beneficial to maintain the patient's body temperature in the range of 33 to 34 degrees to help protect the brain. The inotrope or fluid requirement should be carefully monitored after the clamp is placed. Severe hypotension, sudden arrhythmias, or hypoxia may occur after the SVC and PA are clamped. If the oxygen saturation level is very low, both respiratory settings and oxygen concentration settings can be used and oxygen saturation level can be increased with an increased blood pressure that is induced intravenous administration of dopamine. Severe supraventricular tachycardias, atrial arrhythmias, and even ventricular fibrillation may occur due to the fact that ventricular muscle is very sensitive to hypoxia. If there is supraventricular tachycardia, synchronized defibrillation can be performed, or it can be tried to restore sinus rhythm with drugs such as adenosine and procainamide. In cases where supraventricular tachycardia persists or blood pressure drops rapidly, it is useful to switch to CPB. Therefore, all necessary instruments must be available on the operating table. The literature review showed that the frequency of hemodynamic instability was very low during surgery in cases undergoing BDGS without CPB. In a study by Liu et al. (19) published in 2004, the procedure was completed without CPB and no mortality and neurological complications were reported in 19 of 20 patients whereas CPB was begun in one patient due to severe arrhythmia. The authors reported that BDGS without CPB was safe if SVC pressure was less than 30 mmHg and SVC clamping time was less than 30 minutes. In a study by Kandakure et al. (15) involving 186 patients, which was one of the largest series on this subject, the authors reported no hemodynamic instability and neurological complications in patients undergoing off-pump BDGS with SVC-RA shunt. Luo et al. (36) performed off-pump BDGS with SVC-RA shunt in 28 of 36 patients whereas off-pump BDGS without shunt was performed in eight patients since they had bilateral SVC. The authors

reported no neurological complications in any of the patients. When the authors compared these patients with 35 patients undergoing BDGS with CPB, they reported to find better postoperative results in patients undergoing off-pump BDGS, such as shortened ventilator support, less pleural effusion, less inotropic support, and lower PA pressure. In the study by Hussain et al. (4) involving 22 patients, no mortality and neurological problems were observed, and patients' length of stay in the ICU was reported to be short. Tireli et al. (16) performed off-pump BDGS procedure using different shunt techniques in their study of 30 patients and reported that the best arterial oxygen saturation and hemodynamic status were provided with cavopulmonary shunt and that the neurological condition was perfect except for one patient.

The greatest concern in the BDGS procedure performed without CPB is the risk of neurological dysfunction. Increased pressure in proximal SVC may cause neurological damage (14). This risk is also present in all shunt techniques (13). (41). Using NIRS, Liu et al. (19) observed that the level of oxyhemoglobin in brain tissue decreased significantly as the SVC pressure increased during SVC clamping. Rodrigez et al. (29) reported that the flow velocity of the flow in the middle cerebral artery decreased by 50% when the SVC was clamped. In another study by the same authors, mild electro-cortical changes in evoked potentials were shown during transient SVC obstruction (41). High central venous pressure (CVP) causes a decrease in the transcranial pressure gradient (27). Lee et al. (42) reported that intracranial pressure and brain edema formation increased after SVC clamping and that CVP was high in patients without shunt, which resulted in a decrease in cerebral perfusion pressure. Furthermore, cerebral perfusion pressure can be affected by many physiological factors such as hypercapnia, which causes cerebral vasodilation and an increase in cerebral blood flow (43). The transcranial pressure gradient is the difference between systolic arterial pressure and mean jugular venous pressure (27) and should be 30 mmHg minimum. It seems reasonable to use temporary veno-venous shunts that improve cerebral perfusion and allow SVC decompression to avoid sudden increases in clamped SVC pressure (36). Therefore, Lapar et al. (7) reported that the off-pump BDGS procedure should be performed with shunt. In studies on off-pump BDGS procedure performed by providing SVC decompression using various shunt methods, the authors, including Lamberti et al., who performed such operation for the first time, did not encounter any major neurological complications (7,9,10, 13-20,28-38). Achieving a high transcranial pressure gradient by clamping the SCV underneath the insertion of the azygos vein, as well as using a dopamine

infusion and ensuring a good general circulation volume, can improve the brain protection (35). Furthermore, the use of Fowler position in the operation table can be also beneficial.

Although there are studies reporting that off-pump BDGS procedure not assisted with any shunt for SVC decompression can be performed without neurological complications (4,24,26,27), it is a very controversial issue. In a study by Jahangiri et al. (27) involving seven patients undergoing BDGS without decompression shunt, they reported that there was no need for temporary shunt if cerebral perfusion pressure was maintained at 30 mmHg or above by adjusting systemic arterial pressure using dopamine or alpha agonist medication, or both. They further reported that no neurological problems were observed in the patients in the postoperative period, and SVC clamping time was available, which should not exceed 15 minutes. However, Jonas objected to this and stated that the conduct of off-pump BDGS without proximal decompressing shunt could be associated with significant elevation of the proximal SVC pressure, decreased cerebral blood flow, and neurological damage (44). Rodrigez also supported Jonas and stated that even if it was short-term, unprotected SVC occlusion could lead to minor and subclinical neurological defects that could only be identified by detailed tests (29). In contrast to the comments made by Jonas and Rodriguez, Hussain et al. (4) performed off-pump BDGS procedure with sternotomy without using shunt and reported no neurological problems. In the same study, CT was performed for the brain and developmental evaluations of patients, who underwent off-pump BDGS without shunt, both before and after surgery. Postoperative CT showed no structural changes and developmental delay. Debbis et al. (14) and Mustafa et al. (26) performed BDGS with and without CPB in 57 patients and 50 patients, respectively. They divided the off-pump BDGS group into two: off-pump BDGS assisted and not assisted with shunt. These two studies reported that there was no significant difference between the BDGS procedure performed with or without CPB in terms of operative mortality and morbidity, and that off-pump BDGS without decompression shunt was a simple, economical and safe method. While there were no neurological complications in the study by Debbis et al. (14), Mustafa et al. (26) reported that a treatable convulsion developed in one patient undergoing BDGS without shunt and there was no major neurological disorder in the other cases. Many studies have shown that off-pump BDGS can be performed safely without using a shunt in the presence of bilateral vena cava (4, 36,38).

6. Conclusion

In conclusion, BDGS procedure performed using various shunts without CPB in eligible patients is a safe, effective, simple and cost-effective method. It is possible to avoid the negative effects of CPB with this method. The literature review has shown that operative mortality and morbidity rates of on-pump and off-pump BDGS are similar or in favor of off-pump BDGS. The greatest problem in this method is the possibility of neurological problems due to increased SVC pressure, however, the absence of major neurological problems other than convulsions seen in a few cases supports the use of this method. No neurological problems have been reported in studies using off-pump BDGS without shunt. There is a need for further studies to prove the reliability of BDGS procedure without shunt. Off-pump BDGS can be performed safely in the presence of bilateral SVC.

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CHAPTER XII

POSTOPERATIVE DELIRIUM

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1. Introduction

Delirium is an acute syndrome characterized by disturbances in attention, consciousness, and cognition with a fluctuating course (Ozcan & Gürhan, 2016). The duration of delirium is variable, and the degree of severity ranges from mild to very severe (Avidan et al., 2017). Delirium is one of the most frequent neurological deficits seen after surgical intervention. The incidence of postoperative delirium ranges from 10% to 80%. It can develop 10 minutes after anesthesia, as well as within seven days or after being discharged. It can develop due to many precipitating (major surgical operation, cardiac surgery, or length of stay in intensive care) and predisposing (age, cognitive impairment, or impaired functional status) risk factors (Dasgupta & Dumbrell, 2006; Marcantonio, 2012; Inouye et al., 2014). Delirium is frequently seen in patients who have undergone cardiac surgery or orthopedic surgery, who stayed in intensive care units for a long time, and who received terminal and inpatient treatment (Steiner, 2011). Postoperative delirium may be difficult to diagnose due to many risk factors and its non-specific pathophysiology. This situation makes the diagnosis and treatment of the syndrome difficult. Failure to diagnose the patient in

delirium table may prevent to treat on time and may lead to a negative course in the patient's clinical condition and sometimes to the death of the patient. Therefore, early diagnosis of postoperative delirium has importance.

2. Concept of delirium

According to the definition made by International Classification of Disease (ICD-10), delirium is an etiologically nonspecific organic cerebral syndrome characterized by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behavior, emotion, and the sleep-wake schedule (WHO, 2010). Delirium can easily be confused with dementia, which is chronic brain dysfunction. When the delirium-producing factors are eliminated, also delirium symptoms generally decrease. Possible symptoms such as cerebral disorientation, perceptual disturbances, emotional disturbances, or sleep disturbances may occur in delirium (Oh & Park, 2019).

The clinical presentation of delirium is seen in different subtypes as hyperactive, hypoactive, and mixed type. While it was only differentiated as hyperactive and hypoactive delirium before, since many patients experience hyperactive and hypoactive symptoms together in a short time, mixed-type delirium has also been added to these subtypes. Motor activity and psychomotor features are used to categorize delirium in subclasses. Mixed-type delirium shows both hyperactive and hypoactive features in short periods of time and accounts for about 46% of all cases. Hyperactive delirium is characterized by delusions, hallucinations, agitation, and disorientation and it accounts for about 30% of all cases. Hypoactive delirium, on the other hand, includes depressive, slowed movements or lack of movements, lethargy, decreased alertness and it accounts for approximately 24% of all cases. Hyperactive delirium can be diagnosed more easily than hypoactive delirium and treatment can be started earlier. Since hypoactive delirium does not show any symptoms, its prognosis shows a worse course due to difficulty in diagnosis and delayed treatment (Steiner, 2011; Inouye et al., 2014).

3. Postoperative delirium

Postoperative delirium is defined as an acute onset neurological syndrome that is characterized by disturbances in attention and consciousness with cognitive symptoms and that may develop 10 minutes after anesthesia, as well as within seven days or after being

discharged (Neuner et al., 2018). The incidence of postoperative delirium varies widely, ranging from 10% to 80% depending on the collective of patients observed and the type of surgery (Dasgupta & Dumbrell, 2006; Marcantonio, 2012; Inouye et al., 2014; Bilotta et al., 2019). It may have negative effects such as prolonged hospital stay, prolonged cognitive impairments, increased risk of fall, catheter-related infections, more physical restraints, use of antipsychotic medications, and increase in short and long-term in-hospital mortality (Crenshaw & Presti, 2019).

4. Pathology/pathogenesis of delirium

Studies on the pathophysiology of delirium are limited. There are several hypotheses that factors such as neurotransmitter changes, anatomical considerations, inflammatory response pathways, stress responses, and alcohol withdrawal, and surgical interventions cause delirium (Steiner, 2011; Bogović et al., 2012; Zaal & Slooter, 2012).

4.1. Neurotransmitter changes

4.1.1. Acetylcholine (ACh)

The cholinergic system has been associated with a number of cognitive functions, including arousal, selective attention, memory, and Random Access Memory (RAM) sleep. It can contribute to delirium with a deficiency in the system and impaired cholinergic transmission. Changes in acetylcholine (ACh) levels explain the key features of delirium. Decreased acetylcholine activity and the use of anticholinergic medications can increase the delirium susceptibility in both inpatients and patients undergoing surgical operations (Han et al., 2001). Reducing the use of anticholinergic medications, therefore, can play an important role in relieving delirium symptoms (Zaal & Slooter, 2012; Mulkey et al., 2018).

4.1.2. Dopamine

Dopamine, the catalyzer of norepinephrine in catecholamine synthesis, plays an important role in behavior control, movement ability, memory, control of motor activity, learning, sleep, and hormone secretion. Increased dopamine levels can lead to some of the symptoms of delirium. Symptoms frequently seen in hyperactive and mixed-type delirium in particular, such as agitation, irritability, restlessness, hyperactivity, and inattention can occur. Being intoxicated with dopaminergic medications, disturbed oxidative conditions, increased

toxic metabolic amounts, and changes in electrolyte levels can trigger delirium (Zaal & Slooter, 2012; Mulkey et al., 2018).

4.1.3. Gamma-aminobutyric acid (GABA)

The secretion of gamma-aminobutyric acid (GABA), which is the primary inhibitory neurotransmitter in the central nervous system, poses an increased risk for delirium development. γ -Aminobutyric acid, which is thought to play a role in determining hyperactive and hypoactive delirium, is one of the secondary neurotransmitters. Due to the fact that the sedative agent level in the body decrease in the postoperative period, GABA levels may drop suddenly and lead to delirium. Those randomized to the light sedation had substantially less postoperative delirium than those in the deep sedation (Steiner, 2011; Bogović et al., 2012; Zaal & Slooter, 2012; Mulkey et al., 2018).

4.2. Relation of stress and catecholamine with delirium

Increased stress level induced by surgical intervention performs the activation of the sympathetic nervous system (noradrenaline, hypothalamic-pituitary, adrenocortical) and the release of glucocorticoids. Glucocorticoid hormones have important effects in dealing with stress. As the level of cortisol hormone secreted from glucocorticoid increases, changes occur in the hippocampus. Stress caused by steroid injections, infection, trauma, disease and surgical intervention causes an increase in cortisol levels. Excessive cortisol levels can lead to a delicate state in neurons. Thus, high levels of cortisol cause catecholamine disorders-related memory dysfunction, information processing errors, inattention and confabulation. Increased norepinephrine level increases the risk of delirium in patients who are applied vasopressors and whose sleeping patterns change (Mulkey et al., 2018).

4.3. Glutamate and sepsis

Glutamate that serves as the primary stimulating neurotransmitter is secreted in large amounts in the presence of an infection in the body, activating microglial cells (Zaal & Slooter, 2012). Severe infection and sepsis can increase the risk of delirium. In a study carried out, plasma glutamate levels of 36 of 50 patients, who were hospitalized in the intensive care unit due to sepsis and respiratory failure, were measured. Delirium developed in 12 of the patients who were followed up for fifteen days or until being discharged. As a result of the study, it was found that high plasma glutamate concentrations are associated with

cognitive impairment (Anderson et al., 2017). Besides, changes in glutamate cause disorder of REM, which is known as restorative sleep. Since the risk of developing delirium is higher in patients with liver failure, a history of alcohol use, and severe infections, care should be taken (Steiner, 2011; Bogović et al., 2012; Zaal & Slooter, 2012; Mulkey et al., 2018).

4.4. Surgical interventions

Although the mechanisms responsible for cognitive changes are not fully understood, many risk factors affect postoperative delirium. It may be related to patient characteristics, surgery and anesthesia type. Patients are exposed to many active drugs that will affect cognitive state during general anesthesia. The incidence of postoperative delirium is higher in patients using benzodiazepines. Post-operative cognitive changes are more frequent in younger patients (Steiner, 2011; Bogović et al., 2012).

5. Risk factors of delirium

In the postoperative period, many patients experience pain, stress, anxiety disorders depending on the type of surgery and their sleep-wake cycle can be impaired. This situation paves the way for delirium. Although surgery alone is not a risk factor, there are many concurrent risk factors (Table 1).

Table 1: Evidence-based delirium risk factors

	Delirium Risk Factors	
	Predisposing factors	Precipitating factors
Preoperative Risk Factors	> 65 years old ** Male Basic cognitive Disorders ** Dementia ** Preoperative memory complaint ** Anxiety ** Depression ** Intracranial stenosis ** Carotid stenosis ** Peripheral vascular disease ** Transient ischemic attacks ** Sensory disturbances ** Diabetes B	Surgical or multiple (diagnostic) procedures ** Alcohol or drug withdrawal ** Emotional stress ** Long-term sleep deprivation.

	Hypertension ** Atrial fibrillation ** Alcohol abuse * Smoking.	
Intraoperative Risk Factors	ASA Classification ** Anesthesia, Hip surgery ** Heart surgery ** Emergency surgery, Increased surgery time.	Hyperthermia / hypothermia, Shock, Hypoxia Anemia ** Arrhythmias ** Blood transfusion. Bleeding during surgery **
Postoperative Risk Factors	Liver failure, Kidney failure (BUN / CR greater than 18).	Use of physical restraints, Use of urinary catheters, Pain * Length of stay in the intensive care unit, Prolonged intubation Interfering diseases: Infections, Iatrogenic complications, Metabolic disorders, Dehydration, Severe acute diseases, Hypoalbuminemia and malnutrition. Medicines: Sedatives, Hypnotics Benzodiazepines, Opioids, Meperidine Antihistamine, Dopamine antagonists Anticholinergic drugs, Muscle relaxants, Treatment with multiple drugs. Primary neurological disease: stroke, Intracranial bleeding, Meningitis and encephalitis.

* A: Strong Evidence, ** B: Conditional Evidence. (Steiner, 2011; Aldecoa et al., 2017; Lee, 2020).

6. Diagnosis and evaluation tools for delirium

Delirium can be diagnosed using reference standards such as DSM-5 or ICD. Early and easy diagnosis of delirium is important in the clinic. Therefore, observation, asking for detailed medical history, blood count, physical examination, neurological examination,

electrocardiography (ECG), electroencephalography (EEG), control of Vitamin B and folic acid levels are required (Stainer, 2011). Besides, many evaluation tools that provide mental status examination have been developed (Table 2).

Table 2: Delirium diagnosis and assessment tools

Delirium Diagnosis and Assessment Tools	
Confusion Assessment Method (CAM)	<p>It is the most widely used assessment scale for delirium assessment, developed in 1990. This assessment tool consists of four features. These,</p> <ul style="list-style-type: none"> (a) Acute onset and fluctuating course, (b) Carelessness, (c) Disorganized thinking (d) Changing level of consciousness <p>During detection, the properties of delirium (a) and (b) are mainly detected when they selectively meet the properties of (c) or (d). It has been reported that this assessment tool is accurate between 91% and 94% (Inouye et al., 1990; Oh & Park, 2019).</p>
Confusion Assessment Method for Intensive Care Unit (ICU; CAM-ICU)	<p>CAM (ICU; CAM-ICU), a shorter version of the Confusion Assessment Method (CAM), was developed for use in intubated patients undergoing mechanical ventilation for the intensive care unit with a confidence interval of 93%. This assessment scale guides the patients to be evaluated daily using scales called Glasgow Coma Scale and Richmond Agitation Sedation Scale (RASS). It is used by healthcare professionals to indicate any cognitive fluctuation by comparing the 24-hour period and previous scores. (Ely et al., 2001; Oh & Park, 2019).</p>

<p>Delirium Severity Measure (CAM-S)</p>	<p>To measure delirium severity, the Delirium Severity Measure (CAM-S), developed in 2014, evaluates the progression of clinical care by better understanding the progression of prognosis, its impact and response to treatment (Inouye et al., 2014). Confusion Assessment Method (CAM) CAM and CAM variations are the most commonly used evaluation criteria.</p>
<p>Richmond Agitation Sedation Scale (RASS)</p>	<p>The Richmond Agitation Sedation Scale (RASS), which guides the delirium assessment, is used to evaluate the level of sedation / agitation. RASS is a 10-point scale that is scaled between -5 and +4. A separate expression is used for each agitation and sedation level (Sessler et al., 2002).</p>
<p>Memorial delirium assessment scale (mdas)</p>	<p>It is a tool that measures the presence and severity of delirium by measuring consciousness and cognitive dysfunctions and consists of 10 items with a total score between 0 and 30.</p>
<p>Delirium Rating Scale-Revised-98 (DRS-R98)</p>	<p>It is an assessment tool that includes 3 diagnostic items and 13 severity items, where the total score ranges from 0 to 46 and the high score indicates that delirium is severe. These evaluation tools are not preferred to be used because they take too much time. Electroencephalography (EEG) can be used as an objective diagnostic tool. In the presence of delirium, the indicator of slowing in background activity is a finding detected by EEG. However, it is time consuming and inadequate due to problems with misinterpretation of results in its routine use (Oh & Park, 2019).</p>

<p>4 'A's Test (4AT)</p>	<p>4A test (4AT); It is a short delirium and cognitive impairment test that can be used without a special training developed for use in intensive care units after anesthesia. This test consists of four items under the headings of alertness (a), orientation (b), attention (c) and acute change (d). Delirium severity and cognitive status are evaluated using a 0 to 4 scoring system. 4A test (4AT); It is a widely used assessment tool for delirium, but there are no studies evaluating its use in the post-anesthesia care unit (Saller et al., 2020).</p>
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7. Management of postoperative delirium

7.1. Pharmacologic methods

While reducing the incidence of delirium and shortening its duration, and in both causal and symptom management of disease, haloperidol, atypical antipsychotics (quetiapine, ziprasidone and olanzapine), dexmedetomidine, reductase inhibitors (rosuvastatin) and N-methyl-D-aspartate antagonist (ketamine) are frequently used (Devlin et al., 2018; Guthrie et al., 2018). However, the Clinical Practice Guideline Developed for The Prevention and Management of Pain, Agitation/Sedation, Delirium, Inactivity and Sleep Disturbance in Adult Patients in the ICU (2018) does not recommend the use of pharmacological agents (Devlin et al., 2018).

The most preferred method to manage delirium is the use of haloperidol. (Oh & Park, 2019). In their meta-analysis study evaluating the effects of haloperidol on delirium, Shen et al. (2018) reported that the daily use of 5 mg or more haloperidol for prophylaxis in patients undergoing surgical operations may help reduce delirium (Shen et al., 2018). In another study reviewing the activity and safety of haloperidol, it has been reported that haloperidol can reduce the risk of delirium after the surgery for prophylaxis, and the use of haloperidol will not show a significant increase in side effects (Schrijver et al., 2016). It was reported that the administration of prophylactic haloperidol in the early

period of delirium particularly in elderly patients undergoing elective surgery significantly reduces the incidence of delirium (Fukata et al., 2017). Haloperidol has less anticholinergic and hypotensive effect compared to the side effects of other antipsychotics. Haloperidol needs to be monitored not only for its effectiveness but also for its side effects. In addition to extrapyramidal side effects such as dystonic reactions, akathisia, tardive dyskinesia, and malignant catatonia, the risk of corrected QT (QTC) interval prolongation can be increased with the use of haloperidol (Page et al., 2013). Therefore, follow-up of electrocardiography is recommended in the event of using haloperidol (Oh & Park, 2019). European Society of Anaesthesiology Evidence-based and Consensus-based Guideline on Postoperative Delirium (2017) recommends low-dose haloperidol or low-dose atypical neuroleptics for the prevention and treatment of delirium (Aldecoa et al., 2017). Other atypical antipsychotics used to manage delirium (such as risperidone, olanzapine and quetiapine) are frequently used in the treatment of psychotic and behavioral symptoms seen in agitation, aggression and dementia, as well as psychotic conditions (Oh & Park, 2019).

In the Clinical Practice Guideline Developed for The Prevention and Management of Pain, Agitation/Sedation, Delirium, Inactivity and Sleep Disturbance in Adult Patients in The ICU (2018), it is stated that Dexmedetomidine (Precedex) used in intensive care patients undergoing mechanical ventilation who have the risk of extubation due to agitation assisted a natural sleep and easy awakening without respiratory depression during sedation, reduced the length of stay in the intensive care unit, and was effective in shortening the duration of delirium (Steiner, 2011; Devlin et al., 2018). In a study measuring the effectiveness of dexmedetomidine used in the treatment of patients who developed delirium after open heart surgery, it is reported that 80% reduction in symptoms was observed (Aslankurt et al., 2016). Among the side effects of dextromedetomidine, bradycardia and hypotension are generally included in critically ill patients (Cui et al., 2020). In another study, it was reported that the use of ketamine during surgery may increase the risk of delirium (Elsamadicy et al., 2019).

European Society of Anaesthesiology Evidence-Based and Consensus-Based Guideline on Postoperative Delirium (2017) suggests monitoring the anesthetic depth in terms of delirium (Aldecoa et al., 2017). Monitoring brain functions such as the bispectral index (BIS) reduces exposure to the anesthetic agent by facilitating anesthetic

titration (Chanet et al., 2013). Neuro-monitoring during surgery may result in a lower incidence of delirium by decreasing the bispectral index (BIS) values. Therefore, an operation performed with bispectral index (BIS) and auditory evoked potential (AEP) especially in-patient groups who will undergo high-risk surgical intervention can significantly reduce the risk of delirium (Luo & Zou, 2018).

7.2. Non-pharmacologic methods

European Society of Anesthesiology Evidence-Based and Consensus-Based Guideline on Postoperative Delirium (2017) recommends non-pharmacological methods in the prevention and management of delirium (Aldecoa et al., 2017). In the preoperative period, which is the first stage of perioperative management, collecting detailed data with observation, interview and physical examination methods have importance (Steiner, 2011). In the guide prepared by the National Institute for Health and Care Excellence (NICE) for delirium management, it is recommended that patients who were aged 65 years and over with risk factors such as ex- or present cognitive impairment, and suspected dementia should be evaluated in terms of delirium in the first 24 hours (NICE, 2019). In the European Society of Anesthesiology Evidence-Based and Consensus-Based Guideline on Postoperative Delirium, early diagnosis of postoperative delirium and making a differential diagnosis and starting treatment is recommended (Aldecoa et al., 2017). In a qualitative study on awareness of postoperative delirium and cognitive dysfunction carried out by German healthcare professionals, it was reported that patients with delirium risk create different perceptions among health professionals. They stated that they did not see patients with delirium, but that they encountered patients who were agitated at least once a day. It was emphasized that patients with acute or subacute delirium were not noticed by hospital physicians (Sturm et al., 2019). Therefore, factors such as evaluation and diagnosis of postoperative delirium, knowing the risk factors, providing differential diagnosis, and determining the underlying causes are important in early intervention.

In the guideline of the National Institute for Health and Care Excellence (NICE), to prevent delirium, non-pharmacological interventions are recommended (NICE, 2019). It is stated that patients at risk of delirium should be checked by expert teams, evaluation should be made using screening scales in terms of delirium, the movement of patients within the clinic should be reduced, they should be checked and evaluated for clinical factors causing delirium for the first 24 hours in

the postoperative admission period (NICE, 2019). Ensuring fluid-electrolyte balance, getting help if necessary while managing fluid balance in people with comorbidities (e.g. heart failure or chronic kidney disease), questioning and observing symptoms such as intestinal obstruction, nausea and pain that bother the patient, evaluation of hypoxia, and optimizing oxygen saturation are recommended (Bounds et al., 2016). It has been reported that physical restraints should only be used when pharmacological and non-pharmacological interventions do not avail (Hshieh et al., 2015). Unnecessary invasive procedures and catheterization should be avoided, infections must be prevented and control procedures need to be implemented. Avoiding medical procedures during bedtime, making drug review for patients using more than one medication, providing early mobilization after surgery, and encouraging active movements in the bed in situations that impede walking are recommended (Zhao & Yuan, 2020). Departing from the evaluation results, it was emphasized that a multidisciplinary team should be established for the individual care of the patient, care packages should be used to prevent delirium, and care should be provided by health professionals trained in delirium (NICE, 2019).

According to the recommendations of the American Geriatrics Association; it was reported that delirium should be prevented in at-risk groups underwent surgery, the duration of hospital stay should be shortened, a multi-component intervention program to be provided by a multidisciplinary team should be established in elderly patient groups diagnosed with postoperative delirium and training should be provided to health professionals (Samuel, 2015). In studies carried out with multi-component care package programs; it was reported that this reduces the incidence and duration of delirium and the risk of postoperative low hypoxia. Perioperative multi-component multidisciplinary care package programs can be applied to reduce the incidence of postoperative delirium and these are reported to be effective (Hshieh et al., 2015; Bounds et al., 2016; Hashemighouchani et al., 2020; Zhao & Yuan, 2020). A clinical guideline frequently used in intensive care units for the prevention, diagnosis, treatment and management of delirium was prepared based on the current evidence-based practice guidelines. ABCDE Bundle is grouped under the following six main headings: (a) recovery from sedation, (b) spontaneous ventilation and respiratory coordination, (c) analgesia and sedation selection, (d) prevention delirium and its management and (f) early physical activity. It includes multidisciplinary measures to improve and/or protect the physical, functional and neurocognitive state

of patients (Crenshaw & Presti, 2019). The success of this package depends on the participation of professionals from multiple disciplines in patient care (Ely, 2017).

The orientation of the patient for cognitive impairment and/or disorientation constitutes one of the most important cognitive interventions. Keeping a calendar and clock in an easily visible place, explaining the patient where he/she is, how and why he/she came to the hospital during the day and repeating this step, presenting cognitive activities such as recall, explaining which health professional will provide care, proper lighting, and the use of clear expressions and signs constitute the cognitive interventions to be made in terms of orientation (Oh & Park, 2019; NICE, 2019).

Environmental interventions; as the stimuli cause confusion and insomnia for the patient, it is emphasized that the stimuli that increase delirium symptoms should be decreased and that acquaintances of the family should be allowed to be with the patient. In terms of patient safety, guards of the bed are recommended to be raised and the belongings of the patient should not be relocated, if the patient wears glasses or uses a hearing instrument, it is recommended to wear them to the patient in order to provide orientation (Patel et al., 2014; NICE, 2019).

Psychological interventions; the accuracy of the hallucinations and delusions expressed by the patient should not be discussed with the patient. Instead, distracting the patient's attention, enabling him/her to express his/her fears and feelings, and giving precise and direct commands instead of commands that can draw conclusions or make reasoning are recommended (NICE, 2019).

In conclusion, although it is known that anesthetic substances taken during the perioperative process, sedation and intensive care environment have a profound effect on delirium, the pathogenesis of delirium is not fully known. Most experts, therefore, agree that patients should be observed for delirium and that they should be screened regularly, even there are no postoperative risk factors. In the management and prevention of delirium, non-pharmacological methods are preferred. It is possible to control the incidence, duration and severity of delirium with non-pharmacological methods. When the evidence-based studies are examined; establishment of a multidisciplinary team trained in delirium that can be created in surgical

clinics and using care packages for delirium and creating a multi-component intervention program are recommended.

