ACADEMIC STUDIES IN HEALTH SCIENCES-2019/2

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Cetinje 2019

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PREFACE

The book “Academic Studies in Health Sciences” 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 dentistry, veterinary medicine, medical 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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MULTI DISCIPLINARY HEALTH SCIENCE

THE PROBLEM WITH THE AGE OF TECHNOLOGY: NOMOPHOBIA

Canan BİRİMOĞLU OKUYAN[*]& Süreyya NUR[**]

Introduction

Nomophobia (no mobile phone phobia) is defined as the fear of being away from one's cell phones or not being able to communicate via mobile phone (1, 2, 3). It first became prominent in England with a study (4). This study revealed the symptoms of nomophobia such as using mobile phones all the time and spending most of the time on the phone, feeling uncomfortable when s/he is away from mobile phones, checking the phone for notifications, sleeping with the phone (4, 5). These symptoms indicate that mobile phone usage causes health problems.

One of the groups that use mobile phones the most is university students (6). According to the study of Yıldırım in 2014, university students who are between 18-24 age range use smartphones excessively. Therefore, this group is considered as a risk factor (2, 5, 7, 8, 9). Although there have been many studies about smartphone usage, there have not been enough studies about nomophobia of university students (10). Thus, the study group of the present study consists of university students.

1.The Concept of Mobile Phone

Mobile phones are devices that can be carried around and provide communication via radio stations.

Cell phones are the most practical and preferred mobile devices. Cell phones have been turned into smartphones with the addition of computer features.

Wireless communication was first developed in 1985 (11). Nowadays, there are features like receiving and sending e-mails, accessibility to social media accounts, online shopping, and banking operations (12). These features have increased the number of addicts, especially in the young population.

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2. Mobile Phone Addiction

With the developments in technology, the functions of mobile phones increase together with the rate of use (9).

Smartphones bring various problems as they are becoming more involved in their daily lives. Even though there is no clear definition for it in the field of psychiatry, mobile phone addiction is a condition develops based on the frequency of use of smartphones and has been the topic of research for some time (13). In a study about smartphones, it is stated that smartphones are the latest evolution of 21st-century technology (14).

In a study conducted in Turkey, it was revealed that the majority of the people (92%) owned smartphones. Another study in 2015 found that this rate has increased. Therefore, the increased rate of mobile phone usage implies the number of time spent on the phone. Another study (79% and 72% respectively) it was determined that individuals check their phones 15 minutes after waking up and 15 minutes before sleep (15). Also, visual communication in mobile phones popularize these devices and cause them to have an impact on the daily lives of the individuals (16).

According to the "Digital in 2017 Global Overview" report published by We Are Social and Hootsuite there are more than 4 billion mobile phone users worldwide. 2.5 billion of them are active social users. In Turkey, it was found that the number of active social mobile phone users is 42 million (17). In terms of the usage rate of mobile phone applications, the most frequently used applications at the beginning of 2017 are social media applications (18). The same year, Turkey ranked the second in Twitter usage, the third in Facebook and the fourth in Youtube usage (19). The addiction increases since it is easily accessible to social media platforms that support and meet social needs. Therefore, most of the people obsessively check their Facebook and Twitter accounts day and night. This creates pressure for checking social media activities (20). This pressure encourages people to stay connected with social media. Moreover, primarily because of economic reasons, company owners use various techniques to make sharing more and more accessible by developing notification features of the applications. In this regard, technology addiction has become less controllable since computer-assisted technology has become more fragile (20) Furthermore, peoples' need for staying connected to social media causes them to control the environmental factors less creating problems such as violation of privacy and exploitation of digital labor. Addiction to smartphones cannot be considered independent of the ability of smartphones to connect to networks anytime and anywhere. Also, human-computer (human-smartphone) interaction constitutes an indirect aspect of addiction. The individual connects to a personalized network via a smartphone while interacting with a

technological tool. Two of Sherry Turkle's findings on this interaction are particularly important (20).

3. Dangers of Mobile Phone Usage

The radiation around us is generally divided into two groups as ionizing and non-ionizing radiation. Ionizing radiation can be given as examples of X-rays used for therapeutic and diagnostic purposes, and they have carcinogenic effects. The radiation generated by EM (electromagnetic) waves takes place in the non-ionized group, and its effect is still a research subject (21).

The health effects of electromagnetic fields are divided into thermal and non-thermal effects. Thermal effects are modeled by the so-called Specific Absorption Rate (W / kg). Non-thermal effects are biological, genetic, psychological, and so on. SAR, which is a primary parameter, is not easily measurable but can be obtained by equivalent models in specialized laboratories or by computer simulations. Therefore, electric field strength (E – V / m), a derived parameter, is used. The radio stations are measured accordingly and checked against specified limit values. According to the standards prepared by ICNIRP (International Committee on Non-Ionizing Radiation Protection) for mobile phones, the limit values are determined as 42V / m at 900 MHz and 59 V / m at 1800 MHz for the places people have been in the last 24 hours. Like the US and many European countries, Turkey has adopted these limit values as well. The measurements showed that the limit values could be reduced up to 4-6 V / m without compromising communication quality. The latest regulation of the ICTA (formerly the Telecom Authority, the new Information Technologies Authority) on the subject (Regulation on the Design, Installation, and Sharing of Cellular System Antenna Facilities) was published in the Official Gazette dated 6 December 2016 and numbered 29910 (22) although the directive states that the limit value is 10 V / m at 900 MHz and 15 V / m at 1800 MHz, this is not the general limit value, but the permissible limit value per operator (23).

Turkey met the mobile phone in the mid-1990s, and a few years, the use of it began to increase rapidly in a few years. In the last 20 years, radiofrequency waves emitted from mobile phones have been increasing, and the harmful effects of electromagnetic fields (EMA) on human health have become the subject of much debate. A study has revealed that these waves are harmful to human health, and it may have some side effects on the neuroendocrine system. The period of one second of the EM wave is one hertz (Hz) (24).

Mann et al. found a temporary increase in cortisol levels in individuals within the first hour of EMA (25). According to another study on experimental animals, corticoid levels were higher in experimental animals

exposed to 50 Hz magnetic field compared to control animals (26). Similarly, Arnetz and colleagues found that EM waves emitted from the computer screen significantly increased ACTH levels in their study on office workers (27). Cell phones with 900 MHz EMA, which are widely used, affect the cortex of the adrenal gland, increasing cortisol, a stress hormone, and also reducing testosterone hormone by affecting testes that are rapidly affected by external influences. These two hormones are essential hormones for human health.

Increased EM pollution increases the risk of exposure of living organisms. This field requires long-term interdisciplinary studies. The continuation of interdisciplinary studies on this subject has brought a particular case to the subject. As in any other country in the world, in Turkey, the mean age of cell phone users is quite low as well. More recently, the risks of using mobile phones for young people under the age of sixteen and younger children are being emphasized.

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DENTISTRY STUDIES

THE EFFECT OF PERIODONTAL TREATMENT ON ADVERSE PREGNANCY OUTCOMES BEFORE, DURING AND AFTER PREGNANCY

Ebru SAĞLAM*

Introduction

During pregnancy immunological modifications increase mother's susceptibility to diseases; such as diabetes mellitus (DM), hypertension and periodontal disease (PD) (Armitage, 2013). Also periodontal infection sourced by periodontal disease (PD) may cause adverse pregnancy outcomes (APO) such as gestational diabetes mellitus (GDM), pregnancy hypertension (PH), preeclampsia (PE), preterm birth (PTB), low birth weight (LBW) and fetal loss (Armitage, 2013; Boggess , 2008). It can be said that there is a bidirectional relationship between PD and pregnancy. In this review we aimed to evaluate this bidirectional relationship with current scientific evidence.

Immunological, Microbiological and Physiological Changes in Pregnancy Related With Periodontal Disease

During pregnancy for surviving of fetus, maternal immune system is suppressed. In this process stimulated Th2 cells activate cytokines, such as interleukin-4, interleukin-5, interleukin-10, and suppress cell mediated immune response. Th1 cells secrete cytokines, such as interleukin-2 (IL-2), interferon-c (INF-c), tumor necrosis factor-β (TNF-β) and stimulate cellular immunity. CD25+ CD4+ T-regulatory cells inhibit antigen-specific immune responses which are considerable for maternal immunological tolerance in the presence of fetal antigens. Additionally during pregnancy progresses, amniotic fluid levels of prostaglandin E_2 and inflammatory cytokines, such as tumor necrosis factor -α and interleukin–1 β (IL-1β) increase constantly, until a critical threshold level and overcoming of this level can stimulate rupture of the amniotic sac membranes, cause of uterine contraction, cervical dilation and delivery (Haram, 2003; Madianos, 2013). This signaling process presents a triggering mechanism that can be changed by external stimuli including infection and inflammatory stressors (Armitage, 2013; Boggess , 2008; Madianos, 2013). Also immunosuppressant condition of pregnants can cause higher susceptibility, thus infections induced by some viruses,

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chronic autoimmune diseases and other chronic diseases such as PD; gingival inflammation (Armitage, 2013; Kaja & Watanabe, 2005) or periodontitis (Cruz & Martos, 2010) can develop.

Periodontal disease is defined as a chronic destructive inflammatory condition of periodontal tissues and mostly caused by dental plaque, in which pathogenic oral microorganisms are present. When the inflammation is restricted with soft tissue, it is defined as gingivitis. When gingivitis is not treated, periodontitis may occurs which is related with loss of bone and connective tissue around teeth (Kinane, 2001). The microflora which are responsible pathogenesis of PD is heterogeneous and consist of anaerobic and microaerophilic Gram-negative bacteria in the biofilm. The most important bacteria in this process are *Porphyromonas gingivalis (Pg), Tannerella forsythia (Tf), Aggregatibacter actinomycetemcomitans (Aa), Treponema denticola (Td), Fusobacterium nucleatum (Fn) ssp*, and *Prevotella intermedia (Pi)* (Moura da Silva, 2012). Gram-negative anaerobic microorganisms and endotoxins cause initation of PD (direct damage), and the inflammatory response of the host causes periodontal breakdown (indirect damage) (Offenbacher, 2006). The process of PD involves direct and indirect tissue damage.

The number of periodontal bacteria can change during pregnancy process and according to pregnancy phase. For example the number of *Pi* increases in the subgingival biofilm of pregnants during the 2nd trimester and this was firstly reported in 1980 (Kornman & Loeshe, 1980; Machado, 2012). Highest amounts of periodontal pathogens and the major changes in clinical parameters occur in the 2nd trimester of pregnancy (Kornman & Loeshe, 1980; Gursoy, 2009; Andraens, 2009). In a cross-sectional study 20 pregnants in 2nd trimester of pregnancy were compared to 20 non-pregnants and higher amount of *Pi* was found in pregnants (Machado, 2012). Emmatty et al.(2013) suggested that definite increase in the proportions of *Pi* occurs in the subgingival plaque microflora during pregnancy. The exaggerated gingival response during pregnancy may be associated with enhanced prevalence of *Pi* in the subgingival plaque.

Furthermore, bacterial endotoxins that originate from the periodontal lesions may stimulate systemic activation of the inflammatory response and trigger the synthesis of pro-inflammatory cytokines. The major quantity of pro-inflammatory cytokines are mainly IL–1β, IL–6, TNF–α, prostaglandin E_2 and C-reactive protein (CRP), which may activate the inflammatory response to generate a low grade chronic systemic effects on the host (Offenbacher, 2001; Page, 1991). Additionally PD may burden pregnant patients systematically with oxidative stressors. Increased oxidative stress is cytotoxic to maternal vascular endothelium injury, which may be the key feature in the pathogenesis of PE and reverse obstetric outcomes including miscarriage, stillbirth and PTB

(Moutsopoulos & Madianos, 2006; Klebanoff & Searle, 2006; Boggess, 2003).

Beside this, after stimulation of sex hormones a down-regulation of IL-6 production has been seen in some studies which render the gingiva less efficient to bacterial challenge (Lapp and Lapp, 2005) while other researches recommended that the production of IL-6 was importantly increased by the stimulation of estradiol and progesterone (Yokoyama, 2005; Carillo-de-Albornoz, 2012). TNF-α, another pro-inflammatory biomarker, is affected by hormonal variations. Estrogen deficiency has been showed to enhance T-cell production of TNF-α (Carillo-de-Albornoz, 2012, Weitzmann & Pacifici, 2006), supporting the notion of type 1-cytokine down-regulation by sex steroids (Piccinni, 2010; Shiau & Reynolds, 2010).

Thus, pregnants are more suitable for PDs because the level of sex hormones change during pregnancy. In addition PD as an inflammatory disorder can adversely effect systemic condition and pregnancy process of these patients.

Alteration of Progesterone and Estrogen Levels During Pregnancy

Progesterone and estrogen levels showed a significant increase during pregnancy process (Mariotti, 1994). From the 2nd trimester to the delivery, the level of female sex hormone increase, which are produced by placenta. Hormone reached to the peak level in serum at the end of the 3rd trimester of pregnancy. By the delivery, the placenta is disengaged, so that a significant diminish in female sex hormone levels is seen and within 2 to 3 days, the hormone levels return to their non-pregnant concentrations (Mariotti, 1994).

The high level of these hormones in blood and saliva may cause some periodontal reaction and increase periodontal disorders. Estrogen stimulates wound healing and increases level of vascular endothelial growth factor produced by macrophages, which can be related to increased gingival inflammation during pregnancy (Kanda & Watanabe, 2005) Immunosuppressant effect of progesterone in the gingival tissues against plaque, prevent rapid acute inflammatory response, but increased chronic tissue reaction which results clinically in an exaggerated appearance of inflammation (Ojanotko-Harri, 1991).

Also, during pregnancy, estrogen and progesterone levels lead to hyper-vascularization of the periodontium and changes in collagen formation. These changes can cause the increased of vascular permeability and susceptibility to local irritant factors such as bacterial biofilm at the gingival tissues. Thus, aggravation of inflammatory alterations may happen. This may resulted occurring of pregnancy gingivitis (PG), gingival

hyperplasia, pregnancy tumor and worsening of pre-existing periodontitis (Offenbacher, 2006; Barak, 2003).

The Effect of Periodontal Diseases on Adverse Pregnancy Outcomes

Periodontal disease, such as gingivitis and chronic periodontitis are among the most common microbial and inflammatory diseases affecting mankind. In addition, PD may effect systemic conditions by focal infection theory which was suggested by Hunter in 1900s (Hunter, 1900). Due to the this theory, bacteria and their products from local infections could be spreaded throughout the body and cause diseases in other organs. Periodontal inflammation is known to produce increased secretion of several pro-inflammatory cytokines found in saliva and gingival crevicular fluid (GCF). Most notably, levels of IL-1β, IL-6, TNF-α, and PGE_2 are increased. These inflammatory mediators are seen in the systemic circulation and eventually cross the chorioamniotic barrier so that, finally seen in the amniotic fluid. Thus, pathogens or inflammatory products such as cytokines can affect embryonic tissue or amniotic fluid through haematogenous transport (Offenbacher, 1998). So, maternal-fetal unit may be affected by these processes. Fetal development can be altered and premature uterine contractions may be occurred (Gibbs, 1992; Brown, 1998; Damare, 1997). Gram-negative periodontal pathogens and their products such as lipopolysaccharides (LPS) have been shown to enter the systemic circulation and produce low-grade bacteremia, (Guntheroth, 1984) which may transport to the placenta or uterus and so that birth outcomes may affected negatively by this process (Han, 2006; Barak, 2007). Offenbacher et al. (1996) emphasized that LPS producted by periodontal pathogens are released into the bloodstream and may increase susceptibility to genitourinary infections by decreasing expression of the endothelial receptor E-selectin by endothelial cells. Because a normal neutrophil infiltrate is not produced, Gram-negative bacteria may irrupt the genitourinary tract and cause an infection that affects pregnancy negatively.

Additionally, *Fn* is a gram-negative anaerobe bacteria of the oral cavity, which also was isolated from the amniotic fluid, placenta and chorioamnionic membranes of women delivering prematurely (Kim & Talani, 2006). In another study, periodontal pathogens such as Fn, *Pi*, *Tf*, *Aa* and *Td* were detected in some oral samples taking from high risk pregnants and normal pregnants, while *Fn* alone was defined in chorionic tissues from high risk pregnants (Tateishi, 2012).

The current evidence of studies suggested that periodontal infections lead to haematogenous spread of oral bacteria and bacterial products, which reach the foetal–placental unit. This pathway is related with immune

responses in the foetal– placental unit that induce a range of APO, which are dependent on timing and severity of exposure.

A number of studies have assessed the association between PTB or LBW and PD, with conflicting results. Numerous reviews have assessed these associations (Wimmer & Pihlstrom, 2008; Scannapieco, 2003; Xiong, 2006), some including meta-analysis (Khader & Ta'ani, 2005; Vergnes & Sixou, 2007), and most have expressed a relationship between periodontitis and APO, although 'a high and unexplained degree of heterogeneity between studies' was also noted (Chambrone, 2011). Whereas numerous studies have failed to observe such an association (Davenport, 2002; Mitchell-Lewis, 2001; Machtei, 1992). On account of this, these studies could not establish clear conclusions, mainly owing to methodological differences, which included diverse PD and APO definitions, New studies are required to determine if maternal PD is an independent risk factor for PTB and LBW.

Shortly, two non-reciprocally special hypothesis exist to explain the relationship between PD and APO. The first hypothesis suggests that PD affect the maternal and fetal immune responses systemically, leading to premature delivery. The other hypothesis suggests that oral bacterial translocation into the pregnants uterus may cause localized inflammation and APO in the presence or absence of clinical periodontitis. The oral-uterine transmitting is not restricted to the only well-recognized periodontal bacterial pathogens, but instead may also include the commensal species. The bidirectional mechanism between PD and pregnancy were not clear yet, it is considered that PD have some effects during pregnancy and APO, such as GDM, PE, PTB, LBW, PH.

In conclusion, the number of studies that have proposed to investigate the relationship between PD and APO can still be considered extremely low. The present studies in the literature defined data involved distinct populations, considered heterogeneous exposure to risk factors and lack of appropriate controls for recognized risk factors (age, ethnicity, socio-economic status, smoking, multiple gestations, etc.) and statistical heterogeneity. For this reason, the reported results are contradictory. Because of these methodologic differences among studies, comparison and discussion with this study's results are very difficult. Moreover, differences in criteria for the diagnosis of APO and the description of PD may also have caused great effect on the study results. Further new studies are needed which should be conducted in different population groups, include large samples, and present different methodologic designs.

The Effect of Periodontal Treatment on Adverse Pregnancy Outcomes Before, During and After Pregnancy

Periodontal treatment consist of the preventive, diagnostic and therapeutic recommendations for the oral and periodontal health (Bansal, 2013). When the periodontal treatment could not be performed before pregnancy, to avoid adverse effects of PDs, preventive and therapeutic recommendations can be suggested to pregnants (Sanz & Kornman, 2013; Kaur, 2014). To avoid oral diseases and their adverse effects on pregnancy the best way is the supporting of oral care. Initial periodontal treatment involves scaling and root planning, and is safe and easily applicable in pregnancy. The health professionals, dentists and periodontists should inform the pregnants about that, PDs can be associated with APO and therefore visiting for oral health check-up during early gestation is important (Sanz & Kornman, 2013).

Various strategies about the time and intensity of periodontal treatment has been suggested in the epidemiological and plausibility studies which have found an association between PDs and APO (Sanz & Kornman, 2013; Kaur, 2014; Weidlich & Pihlstrom, 2013; Fiorini, 2013). Organogenesis occurs within the 1st trimester during this process the fetus is highly susceptible to environmental hazards and toxic substances. In the second half of the 3rd trimester, there is a risk of PTB because the uterus is very sensitive to external stimulus. General obstetric guidelines, suggested that in the 1st trimester elective procedures should be delayed due to the possible stress effect on the fetus and preferably made during the 2nd trimester (Sanz & Kornman, 2013). For these reasons the first session of etiologic periodontal treatment, consist of oral hygiene instructions and scaling and root planning must be performed at the end of the 1st trimester of pregnancy until 20th to 28th weeks. In addition, during the dental treatment, prolonged chair time should be avoided and the patient should be positioned on the dental chair in a left lateral supine position to avoid the development of supine hypotensive syndrome (Bansal, 2013).

The other defined factor is intensity of treatment protocol. As the gingival conditions change throughout pregnancy, generally a single session during the 2nd trimester may not be enough to avoid gingival inflammation and PD and provide and maintain periodontal health later in pregnancy. In the current treatment protocol periodontal therapy has been suggested as a possible intervention to prevent PTLBW (Bansal, 2013; Sanz & Kornman, 2013). But, several well-conducted interventional studies, over the past decade showed that, in some cases non-surgical periodontal therapy delivered during the 2nd trimester were insufficient to improve pregnancy outcomes (Bansal, 2013; Sanz & Kornman, 2013; Michalowicz, 2006). A RCT investigating the potential relationship

between maternal periodontitis and APO, including PTB and LBW suggested that intrapregnancy non-surgical periodontal treatment, completed at 20 to 24 weeks, is insufficient in reducing the risk of PTB and LBW delivery in this population (Pirie, 2013). Conversely, Weidlich et al. (2013) were assessed the effect of comprehensive non-surgical periodontal therapy and strict plaque control performed during the 2nd trimester pregnancy on the reduction of PTB and LBW rates. They suggested that comprehensive periodontal treatment and strict plaque control significantly improved periodontal disease and supported periodontal health; but can not reduce PTB and LBW rates. Kaur et al. (2014) suggested intensive instructions and non-surgical periodontal therapy provided over 8 weeks during early pregnancy resulted in decreased gingival inflammation and a generalized improvement in periodontal health and APO.

Shah et al. (2013) in their systematic review showed significant reduction in PTB and LBW rates when periodontitis were treated. A low cost, low morbidity oral hygiene intervention may be beneficial and cost effective in overall improvement of maternal oral and systemic health and to reduce APO in these high-risk populations. Polyzos et al. (2009) suggested a beneficial effect of periodontal treatment on PT and LBW rates. A clinical investigation demonstrated a powerful relationship between periodontal outcomes and full-term birth supporting the notion that possible favorable effects on APO can be dependent on the performance of periodontal treatment (Jeffcoat, 2011). Another study showed that the treatment of periodontitis significantly reduced the occurrence of PTB from 6.8% to 1.1% (Lopez, 2002).

The most common form of PD in pregnant is pregnancy gingivitis, however there is limited data about gingivitis as a potential risk factor for PTB and LBW (Loe & Silness, 1963). There have been very few investigations to assess the effect of intervention on PTB in pregnants diagnosed with gingivitis (Lopez, 2005; Armitage, 2008). A study about Chilean women showed that pregnants with gingivitis who were not treated were at a higher risk of PT and LBW rates than pregnants who received periodontal treatment (Lopez, 2005).

In several RCTs, which conducting in low socioeconomic status populations or low- and middle-income countries, beneficial outcomes of periodontal treatment during pregnancy was showed (Lopez, 2002; Tarannum & Faizuddin, 2007). Several pilot studies (Mitchell-Lewis, 2001; Jeffcoat, 2003; Offenbacher, 2006) or some studies with relatively small sample sizes (Sadatmansouri, 2006; Radnai, 2009) reported that periodontal therapy during pregnancy was decreased rates of PTB and LBW. However, RCTs conducted in high-income countries failed to find that periodontal treatment during pregnancy reduced the incidence of APO

(PTB and LBW) (Michalowicz & Durand, 2007; Newnham, 2009; Offenbacher, 2009). Other interventional studies focusing on the effect of periodontal therapy to reduce the risk of APO have been unable to consistently demonstrate the decrease in PTB and LBW rates (Michalowicz & Durand, 2007, Offenbacher, 2009). In their multicenter clinical study in USA, Michalowicz & Durand (2007) showed that periodontal therapy had no beneficial effect on the occurrence of PTB or LBW. Furthermore, although some studies (Jeffcoat, 2011; Jeffcoat, 2003) have shown the benefit of the treatment of PD during pregnancy on birth outcomes (Lopez, 2002), others have failed to show such effects (Michalowicz & Durand; Macones, 2010; Boggess, 2010). Fogacci et al. (2011) found no beneficial effect of periodontal therapy on the rates of PTB and LBW. Maybe this can be related remaining periodontal inflammation after treatment because of unsufficient performance, thus the lack of effect of periodontal therapy on PT and LBW. Fiorini et al. (2013) aimed to evaluate the effect of periodontal therapy during pregnancy on the levels of six cytokines in GCF and serum, which related with PD and PTB. They suggested that if successful periodontal therapy can be performed during pregnancy, periodontal inflammation and cytokine levels in GCF can be reduced, but it did not have a significant impact on serum biomarkers.

Periodontal diseases, because of its high prevalence, acceptable association with PTB in many studies and in the meta-analyses, and plausible biologic pathway despite the negative RCT results, remains an inviting target for reducing APO (especially PTB and LBW). But, most suitable time and treatment for periodontal treatment during pregnancy is unknown, so that it is essential to support oral and periodontal health care before pregnancy to refrain adverse outcomes. According to a RCT evaluating pre-pregnancy women, providing periodontal therapy during pregnancy may be too late to decrease local and systemic inflammatory responses that lead to APO (Xiong, 2011). Because, once the inflammatory cascade is activated, interventions targeting inflammatory pathways and are not effective, so that intra-pregnancy treatment may be insufficient to prevent APO. Targeting women prior to conception is appealing because the treatments could be more aggressive and include a longer post-treatment maintenance phase, in theory enabling any periodontitis-induced systemic inflammation to more completely resolve. Pre-pregnancy periodontal therapy can be more intensive than which can be performed during pregnancy (eg, the use of adjunctive antibiotics) and can lead to better healing of PD. Preconception periodontal maintenance would be less intensive and designed to maintain health, throughout the hormonal and immunomodulatory stresses of pregnancy (Xiong, 2011). Pre-pregnancy treatments might provide a more definitive conclusion as to whether PD is a causal risk factor for PTB and other APO. Additionally,

periodontal treatment before pregnancy may lead to a reduction in rates of PTB and infant morbidity and mortality worldwide. Jiang et al. (2013) studied the efficacy of preconception PD treatment in the prevention of APO and reported, since periodontal therapy is performed before pregnancy, it can avoid potential risks on pregnants and fetus. Thus, pregnancy may not be an appropriate period for periodontal intervention(s) and there is a lack of knowledge of whether pre-pregnancy periodontal therapy may reduce the risk of APO, future RCTs are needed to test if pre-pregnancy periodontal therapy can reduce the incidence of APO.

In conclusion, although reported inconsistent results; a low cost, low morbidity oral hygiene intervention may be beneficial and cost effective in overall improvement of maternal oral and systemic health and to reduce APO in these high-risk populations. Also, if necessary periodontal treatment can be performed during pregnancy otherwise can be awaited after delivery. This decision can be determined by the assessment of physicians. Thus, to protect pregnants and fetus from unwanted conditions, it can be advised to be under control of gynecologist and periodontologist during the pregnants.

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MEDICAL STUDIES

THE KYNURENINE PATHWAY IN ALZHEIMER'S DISEASE: THE ALTERNATION OF NOGO-A AND KLOTHO ACTIVITIES BY INFLUENCING N-METHYL-D-ASPARTATE RECEPTOR-NITRIC OXIDE PATHWAY

Çagatay Han TÜRKSEVEN*

Introduction

Alzheimer's Disease (AD) is an irreversible neurological disease. It is characterized by progressive deterioration in cognitive functioning due to age, diminished competence in carrying out basic activities of daily life, and fluctuations in personality traits (Castellani et al., 2010). It is the most common cause of dementia, accounting for 50-80% of all dementia (Selekler, 2010). The number of people with AD worldwide is increasing by 3 seconds. There are about 46.8 million people with AD in 2015, and it is believed that this figure is more than 50 million by 2017. The data show that the number of people with AD will double every 20 years. It is estimated to increase to 75 million in 2030 and 131.5 million in 2050 (Martin et al., 2015). In addition, AD is a progressive brain disease which is known to be seen in women higher than in men (Breitner et al., 1988; Jorm et al., 1987; McGonigal et al., 1993; Rocca et al., 1991; Jorm et al., 1998). Considering that AD is an age-old disease, there are studies that show that estrogen has neuroprotective effects on the brain, and that women with relatively high endogenous estrogen levels after menopause have less risk of AD (Manly et al., 2000). However, age-related mitochondrial dysfunction is an important evidence for AD and other neurodegenerative diseases (Lin& Beal, 2006). Loss of cholinergic neuron in the hippocampus and other brain regions, cerebrovascular inflammation, and accumulation of amyloid plaques (Aβ) in the cerebral blood vessels and brain parenchyma occur in AD (Yu&Takahisa, 2017; Elena et al., 2017). Studies show that mitochondrial dysfunction occurs before extracellular accumulation of amyloid plaques (Schuh et al., 2014). The pathophysiology of AD involves complex processes. The histopathology of AD is composed of an excessive amount of senile plaques and neurofibrillary tangles, a significant loss of synapses and cholinergic neurons, and neuronal atrophy in certain brain regions (Askarova et al., 2011). It is known that patients with AD have a synaptic loss of 45-55%,

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especially in the hippocampus (Scheff et al., 2006). The most obvious neuropathologic change in AD is condensation of senile plaques especially in the hippocampus and the cortex. The β-amyloid peptide (βAP) is the major component of senile plaques and has numerous toxic effects on neurons, astrocytes, glial cells, and brain endothelium (Askarova et al., 2011). It is formed by proteolytic processing of a larger transmembrane protein, amyloid precursor protein (APP) (Castellani et al., 2010; Glenner&Wong, 2012). Aβ40 and Aβ42 peptides, which are formed as a result of this proteolytic process, has neurotoxic effects. Aβ accumulates to form plaques in the brain tissues and cerebral vessels of Alzheimer's patients, thus causing neurovascular dysfunction and chronic neurodegeneration. Moreover, oxidative stress triggers long-term deterioration of electrical activity by disrupting apoptosis, calcium balance and structure of ion channels in neuron membranes, thus leading loss of neuronal function and eventually neuronal death (Masters et al., 1985; Yang et al., 2010; Wong et al., 2009). AD, whose formation mechanism contains one or more of these pathways, is the most common cause of dementia.