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CHAPTER XIII

PSYCHOSOCIAL CARE OF AN ELDERLY PATIENT DIAGNOSED WITH CANCER: A CASE REPORT

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1. Introduction

Cancer is one of the main health problems of the 21st century since it is common and has a high mortality rate. [1] 14 million new cancer cases and 8.2 million deaths were stated all over the world in 2012 in accordance with the World Cancer Report (2014) data. Moreover, it is reported that cancer-related deaths will reach 13 million people with the addition of 22 million new cancer cases in the world within 10 years [2]. Cancer is the second most common cause of death with the ratio of 15% after cardiovascular disease and the rate of cancer among the causes of death is gradually increasing [3] in Turkey.

The persons diagnosed with cancer constitute the group of patients to whom nurses frequently give care taking into account the statistics. Cancer patients should be considered as a special group requiring more nursing care since it has been observed that the biopsychosocial problems and unmet requirements are higher in cancer patients in comparison with other patient groups in the studies. [4,5] Nurses should use many functions, carry out different interventions, and are of strong interpersonal communication skills and humanistic qualities in order to meet these requirements.[6]

The patients identify the nursing care as an important and valuable contribution to recovery, the nurse as important, essential, vital, supportive, relaxing, relevant, understanding, sensitive, helpful and the care as compassion, concern and politeness in the study conducted with the cancer patients by Radwin and et al. The patients indicated that they felt that they received the care, they felt comfortable and safe and their anxiety decreased when they received a nursing service including the

mentioned specialties. [7] It has also been reported that it is easier for the patient to be a part of their care when nurses give care by showing positive, friendly and real intimacy with patients in the study of Sainio and et al.(8)

It has great importance to permit the cancer patients to express their feelings and concerns, to increase their ability to deal with the treatment stresses, to help them manage the symptoms, and to increase their compliance with the new condition as cancer is a disease affecting all life so much. However, the attitudes of the patients towards cancer and their adaptation to this new process can vary significantly depending on factors such as cultural, ethnic, social, economic and educational. Therefore, nurses should not only identify their own reactions to patients with cancer, but also put realistic goals for the difficulties they may encounter in the care of patients with cancer (9,10).

Nursing at home of a patient diagnosed with cancer may lead to disruption of daily routines of the family members (11,12), loss of role or role change in the family members. These families may naturally require help in the management of many care areas such as regulating the patient's diet, drug management, pain management, sleep diagnosis, and activity. It is reported that the family members experience more anxiety, depression, fatigue, role conflict, social isolation and distress in due course of the disease, and as a result, the risk of physical illness augments because of the damage of the immune systems (13). The conducted researches show that the patients diagnosed with cancer and their families require several information with regard to the severity and course of the disease and physical, psychosocial, economic and disease/treatment processes arising from the special care need and a chronic problem threatening life. (14,15,16,17,18,19).

The Consultation Liaison Nurse (CLN) can attend a great variety of care services from primary protection to treatment, care and rehabilitation for the patients and their families in the health care system because of existing or potential dysfunction. A holistic nursing care approach of the consultation liaison psychiatry nurse to the patient diagnosed with cancer and an elderly patient at home in the terminal cancer instead of the hospital is set forth in this case report. It is intended to support psychosocial to the patients diagnosed with cancer and their families in their home environment and contribute to the solution of the problems.

This study contemplates an elderly female patient whom was diagnosed with Colon Cancer and registered at an Elderly Center in Turkey. The negative experiences of the patient due to her illness and

inability to maintain adequate health care by herself along with the adjustment process of the patient's disease process, family and social dynamics were evaluated in the context of nursing care. The interviews in the form of home visits included the patient and her spouse.

2. Ethical aspect of the research

The permission was received from the relevant institution in order to carry out the study. The written and verbal consents of the patients and their relatives participating in the study were taken explaining the purpose of the study.

3. Case Presentation

3.1. The introduction of the case

The female patient, N.Ş., is a 65-year-old retired civil servant and of a moderate income in terms of socio-economic point of view. N.Ş. has 4 children and lives with her husband and a daughter in Bolu. The abovementioned patient diagnosed with Colon Cancer 2 years ago was receiving chemotherapy treatment. The patient was receiving chemotherapy in a university hospital out of the province for this disease. She accepted without any hesitation when she was suggested to be interviewed to support her in this process. However, she said that she could not even leave her room due to her ailment such as malaise, fatigue, pain and diarrhea and therefore she requested that it be in the form of home visits. It was figured out that the patient experienced the emotional (such as tiredness, desperation and despair) and physical (such as nausea, alopecia, anorexia, malaise, drop attacks, diarrhea-constipation) negative effects the chemotherapy's side effect that she received also had maladaptive behaviors and thoughts with regard to her disease in due course of this process. The patient also stated that she had lacks of communication among her family members and was uncomfortable with this situation for this reason. She also expressed that she had ambivalent feelings that she could not express and there was a loss of role and function. It was observed that the patient had visual hallucinations, the location and time orientation of the patient weakened and the patient adopted agitated behaviors on home visits following the first meeting. Moreover, this situation was noted by the patient's physician after the first symptoms arose from the side effects of the analgesic that she used due to the intense pain that the patient suffered.

3.2. Home monitoring process

A content utilizing nurse-patient interview principles was created in order to increase therapeutic cooperation of the patient and her family

during home visits. This program consisted of successive four interviews, each taking an average of 40 minutes.

The main topics of the case report whose detailed information is explained below consist of control of the symptoms caused by cancer and treatment, information in relation to the social and economic problems as well as the psychological requirements of the patient and her family, ways to overcome the stress, maintaining normal family relationships, role changes in the family and ways to cope with the mourning period.

The home visits and planned interviews were carried out with the patient and caregiver family members in relation to the identified problems. N.Ş. was experiencing side effects of the chemotherapy, lack of social support, inability to express the emotions, change in the role among the family members, change in sleep and feeding habits, which are among the most common problems in cancer disease and its treatment. The nursing diagnoses discussed during the process of the case study are Chronic Pain, Acute Confusion, Disorder in Sleep Pattern, Nutritional Imbalance, Undernutrition, Diarrhea, Constipation, Nausea, Disruption in Oral Mucous Membrane, Tiredness, Managing Therapeutic Regime Ineffectively, Individual and Family, Weakness, Impairment in Social Interaction and Disorder in Body Image. Her husband and daughter, who are the caregiver of the patient, were also interviewed as well as the patient, they were informed with regard to both the measures to be taken for physical symptoms and what to do in case of hallucinations and disorientation situations and in this direction, the points that can be done and difficult to do were discussed all together. Furthermore, mini mental test was applied to the patient since the patient had visual hallucinations, the location and time orientation of the patient weakened and the patient adopted agitated behaviors. The confusional disorientation status of the patient was assessed at each interview and her family members were also clarified in relation to the necessity to follow this all the time. The compliance of the patient with the person (the caregiver) and the place-time (date, time, day) was assessed in each interaction with the patient. When friend or relative of the patient visited the patient, the effects of this visit on the patient's confusional state and memory were evaluated.

The patient was ensured to recognize false perceptions of the existing facts by open, honest and positive communication. The patient was supported to explain the feelings and thoughts about existing hallucinations and illusions. The caregivers were supported to express their feelings (concern, anxiety, anger) and thoughts about the

confusional status of the patient. The positive and suitable ways of communication were explained to the family members providing care to ensure the patient orientation and they were encouraged to ask questions in regard to this issue. The objects large enough for the patient to see (family photo, clock, calendar, newspaper) were provided to ensure the patient orientation.

The patient's opinions in relation to her disease, her perception, her expectations in the relationship among her family members and social interactions were assessed. In this context, she was supported to explain the problematic behaviors of the patient with her family members that disrupt the communication. The ways that the patient can establish healthy communication were specified and assessed with the patient. The problems about the communication were evaluated together by discussing with other family members. The patient was supported to make contact with her family members and peers

The development of the N.Ş's effective coping skills was strengthened taking into consideration of her views, feelings and ways to cope with these symptoms as she experiences common complications in due course of the chemotherapy. The thoughts and feelings of the patient's husband with regard to the changing family relationship, lifestyle, the disease and treatment process of the disease were evaluated by also interviewing with him.

1st Interview:

The patient's view on her illness, treatment process, inconsistency with the treatment regimen and the factors lay under were articulated. Besides, the patient's nutrition habit was evaluated and pertaining exercise topics were covered. In this context, while being informed about these issues, the patient's resistance to the treatment regimen was also revealed.

2nd Interview:

Objectives of this interview were finding out the symptoms of colon cancer and getting to know the medicines prescribed for these illnesses, getting the patient familiar with the factors impeding regular medicine use, and weighing up the pros and cons of the treatment. At this stage, the patient's opposing feelings (emotional contrast) with respect to treatment regimen adaptation were uncovered.

3rd Interview:

In this interview, the patient was asked to answer open-ended and reflective questions so that the patient could get an in-depth grasp of her

illnesses. In addition, both the patient and her spouse were given home-assignments that involved studying the side effects of her prescribed drugs. Thus, the benefits of treatment and the importance of attaining behavior in consistence with the treatment regimen were emphasized.

4th Interview:

The patient and her spouse decided on implementing the planning, constructed within the supervision of the interviewer, in order to prevent recurring hospital admissions and play current roles. Finally, the patient did undergo change to gain healthy behavior.

4. Discussion

In this study, the patients explained that the interest of their families increased after the cancer was diagnosed, they were satisfied with this situation, but excessive attention disturbed them. It is beneficial to support the patient to sustain his/her daily life, to prevent the disruption of social functioning and to try to comprehend the natural emotional reactions to the disease in order to ease the adaptation of the patients to the disease. The ability of the patient to overcome this process depends upon psychosocial and environmental supports. The social supports facilitate compatibility with the chronic diseases with regard to physical and psychological health and have a positive effect on morale and coping skill even if they do not eliminate the stressful situation [10,20]. The family takes more responsibility in this regard. While the significance of family support is approved by everyone, the family should be concerned with the patient, but not too anxious. The compatibility of the patient with the treatment and subsequent process complicates in the families where excessive protection is dominant. The patients sometimes thought that they were a burden with their families and they reported that they felt weak against their families feeling sorrow and making efforts for themselves also in Tuncay's [21] study.

The patients indicated that the matters such as not being able to do what they did before, to take part in the social activities because of tiredness and malaise, to enter the community easily due to the risk of infection, to eat what they want and also permanent hair loss affect their social lives in our study. It is found out that the side effects of chemotherapy increase the psychological, emotional and spiritual pressures of the individual and create a threat to the individual also in Tuncay's [21] study in a similar way. It is explained that patients diagnosed with cancer are of problems in relation to adapting to the disease and treatment process and cannot satisfy their social needs adequately in the study conducted by Lampic et al. [22] It has been

found out that the patients experience emotional problems such as "mental distress, despair, inefficaciousness in individual coping, change in the performance of role, depressive affect" and social problems such as "failure in sustaining daily work and social isolation" in the same study.

5. Conclusion

The abovementioned patient and her family were dealt all together, and the interventions were applied to them by determining the biopsychosocial problems that they experienced in this case study. The holistic approach has great importance in enhancement their life quality and in the settlement and diminishment of their problems since the psychosocial adjustment of elderly and cancer patients is a multivariate and complex process besides the solution of treatment-related problems of them. In this regard, the service that the consultation liaison psychiatry nurses provide is of paramount significance in the holistic, continuous and sustainable care to be given to the patients and their families at home environment following the discharge from the hospital.

This case study showed that CLP Nurses, whose involvement are benign for the treatment of patient incompliance and patients with chronic diseases, should be knowledgeable with Motivational Interviewing methods.

In this study, the creation of a custom motivational interview taking into account the requirements of patient and the past education of the researcher on the subject of MI had positive impact on the interview process. On the other hand, setting up a time for the home visits were challenging due to fact that the researcher was allocated with her full-time job at the institution.

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CHAPTER XIV

VIDEO-ASSISTED THORACIC SURGERY

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Introduction

Lung cancer is still first place in cancer-related deaths in many countries. Surgical resection is still gold standard curative surgery in early stage non-small cell lung cancers. First time in history of video-assisted surgery, Tulio Cesare Aranzi used a light source for endoscopic examination in 1585 and took sunlight from a bottle with water to nasal cavity. Two centuries later, Phillip Bozzini discovered "Leichtleiter" as an aluminum tube to visualize urogenital path, illuminated by candles and furnished with a mirror reflecting light and image. Also, Antonin Jean Desormeaux improved quality of light source. (1) However, history of video-assisted thoracic surgery (VATS) begins with artificial pneumothorax. Forlanini noticed that tuberculosis cavities healed when a spontaneous pneumothorax or a large effusion occurred in patients. Forlanini performed the first artificial pneumothorax by inserting a needle obliquely into anterior axillary line and this technique was widely accepted. (2) In 1910, Hans Christian Jacobaeus published the Jacobaeus operation. (3) The main principle of the technique was to create an artificial pneumothorax by cutting adhesions with galvanocautery, which narrowed lung and allowed safe access and examination of pleural cavity. However, Jacobaeus used thoracoscopy in treatment of adhesions, infections and effusions, except for diagnosis of tumors, tuberculosis and other diseases. Use of thoracoscopy was expanded in consecutive years, including talc pleurodesis, sympathectomy and spontaneous pneumothorax treatment. With advancement of light transmission in fiber optic environment and development of image processing techniques, VATS was born. In 1992, Giancarlo Roviario performed first VATS lobectomy. (4)

Today, VATS has an important place in diagnosis and treatment of chest diseases. Although there were initially suspicious studies for use of VATS in large pulmonary resections, later studies have successfully

demonstrated many short- and long-term benefits and safety and oncological efficacy of VATS. (5) Uniportal VATS is new approach to return to Jacobaeus' one-way approach. (6) Uniportal VATS is a method in which surgeons may perform increasingly complex chest procedures. (7) This approach has been incorporated into surgical equipment as an extension of the traditional three or two port VATS technique (8) and uniportal VATS approach reduces trauma of access port. (9)

The purpose of this chapter is to explain techniques of video-assisted thoracic surgery.

VATS lung resections in lung cancer and benign case

Videothoroscopic assisted surgery lobectomies started to be used in non-small cell lung cancers (NSCLC) since the beginning of 1990s. In the last two decades, VATS lobectomy has become increasingly common worldwide. (10) Rate of performing VATS lobectomy varies between countries. According to the data of the Society of Thoracic Surgeons General Thoracic Surgery in the 2008, VATS lobectomy rate was found to be 30% in USA. (11) After increasing VATS became widespread, the rate of performing VATS lobectomy in 2013 was 69% in Japan. (12)

First requirement in all new surgical techniques is safe for patients. Even in first years of VATS lobectomy, early results were very successful. In general, surgical mortality rates were between 0-2% and these results were found to be quite sufficient compared to thoracotomy. (13) Also, postoperative major complications and minor complications of VATS were found to be similar even when first performed compared to open surgery. (14)

VATS is considered a similar, reliable and effective method compared to open surgery. In the literature, VATS resections had shorter hospital stay, less postoperative complications and similar long-term survival results. In meta-analysis of Chen et al., it was reported that the duration of operation in VATS surgery, long-term survival results were similar to open surgery, while hospital stay, drainage times and complication numbers were found to be less. (15) In meta-analysis on stage 1 NSCLC of Zhang et al., it was stated that total lymph node dissection was found to be less in the VATS group, although long-term similar oncological results were detected in videothoroscopic surgery. (16) In the study of Sezen et al., it was reported that postoperative similar survival rates were determined between patients who underwent VATS lobectomy and patients who converted to open

surgery at the time of surgery. (17) In the study of Bendixen et al., a randomized controlled trial comparing VATS with thoracotomy, it was stated that quality of life in the first year and pain in postoperative period in patients who underwent VATS were determined better than patients who underwent thoracotomy. (18)

In the videothoroscopic resections performed by Parekh et al. without using wound protectors, the recurrence rate due to tumor implantation was found to be 0.26%. In subsequent studies, recurrence due to implantation was not detected with use of wound protectors and removal of tumor with help of an endoscopic bag. (19) Despite all these short-term advantages, long-term results of VATS and thoracotomy were similar in recent randomized studies. Hopkins et al. (20) examined quality of life of 97 patients, it was stated that although the short-term results were quite successful, the long-term life quality of the patients was similar. In addition, there was no difference in the long-term between patients' chronic pain and psychology.

Segmentectomies are resections performed in patients with limited lung reserve and small tumors. Main criteria for segmentectomy in non-small cell lung cancers, tumor diameter is 2 cm or less. In addition, patients with limited lung capacity should be less than 50% of expected in first second of hard expiratory volume, or tumor should be anatomically convenient for segment resection. If tumor is in intersegmental area, segment resection should not be preferred. Also, segmental resections should not be preferred in cases where surgical margin is less than 2 cm. Sublobar resections may be safely performed with open surgery or VATS method. Which method to choose depends on characteristics of the tumor, preference and experience of surgeon. With VATS segmentectomy method, less pain, shorter hospital stay, low morbidity and mortality rates of patients have been reported in literature. (21, 22)

VATS pneumonectomy is technically easier than lobectomies. However, main problems are high pulmonary artery pressures and risk of higher mortality in complications that may occur due to tumor located centrally. In addition, it is quite difficult to remove specimen from small incisions in lesions of 5 cm and above. Therefore, in cases where tumor is large, utility incision should be extended by 10 cm. Nwogu et al. stated that for main criteria of VATS pneumonectomy, lesion is 5 cm and below and exposure of veins in hiler area is comfortable. (23)

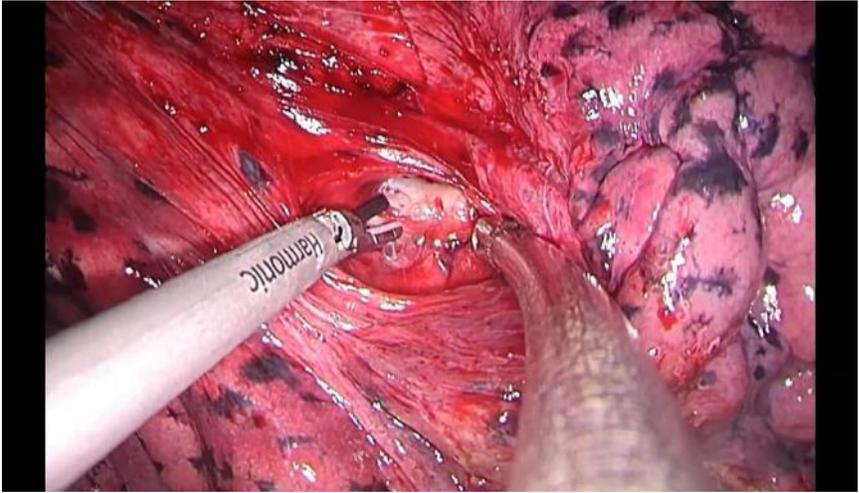


Figure 1: Videothoroscopic lung resection

Sleeve resections

Sleeve resection which is a parenchymal protector surgical technique, is a surgical method that is preferred in patients with bronchial carcinoma instead of pneumonectomy and provides similar survival results. Since introduction of video-assisted thoracoscopic surgery, sleeve resections have been considered a contraindication for VATS. However, thanks to increasing experience and development of technology, sleeve resections may be performed by experienced surgeons with VATS method. The first case of sleeve resection using VATS method in the literature was reported in 2002. Santambrogio et al. performed a left sleeve lower lobectomy with VATS in a 15-year-old patient with mucoepidermoid carcinoma. (24) In 2013, Diego Gonzalez-Rivas et al. published first uniportal VATS sleeve lobectomy case. (25) Thanks to increasing experience and developing technology, many advanced techniques such as bronchovascular sleeve and carinal sleeve resections were performed in various centers with VATS method. (26) Except various case reports, a total of 10 teams have published VATS sleeve resection series in the English literature. (27) In this way, patients benefit from benefits of both sleeve resections and VATS method and have a much more comfortable postoperative period. Today, thanks to developing technology and increasing surgical experience, trend towards minimally invasive surgery has increased even more. Although different methods are performed, VATS

lobectomies and sleeve lobectomies have many advantages compared to open method.

Videotoroscopic surgery in mediastinal diseases

Role of VATS in treatment of mediastinal diseases has increased with increase of experience and skill. Not only treatment of small-sized mediastinal masses, also resection of large-sized masses and more complex mediastinal surgeries may be performed with VATS method. (28)

Anterior mediastinum

While mediastinal lesions appear in a wide range, anterior mediastinal masses draw attention as the most common group among these lesions. Lesions with different histological features cause clinical difficulties in determining diagnosis and treatment. Diagnostic distribution rates in anterior mediastinal masses may be summarized as follows: thymoma 35%, lymphomas 25%, endocrine tumors 15%, malignant germ cell tumors (seminomateous and non-seminomatous) 11% and benign teratoma 10%. (29)

In the literature, in studies comparing minimally invasive interventions with open surgery such as VATS in thymoma surgery, there was no significant difference between groups in disease-free survival and five-year overall survival parameters. (30,31) Long-term survival rates of 90% and recurrence rates of 5% have been reported in resections performed with open surgery in early-stage thymomas. With thoracoscopic and robotic approach, similar and better oncological results were obtained, in addition, less bleeding, lower complication rates and shorter duration of hospital stay were obtained. (32)

Ectopic parathyroid tissue may also be located in anterior mediastinum and surgical excision may be needed in treatment of these lesions. These lesions which, may be located close to thymus in anterior mediastinum in connection with embryological process are also proper pathologies for surgery with VATS approach. Prior to surgery of these lesions, which may be difficult to detect intraoperatively, MRI, CT and nuclear medicine examinations for determination of localizations are important. (33) Germ cell tumors may also be located in anterior mediastinum and may require surgical resection in some cases. It is easy to diagnose benign teratomas from this group with limited encapsulated appearance, fat content, tissue such as cartilage, teeth or bones, and typical radiological features such as cystic appearance. Surgical resection is appropriate treatment for mediastinal benign teratomas.

Thoracoscopic approach may be preferred according to size and location of mass. In general, resection with VATS is recommended for masses smaller than 4 cm. (34)

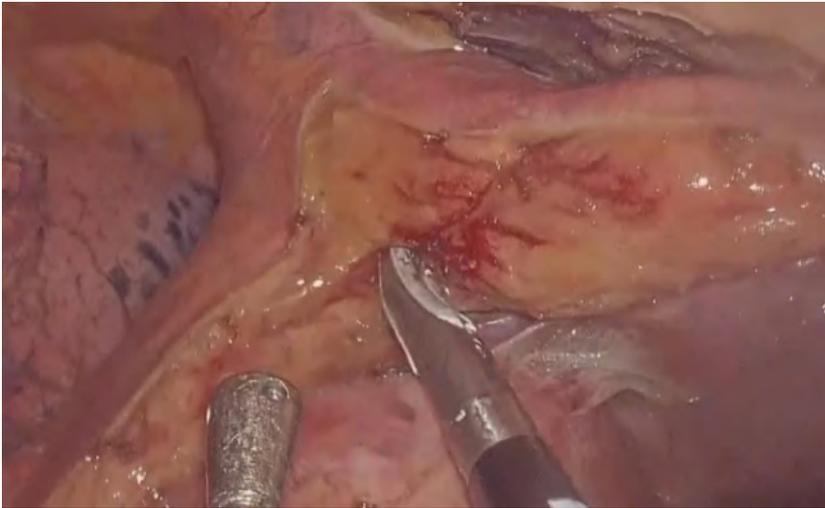


Figure 2: Videothoracoscopic thymectomy

Posterior mediastinum

Majority of posterior mediastinal masses consist tumors of benign nerve origin. Examples of these are neurofibroma or ganglioneuromas, especially schwannoma. Neurogenic tumors located in posterior mediastinal are proper lesions for VATS due to mostly benign, encapsulated and generally small in size, and may be easily removed by enucleation. (35) Open surgery is recommended instead of VATS in malignant tumors, lesions larger than 5 cm and tumors that have advanced beyond borders of thorax.

Middle mediastinum

Majority of middle mediastinal masses are benign cystic lesions (bronchogenic, pericardial). In addition, granulomatous and infectious diseases may occur mediastinal lesions in form of lymph node masses and VATS technique may be used in the treatment. Depending on location of cyst, locations of thoracoscopy ports may be determined.

Minimally invasive approach in esophageal cancer

Esophageal cancer is eighth most common cancer worldwide and ranks sixth among cancer-related deaths. Surgery is accepted as

standard treatment in patients with early-stage esophageal cancer. However, most of cases are diagnosed in advanced stages and surgical treatment may not be applied. (36,37) Today, minimally invasive esophagectomy includes laparoscopic transhiatal, laparoscopic-thoracoscopic three-hole (McKeown) and laparoscopic-thoracoscopic (Ivor Lewis) esophagectomy.

Minimally invasive esophagectomy is performed increasingly with advantages of perioperative results compared to open esophagectomy. McKeown and Ivor Lewis are commonly used procedures of minimally invasive esophagectomy. Deng et al. (38) examined prospective and retrospective studies evaluating short-term results of minimally invasive Ivor Lewis esophagectomy and minimally invasive McKeown esophagectomy in patients with resectable esophageal cancer. The difference between two procedures was not significant, especially anastomosis leakage, 30-day hospital mortality and 90-day mortality. This study shows that two procedures are comparable in terms of clinical safety. Minimally invasive Ivor Lewis esophagectomy may be a better option when case is oncologically and clinically appropriate. Minimally invasive McKeown esophagectomy is a safe alternative procedure in case of clinical indications.

On respiratory complications, minimally invasive esophagectomy is useful in reducing postoperative respiratory complications such as atelectasis. There is no significant difference between the minimally invasive esophagectomy and open esophagectomy for other complications, such as anastomosis leak and recurrent laryngeal nerve palsy. Minimally invasive esophagectomy is associated with less pain than open esophagectomy. There is no significant difference in long term outcomes in terms of quality of life and survival between minimally invasive esophagectomy and open esophagectomy. (39)

Minimally invasive approach in benign diseases of esophagus

Leiomyoma is the most common benign tumor of esophagus and originates from muscularis propria layer of esophagus. In autopsies, its incidence is reported between 0.006% and 0.1%. Leiomyoma forms 10% of all gastrointestinal leiomyomas and 70-80% of esophageal benign tumors (40) and less than 1% of esophageal neoplasms. Which surgical approach will be applied to a case with leiomyoma is decided according to whether tumor is single or multiple, size and localization. Thoracoscopy is mostly preferred when lesion is single and tumor size

is 5 cm and less. As tumor size increases, enucleation becomes more difficult and possibility of mucosal injury increases. (41)

Videotoracoscopic sympatectomy

Sweating is a physiological condition that occurs with apocrine glands. Hyperhidrosis is pathological excessive sweating. It is frequently seen in palms, armpits, soles of feet and head and neck area. It may be focal, generalized or regional.

Generally, though the most common indication is hyperhidrosis in world, thoracic sympathectomy is performed in different indications. Reynauld phenomenon, Q-T syndrome, pancreatic carcinoma pain are main ones. Reynau disease is an episodic digital ischemic attack caused by emotional factors, especially in cold weather. To prevent vasoconstriction, it is essential to quit smoking and avoid cold. Surgical treatment is performed as T2-4 sympathectomy in severe cases that do not respond to medical treatment. (42) A less common indication is treatment of patients with long Q-T syndrome, that especially do not respond to beta blockers. Sympathectomy between T2-5 reduce symptoms was reported in the literature. (43)

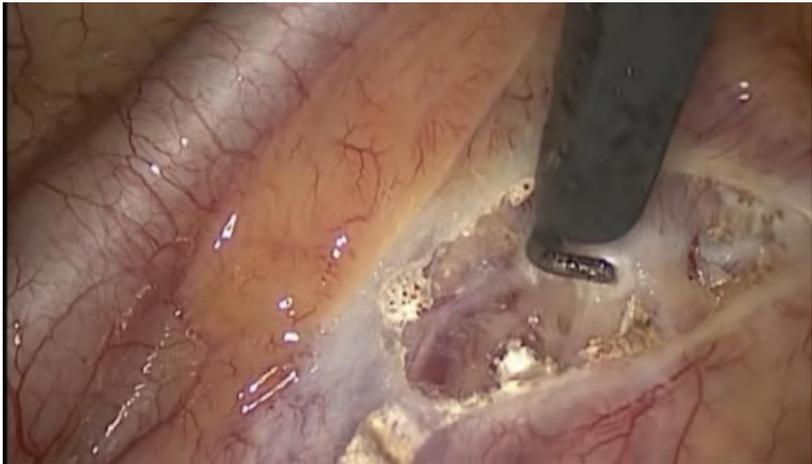


Figure 3: Videotoracoscopic sympatectomy

Patient satisfaction and quality of life are main aims of surgery in thoracoscopic sympathectomy surgery. In diagnosis of hyperhidrosis, although anamnesis and a simple physical examination are sufficient, severity, prevalence and impact on life quality of disease should be accurately determined to evaluate complications that may develop and quality of life. In various studies, it was observed that number of

sweating area in patient do not affect surgical results. (44) In the study on 626 patients who were operated at least six months ago, it was concluded that 25% of patients were satisfied, 64% of patients were very satisfied and 11% of patients regretted surgery. (45)

Main target in endoscopic sympathectomy is to perform a surgical treatment that may provide patient with best quality of life. In patients who do not applied surgery, topical, systemic and iontophoresis methods may be applied.

Minimal invasive pectoral surgery

Pectus excavatum

Pectus excavatum is posterior depression of midline and lower part of sternum and posterior curvature of associated rib cartilage deformity. (46) As sternum corpus is depressed with abnormally growing costal cartilage, ribs protrudes from sternum to anterior and form this image.

Surgical treatment of pectus excavatum was first tried by Meyer by excising costal cartilage in 1911 and bilateral costal cartilage resection was applied by Sauerbruch by performing a sternal osteotomy in 1920. (47) Ravitch method, which is a costochondrol incision or resection, sternal osteotomy and internal fixation has been accepted as a classical surgical procedure. In 1987, Dr. Nuss developed a minimally invasive technique (Nuss procedure) based on retrosternal placement of a metal bar shaped by flexible costal cartilage and ensuring deformity is fixed without need for osteotomy and bar is removed after a certain period of time. (48) Minimally invasive technique has advantage which no need for sternal osteotomy, removal of pectoral muscle flap and resection of damaged cartilage. Also, due to minimal loss of blood, short surgery time, short hospital stay, minimal surgical scar, succesful cosmetic result, starting daily activities early and high patient satisfaction, minimally invasive technique has become first method of choice for surgery of pectus excavatum deformity. In studies on this technique, Osawa et al. also recommended using titanium bar instead of metal bar for Nuss procedure. (49)

Pectus carinatum

Pectus carinatum is deformity which seen on anterior chest wall characterized by convex protrusion of sternum and costal cartilage. It is detected in men four times more than women (50). Majority of patients are aseptomatic.

While deformity is improved surgically, it is aimed to support growing healthy of thorax, to provide a proper posture and to improve

psychosocial situation. Treatment is surgery or orthosis, based on principle of pressure applied to rib cage according to clinical presentation. Pressure force required for improvement deformity in protruded rib cage is measured with a compression test device. Orthotic treatment is recommended if required pressure is less than 10 kg, and surgical treatment is recommended if more than 10 kg. (51)

The first pectus carinatum operation was was operated by Ravitch similar to pectus excavatum surgical treatment. (52) Until 2000s, this classical method continued to be used based on basic principles of separation of malformed cartilage from sternum, subperiosteal resection, if necessary sternal osteotomy, support bar placement behind sternum. In 2005, Dr. Abramson applied minimally invasive technique which is improved by compression of sternum and has replaced classical method with less complication and operation time, smaller incision and less blood loss, reduced hospital stay time. (53)

Minimally invasive approach in mixed type pectus deformity

Mixed type pectus is a combination of excavatum and carinatum deformities. It is generally considered to be a pectus carinatum deformity containing excavatum component and incidence is 0.14%. In improvement of mixed type deformity, "sandwich technique" was applied by Park as an alternative to open surgery. (54) This technique is based on combination of Nuss and Abramson techniques, shaping anterior chest wall thanks to bars placed retrosternal and presternal.

Diaphragm surgery

In parallel with development in minimally invasive surgical techniques, use of video-assisted thoracoscopic surgery has become increasingly common in diaphragmatic surgery after the 1990s. Almost all diaphragm open surgery may be performed with VATS.

Diaphragmatic plication

In diaphragmatic paralysis, as a result of damage to phrenic nerve for various reasons, diaphragm rises and paradoxical movement is observed on same side. Evantration is a rare congenital anomaly. In both cases, the diaphragm rises and compresses lung, causing atelectasis and causing dyspnea. Treatment is to prevent paradoxical motion and correct dyspnea by replacing diaphragm. Therefore, many methods have been applied in open surgery. With development of minimally invasive surgery, diaphragm surgeries began to be performed thoracoscopically. The first successful video thoracoscopic

diaphragmatic plication was reported by Gharagozloo et al. in 1995. (55) While previously this operations were realized with three or four ports, it has progressed to apply with single port. Yalçinkaya et al. reported that such a hybrid operation was performed successfully. (56)



Figure 4: Videotoracoscopic diaphragmatic plication

Diaphragmatic injuries

In blunt thoracic trauma, diaphragmatic injuries occur in approximately 4-6% and 80% are on left side. (57) It is usually associated with intra-abdominal organ injury. Laceration occurs when pushing diaphragm into chest cavity with a sudden increase in intra-abdominal pressure. 15-59% of thoracoabdominal penetrating traumas cause damage to diaphragm. (58) Radiographs in rupture may be normal up to 77%. In these cases, irregularity in diaphragm contours should be suspected in radiography. However, accompanying hemothorax makes diagnosis difficult. Computed tomography and magnetic resonance imaging are more helpful in diagnosis. In minor and penetrating injuries, there are still difficulties in diagnosis. In cases where suspicion continues, VATS provides both diagnosis and treatment. In 1976, first thoracoscopy was performed in trauma of diaphragmatic injury. (59) However, in recent years, VATS has been used more frequently due to less postoperative pain, better lung function, better shoulder function, shorter hospital stay and lower costs. (58)

Congenital diaphragmatic hernias

Diaphragmatic hernia is passage of some intra-abdominal organs into thoracic cavity due to a defect. It is due to complete closure of pleuroperitoneal canal during embryonic development period. It is examined in four groups: posterolateral, non-posterolateral, evantration and mixed hernias. The most common form is posterolateral hernia with a rate of 80-95% and it is frequently detected during neonatal and infant period. Treatment is as soon as patient is stable, surgically pushing herniated organs back into abdomen and closing defect. While this pathology was previously treated only with open surgery, VATS has become popular today on treatment. In a metaanalysis comparing endoscopic treatment and open surgery in neonatal cases, mortality rates were found in favor of endoscopic surgery. However, recurrence rates are lower in open surgery. (60) Although it may be performed laparoscopically, removing thoracic adhesions and having a wide field of view when organs are pushed into abdomen has made VATS preferred method. (61) Non-posterolateral hernia grows through an opening under sternocostal junction. It was first described in 1769. It constitutes 1.5-7.0% of congenital hernias and 90% in right. Although usually asymptomatic, abdominal pain and gastrointestinal symptoms may be seen and VATS operations have been reported in recent years. (62)

Video-assisted ampiem surgery

Pleural empyema is defined as infected fluid in pleural area. Pulmonary infections are most common cause of pleural empyema. Parapneumonic fluid develops in 14-19% of pneumonia. (63) Mortality rate in adults is around 15-20%. (64) Alcoholism, diabetes and immunosuppressive diseases are causative factors. Treatment options should be managed according to multidisciplinary conditions, multiple variables that may be patient-related, characteristic of pleural cavity, experience of surgeons. Fully discharging of infected fluid, ensuring maximum expansion of lung, proper antibiotic treatment for microorganism, cure and supportive treatment are basic treatment principles in pleural empyema. Primary treatment method of complicated pleural fluids is drainage and antibiotic therapy. However, when fibrinopurulent and organized empyema develops, this method is insufficient. The American College of Chest Physicians guide states that VATS and open thoracotomy techniques are all acceptable treatments for these patients. (65)

Since delay in surgery will be a factor that increases mortality, patient should be operated at optimum conditions. It should be remembered that lungs with pneumonic consolidation will cause expansion problems. Decortication is not recommended for patients with damaged lungs. With empyema, option of lung resection with omentopexy / myoplasty should be considered. Aim of surgery is to empty inflammatory material in lung and provide lung swelling. Necessary tissue samples for microbiological, histopathological and biochemical examinations should be taken during VATS procedure. In addition, high success may be achieved with VATS without significant morbidity. VATS decortication may be accepted as one of first treatment methods in early multilocular pleural empyema. (66)

Videotoracoscopic volume reduction surgery

Emphysema is defined as an abnormal dilatation of air spaces remaining distal to terminal bronchioles and accompanying alveolar wall and permanent destruction of surrounding supporting connective tissue without fibrosis. (67) In emphysema, there is no elastic return that throws air out, as disease progresses, expiratory air flow is disturbed and hyperinflation develops inside parenchyma. A clinic similar to chronic obstructive pulmonary disease occurs. (68)

The most discussed topic in volume reduction surgery is patient selection in correct indication. Surgery should be considered in patients who may not provide clinical relief with conservative measures and inhaler treatments. Choosing proper patient is an important factor that determines long-term mortality and morbidity results of surgery. Therefore, prevalence of emphysema, respiratory capacity and comorbidities of patient should be evaluated with a multidisciplinary team with preoperative radiological examinations. Patients who will have least mortality-morbidity after surgery and severe symptomatic (dyspnea, weak physical function) should be identified and directed to operation.

Endobronchial treatments may be used as non-surgical minimally invasive methods. Use of endoscopic endobronchial valves as non-invasive procedures are developing and promising treatments. Minimally invasive procedures used for this purpose are bronchoscopic valves, coils and sclerosing agents. (69) After proper patient selection and proper preoperative preparation, patients are operated. Aim of operation is to eliminate pressure on relatively strong parenchyma, diaphragm and chest wall, by resecting parenchyma areas with nonanatomically evident emphysema and reducing total lung capacity and residual volume. In this way, relatively healthy parenchymal tissue is expanded

and air taken by inspiration tends to areas where gas exchange is better. Quality of life are improved with regulating distribution of ventilation perfusion, FEV1, FVC, cardiac flow and exercise capacity. (70) With this in mind, first time, Otto Brantigan performed lung volume reduction surgery with thoracotomy in 1957. (71) This surgical method was not applied for a long time due to high mortality in early postoperative period. Dr. Copper who is one of pioneers of lung transplant brought this surgery on the agenda again under better conditions with developing intensive care experience and published the principles of volume reduction surgery by performing the operation in 1994. (72) In previous years, although sternotomy, bilateral approach or thoracotomy have been applied, generally accepted method in the world is VATS surgical procedures. Videothoroscopic approaches have advantages such as less pain, less morbidity and more succesful cosmetic incision.

One of important points to be considered during surgery is applying stapler feet to relatively solid area closest to emphysematous area. In this way, stapler is applied to more solid tissue and risk of air leakage is reduced. During operation, stapler line may be supported with synthetic materials such as seamguard or tissue adhesives and air leakage is reduced. (73)

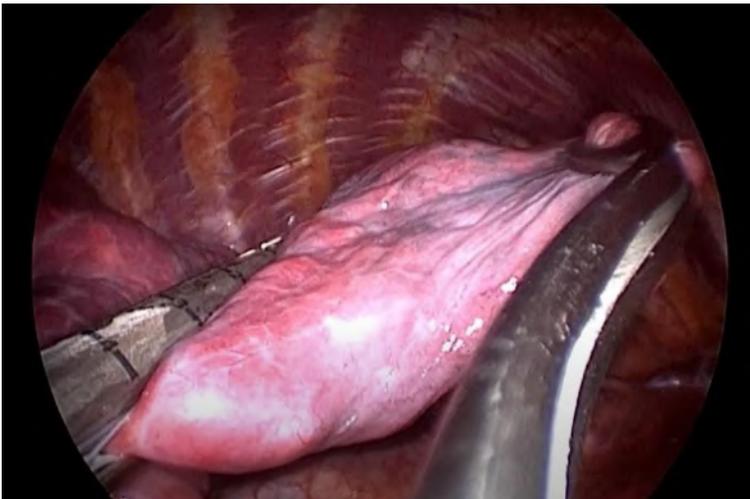


Figure 5: Videotoracoscopic volume reduction surgery

Conclusion

As a result, trend towards minimally invasive surgical methods in all surgical disciplines in the world is quite high. These methods are

especially important in terms of patient comfort and quality of life after surgery. Even in lung cancer surgery where oncological surgical principles are at the forefront, minimally invasive surgical methods may be used safely and with high efficiency. Minimally invasive surgical approach is almost standard, especially in early-stage lung cancer. In the light of this information, when experience gained in VATS method and results of studies in literature are examined, it may be seen that VATS method may be used safely in experienced centers in treatment of almost all diseases that are of interest to thoracic surgery.

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CHAPTER XV

ROBOTIC THORACIC SURGERY

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Introduction

In recent years, there has been a great development in medical technology and one of results of advanced technologies is application of robots to surgery. Idea of producing with mechanical robot has been in imagination of man for last 3000 years. However, using of robots in medicine has a history of only 30 years. Nowadays, FDA approved surgical robotic system is da Vinci robotic system. Robot provides several advantages over traditional open and endoscopic procedures such as 10x magnification, higher precision, vibrate filtration, stereoscopic vision, motion scaling and ergonomically efficient position for surgeons. These advantages have made the robot an increasingly popular treatment option for surgeons and patients. Although it is first used in general surgery, urology and gynecological surgery, successful robotic surgery is gradually increasing in thoracic surgery.

The purpose of this chapter is to describe evolution of modern surgical robotic systems and to explain techniques of robotics surgery in thoracic surgery.

Recent history of robotic surgery

Applying robots in surgery is due to need of modern man to achieve two targets: telepresence and performance of repetitive and correct missions. The first target was reached in 1951. While working for USA Atomic Energy Commission, Raymond Goertz designed the first teleoperation mechanical arm to process hazardous radioactive materials. (1, 2) The second was achieved in 1961, when George Devol developed the first industrial robot called Unimate for General Motors. These successful experiments were decisive factors in robotics entry into all other industrial areas around the world. (3, 4) Although used in

the literature by Karel Capek and Isaac Asimov in the 1920s and 1940s respectively, the first definition of "robot" was published by Robots Institute of America in 1979. (5, 6, 7)

The first 'robot surgeon' used in a patient was a programmable universal machine for assembly (PUMA 200) (Figure 1) developed by Victor Scheinman in 1978 and used by Kwok to perform neurosurgical biopsies in 1985. (8, 9) Due to successful results achieved with PUMA, it was performed in urology surgeries in Imperial College London in 1988. (10) Afterwards, this robot was replaced by prostatectomy (SARP) used in prostate surgery, prostate robot (PROBOT), and UROBOT which were commonly used in urological procedures. (8, 11) These robots were pre-programmed according to patient's anatomical findings and not used in dynamic surgical targets.



Figure 1: Programmable universal machine for assembly (PUMA) 200

The desire to send people into space has prompted NASA researchers to develop research projects to perform long-distance surgeries. Researchers Michael McGreevey, Stephen Ellis and Scott Fischer have developed a 3D vision stereoscopic display unit called a head-mounted display (HMD) to enable astronauts to access real-time data. (12) HMD was combined with data gloves created by Jaron Lanier, allowing the user to interact with virtual area. (8) Also, in the Stanford Research Institute (SRI), Philip Green and military surgeon Richard Satava developed an operating system for instrument telemanipulation. (13) Computer scientist Scott Fischer and plastic

surgeon Joseph Rosen produced the basics of telepressure surgery to perform surgery in space through the combined use of HMD, the data glove, and the SRI telemanipulator. (8) Unfortunately, telepressure surgery projects were not technically possible. (14) HMD has been replaced by handled data gloves for monitors and controllers at surgeon's console. (8) In 1989, Jacques Perissat presented laparoscopic cholecystectomy technique at the American Gastrointestinal and Endoscopic Surgeons Association meeting. This innovation attracted attention team of Richard Satava to develop a robotic system that applied to laparoscopic surgery. (15) United States of America Ministry of Defense was interested in providing medical aid to wounded soldiers on battlefield, that resulted in a project to develop a robotic system. This project was a prototype mounted on an armored vehicle (Bradley 557A) that could take surgeon to battlefield as virtual. (14) The first remote surgical procedure, ex-vivo intestinal anastomosis, performed by Dr. Jon Bowersox. (16)

In the 1990s, scientists developed first “master-slave system” consisting of a robot with remote manipulators controlled by surgeon on Workstation. (8) Various models that designed after development of this system are:

- AESOP:

In 1993, Yulin Wang developed automated endoscopic system for optimal positioning (AESOP). The following year, Food and Drug Administration (FDA) approved AESOP (Figure 2) as the endoscopic camera manipulator controlled by the surgeon's voice commands, thereby eliminating the need for an assistant to perform this mission. (17, 18, 19) There are some literature reports describing AESOP studies in laparoscopic cholecystectomy, hernioplasty, fundoplication and colectomy. (20)



Figure 2: Automated endoscopic system for optimal positioning (AESOP)

- ZEUS:

Yulin Wang who unsatisfied with telemanipulation concept of video camera, developed a robot that provided movements of surgeon's arms.



Figure 3: ZEUS robotic surgical system

As a result, ZEUS robotic surgical system (Figure 3, 4) was created with arms and surgical instruments controlled by surgeon. (15) ZEUS robotic surgical system was first used in fallopian tube anastomosis in July 1998, in Cleveland, Ohio. (21) Reports in literature explained use of ZEUS in digestion (cholecystectomy, appendectomy, bariatric, hernioplasty, gastrectomy, fundoplication, splenectomy and colectomy), urological, gynecological and cardiac surgeries. (22, 23) In September 2001, ZEUS was used for the first transatlantic telesurgery. (24)



Figure 4: ZEUS robotic surgical system

- DA VINCI:

DA VINCI robotic surgical system (Figure 5) is the most common robotic surgical system with more than 3400 units sold worldwide and thousands publications. The first robot-assisted cholecystectomy was performed by Jacques Himpens and Guy Cardiere in 1997 in Brussels, Belgium. (25) Following this successful surgical procedure, myocardial revascularization surgeries were performed at University of Leipzig in Germany in 1998. (26) Although cardiac surgery was main focus of DA VINCI industry, results achieved in this area have not been as satisfactory as in general surgery. (27) In United States of America, use of DA VINCI in abdominal surgeries was approved by FDA in July 2000. (28) Also, it was commonly used in urological and gynecological surgeries, benign diseases and hysterectomy, after the first robotic radical prostatectomy performed in the USA. (29, 30, 31)



Figure 5: DA VINCI robotic surgical system

DA VINCI robotic system surpasses most of limitations of laparoscopic surgery, mainly 2D vision of surgical area, articulated instrument arms. (32) Technical improvements such as highly enlarged 3D vision, precisely control, and preservation of eye-hand alignment provided robotic platform more attractive for surgeons to use DA VINCI in a wide range of surgeries. Some other features such as stable view of the operation area, magnification of up to 10x image, physiological vibrate filtering, motion scaling up to 5:1, and better ergonomics are also stated in scientific articles. (26, 33)

In addition DA VINCI models which lasted for generations in a row, some new auxiliary tools and accessories have also been developed.

- Da Vinci Single-Site: This system eliminated support effect and reestablished instrument triangulation. (34)

- Fire Fly System: This system combined a special video camera with a fluorescent dye injected intravenously during surgery, it provided a detailed picture of vascular and biliary tract. (35)

- Double Console: This system mainly used to train beginner surgeons. (26, 36)

- Til Pro System: This system allowed simultaneous viewing of two image sources (eg computed tomography and intraoperative echography) on monitor. (37)

• Natural Orifice Transluminal Robotic Surgery: One of the most promising practice of this technique has been robotic transanal minimally invasive surgery. (38)



Figure 6: DA VINCI double consol and single site system

Use of robot in thoracic surgery

Robotic thoracic surgery cases have been reported since the beginning of 2000. The first robotic lobectomy report for lung cancer was published in 2002. (39) Early stage non-small cell lung cancer (NSCLC) operations were previously performed using video-assisted thoracic surgery. (40) In 2010, 40% of lung cancers were operated by VATS and 3.4% by robotic systems. (41) According to the annual report of Japanese Society of Thoracic Surgery, 62.9% of lung cancer surgeries were performed with VATS in 2012, but a few cases were performed with robotic surgery. (42) Both VATS and robotic surgery are minimally invasive, but various differences have been reported. (43) Both video-assisted thoracic surgery and robot-assisted thoracic surgery have shown better perioperative results and equivalent oncological results compared to thoracotomy. Compared to VATS, robotic thoracic surgery provides easier operations in lung cancer, robot has better instruments and better view of the field of operation; 3-dimensional instead of 2-dimensional; $\times 10$ magnification instead of $\times 2$ or $\times 3$; and less fogging, thus less camera manipulation.

Robotic lung resections

Surgical resection for early stage non-small cell lung cancer is associated with 5-year survival and the lowest risk of local and distant recurrence. (44) Though thoracotomy for lung resection has developed over time in pain-saving incisions with muscle protective incisions,

catheter systems and long-acting analgesics, variable hospital stay and risk of perioperative morbidity and mortality continue in open surgery. (45) Adoption of minimally invasive lung resection significantly changed management of patients, reduced hospital stay, accelerated return to baseline performance, and shortened recuperation interval for patients who may require adjuvant therapy. (46) Although minimally invasive lung resection has historically been performed in video-assisted method with 2D optical and inarticulate instruments, inclusion of robotic technology in lung cancer surgery also means important technical advantages for surgeons. Robotic system is a useful method in which advanced procedures may be performed, including wedge, anatomical resection (segmentectomy, lobectomy, pneumonectomy), mediastinal lymphadenectomy and bronchovascular sleeve resections. (47)

Determinating appropriate patient for robotic lung resection is similar to other minimally invasive techniques. These procedures are best performed with single lung ventilation; however, unlike VATS, in almost all cases, insufflation with carbon dioxide up to a pressure of 8 to 10 mm Hg is used and significantly improves visualization. Dye marking of preoperative localization with computed tomography (CT) or intraoperative navigation bronchoscopy helped increase preoperative imaging and increased effectiveness. (48) Tumor placement in central structures requiring complex bronchovascular resection and reconstruction may be contraindication for anyone other than an experienced surgeon. In addition, invasion of chest wall may require a hybrid approach (robotic lobectomy and resection with a limited incision) or should be considered only after substantial experience has been obtained in less complex cases. Significant hilar lymphadenopathy surrounding central structures have potential technical challenge, especially in cases where granulomatous disease is common. However, considering technical advantages of articulating instruments and bipolar or energy devices, these cases are performed easier with robot.

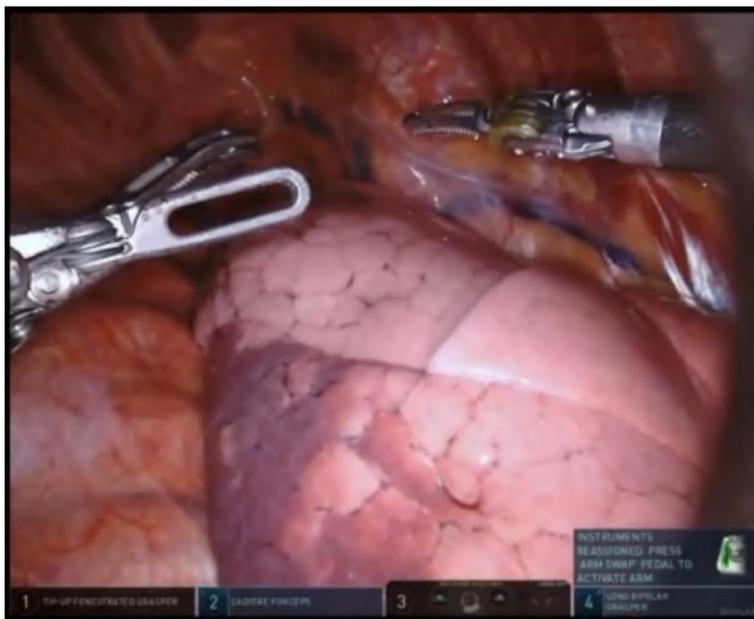


Figure 7: Robotic lung resections

Preoperative chest CT scan is recommended to evaluate tumor placement, pulmonary artery branches, or other complex anatomy that may assist in surgical planning. Staging and cardiopulmonary risk classification are similar to nonrobotic procedures described based on consensus recommendations. (49) These technical features have led to increased use of robotic lung resection over the past decade. Institutional database results show similar positivity and morbidity and mortality rates compared to open and VATS procedures. (50, 51) Reported advantages of robotic lung resection include improved lymph node dissection, greater node resected, decreased blood loss and hospital stay compared to open or VATS procedures. (52, 53)

Robotic mediastinum surgery

Considering mediastinum proximity to heart and large vessels, reaching is hard for surgeons. Surgeries have traditionally been performed with sternotomy, posterolateral thoracotomy or clam shell incision with long hospital stay hospitalization and recuperation. Minimally invasive techniques for mediastinal procedures provided smaller incisions, shorter hospital stay, and faster recuperation. (54) However, emergence of robotic technology allowed surgeons to perform complex maneuvers that mimic traditional open techniques.

Mediastinal pathological condition is traditionally defined according to specific anatomical factors and is divided anterior, middle and posterior. Differential diagnoses for anterior mediastinal pathological conditions include thymoma / thymic carcinoma, germ cell tumors, thyroid masses, and ectopic parathyroid glands. Middle mediastinal masses include lymphadenopathies, bronchogenic cysts, pericardial cysts, and rarely solid ectopic tumors. Posterior mediastinal masses include foregut cysts or neurogenic solid tumors.

Standard preoperative evaluation is according to independently of resection platform, with details of robot-assisted procedures. Intravenous contrast computed tomography helps in determining relationship of a mass with large vessels. In thoracoscopic and robotic procedures, relationship of lesion with ribs in the surrounding area is important for port area. Pulmonary function testing is recommended, because a weak lung reserve may obstruct single lung ventilation. Lung isolation is supplemented by carbon dioxide insufflation at 8 to 10 mm Hg to improve visualization and in cases where single lung ventilation is poorly tolerated.

Anterior mediastinum surgery

Anterior mediastinum is localization in chest between anterior border of pericardium and sternum. Robotic assisted surgery (Figure 8) is used for mediastinal pathological conditions such as myasthenia gravis, thymectomy / thymic carcinomas for thymoma, lymphoma, germ cell tumors, ectopic parathyroid and thyroid tissues.



Figure 8: Robotic radical thymectomy at anterior mediastinum

Performing R0 resection is important for curative treatment. Therefore, thymomas involved in thymic capsule invasion or Masaoka Stage I tumors are considered to be acceptable for minimally invasive techniques. (55) Minimally invasive resections are also acceptable for Masaoka Stage II tumors. (56) Treatment of anterior mediastinal teratomas and dermoid cysts is surgical resection which robotic assistance is appropriate. Seminomas and non-cineminomatosis tumors are treated with radiation and chemotherapy, respectively. If disease continues after treatment, more robot-assisted resection may be performed. Robotic procedures for lymphoma are primarily associated with excisional biopsies.

Middle mediastinum surgery

Middle mediastinum is localization in chest between anterior and posterior border of pericardium. Pathological conditions of middle mediastinum frequently include congenital bronchogenic cysts, pericardial cysts and mediastinal lymph nodes. (57) Use of robotic technology for resection of bronchogenic cysts and pericardial cysts (Figure 9) is described in literature fairly well. (58) Congenital mediastinal cysts may be symptomatic due to mass effect in surrounding tissues. In addition, these cysts may become infected and make resection difficult. (59) Resection is usually indicated for symptomatic or easily accessible cysts with low operative risk to prevent long-term complications due to growth and mass effect.

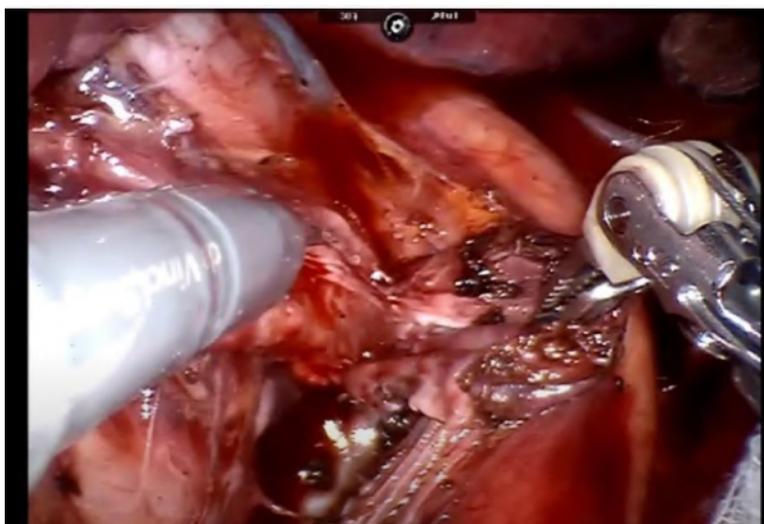


Figure 9: Robotic bronchogenic cyst resection at middle mediastinum

Posterior mediastinum surgery

Posterior mediastinum is localization in chest between posterior border of pericardium and vertebrae. Procedures related to foregut and neurogenic pathological condition, neurofibromas, schwannom, neuroganglioma, ganglioneuroblastoma, paraganglioma and foregut duplication cysts are the most common robotic resection procedures (Figure 10). Similar to middle mediastinal tumors, posterior mediastinal tumors, especially neurogenic tumors may be symptomatic due to mass effect. In these patients, robotic surgical resection requires careful preoperative planning and preparation. MRI of vertebrae is important for describing involvement of intravertebral foramen. If it identified, a procedure combined with neurosurgery may be required. A functional paraganglioma is a possible diagnosis for a posterior mediastinal tumor. Therefore, a comprehensive endocrine assessment for catecholamine levels is important to avoid intraoperative hypertensive crisis. Endoscopy or contrast esophagram is recommended before robotic surgery in emergence of foregut pathological condition.



Figure 10: Robotic schwannoma resection at posterior mediastinum

Robotic esophageal surgery

Esophageal surgery is particularly appropriate for a minimally invasive approach due to its location in multiple anatomical areas and needing several incisions in open surgery. Proximity to important

adjacent structures in neck, chest and abdomen makes robotic approach attractive. Robot-assisted surgery of esophagus (Figure 11) has been described with successful results in malignant esophageal diseases.

Among the most common benign conditions occurring in chest are leiomyoma and epifrenic diverticula. Robotic enucleation of esophageal leiomyoma has been well defined even in very large masses. (60) Management of esophagus malignant disease requires a multidisciplinary treatment. In general, trimodality treatment using induction chemoradiotherapy and surgical resection is gold standard for early-stage disease. Surgical approach varies according to location of lesion, surgical history of patients, and surgeon's preference.