In light of these information, there are three basic hypotheses that occur in the relevant neuroanatomical areas of the brain in AD (Parihar&Hemnani, 2004). These are amyloid cascade, cholinergic and excitotoxicity hypotheses. The amyloid cascade hypothesis occurs as a result of the intracellular accumulation of neurofibrillary tangles and the extracellular accumulation of amyloid beta (Aβ) protein. In the cholinergic hypothesis, the transmission of nerve stimuli deteriorates as a result of a reduction in the level of acetylcholine due to decreased choline acetyltransferase (ChAT) activity and increased acetylcholine esterase (AChE) activity (Parihar&Hemnani, 2004). Dysfunction of the cholinergic system, including the loss of cholinergic cells in the basal forebrain and hippocampus, plays a critical role in the pathogenesis of dementia (Guo et al., 2016; Becker et al., 1988). In people with AD, there is a negative correlation between cognitive impairment and levels of acetylcholine (ACh) found in the cerebrospinal fluid (CSF) (Tohgi et al., 1996). In the exotoxicity hypothesis, neuronal damage occurs after an increase in intracellular Ca^{+2} level as a result of increased glutamate levels and NMDA receptor hyperactivity (Parihar&Hemnani, 2004).

As a result of oxidative stress induced by neuronal damage and chronic neuroinflammation, antiinflammatory and proinflammatory cytokines secreted by astrocytes and microglial activates the kynurenine pathway (Heneka&O'Banion, 2007; Meyer et al., 2011). Kynurenine is an intermediate metabolite that emerges during the degradation reactions of L-tryptophan (Tayfun&Şadan, 2005). The plasma kynurenine/tryptophan (Kyn/Trp) ratio is increased in AD (Gulaj et al., 2010). This altered rate

increases the level of indoleamine 2,3-dioxygenase (IDO) in the brain tissue with AD (Bonda et al., 2010). This increase leads to an increase in levels of quinolinic acid (QUIN) (an agonist of NMDA receptor) and 3-hydroxykynurenine (3-HK) (which produces free radicals) by increasing the activation of kynurenine 3-monooxygenase (KMO). QUIN and 3-HK have neurotoxic effects (Dzamba et al., 2016). Elevation of the QUIN and 3-HK levels is also associated with elevation of the NO level because a study found that the administration of norharman (NOR) (an IDO inhibitor) also reduced the NO level (Chiarugi et al., 2000). This suggests us that Ca^{+2}-dependent inducible nitric oxide synthase (NOS) is activated by an increase in the QUIN level, leading to an increase in the production of NO. Another study also found that the 3-HK and QUIN levels decreased as a result of the inhibition of KMO activity, which causes the formation of 3-HK and QUIN that are associated with neurotoxicity in the kynurenine pathway, with 3,4-dimethoxy-N-[4-(3-nitrophenyl) thiazol-2-yl]benzenesulfonamide (Ro 61-8048), and also that L-kynurenine (L-KYN) increased the formation of kynurenic acid (KYNA) (a NMDA receptor antagonist) via kynurenine aminotransferase (KAT) (Chiarugi et al., 2001). It has been shown that inhibition of KMO activity with Ro 61-8048 led to a decrease in glutamatergic/NMDAR activity and reduced extracellular glutamate levels by shifting the direction of kynurenine towards the production of KYNA (Moroni et al., 2005). It is therefore likely that glutamate/NMDA-mediated excitotoxicity in AD is associated with an increase in intracellular NOS and NO activities (Figure 1).

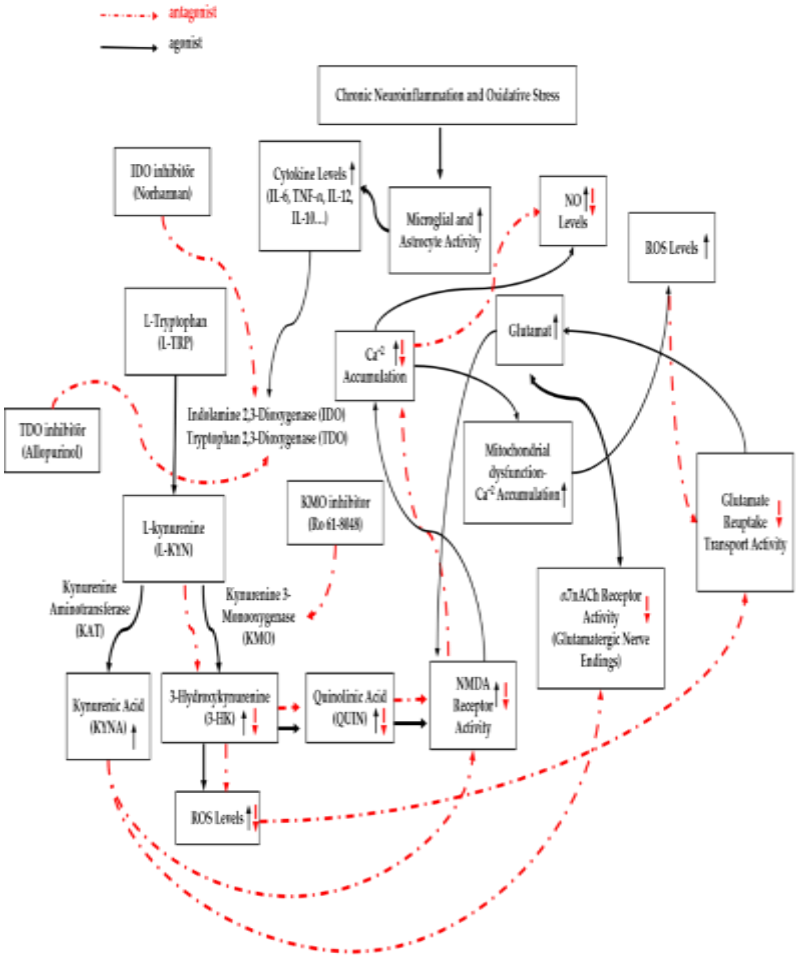

Figure 1. Processes resulting from oxidative stress and chronic neuroinflammation in AD

Nogo-A protein excreted by oligodentrocytes in the central nervous system (CNS) has been found to be responsible for NOS and NO expressions (Fang et al., 2015). It is known that the Nogo-A/NgR pathway inhibits neurite growth. It has also been found to stimulate Aβ secretion via ROCK activity by activating the protein kinase C and RhoA/Rho-kinase (ROCK) pathways (Xiao et al., 2012). The cell enters the process of apoptosis through the interactions of these pathways. However, a different protein called the KL has been found to inversely functions for this process. KL is the key regulator of the aging process, and prolongs mammalian life when overexpressed, and also increases synaptic plasticity and improves cognition (Almeida et al., 2017). It is known that the level of KL is very low in AD and that the overexpression of KL in transgenic mice

(EFmKL46 and EFmKL48) results in suppression of senescence phenotypes and significantly prolongs the life span (Kurosu et al., 2005). There are also studies that show that the excessive increase of pathological findings of AD caused deteriorations in peripheral tissues.

In this section, we will discuss the exact effect and the interactions of the underlying mechanisms in the light of previous studies, although the Nogo-A/NgR and RhoA/ROCK pathways and the KL protein play a role in the treatment and prevention of inflammatory diseases such as AD (Figure 2). It has been shown that amyloid cascade, cholinergic and excitotoxicity hypotheses play a main role in the pathological development of AD. However, recent studies on the associations between structural variants have pointed that there are many underlying biological pathways and that cognitive disorders occur when these pathways become impaired. It sheds light especially on the pathways that develop with oxidative stress and neuroinflammation. Although there are a large number of biological pathways leading to AD, one of these pathways, which is relatively rare in the population, should have a broad influence for useful treatments. It will be argued whether the kynurenine pathway, which is believed to lead to the initiation of the pathologic cascade in AD, may have such a wide effect for treatment. In addition, the results of studies that demonstrated how the inhibition of KMO or IDO in the kynurenine pathway altered the inflammatory mechanisms will be discussed. The predictions on how the relationship between the Nogo-A/NgR and RhoA/ROCK pathways (which have significant roles in the inhibition of KMO and IDO in the kynurenine pathway), the NO and NMDA receptors and the KL protein develops will be revealed. In addition, this section will examine studies that reveal the possible association between the KL protein (whose effects on aging have been understood and which is known to be expressed in the brain) and NMDA and NO. We believe that this interaction may create a new idea for studies investigating the relationship between NMDA receptors (which are the most common receptors in brain cells) and different pathways (which are involved in the development of AD).

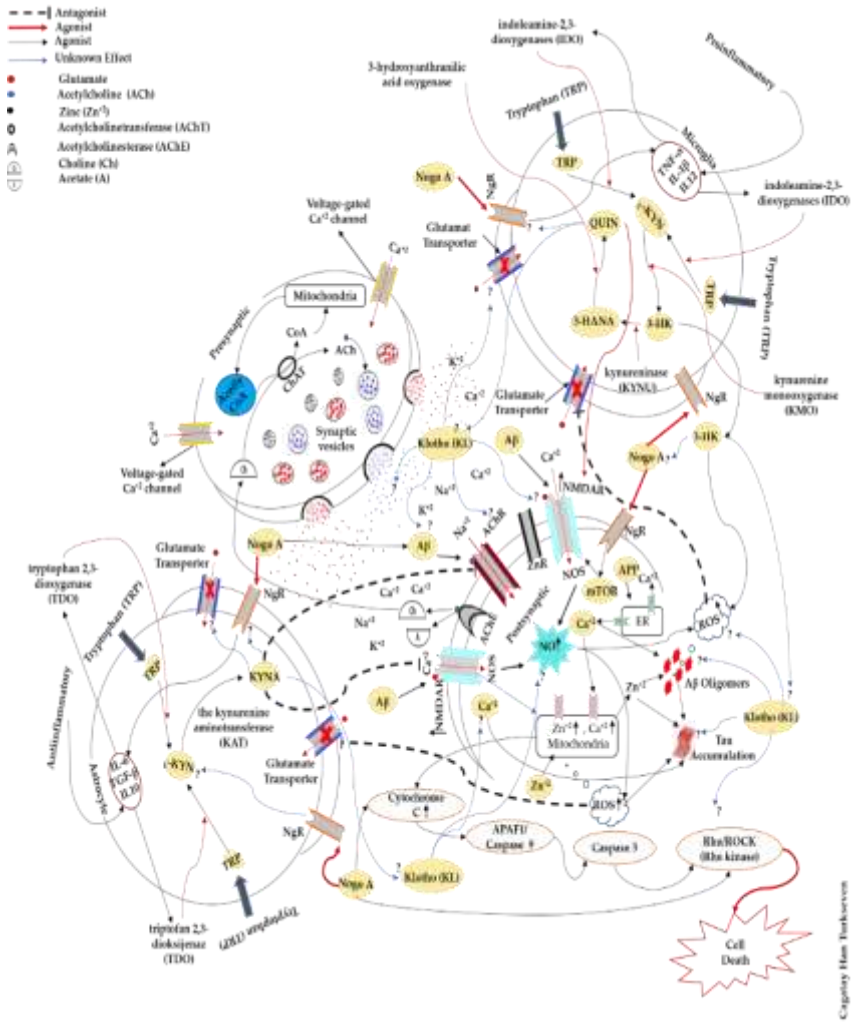

Figure 2. Pathways associated with inflammation in AD

1. Association of Changes in Biophysical Properties of Membrane in Alzheimer's Disease with Neuroinflammation and Oxidative Stress

It has been reported that Aβ reduces membrane fluidity, affects molecular organization and increases membrane conductivity (Corona et al., 2011). Aβ can indirectly affect membrane properties by binding to membrane receptors and by triggering signaling pathways leading to oxidative stress and inflammation. On the other hand, the ability of Aβ to interact with membranes of neurons and other cerebral cells depends on the organization and physical properties of the membranes, such as cholesterol content, lipid composition, Aβ/lipid ratio, pH, surface charge of the double layer, and presence of metal ions. In addition to the presence

of Aβ oligomers and tau phosphorylation, the concentration imbalances of particularly Ca^{+2} and Zn^{+2} ions in the synaptic gap and neurons participate in the development and progression of AD (Corona et al., 2011). Ca^{+2} level is always lower in the cytosol compared with the extracellular space. This equilibrium is achieved by the activity of Ca^{+2}-binding proteins and by transporting Ca^{+2} into the extracellular space through Ca^{+2}-ATPase pump. The increase in intracellular Ca^{+2} occurs by transporting Ca^{+2} into the intracellular space through ionotropic glutamate receptors such as voltage-gated Ca^{+2} channels, NMDA receptor and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor or by releasing intracellular Ca^{+2} in the cytoplasm. Like Ca^{+2}, Zn^{+2} is a metal ion that is lower in the intracellular space. Unlike Ca^{+2}, Zn^{+2} is stored at very high levels in some presynaptic vesicles in glutamatergic neurons in the central nervous system and is released into the synaptic cleft along with neurotransmitters (Qian&Noebels, 2005). Thus, Zn^{+2} can accumulate in the synaptic cleft during intense synaptic activity and enter postsynaptic neurons using some access pathways such as AMPA receptor and less effectively NMDA receptor. The concentration gradient between intracellular and extracellular Ca^{+2} and Zn^{+2} levels are necessary for some central nervous system functions such as neuronal conduction, mitochondrial function, and various enzymatic activities. Imbalances in these concentration changes can be a potential trigger in AD-associated neurodegeneration processes, such as Aβ oligomerization, neurofibrillary tangle formation, and production of reactive oxygen species (ROS) (Sensi et al., 2003; Mattson, 2010). Therefore, Aβ, tau, oxidative stress, increase in glutamate receptor activity, and imbalance in the concentrations of Ca^{+2} and Zn^{+2} can enhance synaptic and neuronal loss related to AD by affecting each other. When Zn^{+2} ion is present in low concentrations, it inhibits NMDA receptor activity. Because the binding affinity of Zn^{+2} to Aβ plaques is increased after the accumulation of Aβ plaques, its blockage on NMDA receptor is removed (Corona et al., 2011). However, as Aβ also activates AMPA receptors that are directly permeable to Ca^{+2}, there is an excessive influx of Ca^{+2} into cells through both pathways. This excessive Ca^{+2} increase in the cell leads to release of mitochondrial ROS and results in increased production of NO due to Ca^{+2}-dependent NOS. Then, ROS leads to the release of Zn^{+2} ions from the mitochondria, bringing Zn^{+2} level in the cell to toxic concentration.

In this situation, it causes more deterioration in mitochondrial function, leading to further formation of reactive oxygen species and release of pro-apoptotic factors. The rise in Zn^{+2} level caused by ROS can also provide Aβ accumulation. ROS begins to be released from the cell after the accumulation of Aβ oligomers in the cell, which prevents glutamate reuptake by blocking glutamate transport in glial cells (Sensi et al., 2003). Therefore, increased glutamate concentration outside the cell causes

excitotoxicity by leading to the hyperactivity of NMDA and AMPA receptors (Annweiler&Beauchet, 2012). For this reason, NMDA and AMPA receptors activity may further increase. Both increased Ca^{+2} level caused by NMDA receptor activity and oxidative stress have been shown to lead to tau hyperphosphorylation in patients with AD (Zempei et al., 2010; Lovell et al., 2004). In addition, the human nicotinic acetylcholine receptor (nAChR) has two functional models. One of these is the presynaptic heteroreceptor which mediates the increase of glutamate release and is found in glutamatergic nerve endings. The other is the presynaptic autoreceptor that mediates the increase of acetylcholine release and is found in cholinergic nerve endings. The autoreceptor represents the α4β2NAChR subtype, whereas the heteroreceptor represents the α7NAChR subtype. The pharmacology of the human nAChRs characterized here is quite similar to the pharmacology of the corresponding receptors in rats (Marchi et al., 2002). Some studies have shown that (nAChR) agonists protect against neuronal excitotoxicity caused by glutamate through alpha4 and alpha7 type nicotinic acetylcholine receptor (Akaike et al., 2010; Shen et al., 2010). However, the progressive loss of nicotinic receptors, which play a role in memory and cognitive impairments during AD, has also been reported (Pettenati et al., 2003). Recent studies have shown that acetylcholine esterase (AChE) inhibitors suppress synaptic dysfunction, Aβ plaque formation, T cell activation, CNS inflammation, and other neuronal damage reasons such as inflammatory reactions caused by cytokines (Kim et al., 2014; León et al., 2013). Increased production of ROS has been shown in mice injected with SCO (a muscarinic receptor antagonist) (Tao et al., 2014). Oxidative stress-induced cell death is an important cause of neurodegeneration in this rat model of AD. Changes in the expression levels of synaptic proteins, neurotrophic factors, and antioxidant enzymes may be responsible for SCO-induced neurotoxicity, and regulation of such factors may be a way to protect the cells or to return them to their original state (Xiong et al., 2015). The brain is highly sensitive to oxidative stress due to its high oxygen consumption and relatively poor antioxidant defense system. In addition, the brain contains a large number of substances such as iron, ascorbate, glutamate and unsaturated fatty acidsCwhich produce free radicals (Walton et al., 2012). Moreover, elevated oxidative stress is strongly associated with mitochondrial dysfunction (Leuner et al., 2012). This induces increased processing of APP and leads to an increase in Aβ production in AD (Anandatheerthavarada et al., 2003). Furthermore, oxidative stress causes degeneration of cholinergic neurons and consequently cognitive and memory impairment (Melo et al., 2003).

2. Association of Alzheimer's Disease with the Kynurenine Pathway

Accumulation of Aβ plaques caused by oxidative stress activates microglias and astrocytes to form proinflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha) and interleukins (ILs) (Heneka&O'Banion, 2007). Proinflammatory cytokines caused by Aβ can cause proapoptotic and synaptotoxic effects which have excessive toxic effects on neurons (Li et al., 2011). Therefore, AD is a complex neurodegenerative disease. Studies on only neurons are not enough to resolve AD. In addition to the degeneration of cholinergic neurons, it is important to recognize the role of glial and microglia cells in the pathogenesis of AD. In a study conducted, it has been reported that glial and microglia cells should be the key elements of AD (Dzamba et al., 2016). Antiinflammatory and proinflammatory cytokines secreted by astrocytes and microglial activate the kynurenine pathway (Meyer et al., 2011). Kynurenine is an intermediate metabolite that emerges during the degradation reactions of L-tryptophan. The vast majority of dietary tryptophan is metabolized by the kynurenine pathway, which begins with the oxidative opening of indole ring and ends with the production of nicotinamide adenine dinucleotide (NAD+) (a cofactor for various enzymes). With the breakdown of tryptophan (TRP) in this pathway, it produces various neuroactive intermediates such as 3-HK (which produces free radicals), QUIN, and KYNA (an antagonist of NMDA and α7 nicotinic acetylcholine receptor) (Tayfun&Şadan, 2005). The kynurenine pathway play a role in various physiological functions such as behavior, sleep, thermoregulation, and pregnancy. In addition, the kynurenine pathway is associated with many diseases such as AIDS, dementia complex, inflammatory brain diseases, Huntington's disease, Down syndrome, sepsis-associated encephalopathy, toxoplasmosis, malaria, epilepsy and traumatic brain injury. It is also thought to be related to the pathogenesis of AD (Tayfun&Şadan, 2005). Although a small amount of L-KYN can be produced in the brain, the kynurenine pathway in the brain is maintained by L-KYNs that enter the brain from the circulation, essentially using the neutral amino acid transporter. L-KYN in the brain is rapidly taken up by astrocytes and microglial cells. Due to its functional significance, KYNA is synthesized mostly in these cells because astrocytes do not contain 3-HK. However, since microglial cells have very low kynurenine aminotransferase (KAT) activity, these cells preferably form intermediates of the QUIN branch of the pathway (Tayfun&Şadan, 2005). As the proinflammatory cytokines secreted by microglial cells (especially TNF-α, IL-12, IL-1 beta) stimulate the enzyme indolamine 2,3-dioxygenase (IDO1 and IDO2), they increase the KMO activity via L-KYN and the levels of QUIN and 3-HK.

QUIN and 3-HK have neurotoxic effects (Miech et al., 2002). As QUIN and 3-HK (a neuroactive metabolite) act as an effective free radical generator, QUIN also exhibits an agonist of NMDA receptor. Furthermore, QUIN induces lipid peroxidation and causes the level of extracellular glutamate to rise, thus resulting in an increase in excitotoxicity (Majláth et al., 2014). As the anti-inflammatory cytokines (especially IL-6, TGF-β, IL10) secreted by astrocytes stimulate the enzyme tryptophan 2,3-dioxygenase (TDO), they increase the KMO activity via L-KYN and the production of KYNA from L-tryptophan (L-TRP). KYNA is a potent antagonist of NMDA and α7 nicotinic acetylcholine receptor (α7 nAChR) (Meyer et al., 2011). KYNA exhibits a competitive antagonist effect by binding to the glycine-binding regions of NMDA receptors (Kessler et al., 1989). KYNA has a dual effect on the AMPA receptors depending on the concentration: It exhibits an agonist effect at low concentrations and an antagonist effect at high concentrations (Prescott et al., 2006; Rozsa et al., 2008). Because KYNA inhibits NMDA receptors, it exerts neuroprotective effect by preventing glutamate excitotoxicity. However, it inhibits α7NACh receptors, which may contribute to this effect. Because these receptors are associated with the regulation of presynaptic glutamate release (Marchi et al., 2002). The L-KYN/TRP ratio was found to higher in the blood and cerebrospinal fluid (CSF) in patients with AD compared to healthy subjects. This situation has been reported to be strongly related to the disruption of the KP (Gulaj et al., 2010). This altered rate has been associated with an increase in IDO1 levels in the brain tissue (Bonda et al., 2010) and in 3-HK levels in blood serum (Schwarz et al., 2013) in AD. IDO and QUIN exhibited a significant immunoreactivity in hippocampal neurons, astrocytes, and microglia in AD. This activity was observed at high levels, especially around senile plaques (Guillemin et al., 2005). IDO and QUIN are also present in the neurofibrillary tangles formed in AD. QUIN is also present in the intracellular granular deposits of cortical neurons (Bonda et al., 2010; Guillemin et al., 2005). Aβ peptides induce IDO1 expression and increase QUIN production in human macrophages and microglia (Guillemin et al., 2003). Studies in both humans and rats have shown that the increased Aβ production is associated with deep induction of KP by inflammatory cytokines which trigger IDO, TDO and KMO activity (Yamada et al., 2009; Lue et al., 2001; Akimoto et al., 2007). In addition, treatment of human neurons with QUIN results in the upregulation of genes associated with tau phosphorylation. This potentially provides a mechanism in which neurofibrillary tangles are formed in AD (Rahman et al., 2009). Various studies have shown that 3-HK and QUIN levels increased in the blood and CSF obtained from patients with AD, while KYNA levels decreased. The fact that this change has led to the development of neurotoxic metabolites instead of neuroprotective species has suggested that it contributes to the pathogenesis of AD

(Maddison&Giorgini, 2015). Another study assessed 3-HK, QUIN (which are neurotoxic metabolites of the kynurenine pathway) and NO levels in interferon-activated macrophages. It was found that 3-HK, QUIN and NO accumulations reached the neurotoxic levels in the incubation medium with the induction of IDO and NOS by interferon-ɣ. The exposure of macrophages with norharman (an IDO inhibitor) has reduced not only the kynurenine pathway metabolites but also the NO formation. (Chiarugi et al., 2000). There are also studies on the inhibition of KMO activity which is responsible for the formation of 3-HK and QUIN associated with neurotoxicity in the kynurenine pathway except for IDO inhibitors.

In a study of mouse model of multiple sclerosis, it was reported that KMO activity was increased excessively and that this increase reached neurotoxic levels with 3-HK and QUIN. It was shown that the inhibition of KMO activity in the kynurenine pathway with 3,4-dimethoxy-N-[4-(3-nitrophenyl) thiazol-2-yl] reduced 3-HK and QUIN levels and also caused the accumulation of KYNA (Chiarugi et al., 2001). In addition, it was found that the inhibition of KMO activity with Ro 61-8048 in the rat brain increased KYNA levels and that the extracellular glutamate concentration decreased in parallel to this (Moroni et al., 2005). In a study of alcoholic rat model performed with the idea that high glutamatergic activity and NMDA receptor activation may lead to drug craving and relapse, it was reported that the inhibition of KMO activity with Ro 61-8048 caused a decrease in glutamatergic/NMDA receptor activity through different mechanisms by shifting the metabolic kynurenine pathway towards the production of KYNA (Vengeliene et al., 2016). In the light of these information, it is possible that the increase in intracellular Ca^{+2} due to NMDA receptor overactivity depending on the increase in 3-HK and QUIN levels in patients with AD leads to the release of mitochondrial reactive oxygen species and that the increase in NO production caused by Ca^{+2}-induced NOS causes an increase in the formation of neurotoxic effects and in the accumulation level of Aβ oligomers.

3. Interaction of NMDA receptor with association between Nogo-A/Nogo receptor and Rho/ROCK pathway in Alzheimer's Disease

Recent studies have shown that the Nogo-A/Nogo receptor (NgR) is associated with pro-inflammatory and anti-inflammatory cytokines or cytotoxic factors released by microglias and astrocytes which are hyperactivated due to inflammation in CNS. Nogo-A has been found to be responsible for the expression of these inflammatory mediators (iNOS, cyclooxygenase-2 (COX-2), IL-1, TNF-α, NO) (Fang et al., 2015). It is a protein that is expressed by oligodendrocytes, an important component of myelin production in CNS (Ineichen et al., 2017). It is known that the Nogo-A/NgR pathway contributes to the inhibition of neurite regeneration by neurons after CNS damage and limits axonal regeneration (Huebner et

al., 2009; Schwab&Strittmatter, 2014; Wälchli et al., 2013). Recent findings have shown that Nogo-A is overexpressed by hippocampal neurons and is associated with Aβ accumulation in patients with AD. Nogo-A and NgR also play a role in the pathology of AH (Park et al., 2006). It has been shown that more than 50% of hippocampal pyramidal cells in the brain with AD have NgR immunoreactivity and that this may be associated with fibrillar tangle formation (Zhu et al., 2007). Loss of both Nogo/NgR in the brain tissue of patients with AD reduces Aβ accumulation (Park et al., 2006). Nogo-A binds to its functional receptor NgR to inhibit axonal growth by activating the intracellular signal molecules with the small GTP-binding protein RhoA and its effector ROCK (Yin et al., 2014; Zagrebelsky&Korte, 2014). One study has revealed that the accumulation of Aβ oligomers which increases via inflammatory mediators in the brain tissue with AD is associated with the Nogo-A/NgR signal (Xiao et al., 2012). It was found that the activation of NgR not only inhibited neurite growth in cortical neurons but also activated Aβ release by ROCK by activating the protein kinase C and Rho/Rho-kinase (ROCK) pathways.

These findings have indicated that Nogo-A overexpression and activation of NgR alter neuronal metabolism by inhibiting neurite growth, leading to overproduction and/or secretion of Aβ (Xiao et al., 2012). In a study conducted on Nogo-A/NgR and glutamate receptors NMDA and AMPA interactions, it was found that the transcription and translation of Nogo A in hippocampal neurons were regulated under the control of NgR1 stimulation via the Rho-ROCK and MAPK pathways and that the interaction between neuronal Nogo-A/NgR1 regulated glutamatergic transmission by altering NMDA and AMPA receptor levels via rapamycin-sensitive mTOR pathway (Peng et al., 2011). Levels of Ca^{+2} and Zn^{+2} ions in the cell increase due to neuronal cell death and glutamatergic excitotoxicity in AD. This leads to the release of cytochrome c and caspase-dependent apoptosis. Released cytochrome c binds to apoptotic protease activating factor-1 (Apaf-1) and procaspase-9 to form an apoptosome, which regulates the caspase activation cascade. The apoptosome complex activates caspase-9, which promotes caspase-3 activation, eventually leading to cell death (Elmore, 2007). Membrane budding, which is observed with the intrusions and protrusions of the cell membrane, indicates the beginning of cell death. This membrane bud formation occurs via some G proteins such as Rho protein. Rho protein is effective in signaling pathways that control gene expression and actin cytoskeleton. ROCKs have been discovered as the first effectors of Rho kinases. ROCK has two isoforms including ROCK1 and ROCK2 (Leung et al., 1995; Ishizaki et al., 1996; Matsui et al., 1996). ROCK1 is cleaved by caspase 3 at the cleavage site DETD1113 during apoptosis (Coleman et al., 2001; Sebbagh et al., 2001). The activation of ROCK1 via caspase 3 is responsible for membrane bud formation in all apoptotic events. Many

studies have shown that this pathway mediates inflammatory events and tissue/organ damage (Büyükafşar et al., 2004). There are many enzymes and proteins involved in neuropathology and neuroinflammation of AD, the most important of which is Rho kinase (ROCK) (Kubo et al., 2008). Agents that inhibit the Rho/Rho-kinase pathway may be new class analgesic and anti-inflammatory drugs (Büyükafşar et al., 2006). On the other hand, the inhibition of Rho-kinase activity may stimulate axonal regeneration (Borisoff et al., 2003). ROCK inhibitors such as Y-27632 and fasudil bind to the kinase domain of the enzyme and inhibit both ROCK1 and ROCK2 (Breitenlechner et al., 2003). In a study conducted using fasudil (a ROCK inhibitor) in rats, fasudil has been found to exert a protective effect by suppressing the inflammatory response to hippocampal neurodegeneration caused by AD (Song et al., 2013). A different study demonstrated that NgR inhibition in murine retinal ganglion cells caused a decrease in the activity of Rho/ROCK (Zeng et al., 2017). On the other hand, the inhibition of the Rho-ROCK or MEK-MAPK signaling pathway in hippocampal neurons caused a similar decrease in neuronal Nogo-A, mRNA and protein (Peng et al., 2011). All these processes are considered to be the main pathways leading to loss of synaptic function and apoptosis of neuronal cells in AD.

4. Association between Klotho protein and Alzheimer's Disease

The Japanese study group found a protein named KL that exert an effect in opposite direction of the Nogo-A/NgR and Rho/ROCK pathways (Almeida et al., 2017). They have identified a new gene (KL) that encodes a membrane protein that suppresses certain physiological properties associated with shortening of life, infertility, atherosclerosis, skin atrophy, aging phenotype in mice, emphysema and osteoporosis (Almeida et al., 2017). Later studies have shown that the KL gene is present on chromosome 13 in humans and encodes membrane-bound and secreted proteins. They have observed that the human KL gene expression decreases in elderly people compared to newborns, and therefore it is thought that decreased KL expression shortens human life (Almeida et al., 2017). One study has demonstrated that increased expression of KL protein in human amyloid precursor protein (hAPP) transgenic mice, which mimic key aspects of AH, reduces premature mortality and network dysfunction. In addition, increased expression of KL inhibited the reduction of NMDA receptor subunits in the hippocampus and enhanced spatial learning and memory in hAPP mice. Increased expression of KL in hAPP mice increased the abundance of the GluN2B subunit of NMDA receptor at postsynaptic densities and the long-term potentiation dependent on NMDA receptor, which is critical for learning and memory. Thus, increased KL expression or activitiy improved synaptic and cognitive functions (Dubal et al., 2015). KL is most expressed in the brain, kidneys and reproductive

organs. In the brain, it is expressed by the choroid plexus and neurons, especially by cerebellar Purkinje fibers in the hippocampus and hypophysis. It is a protein that plays a role in intracellular calcium changes, which we think is involved in the metabolic pathway (Nabeshima et al., 2008). The human KL gene is composed of 5 exons and 4 introns and ranges over 50 kb on chromosome 13q12 (Kuro-o et al., 1997). In mice and humans, the KL gene encodes a transcript of 5.2 kb. In the third exon, there is an alternative splicing donor site that can generate two different transcripts: one encoding a transmembrane form (full-length transcript, 1014 amino acids), and the other, a secreted form of the protein (truncated transcript, 550 amino acids). The full-length transcript encodes a single pass transmembrane protein with a molecular weight of approximately 130 kDa (m-KL). The transcript generated by alternative splicing generates a secreted form of the protein (s-KL) that is formed solely by the KL1 domain, with an approximate weight of 70 kDa (Shiraki-Iida et al., 1998). Studies have suggested that the soluble KL protein, which acts as a circulating hormone, has an effect on ion transport and has anti-aging and anti-oxidant properties (Dubal et al., 2014). Additionally, it plays a role in the regulation of calcium metabolism by suppressing 1α-hydroxylase in the kidneys and in the regulation of parathormone (PTH) synthesis in the parathyroid gland (Olauson et al., 2013). The secreted KL protein has been detected in the blood, urea, and cerebrospinal fluid. In a study investigating whether KL affects physiological brain function and more specifically whether it plays a role in the prevention or inactivation of cognitive impairment in human aging, elevated serum level of KL has been shown to increase cognitive performance (Zeldich et al., 2014).

Cerebrospinal fluid KL levels were found to be lower in patients with AD compared to healthy subjects (Semba et al., 2014). The overexpression of KL leads to a suppression of senescence phenotypes and a significant prolongation of the life span in transgenic mice (EFmKL46 and EFmKL48) compared to healthy mice (Kurosu et al., 2005). Further studies have shown that KL is associated with the regulation of calcium and phosphate homeostasis and the inhibition of intracellular insulin and insulin-like growth factor-1 activity (Kuro-o, 2010). Elevated lipid peroxidation and oxidative DNA damage in the hippocampus of KL mutant mice occurs before the formation of cognitive impairments (Nagai et al., 2003).

5. Conclusion

AD is a progressive neurological disorder that is associated with aging and leads to various mental and behavioral disorders, primarily forgetfulness. Although AD is associated with aging, its pathogenesis develops as a consequence of abnormal brain processes. Early detection of the disease is very difficult, and there is not yet a treatment for AD. For

this reason, studies targeting diagnosis and therapy are very important for AD (Castellani et al., 2010). Many studies have focused on basically three hypotheses that occur in the relevant neuroanatomical areas of the brain in AD (Parihar&Hemnani, 2004). The amyloid cascade hypothesis occurs as a result of the intracellular accumulation of neurofibrillary tangles and the extracellular accumulation of amyloid beta (Aβ) protein. In primary cultures prepared from cortical neurons of Wistar rats, it was found that Aβ increased Ca^{+2} release from the endoplasmic reticulum (ER). It was also shown that the mitochondria could capture large amounts of Ca^{+2} because the endoplasmic reticulum is closely juxtaposed to the mitochondria, and that this also activated the mitochondrial apoptotic pathway. Thus, one of the mechanisms of neuronal loss seen in AD could have been understood (Ferreiro et al., 2008). It is known that disruption of ion balance in neuronal cells plays a role in the pathogenesis of AD. It was demonstrated using standard fluorescence imaging techniques in cell cultures that Aβ modulated Ca^{+2} channels in the lipid vesicles and altered intracellular Ca^{+2} concentration in astrocytes and neuron cells (Abramov et al., 2004). Electrophysiological studies have shown that Aβ enhances long-term potential in the rat gyrus and thus facilitates synaptic plasticity under in vitro conditions. It was shown that whereas acute treatment of young rat (70-120 days) hippocampal slices with low concentration (100-200 nM) of bath-applied Aβ1-40 did not change basal synaptic transmission, there was an increase in tetanus-induced LTP (Wu et al., 1995).

Another function of Aβ that plays a role in neurodegeneration is that when it accumulates in the mitochondrial membrane, it leads to the formation of oxygen free radicals by causing mitochondrial dysfunction (Pieczenik&Neustadt, 2007; Mattson, 2004). Free radicals are toxic because they can interact with most of cellular macromolecules such as proteins, lipids, and DNA. Excessive amounts of oxygen free radicals in various pathological conditions or increased free radicals as a result of insufficient antioxidant system in the structure of the organism lead to cell damage by affecting various components of the cell (Defeng&Cederbaum, 2003). As a result of oxidative stress induced by neuronal damage and chronic neuroinflammation, antiinflammatory and proinflammatory cytokines secreted by astrocytes and microglial activates the kynurenine pathway (Bonda et al., 2010). A lot of evidence suggests that kynurenine pathway metabolites play a role in the pathology of many neurocognitive and neurodegenerative disorders (Maddison&Giorgini, 2015). Levels of IDO and TDO increase in the brain with AD. This increase increases KMO and KAT activities. It is known that this increases levels of QUIN and 3-HK. Increased levels of QUIN and 3-HK exhibit neurotoxic effects (Moroni et al., 2005). It was shown that increased level of QUIN increased tau pathology by inducing tau hyperphosphorylation which occurred in AD, and that this directly caused excitotoxicity (Rahman et al., 2009).

Furthermore, a study in AD Tg2576 transgenic mouse model suggests that a synergistic effect between Aβ and proinflammatory cytokines has an important role in elevating IDO level (Akimoto et al., 2007). This suggests us that Ca^{+2}-dependent inducible NOS is activated by an increase in the QUIN (an NMDA agonist) level, leading to an increase in the production of NO (Moroni et al., 2005). Nogo-A protein has been found to be responsible for NOS and NO expressions (Fang et al., 2015). It is known that the Nogo-A/NgR pathway inhibits neurite growth. It has also been found to activate Aβ release by ROCK by activating the protein kinase C and RhoA/Rho-kinase (ROCK) pathways (Xiong et al., 2015). It is known that the KL protein, which acts inversely to the Nogo-A/NgR and Rho/ROCK pathways, enhances cognitive performance and prolongs the life span (Dubal et al., 2015; Zeldich et al., 2014). There are studies showing that lipid peroxidation and oxidative damage prior to the onset of cognitive impairment are associated with the KL protein and that the interaction of the KL protein with NMDA receptor increases plasticity (Dubal et al., 2015; Ferreiro et al., 2008). Although the Nogo-A/NgR and RhoA/ROCK pathways and the KL protein play a role in the treatment and prevention of inflammation-related diseases such as AD, there is a need for determining the exact effect and underlying mechanism. Recent genetic and pharmacological approaches suggest that KP may be a valid therapeutic approach in neurodegenerative disorders and can complete previous metabolic studies in this direction (Maddison&Giorgini, 2015).

It is clear that increased synthesis of QUIN and 3-HK and reduced production of KYNA have been demonstrated in the majority of neurodegenerative diseases linked to KP and that this can be addressed by reversed interventions (Maddison&Giorgini, 2015). KMO has shown a great potential as a therapeutic target in the treatment of neurodegeneration, especially in KP enzymes. Because inhibition of this enzyme leads to an increase in the production of neuroprotective KYNA and reduces levels of QUIN and 3-HK. In addition, studies have shown that IDO or TDO inhibition can also prove to be an effective neuroprotective strategy (Maddison&Giorgini, 2015). Clinical trials planned with KMO inhibitors may be an important first step in understanding the therapeutic value of KP manipulation in the context of neurodegenerative diseases in general (Maddison&Giorgini, 2015). In light of these findings, KP can be defined as a new underlying mechanism of AD neurodegeneration.

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PRINCIPLES OF PALLIATIVE CARE AND DEMOGRAPHIC ASPECTS OF CANCER PATIENTS

Dilek DÜLGER*

Introduction: In this chapter,the principles of palliative care were examined and the demographic patterns of the patients who were followed up and treated and were examined in the palliative care unit. The primary diseases in this patient group, the age and sex distribution of the patients, the mean length of hospital stay and transferred places to the palliative care were investigated.

Material and Method: Between June 2015 and March 2019,the patient records of the palliative care unit were reviewed retrospectively.Mean and standard deviation in continuous variables and percentage and frequency values in dichotom variables were used. According to Kolmogrov Smirnov test, according to the normal distribution of variables, continuous independent variables;Student t test or Mann WhitneyU test were used in the independent variables, while dichotom variables chi-square were used. Results: Of the 62cancer cases,37(58.7%)were male vs. 26(41.3%) were female.There was a difference between male and female patients in terms of age[(67.4±10.4 vs72.6±13.2)(p=0.048)] There was no difference between the sources of arrival of the patients in palliative care according to gender (p=0.407).When subclassification is made according to the gender of the male and female; Urgent (4vs2),home(15vs8),hospital (16vs12),intensive care (2vs4),liver, 9 colon, 3breast, 1 malignant melanoma, 7 gastric,3ovarian, 4 pancreas,1 esophagus, 1cordoma, 2 prostate, 3 urinary tract,1 rectal and 1 gallbladder cancer.The most common metastatic organ was liver with 8 cases.In terms of male and female sex for length of hospitalization, there was no difference[(31.02±63.7)vs(20.6±29.5) (p=0.536)]. Blood ürea nitrogen(BUN) (6.4 ±18.9) (p = 0.02)] were significantly different and much higher in males.

Conclusion: In this study, in pallative care unit that among the mortal patients the male was found the younger than females.BUN values of the females were more normal than the males. Additionally, we believe that hepatic metastasis are the more frequency according to the other type of metastatic cancers.

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Principles of Palliative Care and Demographic Aspects of Cancer Patients;

Introduction :

Palliative Care:

In fact, at first, when we look at the meaning of this word itself, we see that it means 'Partial'. When used in medical sentences, we see that there is a partial relief of the discomfort that cannot be completely resolved and the prevention or minimization of further complications and cater for patient comfort.

If we look at this term more briefly; It can be describing as, follow-up that requires special treatment, elimination of the patient symptoms that give for suffer to the patient and 24-hour patient care and monitoring, special treatments and specific programs.

At this point, we can say that the principles of chronic patient care should be applied.

So what are the principles of chronic patient care?

1. For good treatment and follow up; Medical partnership formation , with patient.

2. Priority of the patient's concerns forefront.

3. ESTAR (Evaluate, suggest, take, attend, regulate) (In terms of ease of remembering).

4. The case self-managing serving with positive medical management .

5. Requirement of the good organization for proactive follow-up.

6. Include"experienced cases," for education and supporting in your health institution.

7. There is a requirement to strengthing in the patient for the social axis sources .

8. Be faithful to good health registration system for complet follow up.(Please don't forget all points are too important in terms of patient monitoring and treatment)

9. Be a compatible clinical team.

10. Catering of the continuity of care (1) .

Where are the palliative care services is provided?

In the hospital environment

Primary health care / health center

At home

End-care homes

On the other hand the demographic patterns always is so important for description of the patients both palliative care and diagnosis with cancer. In this reason, with this study the demographic patterns were investigated, especially the patients with whom had got with tumour in that palliative department.

Material and Methods :

Between June 2015 and March 2019,the patient records of the palliative care unit were reviewed retrospectively.Mean and standard deviation in continuous variables and percentage and frequency values in dichotom variables were used. According to Kolmogrov Smirnov test; For the continuous independent factors required statistichal tests were determined . On the other hand ; In terms of dichotom variables chi-square had been used. The statistichal results assessed according to $p<0.05$ value, in terms of statistichal significance .

Results : Of the 62cancer cases,37(58.7%) were male vs. 26(41.3%) were female. There was a prominent diversity between male and female patients in terms of age[(67.4±10.4 vs72.6±13.2)(p=0.048)] . On the other hand there wasn't any prominent diversity between the sources of arrival of the patients ,in terms of the palliative care according to gender (p=0.407). In terms of male and female sex for length of hospitalization, there was no difference[(31.02±63.7)vs(20.6±29.5) (p=0.536)]. Blood ürea nitrogen(BUN) (6.4 ±18.9) (p = 0.02)] were significantly different and much higher in males.

This table I is showed that the significant demographic variables

		Male	Female	P<0.05
Gender		37'si(%58.7)	26(%41.3)	0,09
Age		67.4±10.4	72.6±13.2	0.048
The source of the palliative care unit	ES	4	2	0.407
	Home	15	8	
	Hospital	16	12	
	ICU	2	4	
LOS		31.02±63.7	20.6±29.5	0.536
BUN		28.1±45.8	6.4±18.9	0.002

*LOS: Length of stay , *BUN : Blood urea nitrogen, *ICU: Intensive care unit, *ES: Emergency services

For Table 1, we found that, in general, the BUN value was significantly different between genders and was also lower in women.

As a secondary result, we found that men at a younger age were at risk for this care department. Although it was not as prominent as the BUN value, men were found to be younger than women.

In terms of gender as male and female; In our analysis in terms of the sources that transport patients to this unit; We detected the cases were Urgent (4vs2),home(15vs8),hospital (16vs12),intensive care (2vs4), in distribution .

According to our results(Table 1); Among the sources providing patients to this unit, patients who were transferred from another hospital or another unit of the hospital were the first.

The second was the patients who were transferred from home. The third place was the patients coming from the emergency department.

These results show us that for this unit's cases mainly sources from that the patients in hospital worsening or having difficulty in care.

The variables detailed was given below table;

Table II is show that the cancer distrubition of the palliative care patients

Lung cancer	12
Colon cancers	9
Brain cancers	7
Gastric cancer	7
Hepatic cancers	5
Pancreatic cancers	4
Breast Cancers	3
Over cancers	3
Thyroid cancers	1
Chordoma	1
Prostatic cancers	2
Urinary system cancers	3
Rectum cancers	1

Gall bladder cancers	1
Esophageal cancer	1
Malign melanoma	1
Burkitt Lenfoma	1
Totally	62

According to our results; When I look at the frequency of cancer distribution of patients in this unit; As can be seen in Table two, we see that lung cancer takes the first place. Secondly, colon cancer, brain and gastric cancer in third, liver cancer in fourth, pancreatic cancer in fifth, breast, ovarian and urinary system cancer in sixth, gallbladder, malignant melanoma, burkitt lymphoma and esophageal cancer were the least frequent. In addition, liver metastatic cancers; We found it to be the first among metastatic cancers.

Discussion :

Cancer is a process that involves many problems and challenges for patients and their relatives, physical, psychosocial and spiritual. Multiple symptoms seen in cancer patients during this period; it causes deterioration in physical and social functions, decreases in response to treatment and adversely affects survival(2-4).

Failure to control the symptoms relationship with the disease and treatment may result in patients discontinuing treatment, reducing treatment dose, or discontinuation of treatment. Preventing the occurrence of symptoms or controlling the emergence of these symptoms is important for the patient and family to cope with cancer and treatment. During this period, the most effective way to meet all the needs of the patient's family is to provide palliative care with an interdisciplinary approach (5,6,7). In this respect, interclinical coordination and patient care must be ensured.

B.Keleş, F.Aydın and et al. had been stated that Cyto-reduction with HIPEC with high-dose cisplatin and rarely leads to nephrotoxicity and common the more easy manageable metabolic and electrolyte disorders(8). In this respect, it is very important to preserve renal function in these patients who are experiencing the most difficult period of their lives. In addition, renal functions are of particular importance in patient monitoring.

N.Uysal and colleagues stated that in their study, about for cancer distribution and metastasis status as 22% of patients were diagnosed with gastrointestinal system, 19% with hepatobiliary / pancreas, 16% with lung and 13% with genitourinary system cancer. Additionally in their report the

51% of patients had more than one year with diagnosed and 87% were metastasis. On the other hand they stated that found that 9% of the patients were still treated as radiotherapy or chemotherapy and 36% of them were discontinued in the last three months.(9)

In our study, gastrointestinal system-related cancers were more prominent with 23(37.1%) cases.

As in patients receiving palliative therapy and other intensive care patients, blood urea nitrogen is one of the important factors indicating fluid balance, and in our study, it was found to be significantly different between males and females, and blood urea nitrogen was higher in males than the females [28.1±45.8 vs 6.4±18.9 ($p<0.002$)].

A.A Kabalak and et al. (10) they stated that if patients are dehydrated, parenteral fluid administration is not the first choice , in their review(11) Additionally they had been declared in the oral intake is inadequate and severe dehydration due to nausea and vomiting in the early period and this situation increases other symptoms of the patient due to renal failure and drug toxicity (delirium, somnolence, etc.), short-term parenteral fluid replacement can be performed. In short term fluid replacement ; Subcutaneous fluid replacement (hypodermoclysis), which is a less invasive method, should be the first choice for terminal patients. Fluid administration should be performed with careful follow-up, as lymphatic drainage and hypoalbuminemia may cause edema due to tumor invasion. Dry mouth can be prevented by frequent oral water administration and mucosal moisturizers(10)(12). As mentioned in the above literature, it is very important to monitor fluid, that is, strict monitoring of the amount of fluid the patient receives and the amount of fluid released

On the other side the other important corner stone in our study; In terms odf the source of the patient coming primary place 28 hospital, 6 ICU , 23 from home and 6 ES was not found any significance in term's of gender . But furthermore; When we looked in the detailed analysis showed that statisticahlly significantly differences between the hospital (Hospital+ICU+ES) and homedepartments is seen first place with 40 vs 23.

The needs of advanced cancer patients to be met in relation to multiple symptoms and high burden of disease are expected to be high. (13,14)In this study, stated lead to an increased frequency of unmet needs. In studies, advanced cancer patients have been reported to have unmet needs and problems of different sizes, moderate or high levels, 40-89%. 89, daily living activities requirements 1-52%, economic requirements 13-60%, psychological requirements 16-41%, psychosocial requirements 7-44%, communication requirements 34-36%, information requirements 39% and spiritual requirements 14-33% rate (15). Additionally, Ö.Turan and et al.

were stated that in their study on trauma patients in 2019 in critical patients; They stated that early physiological data related to mortality could be identified (16). Therefore, a sufficient number and quality of education personnel are needed to meet all the biopsychosocial needs of this group of patients.

Although our study did not include trauma patients, in terms of end-stage cancer patients; We think that the BUN values determined in this study may be important. On the other hand ; According to our idea too especially gastrointestinal tumours the more higher risk rates over among the these humans. At last point we can say that prominently the most metastasis had included the hepatis structures. Here for hepatic metastasis, we believe that primary source from breast and colon cancer metastases are especially prominent.

Conclusion : Blood urea nitrogen levels may be lower in female cancer patients who come to palliative care than male cancer lines, and most of the patients who are transferred to palliative care are transferred from a hospital that is insufficient for this care to a higher level hospital. However, there was no difference between the genders in terms of the source of admission. According the our idea; Still end stage cancer disorders are overwhelmingly the first line for this risk group patients when compared with the other risk groups (trauma, stroke etc.).

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OFF-PUMP CORONARY ARTERY BYPASS (OPCAB) SURGERY

Erdem ÇETİN*

1-History:

In recent years, although not a new method, OBCAB surgery has become popular again. OPCAB was first proposed in 1910 by Alexis Carrel for the treatment of angina pectoris, and he attempted experimentally to perform coronary artery bypass surgery on the beating heart of a dog (1). After many successful unsuccessful studies by researchers over the years, Vasilii I. Kolesov (1904-1992) initiated modern OPCAB surgery in the sixties (2).

Subsequently, between 1964 and 1976, Kolesov et al. Performed more than 130 coronary revascularizations with OPCAB surgery (3). In the 70s and 80s, OPCAB surgery continued to be performed by some teams due to their economic advantages (3-5). In this period, OBCAB surgery was preferred in selected cases with one or two vessel coronary artery disease on the anterior surface of the heart. Surgeons had to wait until the development and diffusion of coronary stabilizers until the 90s to ensure complete revascularization by safely accessing the posterior wall of the heart. Today, OBCAB surgery has become a part of modern cardiac surgery with developing technology and increasing experience.

2-Advantages of OPCAB Surgery:

Inflammatory Response and Oxidative Stress:

With the introduction of extra-corporeal circulatory technology in cardiac surgery in the 50s, discussions of systemic inflammatory reactions have started. OBCAB surgery has advantages in terms of organ dysfunction and peri-operative morbidity caused by inflammatory reaction.

Brasil et al. (1998) conducted the first of these studies. When prospectively examined 20 patients operated with on-pump and off-pump techniques, plasma TNF increased in 60% of on-pump patients and did not increase in any of the off-pump patients. Clinically, less fever, hypotension, inotropic drug use and postoperative bleeding were found in

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off pump patients. Shorter intubation time was detected in off-pump patients. They concluded that all these data are due to low TNF (6).

Another prospective study by Matata et al. In 20 randomly selected patients, inflammatory mediators such as complement C3a, interleukin-8 (IL-8), elastase and TNFa were evaluated after off pump and on pump surgery. Oxidative stress markers such as lipid hydroperoxide and protein carbonyl were found to increase in the on pump group. They concluded that off-pump surgery can significantly reduce oxidative stress (7).

Myocardial Protection:

Many authors have reported the potential benefit of off pump surgery on myocardial protection. In Pfister's study, it was shown that there was a decrease in the incidence of low cardiac output and decreased intra-aortic balloon pump use in Off pump patients (8).

In a prospective randomized study of 30 patients, Czerny et al. Found that postoperative myoglobin, CK-MB and troponin I values of off pump patients were much lower than those of ten pump patients(9).

Pulmonary Physiology:

Although there are many studies suggesting that extracorporeal circulation and disruption of lung physiology are related, the number of studies on off-pump surgery in this area is scarce. In the studies of Cox et al. And Taggard, no relationship was found between off pump surgery and impaired lung physiology. In these studies, it was concluded that pulmonary physiology disorders observed during CABG were not related to CPB use, but were associated with sternotomy-induced surgical approach (10-11).

Brain Physiology:

The risk of stroke during coronary artery surgery ranges from 1% to 8% (12-13), mainly due to plaque mobilization rupture and peri-operative arrhythmia. Off-pump coronary surgery, despite the use of full arterial grafts, requires manipulation of the ascending aorta for proximal vein graft anastomoses if preferred. However, with the widespread use of off pump surgery, an increase in the studies on this subject has started. As a result of a randomized study of 281 patients by Van Djick et al., Results were reported in favor of OPCAB (14).

Renal Physiology:

After the introduction of CPB in cardiac surgery, it was seen as the main cause of postoperative renal failure. Pulse flow loss, hemodilution, hypothermia, and inflammatory reaction are all contributing factors to this major complication. Off pump surgery can also prevent the deterioration of renal function as it allows avoiding CPB. In a prospective, randomized

study of 50 patients by Ascione et al., They concluded that in off-pump surgery, there is a better conserved glomerular filtration with low N-acetyl glucosidase excretion as a renal tubular biochemical marker (15). As a result of a non-randomized prospective study of 55 OPCAB and 635 ONCPB patients by Maribel et al., They concluded that OPCAB grafting may be a procedure that can be used regardless of the increase in serum creatinine and clearance (16). OPCAB surgery has recently increased its popularity in the world of coronary revascularization. New techniques and strategies are reported and success rates increase as surgeons experience increases. The cost advantage has become the preferred technique for patients and surgeons because of the low risk of complications arising from the inflammatory effects of CPB.

3-Principles of Stabilization and Preservation of Hemodynamics in OPCAB Surgery:

Stabilization of the myocardium during coronary grafting is essential in OPCAB surgery. In the early stages, only the anterior coronary arteries were targeted in OPCAB surgery and simple and primitive stabilization methods were used. However, this was not sufficient to provide safe access to the posterior wall of the heart and caused incomplete revascularization of the circumflex arteries. During the last two decades, various techniques and stabilization devices have been developed and used for myocardial stabilization during OPCAB surgery.

Current Techniques:

Myocardial Mobilization and Preservation of Hemodynamics:

Left Anterior Descending (LAD) Artery:

The LAD artery is usually accessed by simple manipulation. Alternatively, a few sponges to be placed under the heart or pericardial sutures placed just above the left phrenic nerve may be used to lift the apex of the heart. These methods have little hemodynamic effect. Manipulation of the anterior region of the heart with a mechanical stabilizer leads to an interruption of coronary blood flow during coronary grafting, a 6 to 15% reduction in cardiac output, and is generally well tolerated (20-21) (Figure 1).

Hemodynamics may deteriorate during diagonal grafting, Nierich et al. They reported a decrease in left ventricular diastolic volume during diagonal artery manipulation in OPCAB and that they used trendelenburg position and used dopamine to cope with this (22). The use of intracoronary shunt should be used in cases of surgeons with low OPCAB experience and slow anastomosis rate, as well as in all LAD grafts with moderate lesions and less developed collateral.

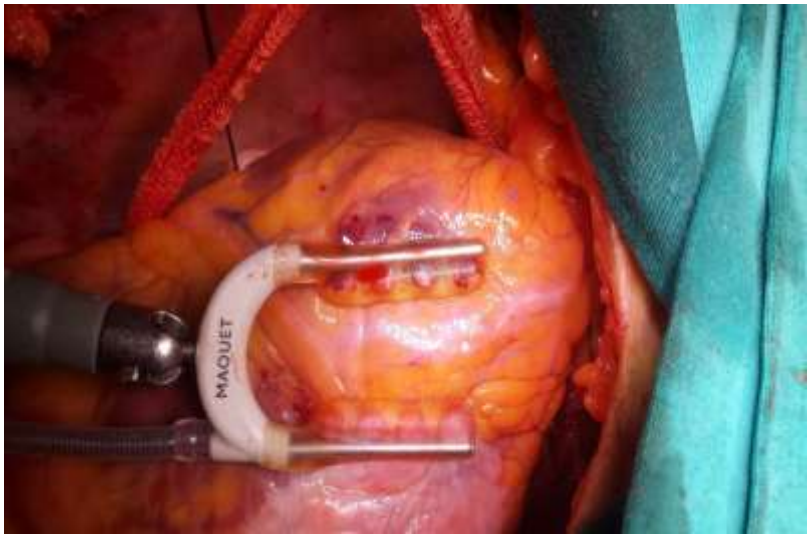

Figure 1. *(Taken from the archives of Op. Dr. Erdem Çetin)*

Pericardial Traction in Posterior Wall Stabilization:

Many techniques have been described, including pericardial traction for stabilization of posterior wall grafts (19,21-22). Four pericardial traction sutures were placed approximately 2 cm close to the left superior pulmonary vein and inferior vena cava, and the vertical apex of the heart was beneficial to surgeons, and the stabilizer was then applied to the targeted marginal branches. With this technique, average cardiac index decreased by 10% and average pressure decreased by 15% (23). There are trends in the use of trendelenburg position and / or inotrop in some studies during the application of similar techniques (24,25) (Figure 2).

Use of Apical Suction in Posterior Wall Stabilization:

Posterior wall stabilization and apical suction devices have been developed. Starfish (Metronic, Minneapolis, MN) and Xpose devices (Guidant Corporation, Cupertino, CA) are the most popular (26,27). These devices allow the heart apex to be vertical and mobilize the apex directly instead of the ventricular base. This technique facilitates the mobilization procedure because it involves little manipulation but has the potential to damage as it exerts direct force on the ventricular wall. Gummert et al. In the comparison of the results of 27 patients who underwent posterior wall grafting, it was stated that the use of suction did not provide superiority to the use of traction sutures (28).