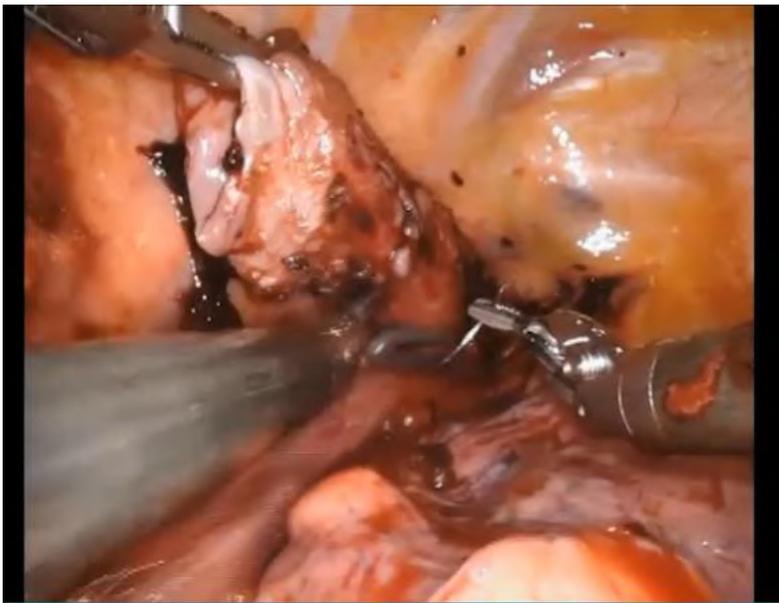


Figure 11: Robotic minimal invasive esophagectomy

Surgical approach of esophagus malignancies is specific to patient and surgeon. Each technique has advantages and disadvantages and requires a analysis for each patient. In literature, many studies were presented that excellent oncological results and quality of life achieved by using robotic surgery to assist surgical resection and reconstruction of esophagus. (61)

Conclusion

With effect of developing technology in thoracic surgery, it has been possible to treat lung resections with robotic surgery in recent years.

Robotic thoracic surgery is considered the next step in the evolution of minimally invasive surgery, since the robot allows a more complex and precise operation than VATS. Compared to open approach and VATS, robotic thoracic surgery provides easier operations in the lung cancer. Robot has better instruments and better view of the field of operation; 3-dimensional instead of 2-dimensional; $\times 10$ magnification instead of $\times 2$ or $\times 3$; and less fogging, thus less camera manipulation.

Retrospective studies show that robot-assisted thoracic surgery is feasible and safe. Limited long-term results show oncological, morbidity and mortality results similar to open and VATS approaches. Robotic approach simplifies surgery with more intuitive movements, greater flexibility, and high definition, three-dimensional vision. High capital and operating costs and limited vehicle availability are main disadvantages of robotic surgery. However, with spread of new generation robots and competition in different manufacturers, it is thought that costs of robotic surgery may be reduced in the future. In the light of this information, it is inevitable that use of robotic technology in thoracic surgery will increase gradually near future.

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CHAPTER XVI

PERCUTANEOUS NEPHROLITHOTOMY (PNL): TIPS AND TRICKS

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Introduction

Minimal invasive or non-invasive method search in urological surgical application has always interested urologists. The situation was also the same in urinary system stone treatment and technological improvements were applied quickly.

Percutaneous nephrolithotomy has a long history although its popularity increased in the last 10 years. The first nephroscopy was applied by Rupel and Brown in 1941 monitorizing the inside of the kidney through a rigid cystoscope during open surgery. Goodwin took the first antegrade nephrostogram through entering the pelvicalyceal system with a percutaneous needle in a hydronephrotic kidney and inserted the first nephrostomy tube in 1955. Fernstrom and Johansson reported a new stone surgery method they named percutaneous pyelolithotomy in 1976 and performed the first percutaneous surgery. Combining this method with ultrasonographic lithotripter, Kurth et al showed that bigger stone particles could be removed from small nephrostomy tract through fragmentation¹. But as extracorporeal shock wave lithotripsy (ESWL) became one of the current urological stone applications and its popularity increased in 1980s and studies on ESWL increased, PNL remained in the background for sometime². When it was observed that ESWL wasn't suitable for the treatment of all stone patients, PNL's popularity started to increase again and PNL

became one of the indispensable methods for stone treatment in the last ten years with the technological developments and new modifications.

Wickham reported that kidney stones which are inoperable through open surgery could be successfully removed through electively applied nephrostomy tract in 1983.³ In another study published in the same year, it was shown that PNL interventions constituted a method preferable by many centers in the treatment of kidney and ureteral stones⁴. When PNL applied by Prof. Dr. Mehmet Arslan in 1985 for the first time in our country is compared to open techniques, it has replaced open surgical interventions in many centers as it has lower morbidity and provides renal stone treatment with shorter recovery time and lower cost⁵. PNL is suggested as the first choice in kidney stones over 2 cm in the stone disease guide of European Association of Urology (EAU)⁶.

Current Developments in PNL:

Tubeless PNL: Tubeless PNL is a good technique which can be used in single access inlets. In the technique first described by Belmann et al⁷ in 1997, nephrostomy tube is replaced by an internal stent at the end of the operation^{8,9}. Tubeless PNL is observed to be more advantageous in terms of hospitalization time, analgesia need, bleeding risk and postoperative morbidity.¹⁰ There are also current studies showing that total tubeless PNL is a safe technique¹¹⁻¹⁴. Studies showing that total tubeless technique is safe in multi-access PNL were also made in recent years¹⁰.

Supine PNL: Valdivia et al.¹⁵ reported first supine PNL experiences in 1998 and defined the advantages of this technique. Supine PNL has advantages such as anesthetic position and time gaining because of simultaneous applications of ureteroscopic procedures and position giving compared to prone PNL. But narrow access area and manipulation difficulty of nephroscope are among the disadvantages of supine PNL. Considering the advantages and limitations of these two positions, disputes on how the most suitable position will be chosen for PNL still continue¹⁶.

Conflicting results are observed especially in stone-free rate when supine PNL and prone PNL are compared. Similar stone-free rates are reported for supine PNL and prone PNL in current studies^{17,18}. Overcoming the restrictions in original supine position through the updates in Galdakao modified Valdivia position and modified supine S-position is considered as the most important cause for this¹⁶.

Due to the acquisition of a larger area for access after defining Galdakao-modified Valdivia position, easiness of access to kidney upper pole stones, provision of the simultaneous application of PNL and ureteroscopic interventions, easiness of emptying stone fragments due to the downward sheath angle and low intrapielocalyceal pressure, supine PNL attracts more attention recently^{19,20}. Lower postoperative fever and higher stone-free rate were shown in supine PNL in current studies. But supine PNL is still a new technique and only supine PNL application rate is around 5%. Thus application of supine PNL in selected patients by experienced surgeons can be considered as an efficient option in renal and upper ureteral stones¹⁶.

Endoscopic Combined Intrarenal Surgery (ECIRS): Simultaneous retrograde intrarenal surgery and percutaneous nephrolithotomy (PNL) and endoscopic combined intrarenal surgery (ECIRS) were recommended as a new surgical treatment in renal stone treatment. One of the advantages of ECIRS is its ability to increase stone-free rates in a single session in complicated renal stones. Intermediate supine position can prevent anesthesia problem in real time simultaneous ECIRS and can lower patient morbidity even in long term operation²¹.

In current studies, provision of high stone-free rate, allowing ipsilateral application, lowering x-ray exposure and anesthetic morbidity in patients with simultaneous ureteral and renal stone and/or complicated renal stone can be stated among the most important advantages of ECIRS application²²⁻²⁴.

The most important disadvantage of ECIRS is the need for two endovision systems and the cooperation of two surgeons. Thus there should be enough free space in the operation room. PNL tract formation difficulties due to intermediate supine position are also available. Since kidneys are more mobile in this position and the renal cavity is not adequately open yet, PNL tract can be longer than normal and may also cause renal parenchymal damage due to the mobility stricture of nephroscope^{25,26}.

PCNL constantly improved in the last 20 years and this improvement was quick due to the development of instruments like mini-PNL and the introduction of supine PCNL and tubeless techniques. Mini-PNL reached the level of Ultra-Mini-PCNL with Karl Storz's MIP system. Supine PNL has now become routine and one of the position options based on the patient and anesthesia condition²¹

At the same time, tubeless technique has also reached total tubeless level because checking bleeding after the operation through radiological interventional approach instead of nephrostomy is considered to be more suitable and advantageous. In addition, use of full HD (1.080 pixels) and PACS system increased image quality. Development of digital flexible urethroscope was revolutionary in RIRS. With a small scale and light video URS, RIRS was very useful in long-term surgeries²¹.

With the development of PNL and RIRS, ECIRS entered a popularization period. The advantage of ECIRS is its ability to minimize renal parenchymal loss through a single way while it can increase stone-free rate in cases with high stone load. It was observed that this increases Stone-free rates even in patients with high nephrolithometry scores. In the future, ECIRS will become a routine stone surgery presenting safe and high stone-free rates in complicated kidney stones²¹. Together with ECIRS, new techniques are also being defined to include technological developments such as electromagnetic guided Percutaneous renal access and real time virtual sonography guided renal access and to lower x-ray exposure during access^{27,28}.

To sum up, no data showing that supine PNL is more risky, complicated or unsuccessful operation compared to prone PNL is available. Prone PNL is still applied more commonly. But PNL is in a fast evolution. Individualized treatment quickly replaces single type treatment.

Surgical Technique; Tips And Tricks

The kidney can be percutaneously accessed in prone, supine and lateral positions. But prone position is preferred in most clinics. Kidney can be accessed through different scopy planes including monoplanary and biplanary.

Percutaneous antegrade access: This approach is defined as follows in literature. A 6 Fr open-end ureteral catheter or occlusion catheter is inserted through guidewire on the side where the stone is located; the patient is laid on the operation table in prone position²⁹. This can be applied through different methods. In the application in our clinic, after laying the water resistant table cloth and green cloth with one side very slightly hanging from the side of the table and the other side left longer, the patient is taken on the table in supine position and is intubated, the catheter is inserted in lithotomy position and the patient is put in supine position again after the bladder catheter

is inserted and urethral catheter is attached to the catheter. Patient's face is closed with a special mask made of sponge. (Figure 1)

Figure 1: Image of the special mask covering patient's face*



*** Application of the special mask prepared for the channel opened for intubation tube and the prone position letting the easy insertion of the face in our clinic.**

An operating room technician holds the green cover below the patient tightly and pulls the patient together with the cover towards him/herself up to the table edge and the patient is brought to the lateral position when the cover is pulled up. Thus the patient is easily taken in the prone position by carefully pushing forward. While the technician is doing this, the assistant provides support in positioning the patient in a controlled way on the opposite side as a precaution. So the patient is located in prone position by a single person safely and without any problem. Long pillows are located on both sides from the shoulder towards iliac crest to facilitate ventilation. An anesthesiologist should attend this maneuver and attention should be paid to endotracheal tube. The lower parts of feet, knees and ankles are supported with the pillows. The table is bent a little depending on the patient's condition to provide skin tension on access line and to

support the kidney. After preparing the skin with povidine-iodine to provide close contact of surgical covers with the skin, alcohol is used for cleaning. (Figure 2)

Figure 2: Positioning the patient*



***Consent of the patient was taken for the photos.**

To prevent the movement of stone fragments towards urethra during intracorporeal lithotripsy procedure, the balloon of occlusion catheter can be inflated with 1 ml contrast matter in ureteropelvic junction. The guidewire is removed and injecting contrast matter or air through the catheter, the detailed imaging of the collecting system during percutaneous access is preferably provided through fluoroscopy. Fluoroscopic imaging is the method most commonly preferred by urologists in PNL operations. One of the most important reasons to prefer fluoroscopy is the clear displaying of equipments such as needle and guidewire³⁰. Putting a sterile cover on the C-arm of scopy device, the surgeon provides the manipulation. C-arm of scopy should have mobility over 90 degrees and a memory so that the image can be saved on the screen. Radiation source is located below the patient to minimize the negative effect of radiation. It is very important to choose a suitable percutaneous nephrostomy tract for the procedure. Posterior calyceal approach is the preferred approach. Thus, the operation is performed away from major vascular structures surrounding renal pelvis. But anterior calyceal access can be

necessary for some stones and calyceal diverticules. But this method is used only if access through posterior calyces is not possible^{29,31}.

Also accessing pelvis through anterior calyx is technically harder. Direct puncture on renal pelvis should be avoided. Because renal artery may damage posterior branch of renal artery. The risk of damaging the large branches of renal artery increases in line with the medial position of puncture in general. Additionally, the resultant tract doesn't provide stability for nephrostomy tube as it lacks parenchymal support³².

Injection of contrast matter through urethral catheter may help the opacification of collecting system. Alternatively, air can also be injected to form an air pyelogram. The advantage of free air is being lighter than urine or contrast matter. Thus it first reveals posterior calyces when the patient is lying. In case of a single stone in renal pelvis or indefinite anatomy, contrast matter use is recommended to completely detect intrarenal anatomy. Air pyelogram satisfactorily determines collective system in cases with multiple radio-opaque calyceal or complete staghorn stones. Thus it prevents misleading artifacts caused by contrast matter³³.

While C-arm of the scopy is in vertical position, collecting system is observed and the suitable calyx is determined. The ideal position is the shortest tract towards calyx below 12th costa. Observation of the C-arm of scopy at 90 degrees determines the medial vertical plane in the calyx entrance. Scopy C-arm is turned nearly 30 degrees towards the surgeon. A direct image of posterior calyces is acquired this way. The covering skin is marked with a hemostat after finding the calyx. Injection can be made on puncture location with 0.25% bupivacaine (marcaine) for postoperative local pain treatment. While the C-arm of the scopy is positioned at 30 degrees, a 18 G (gauge) translumbar angiography needle is advanced in fluoroscopy light plane. While advancing the needle, it is important to see “**bull's eye sign**” to determine the most suitable direction. This effect is observed only when the needle center is superposed with the needle body and it is clearer especially when the needle plane is identical with X ray.

After the suitable plane is determined, radiation effect for the surgeon is minimized and the needle is advanced for 1-2 cm increments with a hemostat. As it provides the safest entry to the posterior calyceal system, the needle should be approached to Brodel line. Returning the C-arm of scopy to vertical position, needle penetration depth is monitored. When the C-arm of the scopy is in vertical position, needle tip's proximity to calyx can be seen and can

be fluoroscopically directed. Both suitable axis and needle depth constitute the absolute conditions for successful percutaneous access. The "stylet" is removed when the needle is in the calyx and the correct location of the needle is validated with the aspiration of urine or air or both. 0.038 inch elastic ended guide wire is sent to the kidney through the needle.

The needle is removed and 1 cm incision is opened in the place of the wire. The tract is dilated up to 30 Fr through the wire. Many techniques can be used for tract dilatation. Amplatz dilatation set or 10 cm balloon catheter and sheath set are the materials mostly used. Both of these systems are applied after a second guide wire is inserted through the collecting system³¹⁻³⁵. When the percutaneous access towards the calyces is performed through 12th costa, hydrothorax and hemothorax risk increases. Different endourological techniques minimizing the complications while providing access to superior calyces are defined³⁶.

Direct percutaneous access in a calyx in upper pole can be difficult through subcostal approach and the urologist should be experienced in intercostal approach. Many urologist prefer this approach as it provides the possibility of access to the upper pole. Although there is a mild and acceptable increase in morbidity in this approach, it is stated to provide direct and optimal access to most staghorn stones. Young and colleagues presented their experiences on 115 supracostal percutaneous nephrolithotomy procedures and reported a complication rate of 8.7%³⁷.

Large pleural effusions and severe atelectasis requiring chest tube were stated among these complications. Access through 12th costa may cause hydrothorax through damaging pleural cavity in posterior costafrenic angle or may damage the lower border of lung's lower lobe or pleura. This technique is not preferred much due to its complication rate. Karlin and Smith defined a technique performed through the relocation of the kidney towards caudal to minimize the potential morbidity of supracostal approach³⁸. The aim is fulfilled through placing an Amplatz sheath inside the calyx at the center or at the lower pole and turning dilatator towards cranial and this condition causes the fluoroscopically visible relocation of the kidney towards caudal. Second puncture or a Y tract is formed inside the upper pole. Occlusion balloon catheter can also be used to apply caudal traction gently and helps the movement of the kidney downwards and below the costal border during the first access. Triangulation is among the techniques commonly used for accessing a calyx in the upper pole.

Biplanary technique is used to determine needle access angle after selecting the suitable calyx to be accessed. In this technique, scopy C-arm is used in two positions as parallel and oblique (45 degrees medial) to needle access. Movement of the needle is adjusted on medial and lateral plane (right-left) when C arm is parallel and on cephalad-caudal plane (up-down) when it is oblique and thus the needle is led towards the calyx to be accessed. Following these adjustments, it is suggested to uniplanarly lead the needle towards calyx and the patient should be taken in expiration during the needle access. In case of suspicion during the advancement of the needle, taking image again on these two planes, the access is completed by re-planning the calyx access of the needle. "Bull's eye" sign doesn't appear in this technique and thus the advancement axis of the needle depends on the surgeon's evaluation in the light of biplanary fluoroscopy imaging principles. Especially the needle tip and calyceal position are considered. Perception of needle advancement angle showing the penetration depth during a certain plane towards the medial requires experience³⁹.

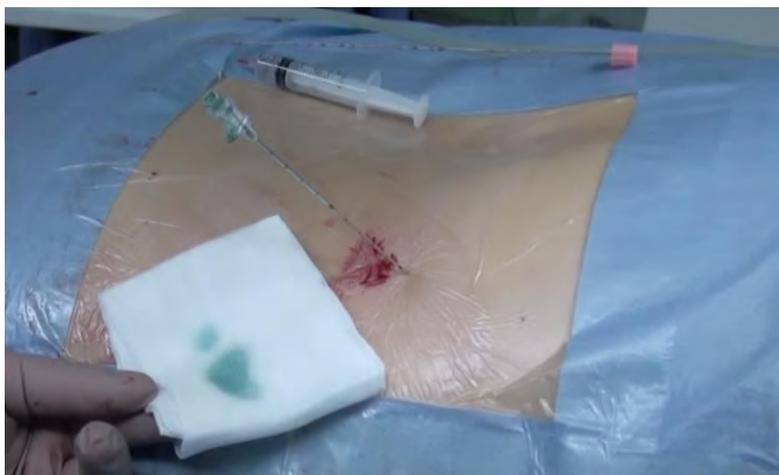
Lateral intravenous pyelogram images may be necessary to distinguish posterior and anterior calyx groups in the presence of malrotated calyx generally seen in ectopy and horseshoe kidney. Additionally, the puncture location on the skin may be located in medial more than normal. The surgeon should know about abnormal vascular anatomy in such clinical cases^{39,40}.

Blind puncture is a fluoroscopic technical variation and this technique is generally needed when there is an obstruction urethral lumen, the urethral catheter cannot be advanced or when pelvicalyceal system cannot be opacified. Renal pelvis is located nearly 1-1.5 cm lateral to L1 vertebral object. A 22 Gauge needle is used for a blinded vertical puncture in the lateral of psoas and right below 12th costa level. Right after the urine is aspirated from renal pelvis, contrast matter can be applied for a detailed view of upper collecting system and the management of suitable calyceal puncture. Access methods accompanied by ultrasonography, tomography and flexible ureterorenoscopy were also defined in literature⁴⁰.

To avoid over-use of scopy in the application in our clinic, needle tip and direction towards the calyx targeted on scopy are monitorized on the skin after the retrograde opacification of the collecting system with methylene blue opaque matter mixture in all stone cases. The point 1-2 cm outside of calyx to be accessed is determined based on the scopy image. While kidneys are more superficial, puncture angle

is narrower and access distance is 5-10 cm in thin patients, kidneys are deeper and access angle is more vertical and the access distance is 10-15 cm. The blue colored fluid coming after entering the calyx is the proof that we have accessed the kidney. (Figure 3)

Figure 3: Access of the needle and methylene blue opaque matter coming from the needle



After the guide wire is sent inside the needle, the dilatation is started with a 1 cm incision after skimming the needle from its edge. Lateral of rear axillary line is the risky area for intestinal perforation. Its 1-2 cm medial is generally safe and provides access the margo lateral of the kidney (brodel line). Thus the access is defined through these data. Following the completion of access and dilatation, amplatz sheaths with a diameter of 26-30 F are generally inserted in standard PNL. These sheaths with large diameter provide the access of large diameter tools in the collecting system and provide operation at low pressure during PNL. Amplatz sheath should appropriately be shortened by measuring skin-calyx distance. This operation prevents the unnoticed movement of the sheath towards the inside during manipulation in the kidney and the related damage. Using large diameter (24F-27F) rigid nephroscope also makes the effective cleaning of the stones easier through the advantages of better image quality, pressurized irrigation solution and rigid stone capturing tools. But complications, especially bleeding, also increase as tract diameter increases in PNL⁴¹. Thus, mini-PNL and micro-PNL methods with

smaller tract size are becoming gradually more popular applications mainly in pediatric group patients³¹. Pneumatic, ultrasonic, laser or combined systems are generally used for stone fragmentation during PNL. We prefer pneumatic lithotripters and holmium-YAG laser while we are applying PNL in our clinic. Nephrostomy tube is generally installed for drainage and tamponization at the end of the operation. In our clinic, we end the operation without using nephrostomy tube (tubeless PNL) at the end of the operation in suitable cases without complications. Tubeless PNL applications have gradually become more common in recent years^{42,43}. Different catheters can be used as nephrostomy tube in PNL (malecot, foley, etc.). We prefer foley catheters in clinical practice. Image and positions of the materials and equipments used during the operation are available in Figure 4.

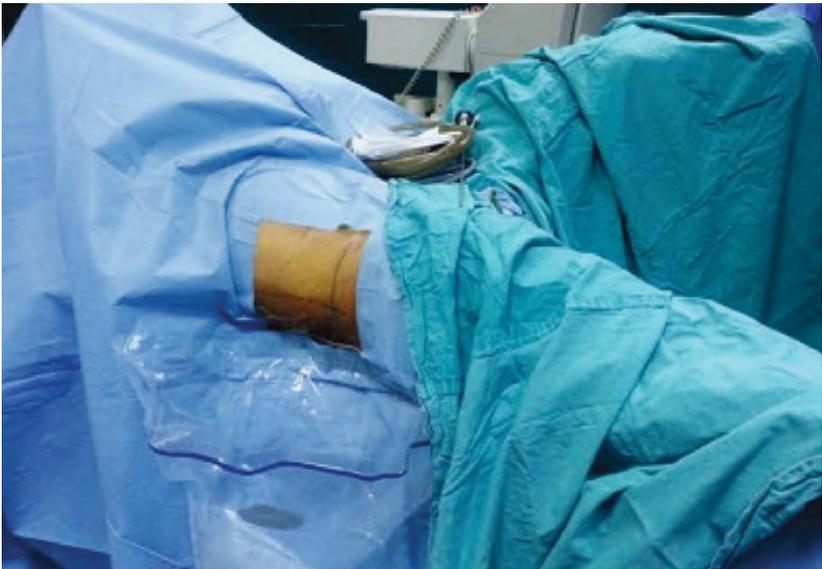
Supine-ECIRS Position and Technique:

There are different approaches in clinics and supine PNL and ECIRS are generally performed in intermediate supine Galdakao-modified supine valdivia (GMSV) position. Shortening of fluoroscopy time is targeted by installing lower pole nephrostomy in interventional radiology before the operation in some clinics. Patient is taken in GMSV position under general anesthesia in experienced clinics performing supine PNL. Positioning 1 L isotonic saline bag in the ipsilateral flank area, flank area is raised 20 degrees and thus posterior calyx access is made easier and then visualizing pelvicalyceal system with opaque or air through fluoroscopy as performed in prone position, posterior calyx is accessed and if ECIRS is going to be performed, the entrance is observed through flexible URS and its performance on the exact position is ensured. Then sending a guide and dilatating, supine PNL and ECIRS can be performed (Figure-5)⁽²¹⁾.

Figure 4: Image and positions of the materials and equipments used during the operation



Figure-5: Galdakao-modified supine Valdivia position ⁽²¹⁾



To sum up:

- While kidneys are more superficial, puncture angle is narrower and access distance is 5-10 cm in thin patients, kidneys are deeper and access angle is more vertical and the access distance is 10-15 cm.
- The collecting system is retrogradely opacified with methylene blue opaque material mixture in all stone cases in order to avoid the over-use of scopy. The blue colored fluid coming after entering the calyx is the proof that we have accessed the kidney.
- Access is safer through the medial of rear axillary line.
- Incision from the needle side before removing the needle after sending the guidewire through the needle makes the operation easier.
- Amplatz sheath should appropriately be shortened by measuring skin-calyx distance.

Indications

The aim in treatment selection is to clean the highest amount of stones causing minimum harm to the patient. European Urology Guideline suggests PNL treatment as the first option especially in the presence of lower calyx stones which are over 2 cm and not suitable for ESWL or are resistant and between 10-20 mm. PNL is suggested as the primary treatment method in the presence of complex, staghorn and/or multiple stones, kidney with anomaly, concurrence of obstruction (such as ureteropelvic stricture, proximal ureteric stone), hard stones (cystine, brushite, etc) and conditions which require certain results (as in pilots)⁶.

Contraindications

PNL is contraindicated in the use of anticoagulant drug, pregnancy, untreated urinary system infections, malign kidney tumor and access tract tumor⁶.

Complications

Complications can be inevitable in surgical applications. A lot of experience is required to predict possible complications. Several studies were made for this. Based on the experiences, meta analyses and reviews of the specialists dealing with S.T.O.N.E. nephrolithotomy system and stone disease, "GUY's Stone score" system was prepared. GUY's system may contribute to the pre-operative estimation of stone-free condition of the patients after the operation and to predict possible complications. Guy's Stone scoring system is divided into 4 grades⁴⁴.

Grade 1: Single stone in medial or lower calyx in a kidney with normal anatomy or a single stone in the pelvis.

Grade 2: Single stone in the upper pole of a kidney with normal anatomy or multiple stones in different locations or a single stone in a kidney with abnormal anatomy.

Grade 3: Multiple stones in kidney with abnormal anatomy or presence of partial staghorn stone.

Grade 4: Presence of staghorn stone or any stone in a patient with spina bifida or spinal cord damage.

Clavien classification used in general surgery for the first time and then modified for stone patients in the field of urology is used for the classification of complications formed⁴⁵.

According to this classification:

Grade 1: Presence of abnormal postoperative findings recovering with the use of antifebrile, antiemetic, hydration and diuretics and not requiring pharmacological, endoscopic or radiological intervention in the postoperative period.

Grade 2: Conditions not included in Grade 1 and requiring blood replacement and parenteral nutrition.

Grade 3: Complications requiring endoscopic, radiological and surgical intervention.

Grade3A: Interventions not requiring general anesthesia.

Grade3B: Interventions requiring general anesthesia.

Grade 4: Complications which are life threatening and require close follow-up and intensive care.

Grade 4A: Singular organ function loss

Grade 4B: Multiple organ function loss.

Grade5: Death of the patient.

Although the most common complications in PNL are problems related to fever, bleeding, urinary leakage and residual stones, major complications with rare but severe results such as organ injuries, acute pancreatitis and perioperative death also occur. In the study by Mannheim group in 2007, it was shown that among the general complication rate of 50.8%, minor complications had a rate of 49.6%.⁴⁶ Clinically insignificant bleedings and fever constitutes most of the total complication rates stated in literature^{6,31} Adamkiewicz

syndrome is another severe and rare complication which is not much mentioned. This syndrome causing paraplegia develops actually develops due to anterior spinal artery vasospasm or injury. Again, clinically significant and transfusion requiring bleeding rates mentioned in literature change between 5-18%.

Treatment of Complications:

Colon Perforation: They are noticed with the observance of gas, water content and fecaloid and the diagnosis is clarified by giving opaque matter. Foley catheter is inserted in the colon and its balloon is inflated with 5 cc. D-J catheter is inserted if the kidney is traumatized. Intravenous feeding is started after ending postoperative oral intake. Double antibiotherapy is started. (for aerob+anaerob bacteria) The foley is pulled to retroperitoneum three days later. Oral is started on the fifth day if there is no problem and foley catheter is removed. Colostomy can be opened in complicated cases.

Hemothorax: Installing nephrostomy tube and chest tube, thoracoscopy and aspiration⁴⁷.

Spleen Injury: Conservative treatment is applied at the beginning and exploration and required intervention are performed if the bleeding continues⁴⁷.

Liver Injury: Generally responds to conservative treatment⁴⁷.

Gram Negative Sepsis: Lengthened hospitalization, suitable antibiotherapy and supportive treatment

Hydration: Maximum diuresis should be provided with furosemide or mannitol and supportive treatment should be given⁴⁷.

Pelvis And Uretral Perforation: Nephrostomy is inserted and urethral drainage is performed.

Post-Operative Hemorrhage: Compression should be made, nephrostomy catheter should be clamped and angiography accompanied embolization is performed in continuing bleedings.

To sum up:

- The doctor shouldn't be overwhelmed by complications
- The doctor should apply the most suitable method in practice to avoid complications even though the learning curve is long.
- The doctor shouldn't be extremely insisting on stone-free condition in complicated cases and second and third sessions should be considered.

As a result, percutaneous nephrolithotomy is a safe and useful minimal invasive surgical method used in the treatment of kidney stones in suitable patients and provides high success rate, low morbidity and short hospitalization time. Due to scopy weighted study, protective precautions for the patient and operation team from radiation shouldn't be neglected as much as possible. Thus experienced urologists modifying kidney access techniques and applying the most suitable method for them would positively affect operation success. PNL primarily preferred in current stone surgery based on present data and the applications in our clinic decreasing open surgical application down to 1% forms a handicap especially for assistant training. Thus open surgery should also be considered in complicated cases.

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CHAPTER XVII

COMPARISON OF THE OUTCOMES OF THREE DIFFERENT STUMP CLOSURE TECHNIQUES IN LAPAROSCOPIC APPENDECTOMY

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1. Introduction

Appendix is the most mysterious part of gastrointestinal (GI) tract. An important disorder of the appendix is the inflammation caused by internal or external causes; as known as acute appendicitis. It still make significant proportion of emergency department admissions. The rates of lifetime acute appendicitis in women and men are 6.7% and 8.6%, respectively (Addiss, Shaffer, Fowler, & Tauxe, 1990). Acute appendicitis is a surgical emergency which requires surgical intervention as a gold standard treatment option.

Laparoscopic surgery is preferred in treatment of the disease. Superiorities of laparoscopic surgery to open surgery are less common infection in surgical site, less common postoperative pain and earlier mobilization (Bennett, Boddy, & Rhodes, 2007; Li et al., 2010; Markides, Subar, & Riyad, 2010). An important issue in laparoscopic surgery is the decision of stump closure technique. Hem-o-lock clips, endo-loop suture and endoscopic intracorporeal suture are three of these techniques.

In present study, we aimed to compare the outcomes of three stump closure techniques in laparoscopic appendectomy cases.

2. Methods

We retrospectively analyzed patients with acute appendicitis that undergone laparoscopic surgery between January 2015 and December 2019. This work has been approved by the directorate of the institution number of 33443051-929. We excluded the patients treated with open surgery and the patients whom necessitated open surgery following laparoscopic intervention.

Three trocars; subumbilical 10mm of camera trocar, suprapubic 5mm trocar and left lower quadrant 5mm trocar used in surgical interventions. Age, gender, findings of appendix in operation, duration of surgery, the need of drainage catheter, hospitalization duration, postoperative complications, the length and diameter of the appendix, histopathological findings of appendices, follow up time after discharge from the hospital and the presence of trocar side hernia recorded from institutional database.

Stump closure techniques in appendectomy were single hem-o-lock clips (group 1), single endo-loop-suture (group2) and endoscopic intracorporeal single suture (group 3). Data of the participants were obtained from institutional data base and patient files. Data of the groups 1, 2 and 3 were compared.

Data were analyzed by SPSS software (SPSS 15.0 for Windows, IBM Inc., Chicago, IL, USA). Distribution of variables between Group 1, Group2 and Group 3 were assessed by Kolmogorov-Smirnov test. Kruskal Wallis test used in comparison of the variables without normal distribution and expressed as median (min-max). Categorical variables were compared by chi-square test. Pearson's correlation test was used whether study parameters were correlated with each other. A p value lower than 0.05 was set for statistical significance.

3. Results

A total of 176 subjects enrolled too the study; 53 in group 1, 53 in group 2 and 76 in group 3. There were 30 women and 23 men in group 1, 25 women, 28 men in group 2 and 41 women and 29 men in group 3. Gender was not statistically different between study groups ($p=0.42$). Median ages of groups 1, 2 and 3 were 37 (17-70), 31 (16-67), 29 (17-72), respectively ($p=0.07$). Duration of operations in groups 1, 2 and 3 were 55 (40-64) minutes, 51 (40-64) minutes and 50 (40-65) minutes, respectively ($p=0.11$). Hospitalization duration of groups 1, 2 and 3 were 2 (1-5) days, 2 (1-5) days and 2 (1-6) days, respectively ($p=0.97$). The findings during appendectomy in groups 1, 2 and 3 were as follows; appendicitis in 83% and perforated appendicitis in 17%, appendicitis in 92.5% and perforated appendicitis in 7.5% and appendicitis in 92.9% and perforated appendicitis in 7.1%, respectively ($p=0.15$).

Surgical complication rate in whole study population was 2.3%; 1.9% in group 1, 1.9% in group 2 and 2.9% in group 3 ($p=0.26$).

The rate of replacement of drainage catheter in groups 1, 2 and 3 were 62%, 43% and 20%, respectively ($p=0.01$).

All patients in study cohort were followed up 2 -95 months. The rate of incisional hernia in groups 1, 2 and 3 were 1.9%, 0% and 1.4%, respectively (p=0.63).

Histopathological examination results of whole study population were as follows: 154 (87.5%) benign, 19 (10.8%) lymphoid hyperplasia, 2 (1.1%) high grade dysplasia, 1 (0.6%) malignant.

Vertical length of the appendix in groups 1, 2 and 3 were 60 (25-110) mm, 55 (30-110) mm and 60 (25-110) mm, respectively (p=0.18). diameter of the appendix in groups 1, 2 and 3 were 10 (6-25) mm, 9 (6-25) mm and 7.5 (6-20) mm, respectively (p<0.001). Study parameters of the groups were summarized in table 1.

Table 1. Study parameters of the groups

		Group 1 (Hem- o- lock)	Group 2 (Endo- loop)	Group 3 (Intracorporeal suture)	p
Gender (n)	female	30	25	41	0.42
	male	23	28	29	
Age (years)		37 (17- 70)	31 (16- 67)	29 (17-72)	0.07
Operation time (minute)		55 (40- 64)	51 (40- 64)	50 (40-65)	0.11
Hospital stay (day)		2 (1-5)	2 (1-5)	2 (1-6)	0.97
Perioperative appendix findings (n,%)	Appendicitis	44, (83)	49, (92.5)	65, (92.9)	0.15
	Perforated appendicitis	9, (17)	4, (7.5)	5, (7.1)	
Complication (n,%)		1, (1.9)	1, (1.9)	1, (2.9)	0.26
Drainage catheter use (n,%)		33, 62	23, 43	14, 20	0.01
Postoperative follow-up time(month) and trocar side hernia (%)		32, (1.9)	39, (0)	60, (1.4)	0.63

4. Discussion

The main finding of present study is stump closure techniques were equally effective in surgical procedure of laparoscopic appendectomy. Complication rates, hospitalization duration, gender and age of the subjects are not associated with closure technique.

Laparoscopic appendectomy is a safe and effective method in surgical treatment of uncomplicated appendicitis (Yu et al., 2017). Stump closure with an effective and easy to assess methods is important for surgeons in laparoscopic surgery. Catastrophic complications due to fecal leakage caused by inappropriate stump closure is inevitable.

Different stump closure technique are available worldwide in laparoscopic appendectomy. These include traditional closures (such as intracorporeal or extracorporeal ligatures or Roeder loops) and traditional devices (such as stapling devices, clips, or electrothermal devices), however, optimal technique is a matter of debate (Beldi, Muggli, Helbling, & Schlumpf, 2004; Delibegović, 2012; Hanssen, Plotnikov, & Dubois, 2007; Mannu et al., 2017; Sohn et al., 2014). In present study, we found that intraoperative and postoperative outcomes of either three closure techniques were similar.

Rakic et al. compared single endoloop and endostapler techniques in stump closure of laparoscopic appendectomy cases and found that there was no significant difference according to complications despite operation duration was shorter in endoloop cases compared to endostapler closure (Rakić et al., 2014). Single endoloop and hem-o-lock clips closure techniques compared by Lucchi et al and complication rates and hospitalization durations were reported to be similar in both techniques (Lucchi et al., 2017).

Double intracorporeal knot and endoloop techniques were compared in a recent study and reported that despite complication rates were similar, operation time was longer in intracorporeal knot compared to endoloop technique (Bali et al., 2015). In another study there was no difference between double endoloop and endostapler techniques according to operation duration and infectious complications (Pedziwiatr et al., 2019). Similarly, single or double end loop closure techniques compared with endostapler and found no difference between these methods according to the infectious complications (Çelik & Erbil, 2019).

Endoloop was used in 109 and double endoloop was used in 99 patients and found that no significant difference was present between

study groups according to postoperative complications (Beldi et al., 2004).

Similarly, with 1.9% in groups 1 and 2, and 2.9% in group 3, complication rates no significant difference of these rates were observed in our study.

Replacement of drainage catheter after laparoscopic appendectomy is controversial. Necessitate of drainage catheter is reduced after introduction of laparoscopic procedures. However, although it is controversial, these catheter may prevent or reduce infectious complications after surgery (Fujishiro et al., 2020). In our study, we found that drainage catheter usage was more common in group 3 compared to others groups, however, complication rates were similar in study groups.

Incisional hernia development is an important complication of surgery. Outcomes of 5541 subjects undergone laparoscopic surgery were studied and 0.14% of incisional hernia was reported during 43 months of follow up (Hussain et al., 2009). In present study, we reported 1.1% of tracheal hernia, without significant difference between study groups, during mean 60 months of follow up.

Histopathological examination of appendectomy materials usually reveals benign conditions. Unver et al studied histopathological reports of 2047 appendectomy cases and found 1.66% of malignant and premalignant diseases (Unver et al., 2019). Histopathological results in present study were not different among study groups and only malignant conditions were reported in 1.7% of the cases.

5. Conclusion

The results of present study indicate that every three stump closure techniques (Hem-o lock, Endo-loop, Intracorporeal suture) were similar according to the operation time, complications, hospital stay and hernia rates. Therefore, we suggest that either of these methods could be used in laparoscopic appendectomy cases.

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CHAPTER XVIII

THE RELATIONSHIP OF INGUINAL HERNIA AND URINARY SYMPTOMS

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1. Introduction

The word hernia is derived from a Latin word meaning rupture. The hernia can be described as abnormal prolapse of tissues or organs from the defect in the wall surrounding them. Although a hernia can develop from any part of the body, it often occurs in the abdominal wall, especially in the inguinal region. While 75% of abdominal wall hernias occur in the groin, the lifetime risk of inguinal hernia development is 27% in men and 3% in women [1]. In parallel with the high incidence, approximately 20 million inguinal hernia surgeries are performed worldwide every year [2]. The incidence of inguinal hernia increases with age, and 90% of the surgeries are performed on male patients [3].

Although many reasons have been investigated in the etiology of inguinal hernia, it is not clear yet. It has been reported that there may be reasons such as age, male gender, smooth muscle cell molecules, and connective tissue components depending on the patient reasons, as well as external causes such as smoking and chronic constipation and cough, pregnancy, and working in jobs that require heavy lifting may cause inguinal hernia [4].

Inguinal hernia may be asymptomatic or have a broad symptomatic spectrum such as life-threatening conditions caused by incarceration. Inguinal hernia symptoms may include inguinal symptoms such as groin pain and swelling in the groin area, as well as extra-inguinal

symptoms such as changes in bowel habits and coexistence with urinary symptoms.

The presence of an inguinal hernia has been shown in 15-20% of patients who underwent prostate surgery. In addition, 11-30% of the patients diagnosed with inguinal hernia were reported to have lower urinary tract symptoms (LUTS) requiring postoperative intervention [5-7]. Whether the coexistence of inguinal hernia and urinary symptoms are due to a common etiology or are separate diseases that trigger each other is still an important research subject.

Although the coexistence of inguinal hernia and lower urinary tract symptoms etiology is not clear, a number of theories have been reported. With increasing age, the incidence of lower urinary tract symptoms secondary to the high incidence of benign prostatic hyperplasia also increases [8]. The fact that age is also a factor in the development of inguinal hernia explains the independent association of an inguinal hernia and lower urinary tract symptoms. Another and more accepted theory is that LUTS and acute urinary retention develop in inguinal hernia surgeries due to the increase of alpha-adrenergic transmitter release in the prostatic urethra and bladder neck due to sympathetic discharge [9]. On the other hand, the relationship between inguinal hernia and lower urinary tract symptoms can be examined under two topics: direct and indirect relationship.

The direct relationship is generally due to a sliding or an inguinoscrotal hernia in which the hernia sac or the herniated organ cause compression on the urinary organs due to the anatomical proximity. The indirect relationship can be examined under the headings of urinary complications that may develop in patients operated on for inguinal hernia or inguinal hernia that may occur in patients who have undergone urological surgery. The relationship between inguinal hernia and lower urinary tract symptoms is handled in line with the algorithm shown in Figure 1.

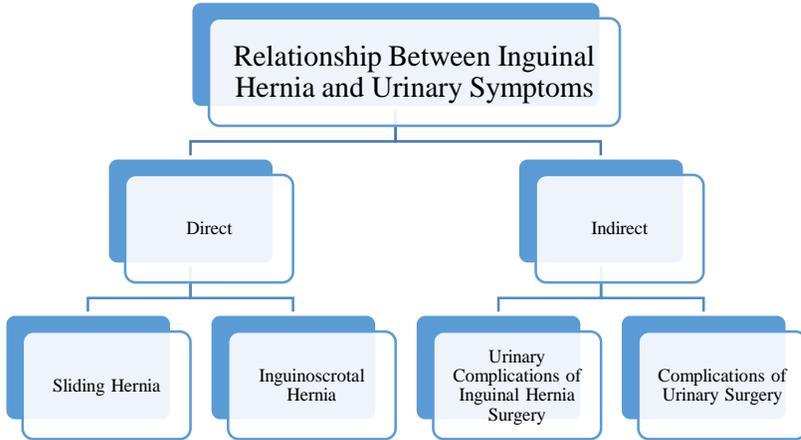


Figure 1. Relationship Between Inguinal Hernia and Urinary Symptoms

2. Direct Relationship Between Inguinal Hernia and Urinary Symptoms;

There are many classification systems for groin hernias. Nyhus classification [10], which is a widely used system among these classifications, is based on anatomical criteria. Sliding hernias and inguinoscrotal hernias are classified as Type 3b according to the Nyhus classification. In order to talk about sliding hernia, part of the wall of the hernia sac must be formed by one of the internal organs. The herniated internal organ is usually the colon or the bladder. Direct relationship between inguinal hernia and lower urinary tract symptoms is generally due to a sliding type hernia that contains bladder. If the sliding hernia is caused by the bladder, the term inguinoscrotal hernia of the bladder is used. This type of hernia is rare and constitutes approximately 4% of all groin hernias [11,12]. Levine B. described the first inguinoscrotal hernia of the bladder in 1951 [13]. Inguinoscrotal hernia is a disease with a broad symptomatic spectrum including inguinal pain or swelling associated with lower urinary tract symptoms or voiding. However, the cases are mostly asymptomatic. Due to its asymptomatic course, only 10% of the cases can be diagnosed before surgery, and less than 20% of the cases can be noticed during the operation [14]. Therefore, preoperative diagnosis of inguinoscrotal hernia is very important in order to avoid urological complications. Branchu B et al. [14] published a systematic review including 51 articles in which inguinal hernia of the bladder is evaluated. According to this review, which includes one of the largest patient samples in the

literature, it has been reported that 95.3% of the patients were male and 47.6% had preoperative lower urinary tract symptoms. The results of this review have shown that male gender and obesity are the main risk factors for inguinoscrotal hernia of the bladder.

Inguinoscrotal hernia may also be caused by indirect inguinal hernia, apart from sliding hernia. In the presence of this type of hernia, the swelling caused by the herniated tissue or organ in the scrotum may mimic hydrocele, which is a urological finding. On the other hand, the symptoms resulting from the compression of the hernia sac on the vas deferens and spermatic vessels may mimic the findings of another urological disease, varicocele. In conclusion, pathophysiology, which plays a direct role in the relationship between inguinal hernia and lower urinary tract symptoms, stems from the close neighborhood relationship between inguinal canal and urinary organs. Hence, the presence of an inguinal hernia may cause urinary symptoms or may mimic urological diseases. Therefore, accompanying urinary symptoms in the presence of an inguinal hernia may provide an idea about the type of inguinal hernia and may be a guide for considering urinary diseases among differential diagnoses.

3. Indirect Relationship Between Inguinal Hernia and Urinary Symptoms;

3.1 Urinary Complications of Inguinal Hernia Surgery

The anatomical position of the inguinal canal is the main risk factor for the development of urological complications after inguinal hernia repairs. The neighborhood relationship of the inguinal canal with the bladder, vas deferens, spermatic vessels, genitofemoral nerve and testis predisposes to the development of possible urological complications. Urological complications that may develop in inguinal hernia repair can be evaluated under two headings as intraoperative and postoperative complications. Intraoperative complications include vas deferens injury, bladder injury, spermatic vessel injury and ureteric injury. Previous surgery and associated adhesions are predisposing factors for the development of intraoperative complications. If recognised of these injuries should be repaired intraoperatively.

Acute urinary retention, one of the most common postoperative complication, and most common reason for readmission to the hospital after hernioplasty [15,16]. Although it is not a life-threatening complication, it is important due to requires additional intervention, prolongs the length of hospital stay and increases the cost [17,18]. Although the cause of acute urinary retention after herioplasty is

thought to be due to adrenergic overstimulation in bladder smooth muscles, it is reported that factors such as age, body mass index, perioperative fluid administration, types of anesthetic and the use of narcotic analgesia can affect this [15,18, 19,20]

Studies have shown that the use of anticholinergic and sympathomimetic agents such as atropine and phenylephrine during surgery will reduce bladder tone and make voiding difficult. Although these agents do not significantly affect voiding functions in some patients, they will be high risk in elderly patients with history of benign prostate hyperplasia (BPH) [16].

BPH presented with lower urinary tract system symptoms such as difficulty of urination, frequent urination, inability to urinate, and it increases with age and is seen in approximately 80% of men in their 80s [21]. Therefore, urological evaluation must be performed before inguinal hernia surgery. In studies, it was reported that alpha-blocker treatment before inguinal hernia surgery reduced acute urinary retention rates compared to control group after the procedure (24.3% vs 3.7%) [9]. Denham et al. reported that peroperative intravenous dexamethasone 4-8 mg reduced postoperative acute urinary retention compared to control group by facilitating smooth muscle relaxation and reducing the affect of adrenergic discharge (3.7% vs 9.8%) [22].

3.2 Complications of Urinary Surgery

While some urological complications can occur after inguinal hernia repair, inguinal hernia can also occur after some urological surgery such as radical cystectomy, open prostatectomy and radical prostatectomy [23]. Radical prostatectomy is the most common cause of inguinal hernia in urological surgeries. Open radical prostatectomy is the most common method which caused to postoperative inguinal hernia compared to laparoscopic or robotic radical prostatectomy [24].

In a recently published meta-analysis, the incidence of inguinal hernia after open retropubic radical prostatectomy was 13.6%, while the incidence of inguinal hernia after robotic and laparoscopic radical prostatectomy was 7.9% and 7.5%, respectively [24]. It has been shown that inguinal hernias after radical prostatectomy are typically indirect hernias and occur within an average of 2-3 years after the surgery.

After demonstrating that inguinal hernia rates are high after the radical prostatectomy, intraoperative prophylactic surgical techniques have been identified to reduce the postoperative incidence of inguinal hernia, but studies are limited [24].

Conclusion

Inguinal hernia reconstruction is one of the most common surgeries in the world and performed by general surgeons and sometimes by urologists. Although the most common complication of inguinal hernia surgery is urinary complication, its causes and solutions are not fully understood. Therefore, the relationship of inguinal hernia and urinary symptoms should be well understood, and methods should be developed to reduce inguinal hernia rates or urinary complications associated with inguinal hernia surgery. More prospective and randomized controlled studies are needed to understand relationship of inguinal hernia and urinary symptoms.

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CHAPTER XIX

ANESTHESIA IN BARIATRIC SURGERY

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Obesity is defined as hypertrophy and/or hyperplasia of fat storage cells. It is a chronic, multisystemic, proinflammatory metabolic disease associated with high morbidity and mortality. The World Health Organization (WHO) classifies obesity by body mass index (BMI); a person with a BMI of $>30 \text{ kg/m}^2$ is considered obese.

It is known that countries such as the US, Turkey, Saudi Arabia, Jordan, Qatar, Egypt, Nauru, Palau, and Cook Islands have the highest obesity rates in the world. WHO reports that 2.3 billion adults are overweight, and 700 million adults are obese worldwide.

Etiologically, 65% of diabetes mellitus, 23% of ischemic heart diseases, and 41% of cancers are attributed to overweight and obesity.

Three-stage treatments are used for the treatment of obesity with such a high prevalence.

1. Behavioral treatments for dietary habits
2. Medical treatments
3. Surgical treatment methods.

Bariatric surgery, derived from the Greek words "baros" (weight) and "iatic" (medical treatment), describes surgical interventions for weight loss. It is very commonly preferred since it improves obesity-related comorbidities and reduces the mortality rate (1).

The most commonly used methods among surgical treatment options are as follows:

1- Sleeve gastrectomy: It is a restrictive intervention in which the calorie intake is limited by reducing the gastric reservoir.

2- Roux-en-Y gastric bypass (RYGB): It is a malabsorptive intervention in which the length of the small intestine is reduced.

3-Biliopancreatic diversion-duodenal switch surgery (for super-obese patients)

Indication for Bariatric Surgery: Bariatric surgery is recommended for

1. Clinically severe obese (BMI > 40 kg/m²)

2. Less obese adults (BMI > 30 kg/m²) with severe comorbidities, such as obesity-related type 2 diabetes mellitus, heart disease or severe sleep apnea.

Physiopathological Changes in Obese Patients:

Central obesity is defined as the waist circumference greater than 102 cm in men and 88 cm in women. Accumulation of fat in the central region is excessive, and the accumulation of fat in this region is known to be metabolically highly active.

In terms of the effects on the cardiovascular system, blood volume, cardiac output, oxygen consumption and CO₂ production have increased due to metabolic requirement. The incidence of left ventricular hypertrophy is seen to increase 16 times in those with a BMI above 30 kg/m². Hypertension is the most common comorbidity. ECG shows changes in P wave morphology, low-voltage QRS, flattening of T wave in inferior and lateral leads, and prolonged QT interval.

In the pulmonary system, functional residual capacity (FRC), total lung capacity (TLC), vital capacity (VC), residual volume and closing capacity do not change, the decrease in FRC causes the lung volumes to remain below the closing capacity, which forms a basis for atelectasis.

Obesity Hypoventilation Syndrome (OHS) is also seen.

When right heart failure is added to this picture, it is called "Pickwick Syndrome". Hypoxemia, hypercapnia, pulmonary hypertension, systemic vasoconstriction, and obstructive sleep apnea syndrome (OSAS) occur in obesity.

In terms of the effects on the hematopoietic system, it is known that adipose tissue secretes various immunomodulators and bioactive molecules.

In addition to resistin and leptin, it also produces cytokines such as TNF- α and IL-6. IL-6 and leptin cause the secretion of hepcidin from adipose tissue. Hepcidin restricts erythropoiesis and causes mild/moderate anemia. Adiponectin is highly anti-inflammatory. In the study by Unamuno X et al., preoperative and postoperative adiponectin/leptin ratios were examined in 25 patients who underwent RYG operation, and it was found that they lost weight very well at the end of 1 year and this ratio increased. (2) Leptin is also known to cause thrombosis by increasing coagulation cascade activity and reducing fibrinolysis. Venous thrombosis is more common as BMI increases. Especially, abdominal adipose tissue and chronic intra-abdominal pressure increase may restrict venous return. Obesity is known to cause thrombosis by increasing coagulation cascade activity and decreasing fibrinolysis via leptin. The effects on the gastrointestinal tract are also very significant. Obesity leads to an increase in intra-abdominal pressure, an increase in gastric acid production, a decrease in lower esophageal sphincter pressure, and motor dysfunction in the esophagus. These pathophysiological changes result in the development of regurgitation, esophagitis and gastroesophageal reflux disease (GERD).

In terms of the effects on the renal and endocrine system,

the LRb leptin receptor is localized in the internal medullary collecting duct of the kidney.

The high leptin level leads to a decrease in sodium and water excretion, and hypertension

Preoperative Evaluation of the Obese Patient

Preoperative preparation period should be very detailed, as it can coexist with many comorbidities.

There are various markers in Risk Assessment. The most commonly used marker is

mortality risk calculation. The 3 most commonly used markers are

1-Obesity Surgery-Mortality Risk Score (OS-MRS)

2- Longitudinal Assessment of Bariatric Surgery (LABS)

3- Metabolic Acuity Score (MAS)

Obesity Surgery-Mortality Risk Score (OS-MRS system) uses 5 risk factors, and 1 point is given for each of the following:

1. BMI \geq 50 kg/m²
2. Male gender
- 3- Hypertension
4. Risk of pulmonary embolism (history of venous thromboembolism, pulmonary hypertension, obesity hypoventilation syndrome)
5. Age \geq 45

0-1 point is classified as "A" or low risk,

2-3 points are classified as "B" or moderate risk,

4-5 points are classified as "C" or high risk.

The preoperative evaluation of the airway:

With excessive adipose tissue increase in the face, neck, breasts, thorax and abdomen, patient's position, neck extension, mask ventilation, and tracheal intubation may cause significant problems.

Mask ventilation is known to be more difficult in obese patients. The neck circumference is an important additional indicator and is associated with a difficult laryngoscopy at a rate of 35% when it is larger than 60 cm.

Points to consider in the Respiratory System:

Preoperative arterial blood gas analysis should be considered in cases of

- Arterial blood oxygen saturation $<95\%$ in room air
- Forced vital capacity <3 L or forced expiratory volume in 1 sec <1.5 L
- Inspiratory 'wheezing' at rest
- Serum bicarbonate concentration > 27 mmol L
- Arterial PCO₂ > 45 mmHg indicates a respiratory failure to some extent and accordingly an increased risk of anesthesia.

The incidence of perioperative complication is estimated to be 2-4 times higher in patients with obstructive sleep apnea (OSA).

ASA uses the apnea/hypopnea index (AHI) to define OSA. AHI is an indicator of the number of apneas and hypopneas that occur per hour of sleep.

According to AHI, 6-20 events/hour are mild, 21-40 events/hour are moderate,

and > 41 events/hour are severe OSA.

The standard method for the diagnosis is polysomnography.

Perioperative Period:

In premedication, oral benzodiazepines can be used for anxiolytic and sedative effects. However, sedative drugs and opioids should be avoided as much as possible, especially in morbidly obese patients diagnosed with OSA, since the risk of respiratory arrest is higher. The risk of aspiration pneumonia should be taken into account during premedication. Gastric acid and/or volume should be reduced by using H₂-receptor antagonists and proton pump inhibitors. Venous thrombosis embolism (VTE) prophylaxis should be administered. However, there is no class I evidence to recommend VTE prophylaxis type, dose or duration in these patients. Mechanical prophylaxis and early mobilization are recommended for all bariatric surgery patients. Devices that perform intermittent pneumatic compression to provide venous return should be used throughout the perioperative period. A combination of mechanical prophylaxis and chemoprophylaxis may be given. Low-molecular-weight heparin (LMWH) has been shown to not only increase the risk of bleeding but also provide better VTE prophylaxis than unfractionated heparin (UFH).

Monitoring and patient's position:

Invasive blood pressure monitoring should be used in patients with severe cardiopulmonary disease and in cases where non-invasive blood pressure cuff is not placed adequately. An appropriate size of the cuff may not be available. Neuromuscular monitoring is recommended. Although peripheral venous access is difficult, central venous catheterization is not routinely recommended. Laparoscopic bariatric surgery position should be the modified Lloyd Davis position (steep reverse Trendelenburg position with legs spread apart and both arms out on arm boards).

Airway management

The patient should be in the "ramped" position before the induction of anesthesia. In this position, pads are placed under the patient from

the lumbar region to the occiput, and the upper trunk, head, and neck are elevated by 20-30 degrees. Thus, the sternum and the tragus are aligned at the ear level, and the arms are positioned below the rib cage. With this position, the appearance of glottic structures is improved and orotracheal intubation is facilitated. Reduced functional residual capacity and increased basal oxygen consumption occur, and therefore pre-oxygenation is mandatory as standard. The use of 10 cm H₂O CPAP/PEEP during the induction period (CPAP during breathing and PEEP after apnea) increases apnea time by 50% before desaturation. As ventilation can be difficult with a face mask, a supraglottic airway tool should be kept available as an alternative airway device in the operation room. If difficult mask ventilation or intubation is considered, intubation can be performed with the aid of a fiberoptic bronchoscope. Video laryngoscopes improve the laryngeal view and allow rapid intubation (3).

Anesthetics

Lipophilic drugs have a larger distribution volume than hydrophilic drugs. However, it is known that distribution volume changes are drug-specific in obese individuals. For most anesthetic agents, dose calculation based on total body weight (TBW) is not suitable due to the risk of overdose. In calculating anesthetic doses, it is recommended to use lean (LBW) body weight instead of total body weight. Cardiac output is an important determinant in peak plasma concentration.

When the thiopental induction dose is adjusted according to LBW, it causes the same peak plasma concentrations as the dose adjusted according to the cardiac output.

It is an appropriate approach to give induction doses based on LBW. However, awakening is faster compared to non-obese patients. The risk of awareness related to thiopental is higher than propofol (4).

Propofol has high lipid solubility. The induction dose is adjusted according to LBW since it is correlated with cardiac output, such as thiopental. When propofol is given as a continuous infusion, the volume of distribution and clearance increases with TBW increase. Propofol infusion should be according to TBW (5). Among the patients who underwent laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass between 2016 and 2017, the optimal anesthesia approach was evaluated by comparing peri- and postoperative outcomes in patients receiving propofol intravenous anesthesia and desflurane anesthesia, and the awakening period was found to be 2 ± 2 min for both intravenous anesthesia and desflurane group. It was found that there

was no difference between the groups in terms of postoperative pain, nausea, and vomiting (6). Retrospectively, 711 patients (72% women, mean age 40 years) in Zurich University Hospital from the period of 2013-2016 were included in the study. In general, it was found that the rate of surgical complications was 34%, and that of anesthetic complications was 37%.

The rate of postoperative nausea and vomiting was 34%, and the rate of intubation-related complications was 4%, while the extubation delay was observed in 2% of patients. Complications of anesthesia were less common in elderly patients and in patients who received volatile anesthesia (7).