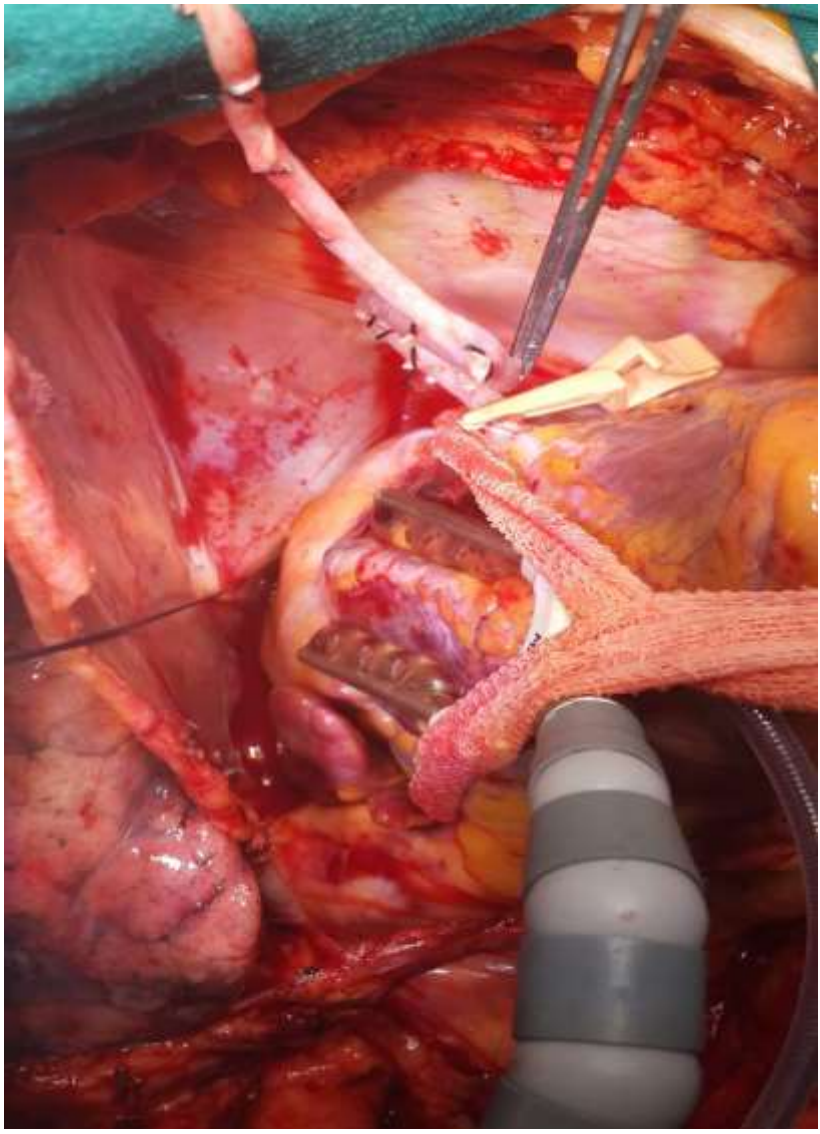

Figure 2. (Taken from Op. Dr. Erdem Çetin's archive)

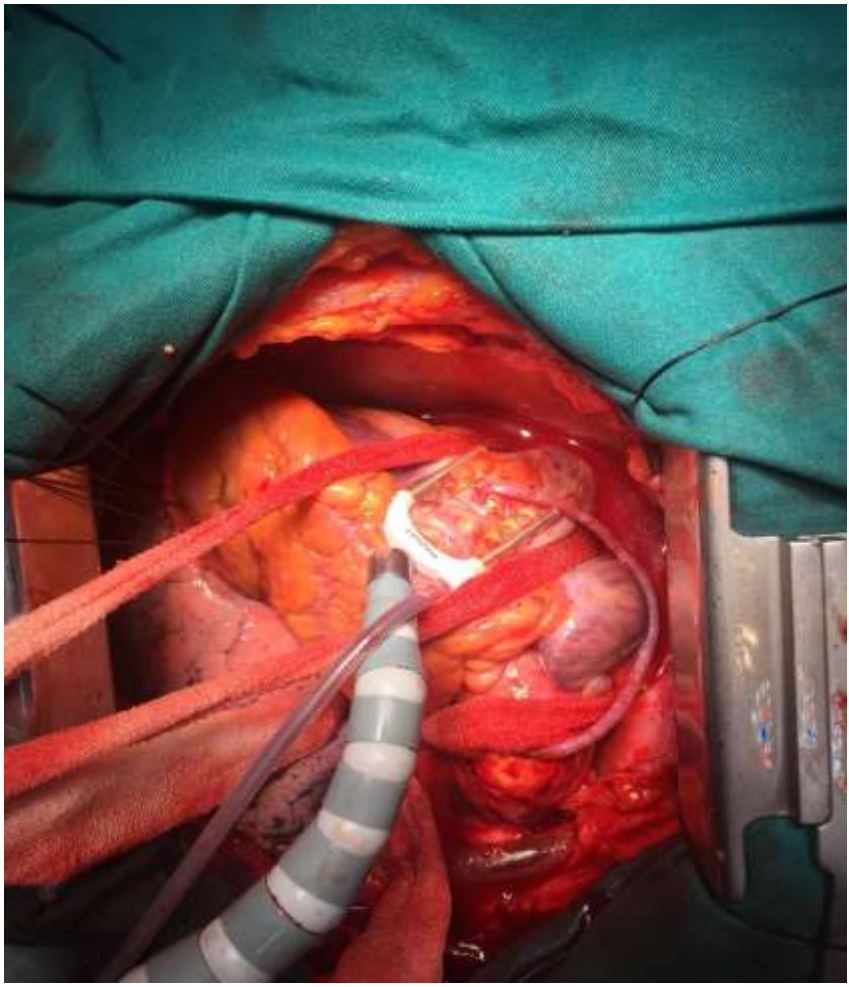

Figure 3. (Taken from the archives of Op. Dr. Erdem Çetin)

Auxiliary Techniques:

Trendelenburg Position:

Many auxiliary techniques have been described for stabilizing the myocardium and maintaining hemodynamics. As mentioned earlier, the use of Trendelenburg position is the most popular.

Trendelenburg position during OPCAB surgery contributes to increased venous hydrostatic pressure. In addition, it is safe to use during apex verticalization and posterior stabilization of the heart, especially in circumflex artery, posterior descending and right coronary artery grafts.

Slope Right and Left:

In addition to the Trendelenburg position, turn the table to the right (towards the surgeon)

It is commonly used during posterior grafting. In posterior descending and right coronary artery grafts, left rotation is applied. Myocardial stabilization has undergone major technological advances since the early 90s. The development and use of coronary stabilizers, the widespread use of coronary shunting, the surgeons' experience in OPCAB surgery, and the development of alternative retraction methods have contributed to the success rates of off-pump operations.

4-Anesthesia in OPCAB Surgery:

Preoperative Evaluation:

The preoperative evaluation of OPCAB patients does not differ from patients who will undergo routine surgery.

Premedication:

It aims to alleviate negative effects such as premedication, anxiety and hypertension. It also provides comfort to the patient during the placement of intravascular catheters. Narcotics (morphine 0.1-0.15 mg / kg IM) and sedative (scopolamine 5 μg / kg IM or midazolam 0.05 mg / kg IM) are the most commonly used drugs.

Prevention of Hypothermia:

Care should be taken to prevent hypothermia, especially if early extubation is planned. All intravenous fluids are applied warmer, washing fluids to be used on the heart are heated.

Normothermia is maintained using sub-patient warmers, thus avoiding the adverse effects of hypothermia, wound healing, clotting and arrhythmia.

Anesthesia Induction:

The purpose of OPCAB surgical anesthesia is early extubation. Medications with short or moderate duration of action are selected. Several drugs can be combined for this purpose (29). Fentanyl 15-50 / g / kg and sufentanil 1.5-3.0 μg / kg are commonly used before intubation. These doses are considerably lower than normal use. Remifentanil, a strong and ultra-short acting narcotic, can be given at an infusion rate of 0.15-0.4 μg / kg / min. In addition, one of the pentotal 2-3 mg / kg, midazolam 0.1-0.2 mg / kg or propofol 1-2 mg / kg may be used. In addition to the narcotics described, anesthesia is provided by propofol infusion. Maintenance of isoflurane or sevoflurane gases is also utilized. Between the induction of anesthesia and the onset of coronary grafting, 2-5 g of magnesium sulfate

is administered. Magnesium has the effect of reducing the incidence of arrhythmias (29-32) and may also reduce arterial graft spasm (33).

Preservation of Hemodynamics:

Since hemodynamic changes can be sudden and obvious, the surgeon and anesthesiologist should be very careful and experienced. If hypotension occurs, fluid loading or phenylephrine (vasopressor) is the most commonly used method and rarely norepinephrine or epinephrine may be necessary. B-agonist drugs should be avoided as they increase myocardial and systemic oxygen consumption during coronary revascularization. At the beginning of the surgery, a low dose of nitroglycerin infusion (0.1-0.3 μg / kg / min) is initiated. Thus, nitroglycerin can be utilized to increase Sub-endocardial flow and to increase myocardial perfusion by reducing preload. In addition, the preventive effect of arterial graft vasospasm is utilized.

Preservation of Hemodynamics by Revascularization Areas:

In OBCAB surgery, revascularization is first initiated from the coronary artery with the highest stenosis. Unfractionated heparin 100U / kg is administered before starting anastomoses. In OPCAB cases, the requirement of heparin is checked by the active coagulation time (ACT) measured every 30 minutes. ACT Add heparin bolus of 25-50U / kg for 300 to 400 seconds.

The perfusionist should be prepared and wait for the operating room at all times, with CPB installed. In appropriate patients, minimal doses of beta-blockers may sometimes be administered (metoprolol 2.5-5 mg IV), thereby reducing myocardial oxygen consumption and keeping the heart rate within the range of 50-75 / min. Despite increasing technical advances in OPCAB surgery, circumflex coronary artery grafting is still the most challenging part of the operation for both the surgeon and the anesthesiologist. The anesthesiologist should have a temporary pacemaker available for hypotension for possible bradycardia which is difficult to predict. Although fluid loading may help hemodynamics due to possible hypotension, it is useful to avoid overloading the fluid. Anostomosis can be performed in all parts of the heart with gentle surgical manipulations and a good hemodynamic protection strategy. Proximal anastomosis of the saphenous vein bypass grafts should be gently manipulated once to reduce the risk of embolism and avoid the risk of dissection of the aorta when performing the ascending aorta (34). To reduce aortic wall stress during aortic anostomosis, it is necessary to lower systemic blood pressure to 90 mmHg systolic levels. Protamine sulfate and heparin should be reversed when surgery is completed without any problems.

Indications and Important Strategies for OPCAB Surgery:

Today, OPCAB surgery is routinely performed by experienced teams in coronary revascularization compared to previous years. But there are, of course, some situations in which this surgical method is contraindicated.

Definite Contraindication:

* Preoperative hemodynamic instability

* Deep intra myocardial LAD

* Moderate (3+) or severe (4+) mitral insufficiency

Relative Contraindications:

* Pulmonary hypertension

* Diffuse myocardial adhesion during reoperative surgery

* Enlarged ascending aorta

With the increasing experience and scientific studies in OPCAB surgery, some strategies of this coronary revascularization technique have been formed.In OBCAP surgery, the most severe stenosis of the corner artery should be grafted first. Proximal anostomoses should be performed with single side clamp technique to the ascending aorta. Moderate hypotension should be observed during proximal anastomosis.

Results from various centers around the world have demonstrated the effectiveness of OPCAB, even in high-risk patients. According to the 2018 ESC / EACTS myocardial revascularization guidelines, OPCAB surgery is recommended in high-risk patients (35). Routine use of this technique, which is recommended in high-risk patients, is undoubtedly used in some centers as a routine surgical procedure. We believe that the prevalence and success rates of OPCAB will increase with each passing year as the technique, which has been the focus of the discussions for years, develops methods that each surgeon feels safe and comfortable while remaining within the indications.

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DEEP VENOUS THROMBOSIS

Ertan DEMİRDAŞ*

Introduction

Deep vein thrombosis (DVT) is a common public health problem characterized by increased morbidity and mortality. It often occurs in deep veins of the lower extremities. Complications of pulmonary thromboembolism (PTE) and related pulmonary hypertension, post-thrombotic syndrome with degeneration of the venous valves of the deep veins and ulcerated ulcers in the lower extremities, is a serious public health problem in terms of labor loss and cost of treatment. Prevention of pulmonary embolism, which is difficult and costly to treat, seems more plausible. In recent years, venous thromboembolism (VTE) has been extensively studied. However, the choice of ideal prophylaxis remains controversial. Numerous factors can be observed in the emergence of the debate. Non-homogeneous patient populations, asymptomatic cases, inadequate diagnostic methods and commercial factors are some of them.

Etiology and Pathophysiology

The three major pathogenetic Virchow triads that facilitate the development of venous thromboembolism were described by Rudolf Virchow in 1856, and this theory is still valid in the etiology of deep vein thrombosis. The slowing of blood flow (stasis), damage to the vessel wall (primarily endothelial damage-dysfunction) and hypercoagulability are defined as Virchow's triad (1) (Table 1).

Table 1: Virchow’s triad and factors affecting formation

Venous stasis	Damage to the vessel wall	Hypercoagulability
Long-term bed rest Long-term travel Inactivity due to surgical intervention Obesity Venous obstruction due to Pregnancy Cardiomyopathy	Vascular injury / trauma Venous catheter insertion Varicose vein formation valve damage Surgical intervention Bone fractures	Acquired thrombophilia History of deep vein thrombosis Surgical procedures Antiphospholipid antibody syndrome Activated protein C resistance

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Congestive heart failure Atrial fibrillation	Cardiovascular diseases Burn Tumor invasion	Factor V Leiden mutation Prothrombin gene (G20210A) mutation Protein C / S deficiencies Antithrombin deficiency Family history Pregnancy

Venous thromboembolism is a multifactorial disease and multiple risk factors may coexist simultaneously. The more risk factors the patient has, the higher the risk of developing VTE (2).

Venous thrombosis is the third most common cardiovascular disease worldwide after ischemic heart disease and stroke. The incidence of lower extremity DVT, which can cause severe sequelae and fatal complications, is 1/1000 person years in the general population but 3/1000 in the elderly population. (3,4). Risk factors of venous thromboembolism can be classified as acute triggering factors and chronic predisposing factors according to their thrombogenic power (Table 2).

Table 2: Clinical risk factors

Acute factors	Chronic factors
Hospitalization major surgical intervention Lower extremity / pelvic trauma or fracture Long-term travel Recently started estrogen therapy Intravenous catheter application Chemotherapy Inactivity Pregnancy and Puerperium	Age Coagulation disorders Obesity Paralysis Estrogen treatment Important medical diseases (chronic respiratory and circulatory diseases, inflammatory bowel disease, nephrotic syndrome, myeloproliferative diseases, etc.) History of venous thromboembolism in individual and / or family Cancer

Deep Venous Thrombosis Diagnosis

In clinical and physical examination of deep vein thrombosis (DVT), clinical symptoms and signs such as pain, hypersensitivity, erythema, elevated heat, edema, swelling or dorsiflexion of the calf, defined as Homans' symptom are found in only less than 50% of DVT cases. These clinical signs and symptoms include extremity trauma, cellulitis, superficial vein thrombosis. lymphangitis, lymphedema and post-thrombotic syndrome. Therefore, it is not a reliable and appropriate method to diagnose DVT only according to clinical signs and symptoms. To confirm the diagnosis, clinical risk scoring is performed and advanced diagnostic procedures such as D-dimer or color doppler ultrasonography (RDUS) should be performed(5). A risk scoring system and a simplified DVT diagnostic algorithm can be used in the diagnosis of DVT (Table 3).

Table 3: Wells clinical risk scoring for the diagnosis of deep vein thrombosis

Klinik özellikler	Skor
Active cancer (treatment in progress, applied in the last 6 months, palliative treatment)	1
Paralysis, paresis or splinting of the lower extremities	1
Bed dependency for more than three days, major surgery in the last 4 weeks	1
Localized sensitivity on deep vein system	1
Swelling in the whole leg	1
Tuberositas tibia increased by more than 3 cm compared to an asymptomatic leg	1
Gated edema (more in symptomatic leg)	1
History of deep vein thrombosis	1
Collateral superficial veins (non-varicose)	1
	1
Risk assessment: Score ≤0 DVT low probability Score = 1-2 DVT probability moderate Score ≥ 3 DVT high probability	

DVT: Deep vein thrombosis

If both legs have symptoms, the leg with more symptoms is evaluated. D-dimer test is recommended for patients with low probability of clinical DVT (test score ≤0, probability of DVT 5%) as shown in figure 1. A negative D-dimer test means that the 3-month cumulative incidence of

VTE is 0.5%. If the D-dimer level is high, ultrasonography should be performed. A positive ultrasonography confirms the diagnosis of DVT, and if negative, the diagnosis of DVT is avoided.3 Direct ultrasonography is recommended for patients with a moderate (test score 1-2, DVT probability 33%) and high (test score ≥3, probability of DVT 85%) of clinical DVT. The negative results of compression ultrasonography do not exclude the diagnosis, but the risk of DVT occurring within 3-6 months continues; 3.6% of moderate-risk patients and 31% of high-risk patients may develop DVT during this period. In this case, D-dimer test is appropriate.

Since D-dimer test is a laboratory test whose sensitivity and specificity vary according to the method used, this issue should be taken into consideration when interpreting. High levels are not always specific to DVT; cancer, infectious diseases, recent surgical intervention, trauma, and pregnancy. D-dimer has a high negative predictive value, especially in cases with suspected DVT from outpatients, ie non-triggered DVT. Color Doppler ultrasonography (RDUSG) is the most appropriate first-line diagnostic method in the diagnosis of DVT because it is non-invasive, fast and easily applicable in patients suspected of DVT. RDUSG has 97% sensitivity and 94% specificity in the diagnosis of DVT (6). However, detection of iliac vein thrombosis can be difficult especially with RDUSG. In these cases, computed tomography (CT), magnetic resonance imaging (MRI) and venography have an important role. The primary diagnostic criteria for DVT is that the vein lumen is not completely compressed. The sensitivity and specificity of compression ultrasonography in the diagnosis of symptomatic proximal DVT is above 95%; In isolated distal DVT, sensitivity is accepted as 70% and positive predictive value as 80% (7).

Pulmonary Embolism

PE, which can also be described as a complication of DVT, is usually characterized by sudden onset dyspnea, tachypnea, tachycardia and chest pain, and these findings are not specific to this disease. So the path to diagnosis begins with clinical suspicion. In addition to initial symptoms and signs, the patient should be evaluated for risk factors(8). The lack of specific clinical findings and the high risk of bleeding from anticoagulant therapy require confirmation or exclusion of the diagnosis as soon as possible. For this purpose, the possibility of clinical diagnosis. The first method to be used for imaging is chest radiography. Chest radiography is normal in 20–40% of patients with PE without cardiopulmonary disease. Normal chest X-ray does not exclude the possibility of PE(9).

Ventilation / perfusion scintigraphy is a reliable diagnostic test in patients with suspected PE. While high probability scintigraphy results are sufficient to confirm the diagnosis, further investigation is required to confirm the diagnosis in case of a medium and low probability result. CT

angiography can be performed for this purpose. If a single-detector CT is performed, normal CT does not exclude PE alone; lower extremity US should also be negative for proximal thrombus. However, the use of multidetector CT in the same case may exclude the diagnosis alone. Pulmonary angiography is the gold standard in the diagnosis of PE but it is an invasive procedure. However, it is used only in cases where definitive diagnosis cannot be made by other methods(10).

Thromboprophylacsia in Deep Vene Thrombosis

Because of the high prevalence of DVT, the incidence of adverse complications of DVT, and the proven efficacy of thromboprophylaxis, routine thromboprophylaxis in high-risk patients is a rational approach to the prevention of DVT(11).

Pharmacological thromboprophylaxis increases the risk of bleeding, but clinically significant bleeding rates are between 1-5%. Thromboprophylaxin is also known to be a good cost-effective method when used appropriately (12). Current anticoagulant drugs used in the prevention and treatment of venous thromboembolism are warfarin, standard heparin (SH), low molecular weight heparin (LMWH), factor Xa inhibitors and direct thrombin inhibitors. The anticoagulants used in treatment and prophylaxis are given in Table 5. The advantages of LMWHs to SH are summarized in Table 6.

Table 4: Anticoagulants used in the treatment of deep vein thrombosis and thromboprophylaxis

Unfractionated heparin
LOW MOLECULAR WEIGHT HEPARIN Ardeparin Dalteparin Enoxaparin Nadroparin Reviparin Tinzaparin Bemiparin Parnaparin Danaparoid
Factor Xa inhibitors Fondaparinux Apixoban Rivaroxaban edoxaban
Thrombin inhibitör Dabigatran
Vitamin k antagonist Warfarin

The main objective of the treatment and prophylaxis of deep vein thrombosis is to prevent chronic complications such as pulmonary thromboembolism (PTE), pulmonary hypertension, peripheral venous diseases, DVT recurrence and post-thrombotic syndrome. Anticoagulation therapy should be started as soon as possible in all patients with DVT diagnosed by objective methods. If the clinical suspicion is strong and the diagnostic tests are to be delayed, treatment should be started without waiting for the tests (13).

Table 5: Basic methods for the treatment of deep vein thrombosis

Unfractionated heparin
Low molecular weight heparin
Fondaparinux
Oral anticoagulants (warfarin and direct FXa / thrombin inhibitors)
Thrombolytics
Vena cava filters
Surgical treatment
Endovenous pharmacomechanical methods
Endovenous mechanical methods

The duration of anticoagulant therapy in deep vein thrombosis should not be less than 3 months. Patients with hypercoagulability syndrome should be treated for a long time if the genetic disorder is combined type or homozygous. If there is an unknown (idiopathic) proximal DVT, there is no risk of bleeding and anticoagulation treatment is possible, treatment should be performed for more than 3 months (14). Patients with acute DVT can be treated in hospital or at home. In the studies comparing the results of treatment in hospital or at home, no significant difference was found in terms of recurrent DVT rate, major bleeding and mortality (15). Table 6 presents the characteristics of the patient group that needs to be treated in the hospital.

Table 6: patient groups that need to be treated in hospital

Patients with high thrombotic load
Patients with high risk of bleeding
Active bleeding
New surgical procedures
Patients with advanced liver disease
Less than 45 kg, heavier than 100 kg children
Pregnant women with complications
Patients with medical illness requiring hospitalization
Patients with venous gangrene

In the studies conducted to evaluate the economic cost of DVT and its associated complications, the annual cost in the United States is between US $ 7.5-39.5 billion in total and the preventable amount of this cost is US $ 2.5-19.5 billion annually (16). With effective prophylaxis and appropriate treatment options, the prevention of DVT and its complications seems to be able to achieve a nearly half reduction in economic cost (17).

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THE IMPORTANCE OF BIRADS 0 IMAGING LESIONS (BREAST IMAGING REPORTING AND DATA SYSTEM), IN TERMS OF MALIGNANCY IN MAMMOGRAPHY

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Introduction:

Breast cancer (BC), is the most prevalent tumour among female gender worldwide and is the main reason of cancer death. In 2012, approximately 1.7 million new BC cases were reported, about a quarter of all newly diagnosed cancer cases occured . The increase in BC incidence remained at the highest level in more developed regions, but was relatively higher in less developed countries due to an increase in mortality, lack of early diagnosis, and inadequate access to treatment facilities (1,2). On the other hand, there is consensus that mammography(MMG) screening can detect breast cancer early and reduce mortality(3). However, Liberman et al. stated that a 7-10% malignancy rate in the 367 high-risk women with normal mammography, in their study(4). At this reason, we tried to touch the BIRADS 0 lesions in the BIRADS evaluation system .

As a first step let's take a look at the BIRADS system used with mammography;

BIRADS 0: Insufficient examination.
Additional examination is required to make a decision (compression, magnification, mammography, ultrasound(USG), other mammographies should be examined)

BIRADS I: Negative.

The breasts are symmetrical and additionally there aren't any mass, no suspicious calcification.

BIRADS II: Benign findings.

Calcified fibroadenomas

Benign calcifications;

Vascular Calcifications

Structural Calcifications. Surgery or biopsy develops at the site.

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Secretory calcifications (seen in ductal ectasia)

Fat-containing lesions

Fat cysts

Breast lipomas

Fibroadenolipoma, hamartoma

Galactocele

Simple breast cysts

BIRADS III: Probably benign

A short interval check is recommended.

BIRADS IV: Suspected of malignancy. Biopsy recommended

BIRADS V: Strong suspicion of malignancy. Necessary actions should be taken.

BIRADS VI: Known malignancy(proofed with biopsy)

Breast Imaging-Reporting and Data System (Breast Imaging-Reporting and Data System). MMG had been developed to standardize breast ultrasound and breast MR reports, making it easier for non-radiologists to understand the report (5)updated in American College of Radiology, 2015).

The feature or advantage of BI-RADS classification is that it not only identifies the lesion but also gives information about what the lesion might be. The more importantly, too, the lesion should be evaluated by considering the possibility of being benign - malignant. For example, normal follow-up, frequent follow-up (3 months-6 months), such as biopsy is required. BI-RADS classification is mostly made according to mammography. Sometimes, however, mamaography alone is not sufficient, old mamaographies are examined, breast ultrasonography and even breast MRI are performed, after all are evaluated and classified according to BI-RADS (6)

Material and Methods:

Between June 2016 and April 2019,the patient records of the radiology BIRADS reporting results were reviewed retrospectively and then among BIRADS 0 lesions the malignancy cases identified. Mean and standard deviation in continuous variables and percentage and frequency values in dichotom variables were used. As a resuult of Kolmogrov Smirnov test, according to the normal distribution of variables, continuous independent variables;Student t test or Mann WhitneyU test were used in the independent variables, while dichotom variables chi-square were used.

Results:

From a total of 3038 BIRADS 0 mammograms resulted in biopsy for 13 patients with clinical suspicion.

All patients who underwent biopsy for BIRADS 0 lesion were female and the mean age was 51.4 ± 9.3 years.

On the other hand, the mean age of 56 patients with BIRADS 4,5 and underwent biopsy was 52.3 ± 14.8 years (p = 0.78).

Four (30.8%) of the patients with BIRADS 0 who underwent biopsy had malignancy.

In addition, 33 of 56 patients who had biopsy with BIRADS 4,5 mammographic diagnosis had malignancy (58.9%).

There wasn't any significance between two patient community in terms of incidence of malignancy (p = 0.121).

Table I: In this table is showed that the incidence of breast cancer for BIRADS 0, 4 and 5 mammography lesions.

	Mean age	**p**	**Breast cancer incidence among biopsy cases**	**P<0.05**
BIRADS 0	**51.4 ± 9.3**		**4vs 13(30.8%)**	
BIRADS 4-5	**52.3 ± 14.8**	**0.78**	**33vs56(58.9%)**	**0.121**

Discussion:

In the most common type of cancer in women is breast cancer(7). Also it's reported that Turkey has doubled in the last 20 years (7,8).Early diagnosis is the most important factor in mortality and morbidity in breast cancer(8).On the other hand, MMG is shown as the first and most suitable radiological imaging method to evaluate the breast. Because breast cancer mortality has been reported the would be decrease by 30-60% due to early diagnosis as a result of mammographic scans(8,9,10).The sensitivity of MMG decreases in dense breasts, especially in cases with high ductal structures. Such cases are interpreted as BIRADS 0 on MMG(11). BIRADS 0 may occured benign diseases, fibroadenomas, chronic mastitis and inflammation, in our series 2 patients had chronic mastitis. As a result, chronic infections of breast infections can also lead to BIRADS 0 lesions too. In this respect, we believe that sometimes breast inflammation and infections with the papabl mass may cause confusion in the clician if there aren't any finding without any the presence of infection or inflammation on the skin in the clinician.

In this reason; Especially in the clinical and radiolical suspicious cases must be breast biopsy with needle (11). However, proper conditions and meticulously breast biopsy are very important for good sample removal and nosocomial infections. D.Dülger and M.Berktaş in their study on the clinical importance of S.Maltophilia strains in the importance of nosocomial infections. It is reported that trimethoprim-sulfamethoxazole should be used as the most effective antibiotic against the agent when it is necessary to start empirical treatment in infections caused by S. maltophilia strains. An interesting point is the increase in S. maltophilia septicemia after the introduction of imipenem, a broad-spectrum antibiotic against gram-negative bacteria(12,13). In this respect, although the breast masses enter the general surgery field, the clinician should always be vigilant and show a multidisciplinary study when necessary. On the other hand, E.Kaya emphasized that cefozolin reduces surgical site infections in breast surgery due to breast cancer. As a result, it should be considered that there may be surgical site infections after the diagnosis of breast cancer starting with MMG(14).The category BI-RADS 0 indicates that advanced evaluation should be made by other available methods other than USG, since precise ultrasonographic evaluation is not possible(15).Additionally, Dobrosavljević A, etal. had stated that diagnostic values of breast USG in MMG BI-RADS 0 and clinically vague or suspicious of malignancy breast lesions six times more common cause for biopsy than BI-RADS 5 category(15) In this study we too detected there aren't any differences between that BIRADS 4 - 5 and BIRADS 0 lesions, in the biopsy cases. In the evaluation of breast cancers, these cases are still overlooked within the scope of screening programs and we think that the experience of the clinician is especially prominent. According to our idea this is depend on attributed to the fact that an experienced clinician does not make decisions based solely on laboratory and imaging methods and attaches importance to physical examination and anamnesis.

Conclusion: As a result, the suspicion of malignancy should always be kept in mind in BIRADS 0 lesions that are biopsied on clinical suspicion.

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SURGICAL APPROACH IN CAROTID ARTERY STENOSIS

Hakan KARTAL[*]

History

The importance of the carotid artery is known from Hippocrates to the present day in Ancient Greece. Hippocrates did not define ‘apoplexy sadece as a term only in the 4th century BC and described the full development of stroke, transient ischemic attacks of the brain and hemiplegia on the opposite side in carotid artery disease (1). Rufus of Ephesus (100 BC) stated that the word meaning of the carotid artery comes from ‘deep sleep ‘(1). In 1552, Ambroise Pare tied the main carotid artery in a traumatized patient and mentioned the relationship of this vessel with deep sleep (2). In 1893, the relationship between extracranial vessel occlusion and hemiplegia was the subject again. Gowers described this condition as otid Carotid hemiplegia.. In a textbook published in 1871, the German clinician Gerhardt emphasized the importance of vascular auscultation in the definition of carotid stenosis. Gluck reported in 1898 that the blood flow of the brain could be corrected for the first time by an animal experiment using a vein graft to the main carotid artery (1,4). In 1896, M. Jaboulay performed an end-to-end anastomosis of the carotid artery. The most valuable information about extracranial occlusive carotid artery diseases came from Rumsey Hunt in 1914. Hunt reported that contralateral hemiplegia and ipsilateral amorosis fugax develop in diseases of the cervical carotid arteries and that examination of pulses of these vessels is important (1).

Epidemiology

Cerebrovascular disease is the second leading cause of death worldwide and accounts for approximately 9.5% of all deaths. Approximately 15% of strokes are fatal, 15% to 20% result in severe disability, and 15% to 20% of patients who recover have another stroke that results in disability in the future. Atherosclerotic carotid artery disease is the most commonly treated vascular disease after coronary artery disease. The incidence of significant carotid artery disease in patients with coronary bypass is 3-12%, while the incidence of symptomatic coronary artery disease in patients with carotid

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endarterectomy is around 50%. A statistical study of the American Heart Association (AHA) in the past years is quite striking. On average, the patient has an American stroke every 24 to 45 seconds. Each year, approximately 700,000 people have new or recurrent strokes. Of this, 500,000 are new and 200,000 are repetitive stroke. 88% of all strokes are ischemic, 9% are hemorrhagic and 3% are due to subarachnoid hemorrhage.