Hydrophilic drugs such as neuromuscular blockers are primarily distributed in the compartment. When rocuronium dose is administered based on the total body weight, it did not cause a significant shortening in the onset of action, but there was a significant increase in duration of action (8)

When vecuronium is administered in doses based on TBW, it causes a longer duration of action in obese individuals than non-obese individuals. Therefore, the use of LBW when calculating the dose is an appropriate approach. In obese individuals, the amount of pseudocholinesterase and the amount of extracellular fluid have increased. Since both of these factors determine the duration of action of succinylcholine, dose should be adjusted according to TBW. The dose of neostigmine and sugammadex is associated with the timing and the total dose of neuromuscular blockers. The dose of fentanyl should be adjusted according to LBW (9). In simulations of remifentanil concentrations, obese individuals who received LBW-based remifentanil infusion had similar plasma concentrations to those of individuals with normal weight who received TBW-based infusion. Infusion according to TBW results in significantly higher plasma concentrations and may increase the risk of side effects such as bradycardia, hypotension. Therefore, dosing with LBW for opioids should be the appropriate approach initially.

Ventilation mode

The ideal intraoperative ventilation strategy is unknown in obese patients.

However, the end-inspiratory pressure should be below 30 cmH₂O, and the tidal volume should be 6-8 mL/kg according to the ideal body weight. In order to prevent atelectasis, the "recruitment maneuver" (RM) should be performed and sufficient PEEP should be used to keep

the parenchyma open. There is no evidence of any difference between pressure-controlled and volume-controlled ventilation (10). High intrathoracic pressures may reduce venous return and cardiac output, causing hemodynamic instability in morbidly obese patients prone to cardiovascular diseases.

Fluid Therapy

There is no evidence-based recommendation. One of the most important factors that play a role in minimizing the negative effects of pneumoperitoneum on kidney and heart functions is intravascular volume optimization. In addition to the direct negative effects of laparoscopic procedures, obese and morbidly obese patients are at risk of muscle damage, especially during prolonged interventions. Muscle breakdown may result in rhabdomyolysis, severe electrolyte disorders, cardiac arrhythmias, and acute renal failure. Aggressive fluid replacement is recommended for the treatment of rhabdomyolysis. Postoperative creatine kinase levels should be checked routinely. In obese patients, hypovolemia is associated with increased hemodynamic instability, postoperative nausea and vomiting. Hypervolemia may increase the risk of decompensated heart failure, peripheral tissue edema, and pulmonary complications in relation to increased incidence of cardiovascular diseases. Therefore, targeting normovolemia in obese patients is essential for cardiac stability. Obese patients undergoing laparoscopic bariatric surgery do not require to be given extra fluids. The use of dynamic indicators such as PVI helps to reduce the volume of intraoperative infusion fluids in laparoscopic bariatric interventions, with no effect on intraoperative or postoperative lactate levels (11).

Postoperative Care

If early non-invasive ventilation is not planned in the patient who comes to the extubation stage, it is necessary to provide awake, cooperative, conditions in which neuromuscular functions return fully and sufficient tidal volumes are created, and the patient should be extubated in a semi-sitting position. In studies comparing sugammadex and neostigmine, which are used for many indications, the use of acetylcholinesterase inhibitors such as neostigmine for reversing conventional non-depolarizing neuromuscular blocking agents has been shown to have significant limitations, such as limited and unpredictable efficacy and undesired autonomic responses. Sugammadex, on the other hand, is preferred due to its potential clinical benefits, ability to rapidly reverse the block, increased patient safety, and reduced incidence of residual block(12).

Postoperative Lung Functions and Oxygenation

Obese patients are at high risk in terms of developing respiratory failure and desaturation in the postoperative period. An obese patient, who is restricted in terms of lung function, can rapidly decompensate when combined with postoperative deep sedation or poor pain control, decreased functional residual capacity, increased airway resistance, and decreased thoracic wall compliance.

In the postoperative period, positioning of morbidly obese patients at 30 °-45° rather than supine position increases arterial oxygenation. The incidence of atelectasis after upper abdominal surgery is 45%. Therefore, in obese patients, it is recommended to initiate CPAP while the patient is in the recovery room and to continue it, especially for the first 24 hours.

The ASA guidelines also state that CPAP should be initiated on patients, who use CPAP or BiPAP devices in the preoperative period, in the early postoperative period (13).

Cardiovascular System

Hypertension: A considerable portion of obese patients, like 50-60%, already have hypertension. Severe postoperative hypertension may develop due to the causes of sympathetic activation such as anxiety, pain, hypervolemia, hypoxia, hypercarbia and bladder distension, leading to myocardial ischemia, congestive heart failure, stroke and bleeding.

Nausea and Vomiting: They are high-risk patients for postoperative nausea-vomiting. Postoperative nausea-vomiting (PONV) is common in obese patients due to difficult mask ventilation-related gastric distension and the slow release of fat-soluble anesthetic agents. Despite multi-drug treatments such as dexamethasone, ondansetron, and scopolamine, more than 40% of patients require additional anti-emetics. Even total intravenous anesthesia(TIVA) only with propofol reduces PONV development up to 20%.

Pain Control

Opioids are still the first and most effective option in acute postoperative pain control, although there are wide variety of analgesic options and strategies. However, central sleep apnea and respiratory depression are the factors that limit its use. Although they are made mostly considering the calculation of the ideal body weight and the dose-response relationship of the additional doses, estimations can be misleading. It was found that laparoscopic-TAP block was associated

with earlier mobilization in bariatric surgeries, and postoperative morphine consumption was decreased too much (14). In patients with and without the application of the Enhanced recovery after surgery (ERAS) () protocol in bariatric surgery, a reduction in the length of hospital stay (from 4.7 to 2.1) and a low morbidity rate were observed (15).

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CHAPTER XX

**DIFFERENT EDUCATION MODELS FOR
ENDOSCOPY**

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Introduction

Endoscopy has been used in the diagnosis and treatment of various pathologies for about a century. On the other hand, particularly major gynaecological laparoscopic surgery practices developed rapidly with the advancement of endoscopic technical equipment and experiences after 1980 (Kelley et al., 2008). The last step of this development includes robotic surgery, virtual reality practices and their variants. Today, almost all open surgical operations can be performed through endoscopy.

Less tissue damage and less postoperative pain are the main factors that have enabled laparoscopic endoscopy to present a rapid development and recognition. In addition, smaller incision areas to relieve cosmetic concerns, fewer complications of the wound, shorter hospital stays, faster return to daily activities and financial advantages

have also contributed to the development of laparoscopy (Campo et al., 2016).

Endoscopy training has changed parallel to the development of endoscopy. The main purpose of this change in the existing training model is to teach endoscopic surgery student how to perform a surgery in a skilful manner in a shorter period. Endoscopic surgery skills of the student, as well as the training model, is an important factor. Another purpose of the current model is to teach students with different levels of endoscopic surgery skills in such a way that they reach the highest level possible since the occupational area of a surgeon involves the human being not tolerating any mistakes. Any mistake could endanger the human life. It is important that training is carried out in the shortest time possible with maximum efficiency.

Training Methods:

The key training model in medical education has been the “master-apprentice” model for centuries. In this model, the students, as the apprentices, observe the surgeons who are the masters, and they get specialized as they start performing on their own. However, this is a time-taking method and it does not allow for being trained everywhere. This training model is insufficient particularly considering the population and the number of surgeons trained today. Besides, this type of training has inconsistencies and it does not have a certain standardization. Student’s skills play an important role in the success of training (Campo et al., 2016). While the training models most commonly used are those developed by Halsted and Peyton, there are also Zwisch, BID and 4C/ID training models whose efficiencies have not been evaluated yet. Self-training materials such as training box, virtual reality applications, robotic training equipment and animal (living/cadaver) are also used in some of these training models (Surgical Education, 2011).

The Halsted Training Model

William Stewart Halsted, the first senior surgeon of Johns Hopkins Hospital, defined a different model in surgical training system in 1890. This model basically uses the master-apprentice training model. It requires a face-to-face training with the teacher like the master-apprentice model. Halsted defines the main steps of training as follows: “see one, do one, teach one”. It was suggested that this could be used not only in surgical training but also in various other fields.

The professional trainer performs the operation in the presence of the student and then the student performs the operation on his/her own.

In the end, the student gets qualified enough to be able to teach other students. This is a rather tiring system requiring long teaching and practice hours. The increase in the number of students and population has caused this model to remain insufficient over time and created the need to develop alternative models. While being suitable for traditional and non-complicated surgical operations, the model has failed to provide sufficient training in complex operations such as endoscopic surgery (Khodaverdi, 2018).

The Peyton Training Model

Another commonly used training model is the one developed by JW Rodney Peyton. Compared to Halsted and the master-apprentice training models, the Peyton training model is more suitable and common for medical training (Peyton, 1998). Several fields of medical science have recognized this model as their fundamental type of training. The training required has 4 steps according to Peyton (Table 1), which are as follows:

1. **Demonstration:** The teacher performs the skill in real time without any comment. This step is taken to provide a benchmark.
2. **Deconstruction:** The teacher performs every step slowly with an additional explanation. The skill should be divided into smaller subsections.
3. **Comprehension:** The student describes every step of the skill whereupon the teacher performs on instruction. The description and execution do not occur simultaneously.
4. **Performance:** The student simultaneously narrates and executes the process step by step.

Table 1: The steps and tasks in the Peyton training model

	Teacher	Trainee
1	Performs	Observers
2	Shows and explains	Observers
3	Performs	Instructs
4	Observers	Explains and Performs

The Peyton model can be basically defined in 3 phases. The first phase, known as the cognitive phase, involves the 1st and 2nd steps. Current surgical practices are learned in this phase. The second phase is the practice and fixation phase. The student learns all mechanical steps gradually and fixes such in the thought system. Autonomy is the final phase. The student uses his/her skills in the relevant training field and gains autonomy with frequent practices (Easton et al., 2012). The Peyton training model can be applied repeatedly on both living cases

and on different training materials. This model has been used in training with various modifications in several different fields of medicine (Münster et al., 2016; Gradl-Dietsch et al., 2019; Krautter et al., 2015). However, it is not superior to the Halsted/master-apprentice training model in every field of training. The Peyton and Halsted training models have been compared in laparoscopic training in several research papers in literature. Romero et al. analysed the efficiency of the Peyton and Halsted training models on laparoscopic suturing and knotting in training boxes. Medical students with no previous laparoscopic experience are included in the research. The first three and final suture placement and knotting skills were assessed according to Objective Structured Assessment of Technical Skills (OSATS), procedural implementation, knotting quality, total time and suture placement accuracy. OSATS scores were evaluated as procedure-specific checklist (PSC) and a global rating scale (GRS). At the end of the study, performance and OSATS-PSC scores were always higher in the Peyton group than the Halsted group. As for task time, the case in favour of the Peyton was balanced with the Halsted in the following practices (Romero et al., 2018). The values and their statistical significance are presented in Table 2 (adapted from Romero et al., 2017).

Table 2: Comparison of student data in Peyton and Halsted Training models

	First Suture			Last Suture			1-3. sutures average		
	Peyton			Peyton			Peyton		
	Halsted			Halsted			Halsted		
			p			p			p
Performance (Score)	15.6±3.3	1.9±3.6	0.001	18.9±3.8	15.0±4.0	0.001	17.6±3.8	13.6±4.1	0.001
Knot quality (Score)	3.0±1.5	3.5±1.1	n.s.	4.0±1.2	4.2±1.3	n.s.	3.5±1.5	3.8±1.2	n.s.
OSATS-PSC (Score)	10.3±2.2	8.6±2.4	0.01	11.9±1.7	10.5±2.9	0.009	11.2±2.0	9.5±2.5	0.001
OSATS-GRS (Score)	6.9±2.5	6.4±2.1	n.s.	11.3±3.3	10.4±3.7	n.s.	9.4±3.2	8.1±2.9	0.01
OSATS total (Score)	17.2±4	15.0±3.9	n.s.	3.2±4.7	20.9±5.6	n.s.	20.6±4.9	7.6±4.9	0.001
Task time (S)	567±1	727±363	0.04	351±18	346±239	n.s.	429±159	506±273	0.03
Accuracy (mm)	1.9±1	1.7±0.8	n.s.	1.3±1.1	1.7±0.8	n.s.	1.5±0.9	1.8±0.8	n.s.

The Zwisch Training model

The Zwisch model helps the teacher in adapting teaching for every surgical operation based on the level of each surgery student. The first phase is “show and tell”, where the teacher demonstrates and tells about the operation. The student just observes the operation carefully. This is like the second phase of the Peyton method. Yet, it differs from the Peyton model since it involves informing the student about practices such as the pre-operation preparations and background practices. The second is the “Smart Help” phase. This process allows for transition from the step providing help to the trainer to the step where the student performs on his/her own. In this process, the student continuously gives feedback to the trainer during the operation to suggest that he/she will be able to perform the operation on his/her own. The third is the “Dump Help” phase. While the student performs the operation, the trainer just helps the student as necessary for fine adjustments in the operation. The final phase is the “No Help” phase. In this phase, the trainer can only help the student in form of advice. This training model must be supported with absolute theoretical information. There is no sufficient amount of researches about its efficiency in endoscopic surgery (Advancing Surgical Education, 2019).

The BID model (The three-phase briefing-intraoperative teaching-debriefing (BID) framework)

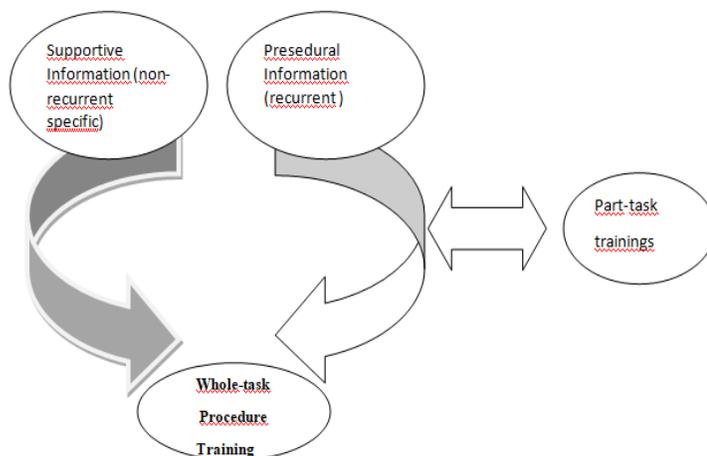
It can be used during, before and after the operation (Gardner et al., 2019). The student is informed about the subjects he/she needs to study prior to the operation and about the goals. Once the goal is achieved, the trainer helps the student focus on technical skills during the operation using previous experiences. This is a very short phase. It is obvious that the desired level of success in this training system cannot be reached in case of insufficient theoretical knowledge. Intraoperative technical skills are developed in the next phase. In the final phase after the operation, the weaknesses and mistakes of the student are frequently emphasized to enable the student to particularly focus on these areas. Utilization of video recording systems is quite useful in training (Advancing Surgical Education, 2019).

The 4C/ID Training Model

This model was designed particularly for developing skills in complex operations. It is divided in 4 main components, which are: learning tasks, supportive information, procedural information and additional part-task training. Learning task is the most important and fundamental step. It must be realistic and involve all steps of the

training. This method is the reverse of the methods that allow for training by dividing into all sub-steps of training. In the 4C/ID training model, the student's direct shift to the application phase will cause cognitive and practical overload and help recovery from factors with negative impacts on learning. For this reason, training should start with the teaching of application in the simplest way. Additions should be made as the student internalizes knowledge, with operations requiring more complicated tasks and practical skills. The operation should progress from the simplest to the most complicated in surgery. Despite all the advantages, its efficiency has not been evaluated in every field of surgical training (Advancing Surgical Education , 2019; Daniel et al., 2018; Maggio et al., 2015).

Table: Components of the 4C/ID training model



Supplementary equipment used in training

Different training materials are used for different training needs of surgical training. Training box, animal (cadaver or living), human cadaver, virtual reality applications, robotic surgery practice areas and simulations (robotic, training box etc.) are used in gynaecological endoscopy training. There are 3 essential skills for endoscopic surgery that all these practices intend to develop; camera navigation, eye-hand coordination and bimanual coordination.

Training box

The major concern for the student in endoscopy training is to be able to access sufficient information and skills. 2D systems with a screen are the most commonly used systems in endoscopy. It requires a high level of knowledge, skills and orientation to perform 3D operations using 2D systems. The perception of depth, hand-eye coordination and bimanual coordination require a certain level of skills. Therefore, it is important to carry out sufficient amount of practice before continuing with actual operations. Since equipment knowledge and training of the surgery team need to be planned by the surgeon, theoretical knowledge, as well as practical knowledge, is essential in endoscopic surgery. Training boxes have an important place in practice fields since they are mobile and widespread. They can be individually created even at home, using a simple webcam, cardboard, a plastic box and a computer; or they can exist in commercial products utilizing complex materials. Adaptation to a 2D image, eye-hand coordination and bimanual coordination as well as the recognition of laparoscopic tools are achieved rather than addressing highly complex procedures. Positive effects of simple training boxes on the development of surgery skills have been revealed in several researches (Scott et al., 2007; Goova et al., 2008).

A recent type of training box has significantly contributed to the development of surgical skills thanks to actual surgery simulations with computer-based programs integrated in the system. Simple peg transfer or suture applications can be performed. Mannella et al. reported a faster increase in Objective Structured Assessment of Technical Skills (OSATS) scores of endoscopic surgery students compared to the traditional method or simple training boxes. The increase in post-training assessment of student scores cannot be observed in professional endoscopic surgeons (Mannella et al., 2019). The quality and success of training could be increased by integrating 3D simulation and virtual reality applications into these training boxes (de Montbrun and Macrae, 2012).

Animal training models

Animal training models are ones that best simulate the endoscopic surgery of a real patient. Pig is the most suitable animal in terms of availability and its similarity with the human structure. Even for training or for experimental purposes, these animals can be used only after certain assessments and criteria. The first and the most important principle is to select an animal fitting the training to be carried out. For example, selecting a male animal for the practical training in gynaecological diseases and birth giving would be waste of efforts.

Necessary conditions for training with the animal must be met before starting to work. i) The animal to be reproduced under controlled reproduction conditions, ii) Legal permits should be received to work on the animal, iii) Necessary assessments should be made and sufficient quarantine period should be considered in order to make sure that the animal has no source of infection. It is also important that all surgical tools complies with normal surgery. The same assessments and conditions must be met for cadaver animal training models, as well. All phases including trocar placement, pneumoperitoneum and laparoscopic surgery can be carried out on animal training models. There are experimental surgery rooms designed for this purpose and courses are organized to train surgery students (Advancing Surgical Education,2019).

Human Cadaver

Fresh cadaver tissue is the golden standard training model for surgical training most similar to the living human tissue. Nonetheless, dead tissue cannot simulate all physiological responses in a surgery. Therefore, it is possible to perfuse cadaver tissues with pressurized blood to make the most real-like. In addition, flap transposition techniques can be performed on cadavers for laparoscopic operations (Imakuma et al., 2016).

On the other hand, high costs and low tissue compliance are the basic problems for cadaver training. Besides, a plant with necessary equipment is needed for the preservation of the cadaver and many operations are non-applicable on a cadaver particularly due to the compliance problem. However, formaldehyde's compliance reducing effect has been improved with the use of *N*-vinyl-2-pyrrolidone. This material helps the tissue expand in compliance with laparoscopy and maintain the flexibility of tissues. Cadaver tissues with high living tissue compliance can be obtained in this way (Nagese et al., 2020).

Virtual reality

Training in surgery rooms are not practical due to high costs and lack of sufficient time for training. Thus, more practical and low-cost surgical training programs allowing for a more efficient training, have been sought for. Besides, training phases in programs not using real patients will naturally help prevention of any patient complications. Over time, all these factors have highlighted simulation-based trainings in modern surgical training. This system has been designed by taking inspiration from pilot training tools. These simulators enable a real-like

and real-time operation area. It is also a great advantage that simulation sessions can be adjusted to the individual's desire, surgical skills and training level. These levels might change from diagnostic procedures to complex urogynaecology laparoscopy. The majority of this system is portable and computer-based. The success of simulators depends on their ability to offer real-life views and reactions (Valentine et al., 2016). Training environments are modernized with advancing computer graphics and power skills to help them achieve the most resemblance to a real-life surgery. Moreover, different environments and surgical experiences can be simulated in a single unit (de Visser et al., 2011). Comparison of virtual reality laparoscopy training with the traditional training box suggested higher scores in favour of virtual reality particularly in terms of pattern cutting and peg transport time (Mohammadi et al., 2010).

360-degree virtual reality simulators were included in training with the ever-advancing technology. The development stages of endoscopic surgery skills can be shorter. While this virtual reality type endoscopy training generally does not provide an additional support to surgeons who are already specialized in endoscopic training, it particularly shortens the learning curve of surgery students that are in the early stage of learning (Aggrawal et al., 2006; Yoganathan et al., 2018). However, no significant contribution was found between the use of virtual reality application alone and the combined use of different methods along with virtual reality in training, in terms of contribution to laparoscopic skills (Brinkman et al., 2012).

Complications are deleted from the system if the operation is repeated, encouraging the surgery student to be able to repeat the operation. Increasing the speed of operation reduces the risks (Alaker et al., 2016; Zevin et al., 2014). Until today, several desk-top training box and virtual reality simulators have been used for training purposes in various operations such as cleft palate correction, bowel anastomose and endoscopic removal of foreign substances (Gause et al., 2016).

Robot-assisted laparoscopic surgery (RAS) simulators

This practice has allowed for small incision areas and has enabled the surgeon to perform operation while sitting comfortably and see the operation area more closely with 3D cams since 2000s. Technical infrastructure of the Da Vinci robot is compatible with virtual reality (Liu and Curet, 2015). There are currently five virtual reality simulator systems for robotic training: the Surgical Education Platform (SEP; SimSurgery, Oslo, Norway), the Robotic Surgical System (RoSS;

Simulated Surgical Systems, San Jose, CA, USA), the dV-Trainer (Mimic, Seattle, WA, USA), the da Vinci Skills Simulator (dVSS; Intuitive Surgical), and the RobotiX Mentor (3D Systems, Symbionix Products, Cleveland OH, USA).

Several researches have revealed these simulators to be useful in the development of surgical skills in RAS (Lyons et al., 2013). Nonetheless, sufficiency of these simulators are yet to be discussed (Moglia et al., 2016). On the other hand, virtual reality application integrated with CT images will enable simulated performance of surgery on the same patient prior to the actual surgery, allowing for knowledge about possible anatomic variations and a great convenience in surgery. It is particularly used in renal and pancreas surgeries (Endo et al., 2014; Makiyama et al., 2015). Furthermore, working with robotic surgery simulators available in the same environment without transition to actual robotic surgery in several surgery rooms, allows for compliance with actual surgery.

In robotic surgery training, operations such as material transfer or suture removal can be performed both directly and as a simulation. Modification of the same systems will also provide a virtual reality environment, allowing for the student to perform, on a simulator, pathologies that require different surgeries. Surgery students are also encouraged towards training with the use of technology. In a review by Bric et al. of 47 research papers on robotic surgery and virtual reality training, virtual reality application was emphasized to be quite useful in the development of robotic surgery skills (Bric et al., 2016). In a review by Thomaier et al., surgery students who had received robotic surgery simulator training were found to have better scores in laparoscopic skills (Thomaier et al., 2017)

Robotic surgery simulator-aided training can be offered under the supervision of certain centres and to a limited number of trainees. Thus, it is a difficult phase for surgery students. Simple simulators designed by the student was compared with the Da Vinci simulators in terms of the development of surgical skills and no significant difference was observed (Lee et al., 2019).

In a review performed over vaginal cuff covering where robotic surgical simulators were assessed in terms of both efficiency and number of practices, significant positive changes were found in OAST scores in robotic surgery simulators minimal surgical application development (Vogell et al., 2015). In a research by Hassan et al. comparing the speed and learning curve durations in laparoscopic surgical skills of the traditional laparoscopic training

box and the Da Vinci robotic simulators, the speed was higher in robotic simulation trainings in terms of basic laparoscopic skills. However, improvement percentages were similar in the development of skills throughout the practice (Hassan et al., 2015). Robotic surgical training is faster and more efficient in individuals who have previously received basic laparoscopic training (Davila et al., 2018).

In conclusion, endoscopy has an important role in gynaecology practice. Most of the practices are almost entirely performed through endoscopy today. Development of endoscopic skills by using different training models and materials will help to specialize in real surgeries and reduce the number of possible complications.

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CHAPTER XXI

**CLINICAL DIAGNOSTIC APPROACH TO DEMENTIA
AND ALZHEIMER’S DISEASE**

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1.Dementia

The word dementia is derived from the Latin word “mens” (mind), and it means the loss of the mind.

Dementia is a major health problem, especially in aging populations. The number of patients with dementia is expected to rise to 81 million in 2050 if there is no major improvement in treatment and prevention (1). In 2015 it was estimated that 46.8 million people worldwide were living with dementia, and this number is expected to increase to 74.7 million in 2030 and 131.5 million in 2050 (2).

Dementia is the impairment in mental abilities that develop as a result of the acquired damage of the adult central nervous system and this impairment affects daily living activities. It is a permanent and often progressive clinical picture.

The first basic feature that should be considered for the diagnosis of dementia is that the patient should have a mental impairment according to the premorbid level. Situations in which mental functions are not acquired from the birth are not covered under the title of dementia.

The second basic feature required for the diagnosis of dementia is the presence of mental and cognitive impairment in more than one area such as the memory, attention, language, visual-spatial functions, executive functions, praxia and gnosis. In addition to all these, there should be disruption in daily life activities including the use of ordinary tools, housework and self-care, professional performance, independence in street and financial affairs and hobbies. In neurodegenerative dementias, the deterioration in daily living activities progresses from mild to severe in the temporal course.

Dementias may be classified as primary and secondary. Primary dementias, including Alzheimer's disease, the most common form seen in patients with dementia, constitute the neurodegenerative diseases of the central nervous system (CNS) that cause dementia. Secondary dementias are those that accompany or occur as a complication in the course of another disease. The most common type of secondary dementia is vascular dementia. Numerous diseases may cause the secondary dementia (3). Some examples of primary and secondary dementia types are given in “Table 1” (4).

Table 1. Classification of Dementia (*)

Primary dementias	Secondary dementias
Alzheimer's disease	<u>Vascular dementia</u> “Multi-infarct dementia, Binswanger, Strategic infarct dementia, Cerebral autosomal dominant arteriopathy subcortical infarcts (CADASIL)...”
Dementia with Lewy bodies	<u>Normal pressure hydrocephalus</u>
<u>Fronto-temporal dementia (FTD)</u> “FTD-behavioral variant, Primary Progressive Aphasia, Semantic dementia”	<u>Intracranial space-occupying diseases</u> “Neoplastic conditions, Subdural hematoma....”
Dementia with movement disorder “Parkinson's disease dementia, Cortico-basal degeneration, Progressive supranuclear paralysis, Huntington's disease, Multi-system atrophies, Wilson's disease, Neuroacanthocytosis	<u>Toxic-metabolic dementias,</u> “Wernicke-Korsakoff disease, Vitamin B12 deficiency, Hypothyroidism, Chronic liver disease, Exposure to organic solvents, alcoholism, drugs....”
<u>Prion hastalıkları</u> “Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease, Fatal familial insomnia...”	<u>Autoimmune-inflammatory diseases</u> “Multiple sclerosis, Behçet's disease, Paraneoplastic limbic encephalitis, channelopathies, Granulomatous angiitis, Primary nervous system vasculitis, Non-vasculitic autoimmune meningoencephalitis syndrome...”
Other rare dementias “Limbic dementia, Polyglucosyl body disease, Argiophilic grain disease...”	<u>Infections</u> “Herpes simplex encephalitis, Neurosyphilis, Chronic meningitis, HIV-dementia complex, Whipple disease...”

*This table is cited from “ www.itfnoroloji.org/demans/demans.htm ” (4).

1.1 Symptomology

The symptomatology of dementia syndrome can be classified into three main (cardinal) categories (Table 2).

1. Cognitive,
2. Behavioral,
3. Functional (daily life activities)

Table 2: The symptomatology of dementia

Cognitive	Behavioral	Functional
-Memory -Attention -Language -Visual-Spatial functions -Executive functions -Praxis -Gnosis	-Personality changes -Mood disorders -Perception disorders -Thought disorders	-Daily life activities outside and at home -Self-care

The most common symptom among cognitive symptoms belongs to the memory area. Patients or their families express some complaints such as asking the same questions and repeating the same issues, losing personal belongings, forgetting appointments, leaving the food on the stove and the stove on. The deterioration of visual-spatial functions is in the form of difficulty in finding direction and sometimes getting lost in foreign spaces. As time progresses, patients begin to have difficulties in recognizing the places they know. Language impairment begins with naming difficulties and a narrowing in the vocabulary knowledge in the early period of the disease. Over time, it can turn into a fluent aphasia in which understanding is impaired, or an aphasia in which the grammatical structure is broken. Due to practical impairments, manipulations of simple current devices (comb, scissors, toothbrush, tableware and etc.) may be impaired and this is called apraxia. Gnostic disorders (agnosia) can disrupt the recognition of objects and faces (prosopagnosia), and the determination of the position of an object in relation to other objects. Another cognitive symptom is the impairment in executive functions. Patients appear to lose their mental flexibility owing to the dysfunction in executive capabilities. Patients find it difficult to plan their behavior, to reason individual and social problems out, and to produce appropriate solutions to the problems with which they encounter in daily life. They cannot perform tasks fitting their purpose in a programmed, planned, sequential and successful manner. Among the

behavioral symptoms, apathy begins with a decrease in the spontaneity of the patient. In time, apathetic patients do not show the initiative, do not demand anything spontaneously, and do not speak unless directed. Another behavioral problem is the opposite of apathy, examples of disinhibition. Disinhibition primarily manifests itself with some devil-may-care attitudes incompatible with the social position. It is called abnormal social behavior, unusual sociability, playfulness, recklessness and childishness. Hypersexuality can range from exhibiting words and actions that carry sexual implications outside of the social norms acquired up to that point, to inappropriate sexual demands by the patient.

In some patients, the sense of hunger and satiety disappears. Hyperphagia is the change in the habitual mouthfeel of the patient and becoming gluttonous. It starts with a fondness for sweets, in particular. There may even be items that cannot be eaten, such as threads, plastic bags, and their own feces. It can be so severe that these items can be stuffed into the mouth. Anxiety, which can manifest itself as restlessness, constantly changing place, and getting bored very quickly, is a common behavioral feature. The patient's anxiety, which increases with the upcoming appointments, draws attention. Phobias can often be seen as the worry of being out of reach of the spouse and therefore the fear of not leaving the spouse or being alone, or it can vary depending on the patient.

Depression, mania, agitation, including physical or verbal violence, purposeless-repetitive movements (aimless wandering-stepping, opening and closing cabinets, repeating the same movement such as folding-unfolding the sheet, collecting objects in inappropriate places, stacking) are among the observable behavioral problems. Thought disorders such as theft, abandonment, infidelity, misidentification, and Capgras syndrome can be seen. Patients may make claims like "the caregiver is stealing my money", "my wife is cheating me with someone else", "you are going to throw me into a nursing home, "this is not my house, let's go home". They can believe that the people they already know are not really them and that they are replaced by other or fake people

Perception disorders, especially visual hallucinations, can occur in all sensory modalities. In general, behavioral disturbances are initially evident in the evening and/or at night, and this is called the "sunset phenomenon". As the disease progresses, these behavioral problems tend to spread increasingly throughout the day. Symptoms related to the functional area include going to work, traveling outside the home, shopping, running

finances (paying bills, dealing with banking operations and etc.), using everyday devices, maintaining hobbies, running household tasks, personal care or hygiene (dressing, bathing, problems with regard to food, toilet and so on.). These draw attentions with the disruption of the daily life activities of the patient at various rates depending on the clinical stage of the disease. In addition to these, other areas such as motor system (gait disturbance, falls, freezing, imbalance, slow movement, weakness, melting, twitching), autonomic system (incontinence, impotence, orthostatic diseases, constipation, sweating) and sleep (REM-behavior disorder, excessive daytime sleepiness, sleep apnea syndrome) (4) often display dysfunction.

The severity of symptoms of dementia is graded by Clinical Dementia Rating (CDR). There are 6 areas in the CDR and the severity of symptoms in each area is graded (4,6).

2. Alzheimer's Disease

Alzheimer's disease is the most common type of dementia, being a progressive neurodegenerative disorder presenting with insidious loss of memory and cognition. Although dementia has been known since ancient times, Alzheimer's disease as the first case in history was written by Alois Alzheimer, who examined and followed up Ms. Auguste D. The prevalence and incidence of AD have been surging with the rise in age. It manifests itself in familial and sporadic forms. Sporadic AD is the most prevalent type of dementia affecting elderly population over the age of 65 years (7).

Although there are the similar neuropathological findings both in the familial form and sporadic or late-onset form of AD, the familial form of the disease is caused mutations in amyloid precursor protein (APP), presenilin1 and presenilin 2 genes. On the other hand, the sporadic form of the disease is multi-factorial disorder in which genetic predisposition and environmental factors contribute to the genesis of the disease (8,9,10).

The main neuropathological lesions of the AD are characterized by abnormal accumulation of amyloid beta protein ($A\beta$) derived from APP and neurofibrillary tangles (NFTs), consisting of precipitates or aggregates of hyperphosphorylated microtubule associated tau protein. There are also extensive synapse and neuronal cell loss. But these lesions may be not always correlated with clinical appearance. Significant AD neuropathology may be observed after autopsy in aged individuals non-demented before death or the cognitive impairment may be much higher in

comparison to existing AD neuropathology. Some presumptions have attempted to explain these contradictory results with the remarks that AD has an insidious preclinical stage and some individuals are relatively resistant to AD due to various levels of brain reserve, protective genetic factors or environmental influences (11,12,13). Moreover, other comorbidities may have contributed to the dementia severity (9,10,12). Although amyloid cascade hypothesis may be positioned to clarify the pathogenesis for the familial form of AD, recently increasing evidence has suggested that other cellular-molecular damage mechanisms such as mitochondrial dysfunction, inflammatory mechanism, some metabolic alterations and oxidative stress may have more crucial roles in the pathogenesis of sporadic AD regardless of being primarily or secondarily (9,11,13,14).

Oxidative stress (OS) associated with the pathogenesis of AD is an imbalance between the production of reactive oxygen species (ROS) and the ability of the body to counteract or detoxify their harmful effects through neutralization via antioxidants. ROS are by-products of cellular metabolism, produced during normal metabolism and are involved in many enzymatic reactions, mitochondrial electron transport, signal transduction, activation of nuclear transcription factors, gene expression, the function of neutrophils and macrophages, and of course, inflammatory responses. If the balance between the production of ROS and elimination becomes unbalanced, OS and its detrimental effects on the cellular functioning emerge in the blood, cerebrospinal fluid, brain and other tissues. ROS can damage proteins, lipids, deoxyribonucleic acid with remarkable negative consequences on the cellular functions (14,15,16). It has been supposed that OS can lead to many chronic diseases in addition to aging and age-related diseases such as atherosclerosis, parkinsonism and dementia (15, 16, 17). A study has reported that young healthy individuals at the risk of developing AD (as determined through genetic analysis, APO E ϵ 4) respond with an overexpression of antioxidants because of increased generation of ROS. Later on, the antioxidant defense system collapses, and OS becomes evident along with the symptoms of dementia (18). Although there are many studies about OS-AD, we indeed still don't know clearly how the role of OS is in the pathogenesis and progression of AD or whether OS is the primary contributor or the secondary effect of the disease or whether OS is a cause or a result like A β .

2.1 Risk factors predicted for AD

Many candidate risk genes have been identified in the AD. Apolipoprotein E ϵ 4 (APO E ϵ 4) is the most consistently associated genetic risk factor for sporadic AD by accelerating onset. SORL1 has also been identified as an important genetic cause of late-onset sporadic AD. Multiple risk factors for sporadic AD have been identified in addition to the genetic susceptibility, age and gender. As well as family history, fewer years of formal education, lower level of income and occupational status under average, depression, traumatic head injury, several metabolic risk factors such as obesity, type 2 diabetes, hypertension and some other cardio-vascular risk factors are considered to be associated with sporadic AD (4,5,9,10,19).

Many epidemiological studies agree that age is one of the most important risk factors for cognitive decline and AD. With advancing age, the prevalence of AD increases. Many studies show a higher prevalence of AD in women than in men. However, this difference in prevalence is generally explained by the longer life expectancy in women. Estrogen functions as a neurotrophic factor in the brain. While testosterone, present in men for life, is converted to estrogen in the brain and continues its function. After menopause, however, women remain estrogen-free. Even though prevalence of AD in females has been higher in recent years, it is recognized that gender is not a risk factor for AD. Now, it is well-established knowledge that low education is a risk factor itself. It is accepted that the increased educational exposure makes it harder for the disease to evolve by allowing the individual's cognitive capacity to expand. A previous history of depression dramatically raises the likelihood of AD. Studies have shown that depression is an early symptom of Alzheimer's disease in elderly people. Vascular disorders, myocardial ischemia, hypertension, diabetes and a history of stroke were reported to increase the risk of AD (4,5,9,10,19). Some of the risk factors and protective factors related to Alzheimer's disease are given in Table 3,4 and 5 (4,5,9,10,19).

Table 3: A summary of some risk factors that have been associated with Alzheimer's disease

Demographic	-Age -Female -Poor education -Poor social relationship and social class
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Lifestyle	<ul style="list-style-type: none"> -Alcohol -Lack of exercise -Lack of cognitive activity -Malnutrition -Poor diet -Smoking
Medical	<ul style="list-style-type: none"> -Cancer -Cardiovascular disease -Congestive heart failure -Immune system dysfunction -Micro-infarcts -Obesity -Poor cholesterol homeostasis -Poorly controlled type-2 diabetes -Stroke -Traumatic brain injury
Psychiatric	<ul style="list-style-type: none"> -Depression -Early stress
Environmental	<ul style="list-style-type: none"> -Air pollution -Calcium deficiency -Geographic location -Metals (especially aluminium, copper, zinc) -Military service -Organic solvents -Occupation -Vitamin deficiency
Infection	<ul style="list-style-type: none"> -Bacteria, e.g. Chlamydomphila pneumonia, Treponema -Dental infections -Fungi -Viruses

Table 4: A summary of genetics risk factors that have been associated with Alzheimer’s disease

<p>Amyloid precursor protein (APP) *</p> <p>Presenilin 1 and 2 (PSEN1/2) *</p> <p>Apolipoprotein E (APOE)</p> <p>ATP-binding cassette transporter A1 (ABCA1)</p> <p>Adaptor protein evolutionarily conserved signalling intermediate in Toll pathway (ECSIT)</p> <p>Clusterin gene (CLU)</p> <p>Estrogen receptor gene (ESR)</p> <p>Fermitin family homolog 2 gene (FERMT2)</p>

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) Histocompatibility locus antigen (HLA class III) Transferrin gene (TF) Triggering receptor expressed on myeloid cells 2 (TREM 2) Vascular protein sorting-10 domain (VpS10) genes Vitamin D receptor gene (VDR) Angiotensin 1 converting enzyme Complement component (3b / 4b) receptor 1 (CR1) Phosphatidylinositol binding clathrin assembly protein (PICALM) Sortilin-related receptor(SORL 1)

*regarded as causal factors

Table 5: Possible Protective factors for AD

Higher education APOE-ε2 Red wine Mediterranean diet Physical and mental activity Antioxidant usage (?) Anti-inflammatory use (?) Estrogen use (?) Statin use (?)

2.2 Diagnosis

The definitive diagnosis of Alzheimer's Disease can only be made by post-mortem brain examination. The presence of Neurofibrillary tangles and amyloid plaques (AP) should be demonstrated in the definitive diagnosis of Alzheimer's disease. In addition, loss of neurons, dendritic and axonal changes, synapse loss, gliosis, inflammation are also pathological findings identified. Although the most noticeable change in neurotransmitters is the loss of cholinergic innervation, changes are also observed in serotonergic, noradrenergic and dopaminergic systems.

There is no laboratory test that can definitively diagnose AD in a patient still alive. Clinicians can not make a conclusive diagnosis of AD disease, but they use some criteria in the clinical diagnosis of AD.

Though some neuro-radiological and biological studies are underway to classify individuals at risk of pre-clinical AD (20,21), the approaches

currently in regular use are only clinical diagnosis after the disease develops.

In the clinical diagnosis, the fundamental concept is impaired intellectual capacity and the following criteria must be met:

- There is impaired ability to learn new information or to recall previously learned information, that is, multiple deficits in intellectual function including memory impairment; and in addition to memory impairment,

- There is at least one of the following as well: (a) aphasia, a language disturbance, (b) apraxia, the impaired ability to carry out motor activities despite intact motor function, (c) agnosia, the failure to recognize or identify objects notwithstanding intact sensory function, and (d) disturbance in executive functioning, which includes planning, organizing, sequencing, and abstracting; and due to these deficits,

- There is impairment of occupational or social functioning, with a significant decline in functioning compared with the previous level;

and

- The deficits are not seen solely during the delirium-typed perturbations of consciousness.

Both the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) criteria, which have been published for the clinical diagnosis of AD, are still widely used by clinicians in clinical diagnosis of AD. National Institute on Aging and Alzheimer's Association 2011 core clinical criteria for all-cause dementia and probable Alzheimer's disease dementia (Table 6,7,8,9) (4,22,23,24).

2.3 AD Treatment and Management for Clinicians

The etiopathogenesis of AD is complex and unclear. Relating to this, the success in the management is limited.

Treatment options for Alzheimer's disease (AD) that improve the condition and stop the progression of the disease are still being investigated. Some research has focused on molecules that can interfere with pathological mechanisms specific to Alzheimer's disease, as well as molecules with neuroprotective and / or neurorestorative properties.

Currently, symptomatic therapy constitutes the core of Alzheimer's disease treatment. Even today, AD therapy can be divided into non-medical and medical (pharmacological) therapy. The key goal of non-medical care is to enhance the life quality of patients and their families and relatives, and to preserve cognitive and daily activity skills of patients (25,26)

Pharmacological medication can be defined as Cognitive Symptomatic and Non-cognitive Symptomatic. Non-cognitive therapy consists of medication options for mood disorders including depression, mania, and anxiety, and psychotic symptoms such as delusions and hallucinations. It primarily includes treatments that regulate behavioral and sleep-related complaints. Anxiolytic and antidepressants are used in different doses and combinations depending on the patient (25,26).

Although several medications have been tested, Cholinesterase Inhibitors and memantine still constitute cognitive symptomatic therapy. Rivastigmine, galantamine, and donepezil are well known as cholinesterase inhibitors used in pharmacological therapy of AD. Another cognitive symptomatic pharmacologic medication is memantine. Memantine is a low affinity N-methyl-D-aspartate receptor (NMDAR) antagonist. Memantine prevents pathological intracellular calcium accumulation by acting as a magnesium plug at the post-synaptic NMDA receptor in the impaired Alzheimer's synapse. These drugs can only relieve symptoms of the disease temporarily and none one of them has proven the ability to cure or stop the progression of the disease. Furthermore, the efficiency of the drugs varies from person to person and from stage to stage and the drugs always cause side effects such as nausea, diarrhea and vomiting. At the same time, failures occur often in AD drug development. Combination therapy has recently demonstrated greater therapeutic effectiveness in contrast with monotherapy, along with comparable tolerability and protection (27).

All of these, however, can not alter the fact that there is an immediate need for a cure that can stop AD and the issue still requires the ongoing search for treatments. And it is worth repeating the fact that about 50 million people worldwide are suffering from dementia, including AD. Moreover, by 2050, this aforesaid number is estimated to double.

Table 6: Diagnostic Criteria for Dementia of the Alzheimer's Type

DSM-IV-TR™ Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), Code Number: 294.1x

- A. The development of multiple cognitive deficits manifested by both
1. memory impairment (impaired ability to learn new information or to recall previously learned information)
 2. one (or more) of the following cognitive disturbances:
 - a. aphasia (language disturbance)
 - b. apraxia (impaired ability to carry out motor activities despite intact motor function)
 - c. agnosia (failure to recognize or identify objects despite intact sensory function)
 - d. disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
- B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
- C. The course is characterized by gradual onset and continuing cognitive decline.
- D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
1. other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
 2. systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
 3. substance-induced conditions
- E. The deficits do not occur exclusively during the course of a delirium.
- F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

Code based on presence or absence of a clinically significant behavioral disturbance:

294.10 Without Behavioral Disturbance: if the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.

294.11 With Behavioral Disturbance: if the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g., wandering, agitation).

Specify subtype: *With Early Onset: if onset is at age 65 years or below. *With Late Onset: if onset is after age 65 years.

Coding note: Also, code 331.0 Alzheimer's disease on Axis III. Indicate other prominent clinical features related to the Alzheimer's disease on Axis I (e.g., 293.83 Mood Disorder Due to Alzheimer's Disease, With Depressive Features, and 310.1 Personality Change Due to Alzheimer's Disease, Aggressive Type).

Table 7: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Work Group Criteria for Diagnosis of Alzheimer's Disease

I. The criteria for the clinical diagnosis of PROBABLE

Alzheimer's disease include:

- dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- deficits in two or more areas of cognition;
- progressive worsening of memory and other cognitive functions;
- no disturbance of consciousness;
- onset between ages 40 and 90, most often after age 65; and
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- impaired of activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if confirmed neuropathologically; and
- laboratory result of:
 - normal lumbar puncture as evaluated by standard techniques,
 - normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and
 - evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;
- other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

<ul style="list-style-type: none"> — seizures in advanced disease; and — CT normal for age.
<p>IV. Features that make a diagnosis of PROBABLE Alzheimer’s disease uncertain or unlikely include:</p> <ul style="list-style-type: none"> — sudden, apoplectic onset; — focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and — seizures or gait disturbances at the onset or very early in the course of the illness.
<p>V. Clinical diagnosis of POSSIBLE Alzheimer’s disease:</p> <ul style="list-style-type: none"> — may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course; — may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and — should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.
<p>VI. Criteria for diagnosis of DEFINITE Alzheimer’s disease are:</p> <ul style="list-style-type: none"> — the clinical criteria for probable Alzheimer’s disease; and — histopathologic evidence obtained from a biopsy or autopsy.
<p>VII. Classification of Alzheimer’s disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:</p> <ul style="list-style-type: none"> — familial occurrence; — onset before age of 65; — presence of trisomy-21; and — coexistence of other relevant conditions such as Parkinson’s disease.

Table 8: National Institute on Aging and Alzheimer’s Association core clinical criteria for all-cause dementia, 2011(*) (23)

<p>Dementia: cognitive or behavioral (neuropsychiatric) symptoms are present that</p> <ol style="list-style-type: none">1. Interfere with the ability to function at work or at usual activities2. Represent a decline from previous levels of functioning and performing3. Are not explained by delirium or major psychiatric disorder4. Cognitive impairment is detected and diagnosed through a combination of<ol style="list-style-type: none">a. History-taking from the patient and a knowledgeable informantb. An objective cognitive assessment, either a bedside mental status examination or neuropsychological testing (neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis)5. The cognitive or behavioral impairment involves a minimum of 2 of the following domains<ol style="list-style-type: none">a. Impaired ability to acquire and remember new information Symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar routeb. Impaired reasoning and handling of complex tasks, poor judgment Symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activitiesc. Impaired visuospatial abilities Symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements or orient clothing to the bodyd. Impaired language functions (speaking, reading, writing) Symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errorse. Changes in personality, behavior, or comportment Symptoms include: uncharacteristic mood fluctuations, such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors

*This table is cited from

<https://www.sciencedirect.com/science/article/pii/S0025712518301317?via%3Dihub> (23).

Table 9: National Institute on Aging and Alzheimer's Association core clinical criteria for probable Alzheimer's disease dementia, 2011 (*) (23)

<p>A diagnosis of probable AD dementia can be made when the patient</p> <ol style="list-style-type: none">1.Meets criteria for dementia (see Tablo 8)2.Has the following characteristics<ol style="list-style-type: none">a.Insidious onset Symptoms have a gradual onset over months to years, not sudden over hours or daysb.Clear-cut history of worsening of cognition by report or observationc.The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories<ol style="list-style-type: none">i.Amnestic presentation: most common syndromic presentation of AD dementia; deficits should include impairment in learning and recall of recently learned information; should also be evidence of cognitive dysfunction in at least 1 other cognitive domain (see article discussion)ii.Nonamnestic presentations<ol style="list-style-type: none">1.Language presentation: the most prominent deficits are in word-finding; deficits in other cognitive domains should be present2.Visuospatial presentation: the most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia; deficits in other cognitive domains should be present3.Executive dysfunction: the most prominent deficits are impaired reasoning, judgment, and problem-solving; deficits in other cognitive domains should be present3.The diagnosis of probable AD dementia should not be applied when there is evidence of<ol style="list-style-type: none">a.Substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burdenb.Core features of dementia with Lewy bodies other than dementia itselfc.Prominent features of behavioral variant frontotemporal dementiad.Prominent features of semantic variant primary progressive aphasia or nonfluent or agrammatic variant primary progressive aphasiae.Evidence for another concurrent, active neurologic disease, or a nonneurological medical comorbidity or use of medication that could have a substantial effect on cognition
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CHAPTER XXII

NEONATAL HIPOXIC-ISCHEMIC ENCEPHALOPATHY: A UPDATE REVIEW FOR THE CLICIAN

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Neonatal encephalopathy is a heterogeneous clinical syndrome, which was born at 35 weeks of gestation and after, manifested by impaired consciousness or convulsions, characterized by respiratory depression and hypotonia. "Neonatal encephalopathy" has emerged as a preferred term to describe central nervous system dysfunction in the neonatal period. The American College of Obstetricians and Gynecologists (ACOG) defines neonatal encephalopathy as a clinically defined neurological dysfunction syndrome in the first days of life in a baby born at 35 weeks of gestation or beyond, and often respiratory depression, and accompanied by hypotonia (1).

Etiology

Neonatal encephalopathy (NE) can occur for a variety of reasons; birth asphyxia and neonatal hypoxic ischemic encephalopathy (HIE) are responsible for most of these. Due to the natural feature of the neonatal brain and the complexity of the causes of the disease, "neonatal encephalopathy" continues to be used as a more inclusive but

more general term because this cause-effect relationship is not fully understood (1).

Risk factors

Except hypoxia-ischemia, few studies have adequately assessed risk factors for neonatal encephalopathy. Studies evaluating prenatal and obstetric factors usually include symptoms, but do not include pathogenic events that can provide information about the timing of hypoxic-ischemic event. Epidemiological population studies of neonatal encephalopathy typically lack brain Magnetic Resonance Imaging (MRI) data to determine the presence and degree of brain damage and also do not contain information about long-term results.

In a study that investigated cases of neonatal encephalopathy in Australia, 69 per cent of patients had only prenatal risk factors, 25 per cent had both prenatal and intrapartum risk factors, 4 per cent had only intrapartum hypoxia evidence and 2 per cent were not at risk. Therefore, about 70 percent of neonatal encephalopathy cases were found to be associated with risk factors that occurred before the start of birth in (2).

Similarly, in a case control study conducted in the UK, 405 infants with encephalopathy were compared to 239 neurologically normal babies. Overall, 7 percent of cases had only prenatal factors, 20 percent had intrapartum factors, 70 percent had both prenatal and postpartum factors, and 4 percent did not have an identifiable risk factor for the development of neonatal encephalopathy. The different results of these reports suggest that neonatal encephalopathy is due to various causes of (3).

In pathogenesis of hypoxic functional encephalopathy, a number of risk factors have been identified that can be grouped due to antepartum, intrapartum and postpartum causes.

1. Antepartum
 - Maternal
 - Endocrine diseases (diabetes, etc.)
 - Hypertension, Cardiovascular Diseases
 - Epilepsy, Preeclampsia
 - Drug addiction
 - Drugs (lithium, MgSO₄, rezerpin)
 - Last trimester bleeding, severe anemia
 - Age of pregnancy (> 35 years)
 - Multiparite, Severe Infections
 - Fetal

- Prematurity
- Postmaturity
- Macrosomia
- RDS
- Twins, triplets
- Intrauterin growth retardation
- Congenital anomalies
- Fetal infections
- Fetal anemia
- Fetus arrhythmias

2. Intrapartum

- Placental
 - Ablatio placenta
 - Placental insufficiency
 - Umbilical and arterial anomaly
 - Cord anomaly
- Other risk factors
 - Abnormal Arrival (breech delivery, transvers)
 - C-section birth
 - Vacuum / Forceps application
 - Early membrane rupture (EMR)
 - Accelerated birth (<30 min)
 - Long-term birth (> 2 hours)
 - Birth induction
 - Sedation use

3. Postpartum

- Risk factors
 - Serious lung diseases (Meconium aspiration, RDS, pneumonia)
 - Congenital heart disease
 - Sepsis and shock
 - Recurrent apnea
 - Severe congenital anomalies
 - Neuromuscular diseases
 - Prematurity
 - Severe anemia
 - Cardiovascular collapse (sepsis, severe blood loss, adrenal bleeding)

Epidemiology: It is incidence varies depending on the condition defined, but It is seen between 2-9 per 1000 births in different series. The gestation age occurs in 9% of infants under 36 weeks and 0.2-0.9% of older people. The inhibition is high in diabetic or gestational toxin breast feds. The risk of perinatal asphyxia in diabetic mother babies is defined as 27%. The incidence has also increased in infants with developmental retardation of intrauterine, breech delivery birth or postmature infants. According to data released in 2008 by the Turkish Neonatology Association's Hypoxic Ischemic Encephalopathy Working Group, 93 babies at live birth in 19857 were examined under the diagnosis of HIE, the frequency was 2.6 per thousand and 1.2% among patients in intensive care units (4).

Pathogenesis: Perinatal asphyxia is the most important cause of HIE and primary event is the deterioration of pulmonary level ventilation due to insufficient gas change in the placenta or postnatal events. As a result, the change in oxygen and carbon dioxide deteriorates and arterial hypoxia, hypercapnia and acidosis develop. Hypotension and the resulting cerebral blood flow causes an increase in harmful events such as acidosis, inflammatory mediators and the release of stimulating neurotransmitters, release radical formation, calcium accumulation and lipid peroxidation. These biochemicals result in vascular autoregulation loss in cerebral hypoperfusion environment. These "events" result in two-phase energy failure in which reperfusion is followed before the eventual neuronal cell death after initial deterioration in cell metabolism (5-6). Phase one; occurs during reperfusion and reoxygenation; The second phase begins hours later, which can take up to 72 hours. During phase one, asphyxia causes the NAD to quickly turn into NADH. When the energy requirement cannot be met, it shifts from aerobics to anaerobic metabolism, which causes glycolysis to accelerate and lactate production increases. As a result of these events, the accumulation of fatty acids, increase in free oxygen radicals, cell apoptosis and cell deaths are observed. Following acute injury and reciprocity, the brain's oxidative metabolism begins to recover in whole or completely, during which period is called the latent phase. Then there is the secondary deterioration period, which is called a late injury period. When cerebral perfusion and oxygenation become normal, the second stage of damage occurs within 6-48 hours. During this period, neuronal and glial cell deaths occur. Causes slow cell death following reperfusion (7).

Diagnosis: It is difficult to determine whether the acute hypoxic-ischemic event contributes to neonatal encephalopathy because there is no gold standard. Various HIE clinical signs, including low Apgar

scores, low cord pH, neonatal seizure and encephalopathy, are not specific and may occur in the absence of acute hypoxic-ischemic brain injury. The markers that help determine the likelihood that the acute peripartum or intrapartum hypoxic-ischemic event may contribute to the development of neonatal encephalopathy are as follows (1).

➤ Neonatal signs compatible with acute peripartum or intrapartum event:

- Apgar score 5 minutes and 10 minutes <5
- Fetal umbilical cord blood pH <7.0 or base deficiency ≥ 12 mmol / L or both
- Magnetic resonance spectroscopy in accordance with acute brain damage or hypoxia-ischemia seen in brain MRI
- Presence of multiple organ failure consistent with hypoxic ischemic encephalopathy

➤ Factors that contribute in accordance with acute peripartum or intrapartum event:

- Having uterine rupture, ablasio placenta, cord prolapse, maternal hypotension, amnion fluid embolism, maternal hypoxia, maternal cardiovascular collapse, vasa previa or fetomaternal bleeding
- Typical findings in imaging, damage to deep gray ore, cortical damage (border zone)
- Lack of these conditions; abnormal fetal growth, maternal infections, fetomaternal bleeding, neonatal sepsis, chronic placental lesions.

The following tests and research are recommended to evaluate the etiology of neonatal encephalopathy(8).

- Blood samples of the umbilical artery and venous pH and cord to determine the base deficit
- Rough and histological examination of the placenta and umbilical cord may be evidence of a contributing cause such as placental vascular lesion or infection/inflammation or umbilical cord thrombosis
- Full Blood Count should be looked at in terms of possible infection, bleeding and/or platelet
- Arterial blood gases, serum calcium, magnesium, glucose and electrolytes should be evaluated when necessary

- Liver enzymes and serum creatinine should be evaluated to identify whether organ damage is present
 - To exclude sepsis, bacterial blood cultures and viral cultures should be taken if there is a specific concern
 - If there is bleeding to exclude common intravascular coagulopathy, clotting tests such as prothrombin time (PT), partial thromboplastin time (PTT) and D-dimer should be performed
 - Electroencephalography (EEG) to determine whether there is a clinical or electrographic seizure and to evaluate electrical activity, because these findings can affect the treatment and prognosis of neonatal encephalopathy
 - EEG is usually performed on the first day of life (before treatment or during treatment) and EEG monitoring persists for at least 24 hours or longer if there are electrographic seizures. Amplitude integrated EEG is an important diagnostic method that can be diagnosed with perpatient application, which can scan seizure activity in infants with neonatal encephalopathy and provide information about electrical activity of the body
 - Four to seven days of brain MRI. Specific findings in brain MRI may be useful for determining pathogenesis and prognosis of neonatal encephalopathy. Brain CT is not as sensitive as MRI and also has preventable radiation exposure
 - Special tests for congenital metabolism failure, including ammonia, lactate and pyruvate, serum amino acids and organic acids of urine to exclude a metabolic cause of neonatal encephalopathy. Genetic testing if the child shows dysmorphic or congenital abnormalities
 - Since meningitis can mimic the symptoms and symptoms of neonatal encephalopathy, lumbar puncture if the patient has concern for meningitis (e.g. fever, high white cell count, rash, positive blood culture, herpes lesion in the mother and a history of proven infection).

Treatment: Therapeutic hypothermia is a treatment option for newborn encephalopathy (within the first six hours of his life) that meets the default HIE criteria. Treatment of moderate and severe neonatal encephalopathy should be performed in an upper-stage neonatal intensive care unit. The main targets are the treatment of symptoms that develop due to physiological homeostasis and brain damage (9-10).