Anatomy

The brain derives from the four main arterial trunks, which originate from the arcus aorta and consist of two internal carotid arteries and two vertebral arteries (10). Carotid System Internal carotid artery (ICA): This artery emerges from the CCA (common carotid artery) with the external carotid artery in the cervical region and passes through the carotid canal to the middle cranial fossa. It then passes through the cavernous sinus and pierces the dura and proceeds to the subarachnoid space. The internal carotid artery (ICA) is divided into two terminal branches lateral to the optic chiasm on the surface of the brain: ACA (anterior cerebral artery) and MCA (medial cerebral artery). The ICA completes this course mainly in four segments: 1. cervical segment 2. petrosal segment 3. cavernous segment 4. cerebral (supraclinoid segment)

-Cervical segment: The main carotid artery from the carotid channel entry, the branch does not branch.

-Petrosal segment: The segment of the temporal bone within the petrosis segment is divided into two branches: the caroticotympanic artery (feeding the tympanic cavity) and the pterygoid artery (waters of the pterygoid channel).

-Cavernous segment: The segment within the cavernous sinus is divided into three branches: 1. Pituitary artery (nourishes the neurohypophysis). 2. Anterior meningeal artery (waters the base of the anterior fossa). 3. Ophthalmic artery (feeding the optic nerve, retina, frontal and ethmoid sinuses and nasal ridge with anastomosis of branches of external carotid artery).

Clinical Findings in Carotic Artery Disease

The most important finding in physical examination is the murmur. However, there is no relationship between murmur and severity and prevalence of stenosis. At 30-30% stenosis on the carotid, murmur begins to be heard.

In carotid artery disease, symptomatology can be determined by 5 main findings (16,17). These:

1. Amarosis Fugax (Transient mononuclear vision loss):

Amarosis is a potential symptom of carotid artery disease with unilateral visual loss occurring in the form of fugax or retinal artery occlusion (18).

2. Transient Ischemic Attack (TIA):

TIA is a focal brain dysfunction that occurs due to ischemia of one of the vascular systems and lasts less than 24 hours (19,20).

3. Reversible Ischemic Neurological Deficit (RIND)

4. Ischemic Stroke:

"World Health Organization WHO (WHO) defined the term stroke as bul clinical manifestations of sudden, focal or global cerebral dysfunction of vascular origin, which may last 24 hours or more, leading to death". Infarction or bleeding due to trauma, infection, tumor or transient attacks due to cerebral ischemia were excluded from the definition (21).

5. Cerebral Infarction:

80-85% of all strokes are cerebral infarction, 10-15% intracerebral hematoma and 6-8% subarachnoid hemorrhage. The main feature of stroke is the sudden onset of neurological findings.

Diagnosis Methods in Carotic Artery Disease:

Dublex Ultrasonography

Duplex ultrasonography is a non-invasive method for real-time two-dimensional imaging, doppler flow analysis, vascular structures and blood flow velocity. Arterial diameter and degree of stenosis are not measured directly with this method. The degree of stenosis is determined by evaluating the blood flow velocity. Speed charts were used to determine carotid stenosis by duplex ultrasound. ICA peak systolic velocity, ICA PSV / CCA PSV values were correlated with angiographic methods in carotid stenosis grading. When compared with conventional angiography, sensitivity and specificity were found to be 85% and 90%, respectively, in the evaluation of 70% carotid artery stenosis (23).

Color Doppler Us (CDUS)

Carotid arteries should be evaluated with RDUS in the axial plane in all areas that can be traced from the most proximal to the distal, as in the gray scale. First of all, whether the carotid arteries and internal and external branches are open or not are evaluated. The level of carotid detachment, if any variation or tortuosity is determined. There are pathologies that can be diagnosed directly by RDUS. A critical main carotid artery stenosis in the proximal and associated external-internal carotid artery stealing phenomenon and main carotid artery dissection can be counted among these (24).

Spectral Doppler Us

The most important criterion for assessing the severity of carotid artery stenosis is flow velocity. Spectral flow samples are taken from the distal part of the plate at the determined level, from the areas where velocity values are expected to be the highest due to jet flow. Peak systolic velocity and end-diastolic velocity values are measured from flow samples and are proportional to the values obtained from the bilateral main carotid artery (24-22).

Computerized Tomographic Angiography (CTA)

It is a radiological examination obtained by combining thin and continuous images after intravenous radiopaque injection. Anatomical imaging of aorta, aortic branches and willis polygon is provided. Multi-plane reconstruction and analysis allows evaluation of highly tortuous veins. In contrast to US and MRA, CTA provides direct assessment of vascular lumen and stenosis. In severe stenosis, the vessel lumen affects the accuracy of the measurement when the gate approaches the BTA resolution limits. With the increase in the number of detectors, higher resolution images of larger areas can be obtained. When compared with catheter angiography, the sensitivity and specificity of CTA is 100%, the specificity is 63% and 70% in patients with carotid and vertebral artery stenosis. (23).

Magnetic Resonance Angiography (MRA)

High resolution non-invasive images of cervical arteries are obtained with MRA. It provides high quality accurate anatomical imaging of the aorta, cervical and cerebral arteries without exposure to ionizing radiation. Compared with conventional angiography, the sensitivity and specificity were 97-100% and 82-96%, respectively.

Digital Subtraction Angiography (DSA)

DSA is the gold standard method for vascular imaging. DSA should be withdrawn when conflicting results are obtained with less invasive imaging methods. DSA may be performed in patients with renal insufficiency (to minimize contrast load), obese, permanent ferromagnetic material, in cases of suspected duplex ultrasonography, CTA and MRA withdrawal. Since it is an invasive imaging method, it may have some complications. The most serious complication is stroke and its incidence is less than 1% when performed by experienced physicians. With the widespread use of stent revascularization, the use of DSA as a diagnostic method is increasing (23,25).

Surgical Treatment Approach

Surgical Treatment Of Asemptomatic Carotic Artery Stenosis

There are two major studies on the application of endarterectomy for the first time in 1954 in asymptomatic carotid stenosis: Asymptomatic Carotid Surgery Trial (ACST) (60-99% stenosis) and Asymptomatic Carotid Atherosclerosis Study (ACAS) (Asymptomatic Carotid Atherosclerosis Study (ACAS)). It was completed with a total of 4782 patients with asymptomatic carotid stenosis (70-99%) and decreased the risk of ipsilateral stroke more than 5 years in comparison with medical treatment.Resar risk reduction with ACAS was found to be 53%. It has been reported with ACST: 0.5% decrease each year, while the 5-year stroke risk with ACST was 6.4% and 11.8% with medical treatment alone, and it was concluded that women benefited less from endarterectomy with ACAS (26). Studies have shown that CEA is beneficial in asymptomatic patients (especially men) between 40-75 years of age, carotid stenosis> 60%, life expectancy> 5 years, and operating mortality <3% (27).

Surgical Treatment Of Symptomatic Carotic Artery Stenosis

There are two major studies, NASCET (North American Symptomatic Carotid Endarterectomy Trial) and ECST (European Carotid Surgery Trial), which show indications for surgical treatment in patients with symptomatic carotid artery stenosis. With NASCET, 2226 patients with symptomatic stenosis were randomized for medical treatment and endarterectomy. Ipsilateral cerebral attack significantly decreased with endarterectomy in patients with a stenosis rate greater than 70%; Surgery has been reported as a more effective preservative in patients with 50-69% stenosis. It was concluded that there is no benefit in patients with a degree of stenosis below 50% (28).

Another major study was randomized 3024 patients with ECST and reported that symptomatic patients with ≥ 80% stenosis had better outcomes than surgical treatment with surgery (33). NASCET and ECST have used different degree of stenosis methods: the stenosis specified by NASCET as 70-99% is accepted as 80-99% by ECST. With ECST, 70-99% stenosis rate corresponds to 50-99% stenosis for NASCET. The 50-69% stenosis group of ECST is in the <50% stenosis group of NASCET. Both studies data showed that surgical treatment is useful in symptomatic patients with carotid artery stenosis 70-99%; In the symptomatic patient group with carotid artery stenosis 50-69%, the benefit of surgical treatment is lower (27).

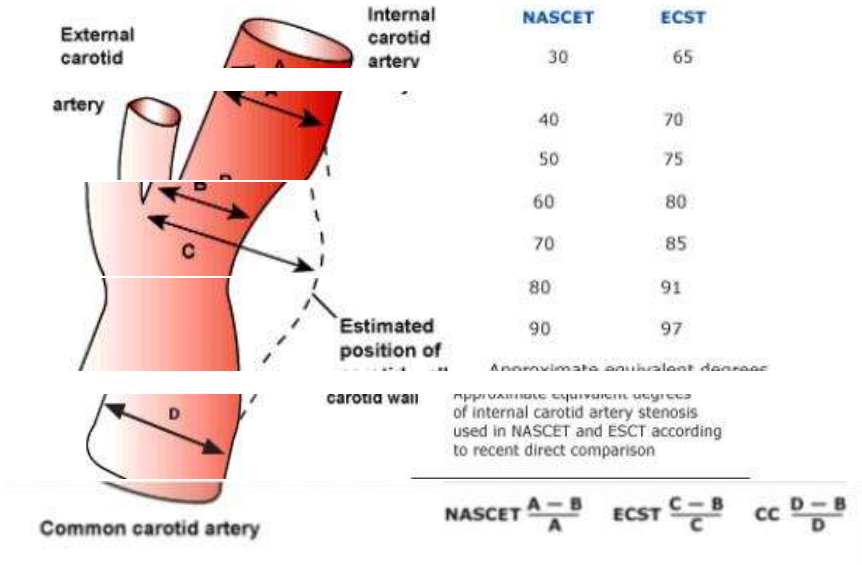

Figure 1: Differences between NASCET and ESCT measurement techniques in internal carotid artery stenosis (27)

Surgical Treatment Methods

Carotid endarterectomy operations can be performed with general anesthesia (GA), deep or superficial cervical block with regional anesthesia (RA) and simple local anesthesia (LA). In the study of General Anestesia versus Local Anestesia (GALA) comparing GA (1753) and CEA results under local anesthesia (1773 patients) in which 3526 symptomatic and asymptomatic patients were included, no difference was found between the anesthesia groups in the GA group. . Although perioperative

stroke, myocardial infarction and death rates in the first 30 days were higher in the GA group compared to the local anesthesia group, no significant difference was found between the two groups (29).

There are 3 options to use shunt in KEA; The lack of routine shunting has been published in very large series. Another is the routine use of shunt in all patients. Although those who prefer this method have published successful results, they have stated the risk of stroke due to technical problems. The last option is to use shunt in patients with high risk of ischemic stroke when shunt is not used.

Various methods are used to accurately determine the need for shunt use in patients under GA; carotid stump pressure measurement (collateral circulation is sufficient if above 50mmHg), electroencepholography, transcranial doppler of the middle cerebral artery, cerebral oximeter. Another method is to evaluate the changes in the patient's neurological responses under RA and make decisions. Intraoperative stroke may be ischemic or embolic. Although our aim in using shunt is to prevent ischemic stroke, there is a risk of embolic stroke (air. Particle) and dissection during shunt placement (30).

The patient should be in the supine position on the operating table, with a slight hyperextension of the neck and with the head facing the opposite side of the lesion. If GA is to be administered, the patient is intubated first. If LA or RA is to be applied, the Mayo stand is placed to prevent claustrophobia (30).

Two types of incisions are used. First; mastoid protrusion and sternoclavicular joint, sternocloidomastoid muscle incision parallel to the anterior border. The incision extends deep through the platysma muscle and reaches the fascia extending between the sternocloidomastoid muscle and the trachea. The second incision is 1-2 cm below the jaw angle and parallel to the skin fold. The incision is deepened along the platysma to reach the underlying fascia. Although this type of incision has more cosmetic results than vertical incision, access to proximal and distal areas is more difficult in this form. There is no difference between these two incisions in the rates of stroke, cranial nerve injury, wound complications or restenosis (31).

Complications after Carotis Endarterectomy

Cardiac Complications: Myocardial infarction is responsible for 25% to 50% of deaths after CEA. Symptomatic coronary artery disease is present

in at least 40-50% of patients with CEA as a result of systemic atherosclerosis (35). But in the last 20 years

11th operative mortality significantly decreased. In a 10-year study on 1566 patients, the rate of postoperative 30-day myocardial infarction was found to be 1.5% (30).

Cranial Neural Injury: It is the most common neurological complication after CEA. The incidence of peroperative cranial nerve damage is 4.7%. The most commonly affected cranial nerve n. And hypoglossal. Although clinical deficit is transient, it usually returns within weeks or months (30).

Cranial nerve injury is more common in recurrent carotid endarterectomy. Cranial nerve injury rate was found to be 21% in 89 patients with recurrent carotid endarterectomy, 88% of which were transient and 22% were permanent damage (35).

Hemodynamic Immunity:

If hypotension develops after CEA, it is usually associated with bradycardia within the first 2 hours. This is often the result of impaired baroreceptor function. After endarterectomy of the atheromatous plaque placed in bifurcation, there is an increase in baroreceptor sensitivity and hypotension and / or bradycardia develops by decreasing the activity of the central nervous system. Hypertension after CEA is thought to develop due to preoperative uncontrolled hypertension, but its mechanism is not fully understood (30).

Eversion endarterectomy has more sympathetic activation and postoperative hypertension than the traditional method. Although this hypertension regresses within the first 24 hours in the first 80% of patients, eversion endarterectomy can last up to 4 days (36, 37).

Hyperperfusion Syndrome:

Cerebral hyperperfusion syndrome usually occurs days after CEA and is usually associated with severe hypertension. Severe headache is usually observed before acute neurological deficit. The most devastating manifestation of hyperperfusion syndrome that may develop after CEA is intracerebral hemorrhage. It occurs between 0.4% and 7.7% after CEA (30). As the cause of hyperperfusion syndrome, increased cerebral blood flow secondary to impaired intracerebral autoregulation is seen after the removal of a high degree of carotid stenosis with severe lesion in the contralateral carotid artery (38).

The SVS clinical guideline recommends that systolic blood pressure be kept below 140 mm Hg diastolic blood pressure below 80 mm Hg after CEA (39).

Infection:

Wound infection is not common due to the rich blood supply to the neck. Cellulitis is usually observed, but its incidence is between 0.09% and 0.15%. The possibility of infectious complications increases in arteriotomies repaired with synthetic patch. However, the true incidence of patch infection could not be detected and is extremely rare (30).

Bleeding:

Postperative hemorrhage is an uncommon complication of CEA, although its incidence is between 0.7% and 3.0%. It is more common in patients receiving clopidogrel. However, we should not stop the use of clopidogrel in cases such as a history of previous coronary artery stents or symptomatic carotid disease that should use this agent. When the neck incision is closed, active red bleeding is observed in the drain and the development of hematoma compressing the trachea is again indications for surgery (30).

Repeating Stenosis:

The most important arterial complication after CEA is recurrent carotid stenosis. It is more common in women, those who continue to smoke, and in hypercholesterolemic, diabetic and hypertensive individuals (30). In the EVEREST study, no significant difference was detected between CEA using eversion and patch in terms of recurrent stenosis at 4-year follow-up (40). Early stenosis occurs within the first 2 years and develops as a result of intimal hyperplasia. Stenosis seen after 2 years is called late stenosis and typically shows atheromatous plaque characteristics (30).

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DIAGNOSIS AND TREATMENT OF CHRONIC VENOUS INSUFFICIENCY AND VARICOSE VEINS

Hüseyin SİCİM & Hakan KARTAL

Introduction

Chronic venous insufficiency (CVD) and related lower extremity varices are a common problem all over the world. Varicose veins affect approximately 32% of women and 40% of men. Varicose veins are seen in 1/3 of men and women between the ages of 18-64 (1). Varicose veins of the lower extremities are divided into three groups as spider veins, reticular veins and varicose veins according to their size and distance from the skin. Varicose veins may be asymptomatic or cause severe symptoms. Standing for a long time may cause pain, itching, burning, tingling, night cramps, edema, skin changes and venous ulcers in chronic cases. It interferes with the daily activities of individuals and may cause loss of work and time (2). Varicose veins thrombophlebitis and associated pulmonary embolism may develop (3,4). Even deaths related to spontaneous variceal bleeding have been reported in the literature (5,6)

Etiology And Pathophysiology

The return of lower extremity venous blood to the heart is a complex mechanism. There are 3 major components of this mechanism. These; stability of the lower limb calf muscle pump, non-obstructed venous flow and venous valves Is the qualification. Valve function has the most important role in venous system physiology (7,8). Normal covers are bicuspid, collagen-containing structures that allow only one-way flow. Normally operating valves are defined as competent and those that allow retrograde flow are defined as incompetent. Primary valve failure is usually loss of elasticity. In secondary valve failure, the causative agent is DVT (9,18).

Venous Anatomy

Superficial venous system

VSM is the longest vein in the body. The median margin of the medial edge of the foot ridge begins as a continuation of the medialis. It passes through the anterior of the medial malleolus on the ankle and on the medial side of the leg. sapheneus. Knee at the level of the joint joint, passing through the medial condyle and the sinephal compartment on the inner face

of the thigh, which is a course between the deep muscular fascia and the saphenous fascia on the surface, passes through the hiatus saphenus in the deep fascia and opens into the main femoral vein approximately 3 cm in the ligamentum inguinal. The saphenofemoral junction (SFB) is where the VSM enters the main femoral vein of the deep venous system at the groin level. Duplication can be observed in VSM at a rate of 1-2% (7,19,20).

Deep venous system

Anterior tibial, posterior tibial and peroneal veins provide drainage of the calf. These veins, which are found as a pair, accompany the arteries of the same name. Proximally, two posterior tibial veins merge into a short posterior tibial root and the peroneal pair becomes a short root in the same way. These two roots m. at the lower edge of the popliteus, popliteal to form the vein. The paired anterior tibial veins form a short root and join the popliteal vein. The most important muscular veins draining the calf muscles are the gastrocnemius and soleal veins. Gastrocnemius veins can be seen in the medial head of the gastrocnemius muscle and drain into one of the popliteal vein or posterior tibial vein. Soleal veins are centrally located and the soleal muscle in the posterior tibia It is located inside. These veins, which may be larger than one centimeter, drain into the posterior tibial or peroneal system. The popliteal vein extends longitudinally along the popliteal fossa at the posterior of the popliteal artery and is directed medially to enter the adductor canal. The popliteal vein is duplicated by 5% (22).

Perforating vein

Perforators are bridging channels between the superficial and deep venous systems. These veins obliquely perforate the deep fascia and play a key role in equilibrating blood flow during calf muscle contraction because of valves that prevent reflux from the deep venous system to the superficial venous system. Perforating veins are numerous and highly variable in arrangement, connection, and size. There are four clinically important perforator groups: upper thigh (Hunterian), lower thigh (Dodd's), at knee level (Boyd's), and in the calf region (Cockett's). Although perforator valve incompetence is always associated with CVI, the cause of perforator insufficiency is not known, and the routine treatment of perforating veins in C2 patients is not supported (16).

Varicose veins of the lower extremities are divided into 3 types as spider (telangiectatic), reticular and varicose veins.

Spider Veins

They are located intradermally and there is no skin protrusion.

Figure 1. Spider Veins

Reticular Veins

They are subdermal. There is protrusion from the skin. They are blue-purple vascular structures with a diameter of 1-4 mm. They can cause pain.

Figure 2. Reticular Veins

Varicose Veins

They are subdermal, vascular structures with a diameter of 3-4 mm to a few centimeters and showing significant protrusion from the skin.

Figure 3. **Varicose Vein**

Diagnosis of CVI

Computed tomography and magnetic resonance venography

Venography is useful in the anatomical and hemodynamic evaluation of the venous system. End Ascending venography için is the gold standard for the diagnosis of DVT. Descendant venography is used to evaluate valvular insufficiency (17,18). In ascending venography, superficial veins are occluded by applying a tourniquet at the ankle level and contrast agent is injected into the vein of the foot back. In the femoropopliteal region, computed tomography and magnetic resonance venography provide information close to US and venography. They are effective in demonstrating pelvic veins and inferior vena cava.

Venous duplex ultrasonography

When creating an image in the gray scale US, the reflection intensity of the rotating echo (amplitude of the rotating wave) and the time between sending and receiving the sound wave reaching the probe are calculated and the rotating wave is coded in different gray tones. In addition to this information, the reflected sound wave includes phase, wavelength and frequency information which is not taken into account when creating images in the B-mode examination. Using this information, an image is generated in the DU (19). Blood is an inhomogeneous medium consisting of a large number of blood elements of various diameters, in which the erythrocytes are distributed randomly. When the wavelength of the transmitted ultrasound sound wave is too large than the reflective surface (such as erythrocytes) The ultrasound waves transmitted show a scattering called Rayleigh-Tyndall scattering from the surface of erythrocytes within the vascular structures. The amount of scattering is directly proportional to the 4th order exponent of sound frequency (19,20). In fixed tissues, the wavelength (λ) and frequency (f) of the ultrasound sound wave are the same as the wavelength and frequency of the wave reaching the probe after

reflection. On moving reflective surfaces, frequency difference occurs in the returning sound waves.

In 1842, this frequency difference was defined by Johann Christian Doppler as 'Doppler Effect (Doppler Shift)'. Doppler found that an increase in the frequency of the energy produced by moving energy sources while moving towards the sensor system and a decrease in the frequency while moving away from the sensor system (20,21).

Classification

The CEAP (clinical, etiologic, anatomic, pathophysiological) system incorporates a range of symptoms and signs of chronic venous disorders to characterize its severity (Table 1). It also broadly categorizes the etiology as congenital, primary, or secondary; identifies the affected veins as superficial, deep, or perforating; and characterizes the pathophysiology as reflux, obstruction, both, or neither. However, this system is not useful for venous severity scoring because many of its components are relatively static and others use detailed alphabetical designations. An adjunctive scoring system (Table 2) allows for a standardized clinical evaluation, the assessment of clinical severity, and evaluation of the response to treatment (18).

Table 1. CEAP classification of chronic venous disorders

Clinical classification (C)[a]	
C_0	No visible sign of venous disease
C_1	Telangiectases or reticular veins
C_2	Varicose veins
C_3	Edema
$^{C}4$	Changes in skin and subcutaneous tissue[b]
C_5	Healed ulcer
C_6	Active ulcer
Etiologic classification (E)	
E_c	Congenital (e.g., Klippel-Trenaunay syndrome)
E_p	Primary
E_s	Secondary (e.g., postthrombotic syndrome, trauma)
E_n	No venous cause identified
Anatomic classification (A)	

^{A}s	Superficial
A_d	Deep
A_p	Perforator
A_n	No venous location identified
Pathophysiologic classification (P)	
P_r	Reflux
^{P}o	Obstruction, thrombosis
$^{P}r,o$	Reflux and obstruction
P_n	No venous pathophysiology identified

CEAP, clinical, etiologic, anatomic, pathophysiological. [a]The descriptor A (asymptomatic) or S (symptomatic) is placed after the C clinical class. [b]C4 is subdivided into A and B, with B indicating higher severity of disease and having a higher risk for ulcer devel-opment.

Table 2. Venous Clinical Severity Score

Attribute	Absent = 0	Mild = 1	Moderate = 2	Severe = 3
Pain	None	Occasional, not restricting	Daily, interfering but not	Daily, limits most daily
		daily activity	preventing daily activity	activity
Varicose veins	None	Few, isolated branch varices,	Confined to calf or thigh	Involves calf and thigh
		or clusters, includes ankle		
		flare		
Venous edema	None	Limited to foot and ankle	Extends above the ankle but	Extends to knee and above
			below knee	
Skin pigmentatio n	None or focal	Limited to perimalleolar	Diffuse, over lower third of	Wider distribution above
			calf	lower third of calf

Inflammation	None	Mild cellulitis, ulcer margin limited to perimalleolar	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration	None	Limited to perimalleolar	Diffuse over lower third of calf	Wider distribution above calf
Ulcer number	0	1	2	3
Ulcer duration	NA	< 3 mon	> 3 mon but < 1 yr	Not healed > 1 yr
Ulcer size	NA	Diameter < 2 cm	Diameter 2–6 cm	Diameter > 6 cm
Compressive therapy	Not used	Intermittent	Most days	Full compliance

An aggregate score for the limb is calculated by adding the individual component scores. The range of the total score is 0 to 30. NA, not applicable.

Treatment of CVI

Conservative Management

The initial management of CVI involves conservative measures to reduce symptoms and prevent development of secondary complications and progression of disease. The use of compressive stockings is the mainstay of conservative management and is further described below. If conservative measures fail or provide an unsatisfactory response, further treatment should be considered on the basis of anatomic and pathophysiologic features (Figure 7). Regarding the management of CVI, the practitioner should be able to recognize the manifestations of CVI and use confirmatory testing, such as venous duplex reflux studies and perhaps APG for advanced and recurrent disease. Specific treatment is based on severity of disease with CEAP classes C4 to C6 often requiring invasive treatment. A referral to a vascular specialist should be made for patients with CEAP classes C4 to C6 (and probably for CEAP class C3 for extensive edema). These patients with uncorrected advanced CVI are at risk for ulceration, recurrent ulceration, and nonhealing ulcers with progressive infection and even veno-lymphedema. A healthy lifestyle including maintaining an ideal body weight or weight reduction if

overweight may improve manifestations of CVI. Obesity is a well-established risk factor for the development of CVI and its complications. Weight reduction after bariatric surgery has been shown to improve manifestations of CVI, including edema and ulcers. It may be extrapolated that weight reduction by other means might also assist in the treatment of CVI.

Compressive Leg Garments

Elastic compression stockings play a fundamental role in the treatment of CVD. Elastic compression stockings are recommended for patients with low complaints or high risk of surgery. Appropriate elastic compression regresses the symptoms of patients with varicose veins, increases venous hemodynamics, reduces edema and provides relief (41,42). Compression stockings are available in different pressure ranges and are used in the required pressure ranges depending on the patient's complaints and the degree of disease. Compression stockings are divided into 5 classes according to their pressure;

Class A: 10-14 mmHg (very little pressure)
Class I: 15-21 mmHg (light pressure)
Class II: 25-32 mmHg (medium pressure)
Class III: 34-46 mmHg (strong pressure)
Klass IV:> 49 mmHg (very strong pressure)

Pharmacologic Therapy

Venoactive drugs used in the medical treatment of CVI are composed of several drug groups. They may be of vegetable origin or synthetic.

Venoactive drugs relieve edema and symptoms of CVD by antioxidant mechanism. While these drugs do not correct the existing disease, they provide symptomatic improvement. They reduce symptoms such as edema, pain, fatigue, and muscle cramps.

Surgical therapy

Open surgical therapy of varicose veins with high ligation and stripping of the GSV combined with the excision of large varicose veins has been the standard of care for more than a century. This therapy is performed in the following sequence: incisions are made in the groin and upper calf; the GSV is ligated (high ligation) below the SFJ, and a wire is inserted into the GSV and advanced distally; the proximal part of the GSV is secured to the wire and retrieved (stripping) via the calf incision. Stripping of the GSV below the knee and stripping of the SSV are not usually performed because of the high risk of nerve injury(19).

Endovenous thermal ablation

Using laser energy for the ablation of veins, EVLA is a minimally invasive method that is an alternative to surgery in superficial venous insufficiency and related varices. The widely used EVLA technique has been reported for the first time in the literature by Navarro and Min (12). EVLA is based on the principle of the energy generated by a laser generator to be transmitted to the vein lumen by fiberoptic catheter and the ablation of the vein with the high temperature obtained from this energy. EVLA releases thermal energy into the blood and venous wall, causing vascular endothelial damage and vein collapse. Diode laser devices with 810, 940, 980 nm wavelengths are commonly used in the treatment of EVLA (20). 810, 940 and 980 nm wavelength diode laser devices by targeting hemoglobin, 1320 nm wavelength laser devices by targeting water, saphenous reflux with minimal side effect was developed to quickly and effectively treat (22). Vein contraction is a gradual process that leads to the resorption of the vein in a few months when endothelial damage, focal coagulative necrosis and thrombotic occlusion of the vein occur. Thrombotic occlusion enables the saphenous vein to become fibrotic cord after endovenous treatment. EVLA was approved by the FDA (food and drug administration) in 2002 for the treatment of varicose veins (22).

The treatment of CVI will be based on the severity of disease and guided by anatomic and pathophysiologic considerations. Compressive garments have been a mainstay in the management of CVI. Traditional surgical techniques and newer interventional methods are often reserved for unsatisfactory response to conservative measures, although earlier use of venous ablation should be considered in symptomatic patients.

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UTERINE SPARING SURGERY in POSTPARTUM HEMORRHAGE

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Postpartum hemorrhage (PPH) is the leading cause of maternal mortality. All women who have a pregnancy of more than 20 weeks are at risk of PPH and its consequences. The World Health Organization indicates that 60% of maternal deaths in developing countries are attributable to PPHs, which account for more than 100,000 maternal deaths per year [1]. A practical bulletin from the American College of Obstetricians and Gynecologists indicates that 140,000 maternal deaths occur annually in the world or 1 woman dies every PPH every 4 minutes [2]. The frequency of PPHs increased from 1.5% in 1999 to 4.1% in 2009, and the level of atonic PPHs increased from 1% in 1999 to 3.4% in 2009. The risk of PPH with placental abnormalities is markedly higher [3].

The definition of PPH is somewhat arbitrary and problematic. A PPH is defined as a blood loss of more than 500 ml after vaginal delivery or more than 1000 ml after a cesarean section [4,5]. This article is about an early PPH that appeared in the first 2 hours after delivery.

Etiology:

PPH has many potential causes, but atony of the uterus is the most common - inability of the uterus to contract after childbirth. PPH, with a previous pregnancy is a major risk factor, and every effort should be made to determine its severity and cause. In a recent randomized study in the United States, birth weight, induction and weight gain, chorioamnionitis, history of magnesium sulfate and PPH, were positively associated with an increased risk of PPH. [6]

To better memorize the causes of PPH, it was proposed to use “4 T” as a mnemonic: tone, tissue, trauma and thrombin [7].

Tone:

Uterine overstretching is a major risk factor for atony. Uterus overdrainment can be caused by multiple pregnancies, fetal macrosomia, polyhydramnios, abnormal fetal development (for example, severe

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hydrocephalus) or structural uterine abnormality. It may also be the result of inhibition of contractions with drugs such as anesthetics, nitrates, nonsteroidal anti-inflammatory drugs, magnesium sulfate, beta sympathomimetics, and nifedipine [7]. Other causes include: low-lying placenta, bacterial toxins (eg, chorioamnionitis, endomyometritis, septic)), hypoxia due to hypoperfusion or uterus Couvelaire with abruptio placentae and hypothermia due to massive resuscitation. Recent evidence suggests that multiparity is not an independent risk factor for PPHs [8].