- Aspects of treatment and supportive care include the following:
 - Ensuring adequate ventilation (hypoxemia or hyperoxia avoidance)

- Maintaining adequate brain and organ perfusion (avoiding systemic hypotension or hypertension, prevention of hyperviscosity)
- Protection of normal metabolic condition (e.g. Normoglycemia, nutritional condition, pH)
- Control of seizures
- Control of brain edema (avoiding excessive fluid loading)

Therapeutic hypothermia: Therapeutic hypothermia, which is maintained for 72 hours at 33 to 35° C (91.4 to 95.0° F) and begins within the first six hours after birth, is the only neuroprotective treatment proven for the treatment of neonatal encephalopathy. Given the data from controlled studies and meta-analyses that benefit from therapeutic hypothermia, hypothermia applies to late preterm infants with term or all criteria of whole body or head cooling (starting from the first six hours of life for treatment) and neonatal encephalopathy (11).

Indications: Eligibility criteria for therapeutic hypothermia are as follows (12).

- Pregnancy age \geq Babies under 36 weeks and \leq 6 hours (although some centers do not have supportive data, they use gestational age between 34 and 35 weeks as an additional criterion)
- Having a cord blood or \leq 7.0 pH or BE: \geq 16 mmol/L in the blood sample taken within the first hour of birth
 - One of the following:
 - ✓ 10 minutes Apgar \leq 5
 - ✓ Ongoing resuscitation at birth (e.g. Cardiopulmonary resuscitation or heart medications) at least 10 minutes
 - Moderate to severe encephalopathy in clinical examination

Therapeutic hypothermia has been shown to only improve the results in infants with moderate to severe encephalopathy. It is not known whether this treatment improves outcomes in infants with lower encephalopathy. Clinical trials use different definitions for moderate and severe encephalopathy. Most centers use a modified Sarnat examination, whether or not additional information about the presence of seizures. Sarnat examination grades the severity of consciousness level, spontaneous activity, tone, posture, reflexes and abnormalities in autonomic function (13).

Hypothermia should be started within the first six hours after birth and should be maintained for 72 hours at the target temperature. Rectal temperature should be kept between 33 and 35 ° C (91.4 to 95.0 °F), and the target temperature should typically be adjusted to 33.5 °C. Head cooling and whole body cooling are seen as having similar safety and effectiveness and the whole body cooling is preferred in most centers in the United States due to ease of application. All body cooling also provides easier access to the scalp for electroencephalography (EEG) monitoring. If the baby needs to be transported to a private center, cooling can be initiated during the newborn transplant and sustainable (14-15).

Table 1. Severity of neonatal encephalopathy, based on modified sarnat Scoring

Category	Normal	Mild abnormality	Moderate abnormality	Severe abnormality	Unable to assess
1. Level of consciousness	Normal	Hyper alert or irritable	Lethargic or poorly responsive	Minimal or no responsiveness	NA
2. Spontaneous activity	Normal	Slightly decreased	Decreased	Absent	NA
3. Posture	Normal	Mild distal flexion	Mild distal flexion	Decerebrate	NA
4. Tons	Normal	Hypertonic	Hypertonic	Flaccid	NA
5. Primitive reflexes a. Suck b. Moro	Normal Normal	NA Low threshold to elicit	Weak or bite Weak or incomplete	Absent Absent	Unable to assess Unable to assess
6. Autonomic a. Pupils b. Respiration	Normal Normal	NA NA	Constricted Periodic breathing	Dilate and either fixed or sluggishly reactive : asymmetric Intubated and ventilated	NA NA

Encephalopathy: at least three of six criteria present. NA: not applicable. Severe : more symptoms in the severe than moderate column. Moderate: more symptoms in the moderate column. Mild: more symptoms in the mild column. If encephalopathy signs are equally distributed between mild, moderate, and severe categories, the severity of encephalopathy is based upon level of consciousness

Exclusion criteria for treatment:

- Infants who have passed more than 6 hours (may vary by consultation decision)
- Infants under 34 weeks

- Babies under 2000 g is a limit of 1800 g for CoolCap
- Documents that are not sure about the diagnosis or other conditions that may cause neonatal encephalopathy are documented, congenital metabolic diseases, family history with sibling history (index case), and other diseases that may occur with early encephalopathy (may change by consultant decision)
 - Babies who are thought to be not benefiting from treatment, very severe or common parenchymal cranial bleeding, very severe life-threatening coagulopathy
 - Maternal chorioamnionitis, trisomy, 13.18 or multiple organ anomaly

Side effects: Therapeutic hypothermia is generally well tolerated, but in randomized studies it has been reported that short-term side effects cause sinus bradycardia and plateletopenia (16).Hypercalcemia or non-hypercalcemic subcutaneous fat necrosis was observed as a rare complication (17).

Supportive treatment: In addition to therapeutic hypothermia treatment, the recommended supportive treatment management includes the following recommendations:

- Seizures are treated with phenobarbital, lorazepam, fosphenytoin or levetiracetam. Optimal therapeutic agent and treatment time not adequately evaluated
- High frequency ventilation, nitric oxide or extracorporeal membrane oxygenation are used for infants with continuous pulmonary hypertension to maintain oxygenation
- Inotropic agents are used as necessary to maintain blood pressure and adequate cerebral perfusion. However, systemic hypertension and volume overload, which can worsen cerebral edema, should be avoided
- If a metabolic disorder is suspected, early treatment may be important. Nutrition should be stopped, acidosis and hypoglycemia should be corrected, and after consultation with a genetic or pediatric metabolism specialist, specific treatment such as vitamin supplementation or hemodialysis should be considered.

Prognosis: The possibility and scope of brain damage is associated with the severity of encephalopathy. While most babies with mild encephalopathy develop normally, long-term neurological morbidity is more likely to develop in infants with moderate to severe

encephalopathy. Severe brain MRI abnormalities are usually associated with pronounced electroencephalogram (EEG) abnormalities and poor results(18).

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CHAPTER XXIII

**METABOLISM-INHIBITING AGENTS:
TISSUE FIXATIVES**

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Introduction

Histology enables to analyse structural characteristics of cells and tissues with a light or electron microscope after some special laboratory treatments on them. Histological analyses are carried out on many materials including organic ones such as live, dead, diseased or normal tissues, diseased or normal body fluids (teardrops, saliva, etc.) or materials (stools, etc.), and inorganic ones such as soil or stone. Although histology uses certain standard procedures, the time and solutions used can vary in practice depending on tissue structure and size, ambient temperature, and researcher experience (Junqueira, 1992; Carson, 2007).

There are some basic stages used in histology including resection, fixation, washing, dehydration, clearing, embedding, blocking, sectioning, staining and mounting. Any error made in these successive stages will eventually affect the acquisition of a proper image during microscopic analysis (Carson, 2007; Kiernan, 2008; Grizzle, 2008).

Microscopic analyses can be made on live or dead samples. Live tissues should be analysed in a short time as they decay rapidly. A live analysis is made either directly with a phase-contrast microscope or with a light microscope using vital or supravital stains. Special vital stains like India ink and trypan blue are used in live analysis methods. Supravital staining (neutral red, cresyl violet, etc.), on the other hand, is carried out by applying a dyestuff into the medium containing cells extracted from an organism or cells reproduced like a tissue culture. Analysis of dead tissues, fluids or matters is carried out directly with a light microscope on tissue sections fixed physically (freezing, drying, boiling) or chemically (formalin, Bouin's, alcohol, mercury) or stained, or on non-stained preparations such as stools. Fixation by drying is used in smearing of blood and bone marrow. Fixation by freezing minimises loss of soluble matters (lipids, enzymes), relocation of cellular structures, chemical changes, and protein breakdown. Although fixation by freezing is seldom preferred for histological assessments of cellular structures, it is advantageous in terms of offering rapid diagnosis. Chemical fixation is the most used method. In this method, samples taken are directly immersed in a fixation solution or, while an animal is under anaesthesia, an isotonic solution is perfused through the left ventricle followed by the fixation solution, and after these solutions come out through the right atrium, the animal is killed, and the immersion technique is applied on the tissues taken. Ultrastructural analyses are carried out on an electron microscope after treatments using various solutions (Junqueira, 1992; Kopturk et al., 1999; Carson, 2007; Grizzle, 2008; Koptagel, 2008).

Fixation

When a living being dies, its cells and tissues are slowly autolysed as they contain various catabolic enzymes. This is called post-mortem degeneration. These changes are also observed on live pieces of tissue resected by an operation. A careful and good fixation is essential for avoiding errors in histopathological assessments. The primary principle for making histological preparations of living beings is to keep cells and tissues as similar as possible to those of the live being. For this purpose, the first target should be to prevent any autolysis in the cells. The purpose of fixation is to store without degeneration a material taken from a living being. Tissues disintegrated or taken out of an organism will soon change and degrade unless special conditions are met. The organelles taking charge in this degeneration are

lysosomes. In living cell lysosomes, there is an osmotic orientation from the cytosol to lysosomes. Therefore, lysosomal hydrolytic enzymes cannot pass into the cytosol. However, under a pathological condition or after death, membrane permeability increases, and other enzymes passing into the cytosol subject cells to autolysis. Therefore, pieces of tissue and organ that can be taken before these occurrences possess a histological value (Dogan, 2005; Carson, 2007; Pabuccuoglu, 2010; Karaman, 2011).

Fixation is a chemical production procedure carried out to prevent autolysis of any piece of tissue or organ resected for a histopathological analysis in the time period from resection to analysis, and to ensure that it remains as similar as possible to its condition in a living organism. Fixation is the primary step for a microscopic analysis of any tissue, and it influences any subsequent stage (Kiernan, 2008). The purpose of fixation is to keep morphological characteristics of tissues as close to their ordinary situation as possible (Fox & Johnson, 1985; Arnold et al., 1996). Fixation also aims to stop metabolism (Braet & Ratinac, 2007), fix the structure of organelles and molecules (Rockey et al., 2009), and obtain a more durable and accessible material for subsequent stages. Factors influencing fixation include pH, temperature, concentration, osmolarity, fixation time, and tissue size. It was also determined that tissue staining also involves a variation depending on the concentration of the fixative used (Grizzle, 2008).

One of the most important results of fixation is coagulation of tissue proteins and building blocks. Thus, losses and diffusions are minimised during follow-up. Fixation also has an important effect in the staining of tissues, and often makes movements of dyestuff easier. Sometimes, a fixation agent might act as a direct link between a special tissue component and the tissue, and then the fixative functions as a mordant. Treatment of a tissue with potassium dichromate for visualising myelin with haematoxylin is an example. Another important characteristic of fixatives is that they enable to take thin sections from tissue pieces easily because they harden tissues (Carson, 2007; Koptagel, 2008; Karaman, 2011).

The Tissue Component-Fixative Interaction

Proteins and fixation solutions establish a cross-link and form a gel-like structure whereby *in vivo* relationships are preserved.

Fixation solutions transform soluble proteins into insoluble proteins, and thus provide a mechanical strength that allows various procedures. During fixation, physicochemical changes occur in the deoxyribonucleic acid (DNA) and the ribonucleic acid (RNA). Ethanol and methanol are widely used for the fixation of nucleic acid, whereby a major part of the DNA collapses. Most lipids are separated from the tissue in classical histopathological analyses. A cryostat or the frozen section procedure should be used when visualising lipids. Formaldehyde reacts with unsaturated fatty acids with double bond. Mercuric chloride special reacts with complex unsaturated lipids and also with the lipids called plasmalogen acetal phosphatides. For carbohydrates, tannic acid and cetylpyridinium can be used for ultrastructural reasons. For glycogen identification, fixatives containing alcohol can be recommended. Water-containing mucous substances such as glycosaminoglycans are broken down in the process (Kokturk et al., 1999; Dogan, 2005; Carson, 2007; Pabuccuoglu, 2010).

Fixation solutions

Systematic research on fixation solutions began in the 19th century. Fixation solutions very similar to each other were produced, resulting in a chaos in this field. In the end of the 1950s, Baker brought this chaos into an end by making it a tradition to name mixtures after their first discoverers (like Bouin's, Helly's, Carnoy's solution). He made a classification consisting of two groups including coagulant and non-coagulant fixation solutions (Baker, 1958; Kokturk et al., 1999). Agents used for fixation are called fixatives. The classification used for these agents in the present:

1. Aldehydes (glutaraldehyde, formaldehyde, glyoxal, acrolein)
2. Oxidisers (osmium tetroxide, potassium dichromate, potassium permanganate)
3. Protein denaturants (methanol, ethanol, acetic acid)
4. Other corresponding agents (carbodiimide)
5. Physical agents (temperature, microwave)
6. Others (mercuric chloride, picric acid) (Hopwood, 1996).

Glutaraldehyde (C₅H₈O₂)

Glutaraldehyde is a dialdehyde widely used for fixation with a molecular weight tripling that of formaldehyde. It provides fixation by cross-bonding. It is assumed to be superior to other aldehydes in terms

of preservation of a thin structure. It is routinely utilised at concentrations of 2.5 to 4%. Glutaraldehyde with cacodylate buffer containing arsenic prevents bacterial growth. However, the one with phosphate buffer is most preferred as it is safer although it causes artefacts. Glutaraldehyde's penetration is slower compared to formaldehyde. It is very useful for electron microscopy and enzyme histochemistry. It is the standard fixative for electron microscopy, and is used as the first fixative before osmium tetroxide (OsO₄) (Junqueira, 1992; Betancor et al., 2006; Koptagel, 2008; Lopez-Gallego, Guisan & Betancor, 2013).

Formaldehyde (CH₂O)

As the simplest member of the organic molecule class called aldehydes, formaldehyde tends to polymerise in a solution. Formalin is a solution of 40% formaldehyde in water. It does not precipitate proteins, and partially precipitates other cellular components. It does not harden albumin, keeps it soluble, and prevents hardening with alcohols in subsequent dehydration. It neither preserves nor damages fats. It is a good fixative for complex lipids but not effective with neutral lipids. Although it is not a good fixative for carbohydrates, it preserves glycogen by preventing it from easily dissolving. While it is suggested as an ideal fixative, it can sometimes cause nuclear swelling. This effect is eliminated if it is post-fixed with acetic acid formalin (Koptagel, 2008; Carson, 2007). The standard fixative used in laboratories is 10% formalin obtained by mixing 1 volume of formalin with 9 volumes of water. Thus, 10% formalin is a solution of 4% formaldehyde in water. Since polymerisation begins to become evident with fixation, molecular weight of formaldehyde also increases. As molecular weight is inversely proportional to penetration rate, manufacturers add methanol into formalin solutions to prevent polymerisation (Titford & Horenstein, 2005; Karaman, 2011; Ganjeli & Ganjeli, 2013).

Formaldehyde is a non-coagulant fixative. When it chemically bonds to a tissue, it does not lead to the formation of a gel-like matrix that would prevent the penetration of a subsequent marker. The primary tissue parts to which formaldehyde binds are reactive hydrogen atoms found in amino acids. It mostly interacts with the N-terminal of proteins, and establishes methylene bridges between protein molecules (H-C-H). Also binding to the sulfhydryl groups in cysteines, it forms cross-bonds that further stabilises proteins.

Although these bridges and cross-bonds stabilise and preserve tissues, they necessitate the step of epitope retrieval in various immunohistochemical procedures (Kothmaier et al., 2011; Karaman, 2011; Robert & Gregory, 2015). The most used histological fixative is 10% formal-saline. It hardens tissues moderately. Thin blocks can be fixed in 10% formal-saline in 24 to 48 hours, but a longer duration, which might cause immunoreactivity, does not make sectioning infeasible. In an alcohol-formalin solution, thin sections can be fixed in 2 to 4 hours. An alcohol-formalin solution is especially used for visualising polysaccharides. Many special dyestuff and immunohistochemistry can be applied to tissues fixed in formalin. However, as the fixation occurs by a cross-bonding of proteins, antigenicity is diminished by time. Efforts will be taken to eliminate this disadvantage with methods for releasing antigens. Formalin is not suitable for fixing tissues to be analysed with an electron microscope. Since an extended formalin fixation will result in excessive cross-bonds, it will adversely affect immunohistochemical analyses. Because formalin will gain an acidic characteristic by time, buffer systems (phosphate, calcium carbonate, magnesium carbonate, TRIS) should be used for controlling pH, which should be between 6 to 8. Ten percent formalin provides 2 to 3 mm tissue penetration and fixation in 24 hours. The fixation, however, depends on concentration and temperature. For shortening the duration, it can be kept in a drying oven with a fixed temperature around 60°C, or irradiated in a microwave oven with a maximum temperature of 65°C. However, it should be remembered that high temperatures can also accelerate autolysis (Koptagel, 2008; Pabuccuoglu, 2010; Karaman, 2011; Kothmaier et al., 2011; Ganjeli & Ganjeli, 2013; Robert & Gregory, 2015).

Formulation

1. 10% formalin solution:

40% formalin	100 ml
Distilled water	900 ml

2. Neutral buffered formalin (NTF):

40% formalin	100 ml
Distilled water	900 ml

Sodium phosphate, monobasic, (NaH_2PO_4) 4 g

Sodium phosphate, dibasic, (Na_2HPO_4) 6.5 g

3. 10% formal-saline solution:

40% formalin	100 ml
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Distilled water	900 ml
NaCl	8.5 g
4. Alcohol-formalin solution:	
Neutral formalin	10 cc
95% alcohol	90 cc

Acetic acid (CH₃CO₂H)

Acetic acid is rarely used alone, and it is insufficient in terms of its likely results. It penetrates fast and well but leads to the lysis of erythrocytes. It swells collagen fibrils, precipitates nucleoproteins, and makes a dissolving effect on some cytoplasmic granules. Acetic acid is usually included in the composition of other fixation liquids (Koptagel, 2008; Ercakir, 2000).

Trichloroacetic acid (C₂HCl₃O₂)

Currently, it is not used as a fixation solution. It well preserves sulphur-containing amino acids such as cystine, cysteine and methionine. It is used as a decalcification agent (Koptagel, 2008).

Ethyl Alcohol (C₂H₅OH)

Ethyl alcohol (70-100%) is rarely used as a primary fixative. Although it is useful for glycogen preservation and for some history chemical studies, it has many disadvantages. By extracting water from tissues, it leads to protein denaturation, tissue hardening and shrinkage, and cellular distortion. It also should not be used for lipid studies or with myelin dyestuff as it can result in fat melting. If it is to be used as a fixative, the pieces to be immersed in it should be 5 mm thick. Pieces with 3 to 4 mm thickness can be fixed in 3 to 4 hours (Pabuccuoglu, 2010; Ercakir, 2000).

Carnoy's fixative

Carnoy's is a fast-penetrating and moving fixative. It is used for rapid fixation and partial dehydration of tissues for urgent diagnoses. Glacial acetic acid consists of absolute ethanol and chloroform. Tissues not thicker than 3 mm should be fixed for 30 to 90 minutes and then transferred into 95-100% alcohol. It is suitable for chromosome studies but it results in lysis and excessive shrinkage of erythrocytes. Collagen is not well preserved, and acid fast bacilli are not stained. Acid-soluble cellular granules and pigments can disappear (Kokturk et al., 1999; Koptagel, 2008; Pabuccuoglu, 2010).

Formulation	
Absolute alcohol	60 cc
Chloroform	30 cc
Acetic acid	10 cc

Acetone (C₃H₆O)

It is used for rapid diagnosis. It is especially preferred for history chemical studies on such enzymes as lipases and phosphatases. It causes loss of nuclear details, and shrinkage of cytoplasm. It does not preserve glycogen well. Rather than being used as a routine fixative, it is included in the composition of other fixation solutions (Koptagel, 2008; Pabuccuoglu, 2010).

Osmic acid (OsO₄)

Osmic acid is a pale yellow crystalline contained in 1 g ampoules. Both the crystal and its solution have an irritant and hazardous fume. Protective glasses should be used when working with it. Osmic acid is easily reduced to grey-black lower oxide by light, temperature or organic factors, and once used, the solution should not be put back into its stock bottle. An effective way for preventing reduction is to add mercuric chloride saturated in a drop of water into each 10 ml solution. Its penetration is poor. It is usually used along with glutaraldehyde for double fixation. While it has little use in general histopathology studies, it is widely used for electron microscopy (Kokturk et al., 1999; Pabuccuoglu, 2010).

Bouin's fixative

It is formed of picric acid, formaldehyde and acetic acid. It is preferred for small biopsies (usually testicles). It provides a sharp haematoxylin-eosin staining. While it gives adipose tissues a yellow colour, lymph nodes are visualised as white, and it thusly enables to find smaller lymph nodes. As it stains yellow for all materials, it becomes difficult to distinguish microscopic details. The yellow colour is significantly eliminated by 50% and 70% alcohol series. Picric acid can lead to DNA degradation and erythrocyte lysis. Fixation for more than 18 hours can make tissues fragile (Eltoum et al., 2001; Koptagel, 2008; Pabuccuoglu, 2010).

Formulation	
Picric acid saturated in distilled water	1500 ml
40% formalin	500 ml

Glacial acetic acid 100 ml

Hollande's fixative

It is formed of picric acid, formalin, acetic acid and copper acetate. It is a modification of Bouin's solution, and involves similar disadvantages. It is used in the fixation of small biopsies primarily including the lymphoid system and gastrointestinal tract. Fixation time is 4 to 18 hours (Leong, 1994; Eltoum et al., 2001; Pabuccuoglu, 2010; Karaman, 2011).

Formulation

Copper acetate	25 g
Picric acid	40 g
40% formaldehyde	100 ml
Acetic acid	15 ml
Distilled water	1000 ml

B5 fixative

It consists of mercuric chloride, sodium acetate and formalin. It is used for fixation of any tissue with suspected lymphoproliferative disorders such as lymph nodes and the spleen. It offers not only excellent cytological details but also a high-level antigen preservation for lymphoid determinants. However, it needs to be prepared freshly. Because excessive fixation results in tissue hardening and fragility, after a tissue is kept in this fixative for 3 to 5 hours, it should be taken into formalin. It can cause problems in preservation of some antigens like keratin. B5 post-fixation can be applied to tissues fixed in formalin (Karaman, 2011; Pabuccuoglu, 2010).

Formulation

Stock solution

Mercuric chloride	12 g	
Sodium acetate anhydrous	2.5 g	
Distilled water		200 ml

Working solution, prepare immediately before use

B-5 stock solution	20 ml
40% formaldehyde	2 ml

Zenker's fixative

It consists of potassium dichromate, mercuric chloride and glacial acetic acid. It is used especially for its benefits on cytoplasmic and fibril dyes. It should be used as a stock solution without acetic acid,

and acetic acid should be added immediately before the work. It can be used for bone marrow biopsies. Fixation time is between 4 and 24 hours. Its erythrocyte preservation is poor. For removing dichromate deposits after fixation, it should be washed in water, and iodine treatment is necessary for removing mercury before routine staining. It is not favourable for molecular analysis and immunohistochemistry (Leong, 1994; Koptagel, 2008; Pabuccuoglu, 2010).

Formulation

Mercuric chloride	5 g
Potassium dichromate	2.5 g
Sodium sulphate	1 g
Distilled water	950 ml
Glacial acetic acid	5 cc (Add immediately before use)

Helly's fixative (Zenker-Formal)

Helly's fixative is an accident fixative despite the fact that it contains an oxidising agent (potassium dichromate) and a reducing agent (formalin). It is especially preferred for bone marrow, spleen, lymph nodes, pituitary gland and pancreas. Blocks should be fixed for 5 to 25 hours, and the mercury pigment should be removed. It can also be applied as a second fixative after 10% formal-saline (Hopwood, 1996; Koptagel, 2008; Pabuccuoglu, 2010).

Formulation

Mercuric chloride	50 gr
Potassium dichromate	25 gr
Sodium sulphate	10 gr
Distilled water	1000 ml
40% formaldehyde	50 ml (Add immediately before use)

Mercuric chloride (HgCl₂)

It is a strong protein precipitant. It rapidly penetrates and hardens tissues. It fixes both the nucleus and the cytoplasm well. It is utilised in mixtures with other fixatives. However, it forms the brown-black granular material called "mercury pigment" that spreads around a tissue uniformly. This material is soluble in alcoholic iodine, and it does not affect any subsequent staining. These granules can be removed from the blocks by adding 0.25-0.5% iodine in 70 to 80% alcohol during dehydration (Hopwood, 1996; Kiernan, 2008; Koptagel, 2008).

Mercuric Chloride-Formalin (Formal-Sublimate)

It is an excellent microanatomic fixative. It shrinks tissues without the distortion observed in formal-saline. It provides a very bright staining with acid dyes, and preserves the cytoplasm effectively. Blocks are fixed in 12 to 24 hours. It is useful as a second fixative after a formal-saline fixation. Being expensive and corrosive for metals are its disadvantages. After fixation, tissues should be taken into 70 to 90% alcohol in order to remove the mercury pigment (Fox & Johnson 1985; Kokturk et al., 1999; Grizzle, 2008; Koptagel, 2008).

Formulation

Water-saturated mercuric chloride	900 cc
Formalin	100 cc

Lison Vokaer fixative (for glycogen)

It is a very good fixative for preserving glycogen. It fixes small pieces in 6 to 10 hours in a fridge. As glycogen is water-soluble, it should be treated with absolute alcohol and embedding immediately after fixation (Carson, 2007; Koptagel, 2008).

Formulation

Picric acid saturated in 96% alcohol	85 ml
40% formalin	10 ml
Glacial acetic acid	5 ml

Clarke's fixative

Clarke's fixative consists of a mixture of 3 parts of absolute ethanol and one part of acetic acid. It preserves nucleic acids well but not lipids. It precipitates alcohol proteins, shrinks cells, and is a very fast dehydrator. With acetic acid, it swells cells by balancing the effects of alcohol. It is a good fixative for chromatin staining. Tissues can be taken into 95% alcohol after fixation. With Clarke's, a fixation time of 4 to 5 hours is sufficient (Kiernan, 2008; Grizzle, 2008).

Formulation

Ethanol (absolute)	75 ml
Glacial acetic acid	25 ml

Susa's fixative

It is convenient for biopsy materials. After Susa's, tissues are weakly stained with Weigert's elastic fibril dye. After a 5 to 24-hour fixation, blocks are directly transferred into 95% ethanol. Swelling is

observed in collagen fibrils after transferred into more aqueous solutions (Hopwood, 1996; Koptagel, 2008).

Formulation

Mercuric chloride	45 gr
Sodium chloride	5 gr
Trichloroacetic acid	20 gr
Acetic acid	40 ml
Formalin	200 ml
Distilled water	800 ml

Sanfelice's fixative

It is a good fixative for chromosomes and mitotic figures. Pieces not bigger than 3 to 4 mm should be fixed for 12 to 24 hours, and then washed in flowing water (Kiernan, 2008; Koptagel, 2008).

Formulation

Solution A: 128 ml of formalin + 16 ml of acetic acid

Solution B: 100 ml of 1% chromic acid

Mixture: 9 ml of solution A + 16 ml of solution B (prepared immediately before use)

Flemming's fixative

It provides a good staining of myelin by using it as the second fixative after formalin fixation. Small pieces 2 mm thick should be fixed for 12 to 24 hours, and then washed in flowing water. Because of its osmic acid content, lipids turn black. After this fixative, haematoxylin nuclear stains cannot be taken easily; safranin should be used instead. It does not equally penetrate tissues (Grizzle, 2008; Koptagel, 2008; Pabuccuoglu, 2010).

Formulation

1% chromic acid	15 ml
2% osmic acid	4 ml
Acetic acid	1 ml

Orth's fixative

Orth's fixative is useful for cytological structures like mitochondria. Blocks should be fixed for 36 to 48 hours before washing with tap water or before chromation with 2.5% potassium dichromate in distilled water. Long treatment with potassium dichromate can cause tissue fragility and difficulty in obtaining

sections from paraffin blocks (Kiernan, 2008; Grizzle, 2008; Koptagel, 2008).

Formulation

Formalin	10 ml
Muller's fluid (2.5 g of potassium dichromate + 1 g of sodium sulphate + 100 ml of distilled water)	100 ml

Discussion and Conclusion

Points to consider as regards practical fixative applications include a researcher's original purpose, tissue size, type and freshness, the sectioning process and the staining technique intended to be applied. No single fixative is ideal for all tissues and techniques.

In a study, Gun et al. found that Clarke's was the best fixative for all regions of the kidney and stomach, and for lamina epithelialis, lamina propria and tunica muscularis in the duodenum, Bouin's for the spleen, and alcohol-formalin for the liver. They also determined separations and disintegration in tissues fixed with Schaudinn's solution. They reported that Regaud and B5 solutions were not suitable for the spleen, Bouin's and 10% formalin solutions for the duodenum, Orth's solution for the liver, and Carnoy's, Zenker's and alcohol-formalin solutions for kidney tissues (Gun, Demirbag & Çinar, 2011). Kokterk et al. reported that 0.1 M phosphate buffered 10% formaldehyde, 0.1 M phosphate buffered glutaraldehyde, 0.1 M cacodylate buffered paraformaldehyde and alcohol-formalin fixation solutions resulted in disintegrations in the tubuli and Bowman's capsule in rat renal tissues, but that they did not observe the same effect with 10% formalin (Kokterk et al., 1999). Another study reported that 48 hours in neutral formalin and 24 hours in Bouin's were suitable periods for any histopathological studies with the pancreas (Öztürk et al., 2002). In a study about the influence of cryopreservation on sperm DNA, the results with acridine orange staining showed that Carnoy's was the best fixative to be utilised (Chohan, Griffin & Carrell, 2004). In another study on testicle histopathology and immunohistochemistry, Bouin's solution produced better results compared to 10% formalin solution (Nur, Nazli & Yildiz, 2014).

Until now, various fixatives have been produced with different structures and each superior to others in one or more aspects. Considering fixation purposes, it is impossible to mention a single

perfect fixative which can completely fulfil all purposes. However, taking study purpose, tissue characteristics and staining characteristics into account, it is extremely important to work with the most suitable one, and to prevent or minimise possible artefacts. In addition to the identification of a suitable fixation solution, it is also essential that a researcher possesses sufficient knowledge and experience in order for study results to be relevant. A smooth and near excellent application can be mentioned only when all of these conditions are met.

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