Tissue:

Contraction of the uterus and its retraction lead to the separation and excretion of the placenta. Complete separation of the placenta promotes better retraction and optimal occlusion of blood vessels. Delay of parts of the placenta in the uterus is often found with an extra lobule. Disturbed separation of the placenta often occurs during very early preterm labor (especially during the 24 weeks of gestation), which can also cause bleeding [9]. Recent studies show that using misoprostol for terminating pregnancy in the second trimester reduces the frequency of latency in the placenta parts in the uterus of the placenta compared with methods based on intrauterine instillation of prostaglandins or hypertonic saline [9]. Anomalies of attachment of the placenta can lead to massive PPH.

Trauma:

Damage to the genital tract can occur spontaneously or during operative delivery. Caesarean section doubles the mean blood loss [10].

Uterine rupture is most common in patients with a scar in the uterus after cesarean section. The risk of uterine rupture exists after conservative myomectomy, metroplasty, uterine horn resection, uterine perforation during dilatation, curettage, biopsy, hysteroscopy, laparoscopy, or the introduction of intrauterine contraceptives. Injury can occur during prolonged labor, especially when clinically narrow pelvis, on the background of rodoactivation by oxytocin or prostaglandins. Finally, an attempt to remove the ingrown placenta manually or with the help of a tool [11] can lead to injury.

Cervical rupture often occur after applying obstetric forceps. Vaginal ruptures are also most often associated with operative vaginal delivery, but they can also occur spontaneously.

Thrombin:

In the early postpartum period, violations of the coagulation system and platelets usually do not lead to excessive blood loss. This reflects the importance of uterine contraction in preventing PPH [4]. However, disorders of the hemostatic system are often the cause of bleeding in the late postpartum period. Thrombocytopenia may be associated with a

preexisting disease, such as idiopathic thrombocytopenic purpura. It may also be secondary to the background of HELLP syndrome (hemolysis, elevated lymphatic lymphocyte), premature detachment of a normally located placenta, disseminated within a lymphatic lymphocytosis, and premature detachment of a normally located placenta, disseminated within a lymphatic lymphocytosis), premature detachment of the normally located placenta, disseminated within the oral lymphocytedenia, and orally, there is a process of lymphocytosis). Functional platelet abnormalities may rarely occur. Most of them are already existing, although sometimes previously undiagnosed [12].

Pathophysiology:

During pregnancy, the circulating blood volume increases by about 50% (from 4 liters to 6 liters). In the period of birth uterine blood flow is 500-800 ml / min, which is 10-15% of cardiac output. Most of this flow passes through the uteroplacental circuit. As these fibers contract after delivery, myometrial retraction occurs. Retraction is a unique characteristic of the uterus muscle to maintain its shortened length after each successive contraction. The blood vessels are clamped and screwed into this muscle mass, which provides uterine hemostasis. This arrangement of muscle bundles is known as “live ligatures” or “physiological stitches” of the uterus [13].

Uterine atony is the complete inability of the uterus to contract. This is the most important reason for early PPH. and usually occurs immediately after childbirth, up to 4 hours after birth. Trauma to the genital tract (rupture of the uterus, cervix, vagina, labia, clitoris) during pregnancy leads to significantly more bleeding than in the non-pregnant state due to increased blood supply to these tissues [13]. Tissue injury during vaginal delivery, as well and operative abdominal delivery can be quite significant and involve PPH.

Surgical treatment:

Surgical treatments for postpartum hemorrhage include both hysterectomy and organ-sparing approaches. The purpose of this article is to systematically evaluate all existing methods. Methods to preserve the uterus with PPH are listed below: ligation of the uterine and uterine-ovarian vessels; compression stitches on the uterus; balloon uterus tamponade; ligation of the ileal artery; selective arterial embolization; ligation of the uterine and uterine ovarian artery [14,15,20,24,27].

When applying these surgical methods, it is not necessary to follow a certain order. Depending on the clinical experience and the capabilities of the operating physician, one of them or a combination of these methods can be used.

1. Uterine artery ligation

Ligation of the uterine artery is a relatively simple procedure and can be very effective in controlling bleeding from the uterus. These arteries provide approximately 90% of the blood flow to the uterus.

The first choice is ligation of the uterus vessels in postpartum bleeding [14]. may be insufficient with uterine atony, but can save time and reduce blood loss during hysterectomy. Easy access to the uterine arteries and branches, as well as simplicity, are an advantage of the method. The risk of injury to large vessels and ureters is minimal [15].

The technique was first described by Waters in 1952 and Oleri in 1966. In 1972, in addition to ligation of the uterine vessels, the utero-ovarian vessels and the round ligaments of the uterus were first tied to stop M.C. Tsirulnikov [16].

Ligation of the uterine artery requires abdominal access, and usually the Pfannenstiel incision can provide sufficient visibility for the surgeon. Intersection of the round ligament is not required when ligating the uterine vessels. Absorbable suture material is used for suturing the vascular bundles about 2 cm below the incision of the uterus for cesarean section. If the control of bleeding is insufficient, closer to the corners of the uterus can be tied uterine-ovarian vessels.

Ligation of the uterine and uterine-ovarian vessels successfully controls bleeding in approximately 90% of patients [14,17]. Necrosis of the uterus and placental dysfunction during subsequent pregnancy was not observed in the studies [17,18]. However, in several cases, dysfunction of the ovaries and postpartum synechia of the uterus were found. In a series of 265 cases, 95% success was reported using this procedure for uterotonic uterotonic atrophy after cesarean section [14]. Another series of 103 cases was 100% successful against the background of the use of the step-by-step approach [19]. After the initial ligation of the uterine artery, subsequent sutures were placed 2-3 cm below this level after the bladder was lowered, and finally, if necessary, were performed by ligating the ovarian vessels. Subsequently, menstrual dysfunction and fertility decline were not observed.

2.Uterine compression sutures:

Uterine compression sutures are effective methods for atony of the uterus. Stitches uterus and reduce blood flow. Although the seams by B-Lynch are the most commonly used method, but there are various methods, such as the seams by Hayman, Pereira, Cho [20]. Complications such as uterine necrosis, erosion and pyometra have been reported in patients treated with compression joints [21]. It has been reported that in some women, the presence of intrauterine synechia was noted. No adverse

effects on fertility were found during long-term observation of women who were subjected to compression stitches on the uterus [22].

The use and localization of compression joints of the uterus can vary depending on the experience and decision of the surgeon. Longitudinal sutures are preferable to comparing transverse sutures. Against the background of uterine atony, this procedure must be performed very quickly, otherwise the need for hysterectomy increases [23].

B-Lynch suture: The technique was first described in 1977 by B-Lynch and his colleagues. In a small number of cases, patients who did not respond to other types of treatment were quite successful [24]. The technique is ineffective in bleeding, which is associated with abnormalities of attachment of the placenta, such as plasenta assreta, although it is quite effective in atony of the uterus. At the first stage, the needle, which begins under the hystereomy incision, pierces the lower segment of the uterus and enters the uterus, then the needle passes through the incision and is released. Secure the suture and make a ring around the bottom towards the back of the uterus. Then the needle enters the uterine cavity again through the back wall and is brought out from the other side to continue the suture in the opposite direction. At the last stage, the needle enters the uterus above the incision. Then it comes out through the lower lip of the incision and the stitches under the incision are tied.

Other methods are less commonly used as modifications to the seams of B-Lynch. In the technique described by Hayman, vertical sutures are used without cutting hysteretomas. In the Pereira technique, many transverse and vertical sutures are connected through a layer of myometrium, without entering the uterine cavity. In the Cho technique, multiple square or rectangular sutures are superimposed on the uterus [20].

3. Balloon tamponade of the uterus:

Tamponade balloon can be applied after vaginal delivery and cesarean section, which acts by increasing the pressure in the uterus. It is used for bleeding from the lower segment due to placenta previa or placenta accrete. Use balloons Bakri, Belfort-Dildy, BT-Cath. The balloon is introduced directly into the uterine cavity through the cervix. Up to 500 ml of fluid is injected into the balloon. In double-lumen balloons, drained blood indicates continued bleeding. Complications include uterine rupture and infection [25].

4. Ligation of the internal iliac artery:

The first cases of ligation of the internal iliac artery were published in the 1960s. This is one of the most well-known conservative surgical methods [15]. It acts by reducing blood flow and pressure on the uterus. During ligation of the distal arteries, the pulse pressure in the uterus is

reduced by about 85%. This method is effective not only for uterine bleeding of the uterus, but also for bleeding due to anomalies of attachment of the placenta, deep ruptures of the neck and vagina. Ligation of the internal ileal artery requires retroperitoneal access. According to the literature, the ligation success rate of the internal iliac artery varies from 42% to 93%. Complications include damage to the internal iliac vein, damage to and ligation of the ureter, ligation of the external iliac artery, injury to the peripheral nerves and necrosis of the gluteal muscles. These complications are associated with insufficient experience of the surgeon [15.26]. It is preferable to perform a lower median laparotomy. The retroperitoneal space should be opened to reveal the ileal artery bifurcation. After detecting the iliac artery about 2 cm below the bifurcation, an absorbator suture material should be ligated under the artery without any effort. After ligation, check the pulsation of the external iliac artery and go to the other side. Unilateral ligation of the internal iliac artery does not affect PPH control. Therefore, the arteries should be ligated on both sides.

5. Selective arterial embolization:

Angiographic embolization for the treatment of PPH was first described more than 30 years ago [27]. Since selective uterine artery embolization showed outcome for PPH in 1979 by Brown et al. [28], it has showed as a safe, effective and minimally invasive alternative to traditional surgical treatments such as hypogastric artery ligation or hysterectomy. Later, some authors have reported the usefulness of this technique as a first-line treatment for PPH in those patients refractory to conservative treatment [29].Several series of cases have shown that selective arterial embolization may be useful in situations where preservation of fertility is desirable, when surgical options have been exhausted, and also in the presence of pelvic hematomas[30]. In a retrospective study Park showed that transcatheter arterial embolization (TAE) is safe and effective at pc. In the study, this procedure was clinically successful in 47 of 52 patients (90.4%) with PPH, caused by an increase in the placenta in 23 cases. Gelatin sponge particles were used in 48 patients either alone or in combination with permanent embolic materials (for example, microcolys, N-butylcyanoacrylate). Embolization was performed only with permanent materials in the remaining four patients. Regular menstruation occurred in 44 patients who were observed (average of 12.6 months), and five patients subsequently became pregnant [31].

Summary:

Postpartum hemorrhage is the leading preventable cause of maternal mortality. Determining patients with a high risk of postpartum hemorrhage, early diagnosis and attempts to prevent bleeding play a key role in preventing maternal mortality. Although many risk factors for postpartum

hemorrhage have been identified, most cases do not have an identifiable risk factor. Active management of the third stage of labor is recommended for the prevention of postpartum hemorrhage. Managing postpartum hemorrhage requires a multidisciplinary approach.

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FOOD ADDICTION/OBESITY AND SPORTS

Kerim GÜZEL* & Nermin GÜRHAN**

Introduction

In recent years, food addiction-obesity has been an important one among the world's serious health problems, and it still is. According to the studies, especially very delicious and high-energy processed foods cause addiction. According to DSM-5, the criteria of the substance addiction and food addiction are similar. Popularization of high-calorie foods, alienation from pot meals, intake of calories more than we burn, doing exercises like walking, sports, etc. very limitedly or not doing them at all can be mentioned among the most important reasons of obesity. Likewise, since the high-calorie foods generally include fat and sugar combination, there is a relation between compulsive eating disorder and reward dysfunction, as is the case with substance addiction. While the fat increases body weight, sugar causes addiction-like behaviors. Obesity is not a simple overweight problem that can be solved with conventional methods; to the contrary, it is a clinical and social health problem having serious health risks, which is thankfully preventable. It is a situation requiring individuals to change their lifestyles by adding walking and sports to their medical treatments (1, 2, 3).

Sports

The word sports, coming from “disportare and desport” in Latin, means “distributing, separating from each other, entertainment, joy”. It is suggested that it has become “sports” over time through haplology of the first syllable. Sports is a pattern of behavior carried out in series, for a certain purpose, individually or as a team, as per certain rules, and can be observed in a certain place and a certain timeframe (4).

In addition to their positive and desired effects on body health, the benefits of sports and physical activities with regard to mental health are a well-known and unignorable fact. The sports and physical activities in the adolescence period especially do not only have profound effects on the psychological and physical health at later ages but also constitute a good agent of socialization. It is a well-known fact that playing sports and participating in sporting activities increase the individual's interest in their own body, have positive effects on the psychological and social structure,

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and affect the self-respect positively through satisfaction with the body image, being pleased with oneself, etc. (5, 6)

Being engaged in sports since childhood provides the individual with a more desired body structure and a healthy life at later ages thanks to building up of the muscular tissue instead of the adipose tissue.

Obesity

Today, obesity is a serious health problem we encounter in all societies and all age groups. We can define obesity simply as high fat percentage. The normal fat percentage is specified as 30% for women and 25% for men. Numerous studies specify the obesity/overweight, etc. with Body Mass Index (BMI). It is also a beneficial and useful technique for classification on the basis of body fat percentage. According to several sources, the obesity percentage in developed countries is 31% for adults, 15.5% for adolescents, and 15.3% for children. The obesity that is a problem that has multiple factors such as genetics, psychology, lifestyle, etc. occupies a considerable place in our daily lives due to health problems it causes each passing day increasingly. Sports (physical activity) have an important prophylactic effect in addition to numerous other psychological, social and physical positive and important effects. Today, lack of physical activity, malnutrition, and overweight constitute the most common secondary reason of death. In 2009, Slentz et al. discovered that regular physical activity/sports burns and reduces the body fat of obese individuals (7, 8, 9, 10).

Food Addiction

In recent years, food addiction-obesity has been an important one among the world's serious health problems. According to the studies, especially very delicious and high-energy processed foods cause addiction. According to DSM-5, the criteria of the substance addiction and food addiction are similar.

Similarities have been found between the hyperactivity findings discovered in the reward-related brain areas, caused by the dopaminergic signalization changes caused by obesity and binge eating, and the process observed in the drug addicts. These results have raised the scientific interest in the subject, and laboratory studies have been conducted on the matter. In consequence of these studies, evidences have been found such as clinical similarity between obesity and substance addiction, common sensitivity between obesity and substance addition, compulsive food search behavior-deprivation and tolerance in animals subjected to high sugar/fat diets, similarity between the low levels of the striatal dopamine receptors and the findings discovered in drug addicts, and changing brain

replies to food-related stimuli in obese individuals compared to non-obese control individuals in functional imaging studies (11, 12, 13).

Sports/Food Addiction/Obesity

Two important reasons of the recent increase in obesity are the shift from active lifestyle to a more limited and sedentary lifestyle in parallel with the industrial-technological developments simultaneously with the shift from traditional pot-meal-based eating habits to fast-food-based eating habits (14).

It is said and argued that children are always active, but a fall in children's activity and a rise in time they spend inactively by using tablets, phones, etc. have been observed in recent years. Therefore, especially the industrialized and developed countries develop various policies to guide children to sports. Obesity, which we have said to arise in children who are future's adults due to inactive and monotonous lifestyle, does not only affect the children's lifestyles negatively but also paves the way for obesity in the future's adults. One of the important factors affecting obesity in childhood in particular is obese parents; and malnutrition and unrestrained eating habits of the family also constitute an important factor increasing the risk. The studies conducted show that the ignorance and denial of treatment of the obese children by healthcare professionals causes the obesity to increase and become chronic (15, 16, 17, 18).

According to the result of the study conducted by Altunkan in 2013, of the children over six years of age studying in Karaman, 8.6% were overweight and 7.9% were obese (17). In a four-year study conducted on the children living in Isparta downtown by Akçam et al. in 2013, the first measurements revealed 12.2% overweight and 11.6% obesity while the same measurements at the end of four years revealed 11% overweight and 12.5% obesity. Likewise, another study conducted by Süzek et al. discovered the prevalence of obesity among the children of 6 to 15 years of age in Muğla as 57.6% for girls and 9.1% for boys (18, 19). Another study conducted in Istanbul has discovered the prevalence of obesity among the children of 6 to 15 years of age as 8.4% (20). Many such studies show that obesity has become a serious social problem in our country as is the case with many other countries. According to the World Health Organization, there are approximately 250 million obese people across the world, which is going to rise to 300 million in the year 2025 (21, 22, 23).

The last resort treatment of obesity, which is selected when all other methods remain incapable, is surgery. In obesity, the surgical approach is categorized in two groups: bariatrics and reconstructive. The purpose of bariatric surgery is to reduce absorption of foods in the gastrointestinal system to reduce the energy intake from foods. To that end, the methods such as bypass, gastroplasty, gastric balloon, etc. are used. In

reconstructive surgery, on the other hand, the purpose is to remove fat tissues localized in certain parts of the body. However, even in those treatment methods, if eating and exercise rules are ignored, re-accumulation of fat and re-emergence of obesity constitute an inescapable truth (24, 25, 26).

Prevention of obesity or its post-treatment recurrence definitely requires teamwork and behavioral change. The basic purpose of behavioral change treatment is to enable individuals to change their eating habits, activities, and mentalities positively, and discipline themselves. The treatment plan generally includes these steps: self-observation, stimulant control, development-reinforcement of alternative behaviors, self-rewarding, cognitive structuring, and social support. Behavioral strategies are very important for improving the health and preventing unhealthy weight gain. This treatment is also very important for preventing or treating obesity as well as maintaining its absence for it eliminates the food addiction (24, 25, 26).

Place and Importance of Sports in Prevention of Obesity and Food Addiction

It is an important issue that must be handled starting from the childhood. It is a well-known fact that the obesity can be prevented through correct eating habits and sports/physical activity starting from childhood. Starting from childhood, treatment of obesity and the diseases it causes is rather costly. On the other hand, it is an obvious truth that the children fed healthily since infancy and enabled to do sports and physical activities starting from very early ages will have a healthy life at both childhood and later ages, and this in return will provide a great profit in economic terms. Body fat reduction and weight loss are rather important in prevention of obesity and minimization of the obese persons' risks. The obesity is treated through reduction of body fat percentages and the changes created in the energy metabolism through sports and physical activities. Light and regular sports not only provide regular weight loss but also prevent regain of the lost weight. Sports included in the lifestyle starting from childhood are rather important in prevention of childhood and adult obesity.

The childhood period is the period when sports are most effective. Considering a child's physical features and psychological composition, the sports played in the childhood period will assist the development of their physical capacity, boost their self-confidence, teach them to follow the rules and respect other people's rights, and protect them against addiction and obesity by ensuring their self-confidence (27). According to the results of a study conducted in Germany in 2002 on 1000 high-school students of 14 to 18 years of age, divided into two groups as those who play sports and those who do not, the students who play sports have more positive self-

image, consume less alcohol and drugs, and have lower depression and anxiety scores compared to the students who do not play sports (28). It is a well-known fact that depression-related alcohol consumption is also a reason of weight gain as it includes surplus energy. In addition to its direct effect indicating itself with positively developing body perception, developing muscular tissue, and in parallel to this, decreasing adipose tissue, sports also prevents weight gain and obesity indirectly by reducing depression scores and alcohol consumption.

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WOMAN – SPORTS AND SOCIAL GENDER

Nermin GÜRHAN & Gökççen ERDOGAN

Introduction

It is useful to know the concept of asymmetry between genders in order to understand how gender relations are shaped within societies. Asymmetry between genders means that one gender in a society is in a worthless/non-preferential position compared to the other gender. In this social order, the biological differences between men and women and the idea of male superiority created by these differences are the factors that enable women to gain experiences and be successful in sports fields, etc. While the biological differences of women create the idea of the "other" second class against male superiority, they also reveal the sexuality and protection of men (1).

Woman

While a matriarchal life was lived in the primitive ages with female fertility and their active roles in production, later on there has been a decrease in the status of women due to the effect of private property, religion, class distinctions, pressures and gender distinctions and it was switched to a patriarchal society from a matriarchal society.

For women and femininity, women have been defined and continue to be defined through "home" in line with the culture they have started to live in today, regardless of the variables such as age-education-class etc. For this reason, it is almost always encountered as a key area for the establishment and making sense of women's care. Housings and housework, which have always occupied and continue to occupy an important place for ages, are differentiated depending on the class, status, generation and education level of the women. The in-house space that constitutes the definition of women is a place where gender inequality is produced. The family where the women first get in contact and start to socialize has been an important key point for the identification of women (2,3).

The results of the study carried out by the SPO (State Planning Organization) in 1988 with approximately twenty thousand households

indicate that, among the most important tasks of women within the family such as doing housework, raising and upbringing their children, giving moral support to their spouse and children, taking care of their children and husband, giving birth to children and contributing to the family budget, have not changed today. The results of the study conducted by TSI (Turkish Statistical Institute) in 2006 indicate that while women undertake more roles in traditional housework such as cooking, ironing and laying the table, men undertake more roles in the payment of bills, maintenance and repair. The same study indicates that a large part of men do not have any expectation from women to work and generate income (2,4).

The study conducted and similar studies indicate that women belittle themselves as insignificant, worthless and under submission compared to men as they have perceived and learned the responsibilities in the house as their natural tasks. They are first dominated by the father and brother and then the husband/spouse. The woman is either someone's daughter, his sister or his wife. She is not an individual in her own and such a woman cannot take decisions about herself and cannot do anything without their permission. A dependent woman and independent men, who can take their own decisions, are formed with the influence of games, family, close relatives etc.

Sports

The sports, which initially emerged as being away from work, relaxation and leisure time, became professional later on and have been a profession. Over time, the competition that emerged within the game gave rise to interest in sports, and the sports became more important not only for those who do it, but also for those who watch it, and the increasing interest has created more audience and more political importance and support.

If we define sports according to Kurthan Fisek, sports control the aggressive impulse of human nature and make it a desired race. It ensures the adaptation of the individual to the society and his/her socialization. It provides the mental and physical health of the individual. It is a process that develops success and requires effort for winning and being elected (5). Sports, which constitute such an important place for human life and development, has unfortunately been and established historically almost always for men. Hence, sports were included especially in military trainings. Importance has been given to the sports for the formation of healthy young men before the military service and creation of warriors with healthy physical strength during military service. Sports, which have an important place in military training, have gained a great importance later on in terms of public health, as well (6,7,8).

Nowadays, it is accepted that sports prepare individuals psychologically for daily life together with cultural activities. The sport,

which was a game previously, has become a profession that provides economic income together with professionalization with the influence of globalization. Factors such as winning culture, achieving success and recognition have taken precedence over sports (9,10).

Social Gender

Gender/Social Gender; While gender explains existing genetic, biological and physiological changes, social gender is a situation that includes the duties and responsibilities given by the society, how it is deemed and perceived by the society, and the expectations of the society (11).

Social gender equality due to gender differences has been discussed for years and continues to be discussed in the 21st century. Babies who are born as boys or girls become men or women with their experiences and living conditions according to the societies in which they live. As can be understood, while the nature determines the gender, cultures determine the social gender. Women exposed to social gender discrimination suffer inequalities legally, in ownership of land and property, and having and gaining social, economical and political rights.

However, when we look at the women in Turks from a historical perspective, Turkish women were under equal conditions with men before Islam. Turkish women were mentioned with respect in VIII. century Orkhon inscriptions. During this period, Turkish women were riding horses, girding on swords, shooting arrows, and taking part besides their men in the battles (12). There was even a cavalry troop constituted of women during the period of Gokturks. They were primarily responsible for the training of children, they were participating in social and political decisions and were involved in all aspects of everyday life. Turkish women were negatively affected by the adoption of Islam during the Ottoman period. The social life of women was strictly limited in the Ottoman Empire, which had a theocratic structure. Women who are voiceless in the family could not receive equal rights from the inheritance. Divorce was a unilateral right entitled to men and the testimony of two women was equal to the testimony of a man in the courts. Changes started with the imperial edict of Gulhane, high schools started to be opened only in Istanbul in 1913-1914 and the first university where girls could attend was opened in 1914 (13,14).

When we look at the applicable laws in our country, it is seen that there is an attitude towards equality. According to some sources, although it is stated that this equality table started and developed with the Convention on the Elimination of All Forms of Discrimination Against Women (CEDAW), which was signed in 1985, the “Advisory Board on the Policies for Women” developed in parallel to this and established in 1987 in the

State Planning Organization, and in 1990, “Directorate of Women's Status and Problems” affiliated to the Prime Ministry, in fact, equality and appreciating women was started and developed with the declaration of the Republic in our country before many developed countries in the world (15,16,17). After founding the young Republic of Turkey, Ataturk attached great importance to the women's rights. “The reason for the failure of our social society results from our neglect against our women. Living means activity. Therefore, if one organ of a social society does not function while the other does, that society is paralytic” he said and well summarized the importance he attached to women. With switching to coeducation and granting to women the right to elect and to be elected before many developed European countries, the ongoing reforms have also found a place in sports. Atatürk gave great support and contribution to sports, did not restrict the sports depending on gender, religion, race, etc., and despite all the impossibilities, he ensured participation in the Paris Olympics in 1924. In 1926, Turkish women showed themselves on the athletics track for the first time. Now, we began to regress to a situation, where social gender prevails, from a system in which social gender was eliminated and both men and women were equal (13,18). Compared to the rights entitled to Turkish women and the steps taken in sports field in the 1924s with the establishment of the Young Republic, women in Europe took their place again in the sports with the trend initiated by the modern olympics and great struggles at the end of the 19th century (19).

Sports and Social Gender

We can say that the ideological process that legitimizes women's sports experience and engagement within the gender order and the biological difference between men and women adversely reinforce that women are second-class against men. As sport activities are defined by top performance, superior physical characteristics, talent, ambition, success, and records and as a result of sports activities are limited to those other than these definitions, biological differences were normalized and women became socially second. It is because of a patriarchal perspective that sports are integrated with the athletic structure of men and regarded as a situation specific to men. This patriarchal perspective is closely related to the participation and experiences of women and men in sports. As a patriarchal society, family and teachers play an important role in learning the social gender roles and socialization in our country. While boys are directed to sports to have an athletic body and reinforce their masculinity, it is claimed that girls are especially kept away from heavy sports that require strength for not losing their femininity and protecting their body and therefore the number of girls engaged in sports is less than boys. The rate of quitting sports early is higher among Turkish female athletes. The reasons for this are stated as early marriages, young motherhood, high

domestic responsibilities and increase in the pressure of the father or spouse as a result of the activation of women in sports (20,21).

In a sense, sports have been and continue to be one of the important tools in which the masculinity is built against femininity in the formation of the hierarchy of cultural power. Although there are recent studies indicating an increase in participation of especially women in sports activities, these sporting activities include mostly the light exercises such as aerobic and fitness. The sports field has always been identified by masculine references. As a field that concentrates on physical performance and power and normalizes the differences in this way, sports have been and continue to be an ideological mechanism that serves the most for the social gender ideologies. Some sports are privileged for men; while they are football, wrestling, weight lifting and boxing for our country, they include ice hockey, baseball and rugby in addition to these for the EU and USA (22,23). The evolution has started with tennis, ice skating, etc., among these sport branches which are considered as specific to men only, and women have started to be involved also in the elite discrimination category such as weight lifting and wrestling which are considered more masculine. In order to be involved in these elite female athletes, they are expected to perform more masculine behaviors and it is an inevitable fact that they are excluded because of their socially masculine appearances and behaviors.

Today, some Scandinavian countries have made significant progress inachieving equality between men and women. For example, the position of women in Norway is much better than in many other European countries. They are equal with men in many fields such as participation in labor force, wage received, and their position in politics. However, because of the male-dominated structure of the Physical Education and Sports Committee, the curriculum prepared in schools that train physical education teachers show male dominance. This shows us that, although it is stated that it is developing and it is told that women now take part in sports, women's participation in sports is still not at the desired level and conditions (24).

Coaches also have an important role in the maintenance of social gender. In particular, the language they use reinforces social gender and gives rise to violence. For example, they say to passive or weak players “do not play like a girl”, “play like a man” (25). Hence, according to the results of the study conducted by Karahuseyinoglu in 2008, it was determined that traditional sports branches were mostly based on physical strength and 13 female athletes participated in traditional sports branches compared to 787 male athletes due to the lack of facilities and opportunities provided for female athletes to participate in them. These 13 female athletes who participated in the sports took part in a javelin sports team (26). While Turkish women were shooting arrows, wrestling and

competing with men, etc. during the pre-Islamic period, today it is seen that we are regressing seriously.

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SURGICAL WOUNDS AND WOUND HEALING PROCESS

Özgür ALBUZ*

Introduce

It can be described as, a pysical damage source from an agent that arising from inside or outside the organism.

Wound Types:

1- According to the time of occurrence; Acute or chronic wounds

a)Acute wounds

• Usually secondary to trauma

• The agent is temporary

• Improves sooner than expected

• There are few factors that prevent recovery

• Continuous improvement

b)Chronic wounds :

There is a healing problem in the wound.

• There is a continous negative effect that disrupt wound healing process.

• If these factors depend on the organism itself; It can be vascular, neural, cellular.

Clinically; Examples include venous ulcer or arterial ulcers, cancer-related ulcers, pyoderma gangrenosum due to immunological reasons, and diabetic foot (F.C.Brunicardi, 2013),(Onat DA.,1989).

Factors that can be considered as the main causes of chronic wound;

* Physics: Thermal, cold, radiation, trauma

* Bite

* Infection

* Op. Dr. , Keçiören Eğitim ve Araştırma Hastanesi-Genel Cerrahi Kliniği- Ankara.

* Arteriosclerosis

* Increased coagulation

* Vascular occlusive diseases

* Pyoderma gangrenosum

* Cancers

* Systemic sclerosis

* Blood diseases

* Medicines (Warfarin, heparin, etc.)

* Gout

* The reasons preventing leukocyte migration

2- According to skin integrity;

a) Open wounds
b) Closed wounds

3- According to the change caused by the skin (According the shape of wound)

Scraped wound: As a result of the rubbing of the skin on the hard surface, the loss of a part of the outer layer of the skin, capillary hemorrhage ,also nerve endings are also damaged because it is very painy.

• **Cut wound:** Comes with sharp and pointed objects. It can be superficial and deep. Tissues such as nerves, vessels, muscles can be damaged deeply.

• **Crushed wound:** It is caused by debris, weight, stone sticks, fist shock, traffic accidents. The wound edges are dented. There is less risk of bleeding. Life can be endangered by internal organ damage.

• **Pierced wound:** knife, pocket knife, spit, broken glass, bullet wounds. Depth is high. Puncture of large vessels and organs.

• **Segmented wound:** It is caused by a death or separation of the skin or subcutaneous tissues. Tissues are usually separated from anatomical regions. There is a lot of bleeding.

4- According to the contamination:

*Clean

*Clean – Contaminated

*Contaminated

*Dirty(infected)

(Mc Graw Hill Eight edition. 2005), (Bruce E. Jarrell, 1999)

The classification of surgical wounds:

Clean wounds: It includes incisions in the skin that have been cleansed with disinfectants. It hadn't been entered any gastrointestinal or genitourinary system. The infection rate is at most 2%.

Clean contaminated wounds: In the incisions with made to the skin prepared with disinfectant in accordance ; It is done with the conrolled enterance for minimal contamination to the genitourinary, gastrointestinal or respiratory systems. The expected infection rate is between 3-5%.

Contaminated wounds: There is a major contamination of the wound.

All trauma-related wounds are included in this group.The expected infection rate is between 5-10%.

Infected wounds: There is a built-in infection before the wound forms and expected infection rate is 50% or higher.

(F.C.Brunicardi, 2013), (Bruce E.Jarrell,1999)

Additionally other describments relationship with wound :

Erosion: Superficial loss in the dermis, There aren't any trace.

Fissure: It is shaped as cracked a vertical wound.

Ulcer: Deeper than erosion, passes into the dermis, becomes chronic, difficult to treat and it leaves a scar.

(Alarcon LH et al. 2008), (Khir. 2006 Nov-Dec), (J.M Velesko et al. , 2011)

Wound Healing Phases:

There are four main phases in wound healing;

a) Hemostasis and inflamation phase
b) Migratuar phase
c) Proleferative phase
d) Maturation and remodeling phase

a) Hemostasis and inflamation phase(It covers first 5 days): After tissue injury, the cell contents and the debris flow into the wound. At this stage, the inflammation phase lasts until the leukocytes clear out all inflammatory waste.In clean wounds, this period is approximately 1 week.

- In the first step, vasoconstriction that causes the damaged area to appear white view. In the second stage, there is vasodilatation causing erythema.
- As a result of increased capillary permeability; Erythrocytes, leukocytes and platelets pass to the wound. Chemoattractants in the injured tissue increase white blood cell migration to the wound.
- Depending on cell migration, fluid accumulation results in a marked wound edema.

(Khir. 2006 Nov-Dec), (Bruce E.Jarrell,1999).

In another way of expression, we can summarize it as ;

Following tissue damage, cytokines are immediately secreted within seconds.

The tasks of cytokines at this stage; Directing complex events in hemostasis and healing process.

- When vascular endothelium is damaged, platelets drop contact with the collagen in the wall to form a temporary clot, and hemostasis (TXA2 activates platelets).

In the same time it is vasoconstructive.

Coagulation factors are activated after the first coagulation.

Afterwards; Fibrin is formed and the loose clot formed by platelet becomes convert to the more resistant form.

b) Migratuar and proleferative phase phase: (Covers days 5th and 14th days):

As inflammation decreases, macrophages replace polymorphic leukocytes.
Bacteria and debris from the wound are cleaned by macrophages. Macrophages also secrete growth factors necessary for wound healing.

The dominant cells were macrophages 72 hours after injury.

Fibroblasts move towards the wound at this stage to initiate wound healing.

Angiogenesis has not started at this stage and the wound tissue is hypoxic.

Hypoxia and growth factors stimulate angiogenesis and begin to develop into the wound tissue.

Granulation tissue formation begins on 5th day. Good oxygenation and nutrition are essential for this phase to begin. At this stage, vitamin C is essential for the conversion of proline to hydroxyproline.

The epithelium on the wound edge develops onto the wound. On the other hand, this epithelium is thinner than intact skin and does not contain real skin characteristics.

It is the stage in which the inflammation phase begins to decline and fibroblasts migrating to the wound begin to synthesize collagen.

This is the stage in which the wound tensile force begins to strengthen.

Myofibroblasts initiate wound contraction at this stage.

In addition, endothelial cells begin to proliferate.

Collagen production takes about 3 weeks at this stage and then gradually returns to normal.

(F.C.Brunicardi, 2013), (Khir. 2006 Nov-Dec), (Bruce E.Jarrell,1999).

c) Maturation & Remodellling phase: Usually covers period from day 15th day (This phase continues for years

*Approximately 3 weeks after the injury, mainly wound healing and scar tissue were formed. The wound continues its shaping for years.

*Collagen which is scattered in different directions in the wound tissue is rearranged along the stress lines.

*In the remodeling phase, type III collagen eventually convert in to condense type I collagen.

*Wound tissue reaches 90% strength only on average after 6 weeks or more with respect to the original tissue strength

(F.C.Brunicardi, 2013), (J.M Velesko et al. , 2011), (Alarcon LH et al. 2008).

Leading wound chemoattractants;

Factors affecting wound healing positively and negatively:

****Positive affecting factors***

High dose of vitamin A
Hyperbaric oxygen
Growth factors
Cytokines

Negative affecting factors

Diabetes mellitus

Obesity

Chemotherapy

Radiotherapy

Infections

Hypoxia

Anemia

Steroids

Jaundice

Uremia

Cytokines, molecules of protein structure that enable communication between cells in the body, are critical in wound healing.

Cytokines involved in wound healing:

- FGF (Fibroblast growth factor)

- IL 1, IL 2, TNF (Tumor necrosis factor) alpha

- EGF (Epidermal growth factor)

- TGF-Beta (Transforming growth factor-Beta)

- IGF (Insulin-like growth factor)

-Platelet derived growth factor (Platelet derived growth factor)

- GMCSF (Granulocyte macrophage colony stimulating factor)

When we look at the role of these cytokines in wound healing;

- Chemotactic effect of inflammatory cells and fibroblasts provide

Healing phases	**Postinjury time**	**The cells that in task**	**The role of mediators**
Hemostasis	Instantly	Platelets	Coagulation
Inflamation	1th-4th day	Neutrophils and macrophages	Fagositosis
Proliferation [Granulation & Contraction]	4th-21th day	Macrophage, Lymphocyte Fibroblast, Keratinocyte, Angiocyte, Neurocyte	Repairing the defect, restoring skin functions
Remodeling [Maturation]	22th day - 2 th year	Fibrocyte	Provides damaged tissue tension force

migration to the wound site.

- They provide cell proliferation (proliferation)

- Activation ff angiogenesis

- They provide extracellular matrix formation and structuring

We see that they provide above specific functions.

(Kuehn BM.,2007)),(J.M Velesko et al., 2011).

The types of the wound healing ;

Primary healing:

*Closed with consecutive surgical sutures, tissue wound lips composed.

* Synthesis, storage and collagen fibers of collagen and matrix proteins the formation of bonds between the balance continues.

* Healing is complete without minimal edema, very thin scar (scar) and infection

* After healing, the wound will wins recover 85-90% of its previous strength without injury.

* Operation wounds without clean and clean contaminated tissue defects are example

(Alarcon LH et al. 2008),(J.M Velesko et al., 2011).

Secondary healing:

There is full-thickness wound and particularly occur in the cases with tissue defects.

After occurance of the granulation tissue, wound contraction and epithelization occur.

Sutures must not be put for sew these wounds .

• As like primary healing; Matrix formation, epithelialization and scar tissue maturation occur.

It is important to maintain the integrity of epithelialization in secondary healing.

• Epithelialisation is more important in forming the tensile force of the scar tissue.

• Secondary healing is a slow-growing process and may take 4-8 weeks for epithelial development. The scar is wider.

• Secondary healing is preferred in cases where primary closure is not preferred in patients with plonidal sinus and perianal fistulotomy(J.M Velesko et al., 2011), (Kuehn BM.,2007) (Alarcon LH et al. 2008).

Tertiary healing (Delayed primary wound healing)

In large tissue injuries, due to the foreign body the risk of severe bacterial wound infection to prevent wound infection with contamination; The wound is closed after a few days. In this process, the wound is left open and sterile serum covered with physiological pads.

*The wound is left open for several days to reduce the risk of infection.

*At the end of the primary closure is reached values equal to the tensile force reached.

*Contaminated and dirty postoperative wounds due to peritonitis or empyema and such healing in infected traumatic wounds beyond 24 hours may be preferred (Onat DA., 1989),(J.M Velesko et al., 2011), (Kuehn BM.,2007).

Covering complex physiological and biochemical events and compatible with each other for effective tissue repair progression is a dynamic event in which different processes continue sequentially.

• The main cells are macrophages, fibroblast and collagen fibers, in the wound healing process.

• In conclusion; The most appropriate and least scarring wound healing model is the primary healing model

(F.C.Brunicardi, 2013), (Kuehn BM.,2007) (J.M Velesko et al., 2011).

Basic principles of wound healing;

*To minimize tissue damage and loss

* Ensuring adequate tissue perfusion and blood oxygenation

* Ensuring good nutrition and moistening of tissue

* Ensuring adequate tissue epithelialization

* The most important result of all reactions during wound healing is to try to normalize the wound tension force.

(J.M Velesko et al., 2011)

Basic principles for surgical wound incision healings;

There are tension lines in the human body known as Langer's lines.

When incision is made, the incision should be planned parallel to these lines.

If the incision is made perpendicular to these lines, the wound will heal by pulling the lips and a bad form will occur.

In addition, scar formation and wound healing are related to the surgical technique used during wound closure.

Minimal traumatic approach, debridement of necrotic tissues, absence of foreign bodies in the wound and tension-free suturing are necessary for a minimal scar tissue(Sherris DA,1999), (Khir. 2006) (F.C.Brunicardi, 2013).

Prolonged surgery, prolonged exposure to air and trauma of tissues may adversely affect healing. In addition, factors such as the temperature and light of the operating room may dry the wound. During surgery, hot serum soaked compresses will reduce the drying of the wound(J.M Velesko et al., 2011), (Barbul A., 2005).

In the incision line; Squeezing the suture too far away from the wound will also result in poor scarring. The reason for this is ischemia in a wider area (Sherris DA,1999) ,(Peacock EE Jr.,1984).

The type of suture material also affects scar formation. Especially silk is one of the materials with the highest rate of reaction and infection. On the other hand, suture materials such as polyproprolene, polyamide and polyglecapron have the lowest reaction and infection rates. The suture should be removed as soon as possible. Scar formation will be adversely affected as the time elapses. Face and neck sutures should be taken 1-3 days and other incisions should be taken within 7 days at the latest(Kuehn BM.,2007) (J.M Velesko et al., 2011), (Barbul A., 2005).

In particular, it is essential to manage this process within the principles appropriate to the wound healing process after surgery. As a result; The wound healing process is a vital issue that needs to be managed carefully in the event of different diseases or surgical interventions and in one step. In addition, diseases such as direct wound healing and diabetes are need to a very focused and meticulous process management.

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ANTIBACTERIAL EFFECTS OF HONEY AND HYPERTONIC SALINE

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Introduction

Honey is a super-saturated sugar solution with 82.4% carbohydrate. Honey also contains 17.1% water, 0.5% protein, organic acids, multiminerals, amino acids, vitamins, phenols, and numerous other minor components. Phenolic compounds in honey contribute to its antioxidant, antimicrobial, anti-inflammatory, wound healing and cardioprotective effects (1, 2). The use of honey for medical purposes has been indicated throughout history since ancient Egyptians (3). Honey is commonly used for wound dressing and it is the oldest wound dressing material known to humankind (3-5). The antimicrobial activity of honey was first reported by Van Ketel in the late 19th century (6). Hypertonic saline solution is also reported to inhibit bacterial growth with hypertonic environment (7).

Decubitus ulcer (DU) is the localized tissue damage in the skin and subcutaneous tissues, usually where the bone spurs are, with the effect of pressure, friction, tearing, and other factors (National Pressure Ulcer Advisory Panel (NPUAP) ve European Pressure Ulcer Advisory Panel (EPUAP)) (8). Decubitis ulcers are localized pressure sores on the skin and in subcutaneous tissues (9). It is reported that an estimation of 1.6 million patients develop pressure ulcers annually in the Intensive Care Units (10). Decubitis ulcers lead to increased hospitalization and high treatment costs, as well as increased workload for health workers (11). A number of treatment methods, including wound dressings with antimicrobial properties, are widely used in its treatment (9).

Especially in infected decubitis wounds which are seen frequently intensive care units, choosing effective and low cost dressing materials, taking into account the difficulties of wound care and the high cost of treatment, is very important in terms of increasing treatment success and reducing treatment costs. For this purpose, in this study, the antibacterial

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activities of honey and HS solutions used in wound treatment were tried to be revealed comparatively with mupirocin, an antibacterial agent.

The primary aim of this in vitro study is to reveal the most effective wound care method for wound healing in difficult infected wounds, in order to contribute to the reduction of treatment costs and hospitalization time, as well as clinically fast wound healing.

Method

S. aureus ATCC 29213, *P. aeruginosa* ATCC 27853 and *E. coli* ATCC 25922 origins were plated on liquid Müller Hinton broth (Oxoid, UK) and Group C (Control): 1 mL sterile physiological saline solution, Group H (Honey): 1 mL honey, Group M (Mupirocine): 1 mL mupirocine and Group HS (Hypertonic saline): 1 mL of 3% isotonic solutions' in-vitro effect to these bacteria after 24 hours of 37ºC incubation was investigated. 0.5 McFarland turbidity standard suspension (with the final measurement concentration of 10^6 CFU / mL) were prepared in 2 different tubes for each origin. While honey and liquid Müller Hinton broth (Oxoid, UK) medium were mixed to be 10% (volume/volume) for Group H and Group HC; 100 microliters of mupirocin and 3% hypertonic saline were mixed with liquid Müller Hintron broth (Oxoid, UK) medium to be 10 mg/mL for Group M and Group HS, respectively. Müller Hinton medium was used for Group C. By using Epoch spectrophotometer (BioTek Inst. Inc. Vermont, USA) for OD600 (in 600 nm wavelength) at 0th and 24th hours, the growth in the wells was checked by comparison with the standard curve.

Statistical analysis: In the study, the data were analyzed with SPSS 23 (IBM) packaged software. Central and prevalence criteria such as number, percentage, minimum, maximum and median were used to create descriptive statistics. Conformity of numeric variables to the normal distribution was visually (histogram) and analytically (Shapiro-Wil) tested, while Kruskal Wallis test and post hoc Mann Whitney U test were used for determining the difference between independent variables that don't conform with the normal distribution. Wilcoxon test was used to determine the difference between the dependent variables that did not conform with the normal distribution. A p value that is less than 0.05 was considered statistically significant in the study.

Results

The quantitative distribution (CFU/mL) of the origins of *S. aureus, P. aeruginosa and E. coli* against active substances at 0th and 24th hours was shown in Table 1.

Table 1. The quantitative distribution (CFU/mL) of the origins of *S. aureus, P. aeruginosa and E. coli* against active substances in 0th and 24th.

The reproduction inhibitory effect of S. aereus was significantly higher in Group B, Group M, Group HS than Group C (**p<0.01**) (**Group H=Group M=Group HS>Group C**). The reproduction inhibitory effect of P. aeruginosa was significantly higher in Group B and Group HS than Group M and Group C (**p<0.01**) (**Group H= Group HS> Group M= Group C**). The reproduction inhibitory effect of E. coli was significantly higher in Group HS and Group B than Group C and M (**p<0.01**) (**Group HS> Group H>Group M= Group C**). Table 2 shows the comparison of bacterial amounts at the beginning and 24th hour according to different groups of substances applied.

Table 2. Comparison of the amounts of bacteria at the beginning and 24th hour according to the different groups of substances applied

In Group H, the inhibitory effect on S. aureus and P. aeruginosa was found to be significantly higher than that of E. coli (**p<0.01**). In Group M, the inhibitory effect on S. aureus was significantly higher than that of P. aeruginosa and E. coli (**p <0.01**). There was no significant difference between the groups in terms of inhibitory effect in Group HS (p=0.45). There was no inhibitory effect on bacterial colonies in Group C, and P. aeruginosa reproduction growth was significantly higher than S. aureus and E. coli (**p=0.02**). Table 3 shows the comparison of the amounts of bacteria at the beginning and 24th hour in all groups.

Table 3. Comparison of the amounts of bacteria at the beginning and 24th hour in all groups

A significant inhibitory effect was detected in Group H and Group HS against all bacteria (**p <0.05**). In Group M, a significant inhibitory effect in S. Aureus, and significant reproduction growth in P. Aeruginosa and E. coli were detected (**p<0.05**). In group C, a significant increase of reproduction was detected in all bacteria (**p<0.05**).

Discussion

There are clinical trials that have demonstrated the efficacy of honey in wound healing, and some cases have been reported which show its accelerating effects on wound healing, even in antibiotic-resistant infected wounds. Honey also contributes to autolytic debridement and accelerates wound healing (1, 12, 13). With the application of honey to the wounded area; therapeutic effects such as rapid healing, cleaning of the wound and infections, tissue regeneration, minimization of inflammation, and low tissue adhesion are observed (1, 14). In our study, in accordance with the results of the studies in the literature, it was determined that honey had a significant antibacterial effect on S. Aureus, P. aeruginosa and E. coli. In fact, the antibacterial effect on S. aureus was found to be statistically at the same level with mupirocin.

Recently, honey has been shown to be effective in decubitus ulcers, cesarean section wounds and chronic venous ulcers in lower extremities (15). Complex wounds such as decubitus ulcers create an ideal environment for microbial contamination (16). Wound infections also negatively affect wound healing (17). This leads to prolonged hospitalization, high cost of treatment and increased morbidity (18). In a study on DUs by Khadanga et al. (15) , it was reported that honey showed an antibacterial activity similar to povidone iodine and also showed a significant reduction in Visual Pain Scores (VAS). Therefore, it has been reported that honey can be used safely in DUs because of its effective antibacterial effect and significant decrease in VAS. Considering the results of this study, it can be thought that due to the significant decrease in VAS levels, it may contribute to decrease in the doses of analgesics, especially in intensive care patients, and this may contribute to decrease in morbidity. Many studies have shown that honey has antibacterial effect against a variety of gram-positive and negative bacteria. (15). In our study, it was determined that honey has a strong antibacterial effect on both gram-positive and gram-negative bacteria. In the study performed on 20 patients with spinal cord injury by Biglari et al. (19), it was reported that honey stopped bacterial growth in Grade 3 and Grade 4 DUs in all patients after 1 week, and complete wound healing was observed without any side effects in 18 patients after 4 weeks. In our study, a meaningful antibacterial effect was detected on all bacteria at the 24th hour. In a clinical study conducted on 50 patients by Molan et al. (20), it was reported that honey had eradicated infection in postoperative wound infection in the group treated with honey, and that group had a faster wound healing than the antiseptic group which was treated with 70% ethanol and povidone iodine. Considering all these clinical and in-vitro studies, honey can be safely used for treatment purposes, especially in infected wounds, due to its antibacterial activity and lack of side effects. The use of topical honey may be a good alternative in terms of cost due to the development of resistance due to antibiotic use and the high cost of antibiotics used in treatment. (15).

There are limited studies on the use of HS solution in wound treatment in the literature. Hypertonic saline solution is also reported to inhibit bacterial growth with hypertonic environment (7). In the study conducted by Elkins et al. (21), it was observed that the use of HS in patients with cystic fibrosis decreased the use of antibiotics in exacerbation, compared to isotonic saline. This result demonstrates the antibacterial activity of the HS solution. A comparative study showing the antibacterial efficacy of honey and HS solution was not found in the English literature. In our study, it was determined that both HS and honey showed significant antibacterial effect on S. Aureus, P. Aeruginosa and E. coli. However, it was seen that HS solution showed significantly stronger antibacterial effect than honey against E. Coli. This result suggests that HS solution may be preferable to

honey in the treatment of DU in gluteal and sacral regions, where E. Coli growth due to fecal contamination is a high risk.

In conclusion; DUs, which are frequently encountered in intensive care units, cause increase the workload of health workers, long hospitalization and high treatment costs. Wound infections also adversely affect wound healing, increasing hospitalization time and morbidity treatment costs. In the light of the results obtained in our study, considering the strong antibacterial effects of HS solution and honey; a significant reduction in hospitalization time, morbidity and treatment costs can be achieved through its use in wound care. Considering the facts that honey's analgesic efficacy is high in clinical trials in the literature and the HS solution is more effective than honey on E. Coli, we believe that HS or honey can be preferred in wound care depending on the patient's clinical condition and wound localization. If these study results are supported by clinical trials; wound healing can be accelerated, and a significant reduction in hospitalization duration and treatment costs can be achieved.

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Key messages

1. Wound infections delay wound healing and lead to an increase in treatment time and costs.

2. Effective treatment of wound infections accelerates wound healing and shortens hospitalization duration.

3. The cost of treatment can be significantly reduced through the use of effective and low-cost antibacterial wound dressing materials in wound care.

4. Infected wounds and DUs, which are frequently seen in intensive care units in particular, significantly increase the duration of hospitalization and treatment costs, and cause labor loss.

5. According to the results of this study, through the use of honey and HS solutions in wound dressings, wound healing can be accelerated and the treatment costs can be reduced significantly with an effective anti-bacterial treatment.

6. In addition, through the use of honey and HS solutions, antibiotic doses and thus treatment costs can be reduced, especially in patients with infected wounds in intensive care units.

7. In the wound areas where the risk of fecal contamination is high, such as perianal and sacral regions, HS solution may be preferred over honey, due to its stronger antibacterial effect on E. coli.

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TABLES

Table 1. The quantitative distribution (CFU/mL) of the origins of *S. aureus*, *P. aeruginosa and E. coli* against active substances in 0th and 24th.

	Group H (Honey)		**Group M (Mupirocine)**		**Group HS (Hypertonic saline)**		**Group C (Control)**	
Hour	**0**	**24**	**0**	**24**	**0**	**24**	**0**	**24**
S. aureus ATCC 29213	1090000	307	1140000	1860	1050000	1080	1050000 2130000	
P. aeruginosa ATCC 27853	1120000	2460	1070000 2190000		1070000	940	1040000 2250000	
E. coli ATCC 25922	1100000 616000		1060000 2150000		1060000	640	1070000 2190000	

Table 2. Comparison of the amounts of bacteria at the beginning and 24th hour according to the different groups of substances applied

Group	H	M	HS	C	
Bacteria difference (0-24. Hour)	**Med (Min, Max)**	**Med (Min, Max)**	**Med (Min, Max)**	**Med (Min, Max)**	**p***
S. Aureus	1130[a] (980,1180)	1121[a] (1061,1162)	1039[a] (979,1159)	-1060[b] (-1160,-1059)	**<0.01**
P.Aeruginosa	1117[a] (1037, 1227)	-1140[b] (-1150, -1020)	1059[a] (1039, 1109)	-1220[b] (-1240, -1150)	**<0.01**
E. Coli	484[a] (386, 564)	-1080[b] (-1140, -1030)	1059[c] (989, 1119)	-1140[b] (-1160, -1050)	**<0.01**

***Kruskal Wallis Test p value

a, b, c : The difference between the groups shown in different letters is significant
-:Bacterium increase

Med: Median

Table 3. Comparison of the amounts of bacteria at the beginning and 24th hour in all groups

Bacteria difference (0-24. Hour)				
	S. Aureus	**P.Aeruginosa**	**E.Coli**	
Group	**Med (Min, Max)**	**Med (Min, Max)**	**Med (Min, Max)**	**p***
H	1130[a] (980,1180)	1117[a] (1037, 1227)	484[b] (386, 564)	**<0.01**
M	1121[a] (1061, 1162)	-1140[b] (-1150, -1020)	-1080[b] (-1140, -1030)	**<0.01**
HS	1039 (979, 1159)	1059 (1039, 1109)	1059 (989, 1119)	0.45
C	-1060[a] (-1160, -1059)	-1220[b] (-1240, -1150)	-1140[a] (-1160, -1050)	**0.2**

***Kruskal Wallis Test p value
a, b, c : The difference between the groups shown in different letters is significant
-: Bacterium increase
Med: Median

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS COLONIZATION IN NASAL CULTURES OF THE BABIES HOSPITALIZED AT NEWBORN INTENSIVE CARE UNIT

Asst. Prof. MD. Sinan TÜFEKÇİ

Introduction

Prevalence of *Staphylococcus aureus* carrier status is among 30-70% in humans. This ratio is 0.3-25.9% for nasal MRSA carrier status at NICU. Likelihood of *S.aureus* exposure just after delivery is high for the newborns. *S.aureus* colonization is most common in umbilical cord, skin, naso-pharynx and gastro-intestinal system. Nose and umbilical cord are the most common origin for MRSA.

About 20-30% of the hospitalized patients are colonized with the microorganism which is common at the hospital within the first 5-10 days. *Staphylococcus aureus* is in normal flora in skin, mucosa and many other body parts in humans. *S.aureus* which is colonized in nasal mucosa of the patients and the health staff is one of the important risk factors for nosocomial staphylococcus infection development. Epidemics originated from the *S.aureus*-colonized patients and health staff were reported. The main source for *S.aureus* colonization was reported to be maternal *S.aureus* carrier status in the newborns in several papers published in recent years. Methicillin resistance is important for *Staphylococcus* colonization. MRSA is resistant to many antibiotics. MRSA leads to infections which requires long-term hospitalization and antibiotic use and which has a high mortality rate at intensive care, newborn, hemodialysis and burn units. MRSA colonization facilitates bacteria spread in hospital environment and intensive care units. Detection and isolation of MRSA carriers is one of the infection control measures and this may both reduce nosocomial infection prevalence and control MRSA epidemics (1,2).

The present study investigated the prevalence of MRSA colonization in nasal cultures at the first admission of the patients who were hospitalized at NICU.

Methods

Nasal cultures were obtained from 560 out of 643 patients who were admitted to intensive care unit from the delivery room of Afyonkarahisar State Hospital or at another institution between January 1, 2016 and December 31, 2017. The study design was prospective. Informed consent

was obtained from the family and ethics committee approval was obtained from the local ethics committee prior to the study. Babies who were under 30 weeks of gestation and/or 1000 gr of birth weight, who had multiple congenital anomalies, open wounds like meningo-myelocele, neural tube defect, who were not screened for MRSA at the first hospitalization and whose families did not give consent for participation were excluded from the study. MRSA isolation from the nasal mucosa without the presence of infection signs was defined as "colonization" (carrier) and, presence of MRSA in normally sterile regions and presence of clinical signs was defined as "infection".

Nasal cultures were obtained by using a swab at 1-2 mm depth of nostrils. Smear cultures were cultivated in 5% sheep blood agar and incubated at 35 °C for 24 hours. The colonies which showed gram positive coccus morphology were applied catalase and coagulase tests. Methicillin resistance was determined with disc diffusion method in accordance with the recommendations of National Committee for Clinical laboratory Standards (NCCLS) (3). Babies who had nasal MRSA positivity were taken into an isolated room and applied decolonization protocol with local mupirocin tid for 5 days. Control nasal cultures were obtained one week after the treatment protocol.

Maternal age, gestational week, gender, type of delivery, birth weight, Apgar scores at 1^{st} and 5^{th} minutes, low birth weight (birth weight less than 10% according to gestational week), time of admission, premature rupture of membranes (longer than 18 hours), blood pressure during pregnancy, gestational diabetes, time of nasal culture were inquired. Data were analyzed with SPSS 18.0 statistical package program by using Fisher's test, chi-square test and Wilcoxon for calculating median and a p level of <0.05 was accepted as statistically significant.

Results

Prevalence of MRSA colonization was found as 6.8% (95% CI 2.6-10.9) in nasal culture of 560 babies hospitalized at NICU. This ratio was 6.1% (95% CI 2.8-10.6) in 2016 and 7.5% (95% CI 2.7-11.7) in 2017 and it was seen to tend to increase. Of the babies, 288 (51.5%) were boys and 272 (48.5%) were girls. While ratio of MRSA colonization was higher among boys (55% vs 45%), the difference was not statistically significant. Number of normal vaginal deliveries was 354 (63%) and number of Caesarean sections was 206 (37%). Ratio of MRSA colonization was higher among the babies delivered by normal vaginal delivery compared to Caesarean sections (8.5% $_{VS}$ S 3.9%). 0f 38 babies colonized by MRSA, 8 (21%) were delivered by Caesarean section and 30 (79%) were delivered by normal vaginal delivery. Mean gestational week was 36.8 (range 31-42 weeks , median 37.3 weeks), mean birth weight was 3000 g (range 1210-

4790 g, median 30160 g) in the group with negative nasal culture for MRSA. Mean gestational week was 36.9 (range 31-42 weeks , median 37.4 weeks), mean birth weight was 3020 g (range 1170-4870 g, median 30950 g) in the group with positive nasal culture for MRSA.

Ratio of nasal MRSA positivity was higher among the babies who received care by the mother after delivery or who were monitored for 1-4 hours in delivery room (10.4% vs 5%) compared to the ones who did not receive care. Ratio of nasal MRSA positivity was 3.8% in the babies who were hospitalized within the first 24 hours after delivery and 15.2% in the babies who were hospitalized after the first 24 hours. Ratio of admission to NICU from another center was 10.5% within the first 24 hours (42/400) and 25.4% (31/122) after the first 24 hours. Ratio of nasal MRSA colonization was higher among the babies who were hospitalized after the first 24 hours.

No significant difference was detected between groups with regard to gestational week, gender, birth weight, Apgar scores at 1^{st} and 5^{th} min, low birth weight, premature rupture of membranes, pregnancy-induced hypertension, gestational diabetes, duration of hospital stay. Impetigo, boiled skin syndrome or sepsis did not develop in the patients who were colonized with MRSA. MRSA-related sepsis developed in two babies who were not detected nasal MRSA colonization and who were referred from another center. Risk factors were endotracheal intubation and umbilical venous catheterization in these babies however growing did not occur in tracheal aspirate and catheter cultures.

Characteristics	MRSA negative group (N=522)	MRSA positive group (N=38)	P value
Gestational week	36.8±5.1	36.9±5.3	0.74
Birth weight (gram)	3000±1790	3020±1850	0.71
Male gender Female gender Apgar score at 1st min Apgar score at 5th min SGA PROM PIH GDM	267(51%) 255(49%) 8.1±1.5 8.3±2 11(2.1%) 7(1.3%) 8(1.5%) 9(1.7%)	21(55%) 17(45%) 8.0±2.1 8.5±1.8 1(2.6%) 3(7.9%) 2(5.2%) 1(2.6%)	0.22 0.26 0.16 0.17 0.07 0.09 0.23 0.22
Caesarean section Normal vaginal delivery	198(38%) 324(62%)	8(3.9%) 30(8,5%)	<0.05
Received post-natal care Not received post-natal care	163 359	19(10.4%) 19(5.0%)	<0.05
Time of admission <24 h >24 h	 400 122	 16(3,8%) 22(15.2%)	 <0.05
MRSA blood culture	2(%0.38%)	0	0.12
Duration of hospital stay (median) (day)	16.5 (5-68)	17.4 (6-63)	0.65

Table 1 (N=560); Comparison of MRSA groups by using x^2 and Fisher tests ($p<0.05$ significant) SGA, small for gestational age, PROM, premature rupture of membrane, PIH, pregnancy induced hypertension, GDM, gestational diabetes mellitus.

Discussion

MRSA is among the most common nosocomial pathogens worldwide and associated with significant mortality and morbidity in NICUs. Only nasal or nasopharyngeal culture is sufficient for detection of MRSA colonization in newborns. Polymerase chain reaction (PCR) is also used for diagnosis of MRSA. While PCR test yields the result within 24 hours,

culture results are obtained within the first 48 hours. Sensitivity and specificity of PCR test is reported to be higher for diagnosis of MRSA (4). In our study, culture method was used for diagnosis. MRSA colonization leads to prolonged duration of hospital stay, increased treatment costs, pneumonia, osteomyelitis, sepsis, endocarditis, muco-cutaneous infections (5,6,7). The source of MRSA colonization and infection development thereafter at NICU could not be fully understood. MRSA contamination occurs through the contaminated clothes and hands of the health staff, family members of the baby, equipment, breast milk or vertical route (8,9). The unit's being overcrowded, insufficient number of staff, antibiotic use, long-term use of catheters were reported to contribute to MRSA-related epidemics in NICU (10,11). Control of nasal MRSA colonization is recommended for reducing MRSA-related infection and sepsis in newborns.

In our study, prevalence of nasal MRSA colonization is 6.8% among the babies at NICU. This ratio was found to be 6.1% in cultures obtained from nasal mucosa, axilla and diapers of the babies in literature (12). Nasal MRSA colonization was found to be 5.7% among pregnant Chinese women and nasal MRSA colonization was detected as 4.4% at NICU in Taiwan (13).Ratio of nasal MRSA colonization varies among countries and regions during the first month of life. This is suggested to be associated with hygiene conditions of the mothers, hand hygiene of the staff at NICU and environmental hygiene. Nasal MRSA colonization is higher in the patients hospitalized at NICU compared to healthy newborns. In the present study, nasal MRSA was not investigated in mothers and in the staff as MRSA epidemic was not seen.

Nasal MRSA colonization is reported 2.9 fold greater in normal vaginal deliveries compared to Caesarean sections (14). Ratio of nasal MRSA positivity was 3.9 in Caesarean sections and 8.5% in normal vaginal deliveries. However papers are available in literature reporting that nasal MRSA colonization is higher among babies delivered with Caesarean section and hospitalized at NICU, particularly in preterm and low birth weight group (12). Vertical transfer of MRSA from the mother to the baby was reported recently (15,16). Maternal MRSA was associated with maternal chorio-amnionitis and MRSA sepsis in the newborn (17).

MRSA colonization leads to severe conditions through facilitating spread of bacteriae in hospital environment. Prevalence of Staphylococcus infection is four-fold greater than methicillin-sensitive *Staphylococcus aureus* (MSSA) infection in presence of MRSA colonization (18). Systemic or local MRSA infection did not develop in babies who were detected to have MRSA colonization in our study. Mupirocin, vancomycin and teicoplanin resistance did not develop in our patients who were detected to have MRSA growing in nasal smear. Topical drugs (mupirocin,

bacitracin) is recommended for treatment of MRSA-colonized individuals and controlling epidemics (19). In our study, decolonization could be achieved in all babies one week after administering local mupirocin tid for five days when the nasal MRSA-colonized babies had been transferred to isolated rooms.

In Maraqa study, MRSA colonization was detected in 138 out of 2048 NICU patients (6.74%) between 2004 and 2006, and infection was reported in 30 (21%) of the colonized patients. Duration of hospital stay and colonization was shown to be significantly associated with infection in logistic regression analyses (20). In the present study, not encountering sepsis in nasal MRSA-colonized patients may be explained with decolonization, strictly following hand hygiene rules in the clinic, isolation measures and not including high risk babies. Analysis of molecular characteristics of MRSA isolates was not required in newborns with nasal MRSA colonization in our study.

Conclusion

In our study, nasal MRSA colonization results are consistent with the literature and colonization-related sepsis did not develop. Early detection of colonized patients before infection development may reduce MRSA spread in babies hospitalized at NICU. Detection of risk factors, isolation measures, hand disinfection and decolonization with local therapy are the required surveillance measures in patients with nasal MRSA colonized patients.

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ADENOVIRUSES IN OPHTHALMOLOGY REVIEW

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Introduction

Adenoviruses are icosahedral, enveloped and double-stranded DNA viruses and cause a number of diseases such as conjunctivitis, gastroenteritis, hepatitis, myocarditis and pneumonia.[1] Adenoviruses are highly contagious organisms with different antigenic identifiers and over 50 known serotypes. The most common type of adenoviral eye involvement is epidemic keratoconjunctivitis (EKC) followed by pharyngoconjunctival fever (PCF). The appearance of all ocular surface involvement, including conjunctiva and corneal epithelium, is a distinctive feature of EKC. Pseudomembranous, symblepharon, and multifocal subepithelial infiltrates, which are seen in severe cases, may result in decreased visual acuity.[2-4] PCF is characterized by fever, pharyngitis, acute follicular conjunctivitis and preauricular lymphadenopathy. Also isolated adenoviral conjunctivitis can be seen without corneal or systemic involvement. Contact with hand eye contact, ocular secretions, aerosols, ophthalmic caregivers and ophthalmic devices are main routes of transmission.[5] Adenoviral conjunctivitis is a biphasic disease that begins with an infectious phase followed by an inflammatory phase. Viruses continue to shed in ocular secretions for up to 7-10 days from the onset of infection. The patient will continue to be infectious until 2-3 weeks.[6]

Adenoviruses are the most common cause of acute viral infections of the conjunctiva, affecting up to 75% of cases.[7] According to the data from the Japan national surveillance center, adenoviral conjunctivitis affects 1 million people every year.[8] Precise statistical data, prevalence and incidence values are not available because of the inability to access medical care or access to health facilities. According to the data of Germany; while most affected group is adults by disease, the disease is seen in all age groups and gender dominance is not observed.[9] Although EKC is generally observed between 20-40 years, PCF tends to be seen mostly in children.[10,11]

Adenoviruses are divided into 7 different species (A-G) and a number of serotypes according to their immunohistochemical properties, nucleic acid similarities, hexose and fiber protein lengths, biological properties and phylogenetic analyzes.[12,13] Adenoviral conjunctivitis may occur sporadically or epidemically throughout the year. The severity and prevalence of the disease is related to the serological subtype. Serotype 8,

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9 and 17 (type D) were associated with EKC; serotype 3, 5, 7 and 11 (types B and C) PCF; serotype 1-11 (species B-E) is associated with isolated follicular conjunctivitis without sore throat and auricular lymphadenopathy.[14,15] According to the results of epidemiological studies in Japan, adenoviral conjunctivitis cases with serotype 3, 4 and 37 were found to increase with increasing air temperature.[16] Germany's data also support an increase in adenoviral conjunctivitis cases in hot weather.[10] Outbreaks of EKC are common in hospitals (especially in ophthalmology units),[17-19] intensive care units,[20,21] and care homes;[22] PCF outbreaks are more common in schools, nurseries and summer camps.[23]

Both the EKC and PCf tend to be more frequent in the environments where close relationships need to be demonstrated. Direct contact with ocular secretions is the most common route of transmission. The infection can also be transmitted through the tonometer used by the eye caregiver, the cover speculum, and the split lamp. In one study, the positivity rate of hand sweep of infected patients was 46%.[5] Although the risk of infection with a family-friendly contact infection is 10%, the risk is increased when the infection is prolonged.[24] Nasocomial EKC outbreaks are widespread especially in ophthalmology units; postponement of ophthalmologic surgery, early discharge after surgery and closure of the operating room for a while.[8]

Epidemic Keratoconjunctivitis (EKC)

At least 19 of the adenovirus serotype that is 60 or more can cause EKC. Serotypes 8,9 and 17 are the most common causes, and less frequent 2-5, 7, 9, 10, 11, 14, 16, 21 and 29 can lead to the EKC table. The incubation period varies from 4 to 24 days and the symptoms tend to last for 7 to 21 days. After the symptoms have cleared, the patient continues to be contagious for 10-14 days. The virus can not be detected by PCR analysis in ocular secretions before the onset of symptoms.[25] Although the first phase of the EKC is unilateral; has been shown to cause double-sided disease in up to 70% of cases.[11] Red and pink eyes, excessive watering, foreign body sensation and photophobia are the most common symptoms. In severe cases, the patient may complain of decreased visual acuity associated with orbital and periorbital pain.

They are usually have recent eye examinations, affected family members or professional contacts in their anamnesis. Sometimes there may be flu-like symptoms, fever, vomiting, diarrhea, myalgia and difficult breathing before infection. Ocular findings are marked conjunctival redness, chemosis, tarsal follicular reaction, petechiae or subconjunctival hemorrhage.

Pharyngoconjunctival Fever (PFC)

PFC is most often caused by adenovirus serotype 3 and less frequently by serotypes 2, 4, 7, and 14. Serotypes 1, 5, 6, 8, 11 and 19 are the cause of sporadic outbreaks.[26,27] It is an acute and highly contagious disease accompanied by fever, pharyngitis, rhinitis, acute follicular conjunctivitis, and sensitive preauricular lymphadenopathy. Ocular inflammation is unilaterally starts and affects other eye within 1-3 days. The most common ocular findings are swelling and scaling of eyelids, epifora, conjunctival injection, conjunctival chemosis, follicular and papillary reaction, and subconductival haemorrhage. Contamination pathway is direct contact with droplet inhalation and ocular secretions. Although the incubation period varies between 5-12 days, the symptoms end within 3-5 days, limiting themselves and often without causing any complications.

Complications

Pseudomembranes containing a fibrin-rich exudate lacking blood vessels and lymphatics adhering to the upper and lower tarsal conjunctiva are more common in EKC cases and have been shown to be associated with adenovirus serotypes 8,19 and 37.[28] Unlike the true membranes, pseudomembranes can be separated without damaging the underlying epithelium, thus leading to little or no bleeding. Although pseudomembranes are generally observed in EKC cases, true membranes can also be observed according to the degree of the disease and the intensity of inflammation. Removal of true membranes leads to bleeding, leaving it in situ leads to subepithelial fibrosis and symblepharon formation.[29]

Another common complication observed in EKC cases is multifocal subepithelial infiltrates, which are pathognomonic for adenoviral infections. It has been shown in up to 50% of patients and has been shown to occur more frequently with serotype 8.[29] These infiltrates are a type of cellular immunological response to viral antigens stored in the corneal stroma beneath the bowman's membrane.[30] In vivo confocal microscopy study showing the clinical course of the EKC has shown that dendritic cells at the 1 st stage of diffuse epithelial keratitis are associated with subepithelial bowman membrane level accumulation. During the second week of focal epithelial keratitis, it has been shown that the hyperreflective basal cell clusters on dendritic cells are surrounded by a complex network of leukocytes. There is a hyperreflective layer of cells on the subepithelial infiltrate area in the anterior stroma.[31] The reduction in corneal sensitivity seen in the early phase of the disease probably improves on average of 8.5 days.[32]

Disease Progression and Treatment

Subepithelial infiltrates persist for weeks to years. These can cause visual impairment if they involve the visual axis. Most of these infiltrates heal spontaneously without scarring. Although topical corticosteroids shorten the healing time of infiltrates, there is no effect on long-term outcomes.[33] It has been shown that phototherapeutic keratectomy treatment combined with low dose mitomycin has a positive effect on photophobia, visual acuity and contrast sensitivity in the treatment of persistent corneal opacities developing as a result of EKC.[34]

Adenoviral conjunctivitis is usually a self-limited disease which results in complete recovery within about 3 weeks. Conservative approaches such as artificial tears and cold application provide symptomatic relief without any side effects. Topical antibiotics are used to prevent or treat bacterial superinfection.[35] The use of topical antihistamines and vasoconstrictors may also reduce the duration of the disease and complaints related to the disease, but there is also a risk of local toxicity.[36] Topical steroid use is controversial. Topical steroids are generally preferred in the acute phase of the disease and the effect is transient. The use of topical steroids in animal studies has been shown to increase the adenovirus replication rate and therefore the disease recovery process is prolonged.[37-39] Steroid therapy should be restricted for complicated disease with visible pseudomembranes or subepithelial infiltrates with decreased visual acuity.[33,37] It has also been shown that topical nonsteroidal antiinflammatory use does not reduce adenovirus replication in animal models.[40] Because topical nonsteroidal antiinflammatory use has no effect on subepithelial infiltrates, it may be a safer alternative to steroid use for symptomatic relief.[41]

The effects of the virustatic agents trifluridine, vidarabine and ganciclovir on adenoviruses are limited, and the use of adenoviral conjunctivitis therapy is still controversial.[42-44] Topical ganciclovir experimentally reduces adenovirus burden[42-45] but clinical studies have shown no effect on adenoviral conjunctivitis.[46] Significant antiviral activity of topical cidofovir against adenoviruses has been demonstrated in experimental studies and in animal models.[47-50] Topical cidofovir administration reduces the duration of the disease by reducing viral titers and is also effective in the prophylaxis of adenovirus.[51] In a clinical trial comparing the rate of symptomatic treatment of acute adenoviral conjunctivitis, combining topical cidofovir alone or with topical cyclosporine has not been shown to be a superior superiority of the disease to the disease.[52,53] It has been shown in animal models that the

antiadenoviral effect of 2'3'-dideoxycytidine, an antiviral agent, is higher than that of sidofovir.[54]

Interferons are proteins that are responsible for stopping viral spread in response to viral infection and released from the cells. In some studies, topical interferon beta treatment has been shown to be effective in reducing the duration and complications of the disease.[55-57] Interferon gamma therapy can also be used as a treatment option because of its antiadenoviral activity.[58-60] Therapeutic effect of interferon alpha treatment has not been demonstrated.[61-63] Anti adenoviral activity is shown in animal models of topical immunoglobulin treatment; there is no human study.[64]

Povidone-iodine is a broad-spectrum antiseptic and, despite high activity against free adenoviruses, its activity against intracellular adenovirus particles in infected cells is poor.[65,66] The combination of topical povidone-iodine and dexamethasone has been shown to reduce viral secretion and disease duration.[67,68] Topical steroids provide symptomatic relief; topical povidone-iodine also kills viruses that shed in tears, thereby reducing the risk of spreading the disease. In a recent study, it has been shown that conjunctival washing with 2.5% povidone-iodine in infants is effective in the treatment of adenoviral conjunctivitis.[69]

Unlike acute disease, topical steroids have been shown to reduce adenovirus-associated subepithelial infiltrates.[33,70,71] However, this condition recurs after the cessation of treatment. This does not only lead to treatment dependency; at the same time steroids may result in cataracts and increased intraocular pressure. Cyclosporins used as an alternative to steroids do not provide symptomatic relief in the acute phase of the disease and have no activity on the natural course of the disease but are used in the treatment of subepithelial infiltrates following adenoviral conjunctivitis.[52,53] Topical cyclosporine treatment, varying between 0.05% and 2%, reduces subepithelial infiltrates and associated foreign body sensations and visual complaints.[72-75] Although topical cyclosporine treatment increases viral efflux in an animal study and therefore poses a risk for local epidemics, it is still a relatively safe treatment.[76] Phototherapeutic keratectomy therapy combined with low dose mitomycin C should be reserved for chronic subepithelial infiltrates with severe visual disturbances and treatment has shown positive effects on photophobia, visual acuity and contrast sensitivity.[77,78]

Since adenovirus conjunctivitis and complications are not effective treatments, strict sterilization of the hands and instruments is essential controlling the spread of the infection.[10,11,80] Because adenoviruses are resistant to many antiseptics, the type and amount of antiseptic used is important.[81] Human adenoviruses are resistant to dryness and can survive significant periods of time outside the human body. Plastic and metal

surfaces have been shown to produce infectious concentrations even 28 days after settlement.[82,83] Simply deleting surfaces with general disinfectants such as isopropyl alcohol or hydrogen peroxide is ineffective against adenoviruses.[81,84] When adenovirus is suspected, it is recommended to be taken into an isolated contamination room and all surfaces and instruments should be disinfected with 70% ethyl alcohol and 1/10 of bleach after examination.[81,85] Disinfection should be done starting from the cleaning of organic matter.[81] The use of gloves, single-use tonometer heads and disposable eye drops can reduce transmission.[5,80] Patients should be informed about the course of the disease when they arrive in the acute phase of the disease and be cautious at the point of call for control at this time that they are contagious.

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PERIANAL HIDRADENOMA PAPILLIFERUM

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Introduction

Hidradenoma papilliferum (HP) was first reported by Worth in 1878 (1). HP is a rare papillary apocrine gland tumor often seen in women (2, 3). For some authors, it can be considered an analog of intraductal papilloma of the breast (4). It is most frequently located in vulvar and perianal area. Rarely, it may also be located outside of genital area. Extragenital localization of HP is defined as ectopic HP (2). Ectopic HP is generally encountered in head and neck areas (4). The ones localized in genital area are most frequently seen between 30-60 years of age, while extragenital localization may be encountered in different age groups (between 8-78 years of age).

Though it is generally asymptomatic, sometimes it may manifest itself with itching, pain, bleeding and ulceration (2). They usually appear as slow-growing, solitary, red or skin-colored nodular lesions (4). In this case report, the discussion topic was a female patient that sought medical advice due to painful nodular lesion in perianal area.

Results

In this case report, a 60 year-old female patient who was operated due to a palpable mass in perianal area and reported to be HP as a pathological result was discussed. The patient complained of having a slow-growing painful mass around the anus for approximately 9-10 months. No finding was detected in patient history. Palpable mass was not detected during rectal examination. A nodular lesion with similar appearance to thrombosed hemorrhoid was present at perianal area at 9 o'clock lithotomy position. Excision was planned due to pain complaint of the patient. Gross total excision together with mass base was applied to the patient under spinal anaesthesia. Histopathological examination of surgical specimen was reported as HP.

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Discussion

HP which was previously thought to be an apocrine tumour, is now believed to be a mammary-like gland (MLG) adenoma (5, 6). HP is a benign tumor often localized in anogenital area, mostly seen in women and clinically asymptomatic in general (2, 4). But rarely, it may manifest itself with symptoms such as itching, pain, bleeding and ulceration. While lesions are typically smaller than 2 cm, in literature there are lesions reported to be bigger than 4 cm (2). In this case report, the patient had a painful red-colored nodular lesion sized around 1-1.5 cm located in perianal area.

In differential diagnosis, perianal abscess, genital warts, external thrombosed hemorrhoidal disease along with less commonly encountered perianal localization diseases such as epidermoid carcinoma, lipoma, neurofibroma, angioma and sebaceous cyst should be considered (2, 7). Also, very rarely seen but clinically quite similar granular cell tumors with perianal localization should also be taken into account in differential diagnosis (8).

Definitive diagnosis is not possible clinically and it may only be reached by histopathological examination. Generally benign and rarely malign transformation is reported histopathologically and it may incorrectly be diagnosed as adenocarcinoma. If there is mitotic figures, cellular pleomorphism or atypia in histopathological examination, existence of malign transformation is accepted (2). In literature, while malign transformation is reported in cases with perianal localization, it is not reported in cases with ectopic localization. (4). In the study performed by Scurry et al. malignancy was not reported in 46 patients with vulva located HP (5). In this case report, histopathological examination results of the patient did not show any malign transformation.

Gross total resection with negative surgical margin is recommended for treatment and recurrence is quite rare (2, 9). Patient in this case report had a total excision with lesion base and recurrence was not detected after 18 months follow-up.

Conclusions

HP is a rarely encountered benign lesion with perianal localization that shows slow progression and is generally asymptomatic. For this reason, it is quite difficult to diagnose. But after considering the fact that it can seldom go through malign transformation and definitive diagnosis can only be reached after histopathological examination, we are of the opinion that

all surgeons should be quite alert regarding surgical excision of slow progressing, asymptomatic nodular lesions with perianal localization.

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CURRENT TRENDS IN THE TREATMENT MODALITIES OF OPEN ANGLE GLAUCOMA

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Introduction

Glaucoma includes the conditions having the common feature of an acquired, degenerative optic neuropathy [1,2]. Glaucoma-related optic neuropathy is characterized by abnormalities of the optic nerve complex (optic nerve head [ONH], retinal nerve fibre layer [RNFL], and peripapillary region) in a specific pattern and corresponding damage to the visual field (VF) [3]. Glaucoma is frequently associated with elevated intraocular pressure (IOP), but an increase in IOP is not necessary to diagnose this condition [1,2]. Changes in the optic nerve are permanent, progressive resulting in reduced quality of life [4]. In this article, we would focus on the current modalities in the medical and surgical management of open angle glaucoma.

Epidemiology And Risk Factors:

Globally, It is estimated that 64.3 million people have glaucoma, of which three fourths are open-angle [5]. Glaucoma (both open-angle and angle-closure) is the second leading cause of irreversible blindness both worldwide and in Europe, with approximately 8.4 million people becoming blind from the disease [5]. Globally, the number of people with glaucoma is estimated to become 111.8 million in 2040 [5]. The estimated prevalence of glaucoma is 2.65% in people above 40 years of age [6]. In Europe, the prevalence of glaucoma varies from 1.54 to 3.89% [7-18], which amounts from 3.99 millions to 7.11 millions. [7-18]. The risk factors of Primary open angle glaucoma are increasing age, high refractive error(both myopia and hypermetropia), thin central corneal thickness, Large optic disc diameter, elevated IOP, hypertension, cardiovascular disease, thyroid disorders, low physical activity, positive family history. African people and Hispanic people have higher prevalence of Open angle glaucoma than other ethnic groups [1,19,20].

Classification and Subtypes:

Glaucoma is classified based on the underlying anatomy and pathophysiology, with open-angle and angle closure representing the two

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major subtypes [1,2,21]. Idiopathic or primary glaucoma occurs with no identifiable cause. Glaucoma in which there is an identifiable cause of increased IOP, resulting in optic nerve damage, is known as secondary glaucoma. Pseudoexfoliative glaucoma is the most common type of secondary glaucoma [22]. Normal-tension glaucoma, one of the sub types of POAG, is characterized by glaucomatous optic neuropathy in patients with IOP measurements consistently lower than 21mmHg [23-25]. Optic nerve damage occurs at relatively low IOPs in NTG patients as compared to patients with POAG. Angle closure can be either acute or chronic. Mixed-mechanism glaucoma includes characteristics of both open and closed-angle glaucoma.

Pathogenesis:

Although the pathogenesis of glaucoma is not fully understood, the level of intraocular pressure is related to retinal ganglion cell death. Intraocular pressure is determined by the balance between secretion of aqueous humor by the ciliary body and its drainage through 2 independent pathways—the trabecular meshwork and uveoscleral outflow pathway. There is increased resistance to aqueous outflow through the trabecular meshwork in patients with open angle glaucoma. In contrast, the access to the drainage pathways is obstructed by the iris in patients with angle-closure glaucoma. The sclera is perforated at the lamina where the optic nerve fibers (retinal ganglion cell axons) exit the eye, because of the mechanical stress and strain on the posterior structures of the eye, resulting in mechanical axonal damage and disruption of axonal transport [26,27,28]. Disrupted axonal transport occurs early in the pathogenesis of glaucoma in experimental systems resulting in collections of vesicles and disorganization of microtubules and neurofilaments in the prelaminar and postlaminar regions [26]. There may be mitochondrial dysfunction in retinal ganglion cells and astrocytes [29]. Even in individuals with normal IOP, glaucomatous optic neuropathy can occur. Impaired microcirculation, altered immunity, excitotoxicity, and oxidative stress may also cause glaucoma [30].

Dıagnosis:

Although increased intraocular pressure is a significant risk factor for the presence of glaucoma, in many studies, it was found intraocular pressure was lower than 22 mm Hg in one fourth to half of the individuals with glaucoma [1]. Glaucoma progresses without causing symptoms until the disease is advanced with substantial amounts of neural damage. When symptoms do occur, the disease results in vision loss with concomitant reduction in quality of life and inability to perform daily activities, such as driving. Early detection and intervention is essential to slow the progression of the disease. With retinal ganglion cell death and optic nerve

fiber loss in glaucoma, characteristic changes in the appearance of the optic nerve head and retinal nerve fiber layer occur [31]. Diagnosis can be confirmed by the presence of characteristic visual field defects, but as many as 30% to 50% of retinal ganglion cells may be lost before defects are detectable by standard visual field testing [26,31]. However, subjective identification of optic disc damage from glaucoma can be challenging, with large disagreement in grading observed even among glaucoma specialists [32]. Several recently developed laser scanning imaging techniques provide more objective and quantitative information about the amount of optic nerve fiber loss [32-35].

Management:

Glaucoma management is aimed at reducing IOP, but the ultimate goal is to slow or halt the structural and functional progression of disease so that overall quality of life would be maintained or improved. [36-39] The target IOP range is a dynamic concept and it should be individualized and constantly reevaluated, taking into consideration stage of disease, patient risk factors, life expectancy, and social circumstances.

Medical Management: Unless contraindicated, medical therapy remains the most common initial treatment modality for lowering IOP and are delivered topically as eye drops [1, 2].

Prostaglandins; First Choice for Glaucoma Treatment: The effectiveness and tolerability of PGAs such as latanoprost, bimatoprost, and travoprost makes them popular first choices for treating glaucoma. PGAs have better IOP-lowering ability and fewer systemic adverse effects than -blockers [40-42]. They act by increasing uveoscleral and TM outflow and reduction in IOP starts 2–4 hours after first administration. Peak therapeutic effect is reached at 8-12 hours. IOP fluctuations are minimized during a 24-hour period and maximum effect is achieved 3–5 weeks after initiation of therapy. Although prostaglandins have an excellent systemic safety profile, they are associated with several cosmetic ocular adverse effects like conjunctival hyperemia, elongation and darkening of eyelashes, and induced iris darkening. Prostaglandin-associated periorbitopathy can occur which includes manifestation like periocular skin pigmentation and fat atrophy can result in a sunken looking appearance, deepening of the upper eyelid sulcus, upper lid ptosis, enophthalmos, and loss of the inferior orbital fat pads [43-45].

-BLOCKERS: Topical -blockers, indicated for once or twice daily use, have a proven efficacy and known contraindications. As -blockers are systemically absorbed, they were historically contraindicated in patient with cardiac or pulmonary disease [46-48]. Tachyphylaxis can occur during treatment with -blockers due to rapid increase in the density of -adrenergic receptors on the cell surface. Morning administration of -

blockers may provide more benefit since circadian variation exists in the rate of aqueous humour production, with the rate approximately 50% lower at night compared to daytime [46-48].

-2 AGONISTS: -2 Agonists works by constricting of the afferent ciliary vasculature, leading to decreased aqueous humour production and also by increasing uveoscleral outflow resulting in decreased IOP [49]. -2 agonists are relatively safe long-term IOP-reducing agents. Ocular allergy is the major side effect leading to discontinuation of treatment in 10% to 20% of patients [49,50].

CAIs: The misconceptions about contraindications for CAIs in patients with proven or putative sulfa drug allergies have been clarified resulting in wider use of CAIs. [51-53]. With proper monitoring and follow up, patients with a documented sulfa allergy might still benefit from CAIs.

Fixed Combination Therapy: European Glaucoma Society (EGS) and COS guidelines recommends least amount of medications to achieve the desired IOP reductions [1,2]. However, many patients require more than one agent to reach the desired target IOP [54]. Benefits of fixed-dose combinations [55,56] are as follows: Washout of the first drug by the second is avoided, It is convenient to use single medication bottle and to dispense reduced number eye drops, lower cost, ocular exposure to preservatives is reduced and hence ocular surface disease is prevented [57,58].

Certain combination therapies that include -blockers and/or agonists have negative effects on diastolic ocular perfusion pressure (DOPP), especially in NTG patients and in smaller patients or children [58,59]. Most fixed combinations include the -blocker timolol along with either a PGA, CAI, or agonist. The most recent fixed-dose combination entry on the market is brinzolamide/brimonidine. This first non- -blocker combination provides an additional, costeffective option that is expected to have a positive impact on patient adherence. Both brinzolamide and brimonidine are used as a part of fixed dose combination theraphies, either with timolol or PGA resulting in relevant IOP reductions [60-63]. Brinzolamide/brimonidine eye drops were statistically significantly superior to either constituent drug administered alone as monotherapy in reducing IOP at threemonths in two phase 3 RCTs [64,65].

Generic Fixed Combination Drugs: Although it is generally accepted that generic drugs are bioequivalent to that of brand-name drugs, a study of latanoprost showed that the IOP-lowering effect of the brand-name drug was better compared with the corresponding generic drug in POAG and ocular hypertension patients [66]. The difference in IOP lowering could be due to the difference in adjuvants and/or the stability of the active ingredient once the bottle is opened [66]. Difference in adjuvants results in

differences in viscosity, surface tension, and pH, which could affect efficacy and safety eventhough generic drugs have the same quantitative compositions in terms of active ingredients [67-72].

The Need for Novel Therapies: No novel class of drugs for the treatment of glaucoma has been approved since latanoprost in 1996. In spite of recent advances, currently available medical therapy often fails to meet the desired outcomes. Hence, effective alternatives are needed that have a longer duration of action and offer patients simple dosing regimens.

One of the emerging therapies is the **kinase inhibitor** [73-75]. kinase is a serine/threonine kinase that plays a key role in regulating the contractile tone of smooth muscle tissues in a calcium-independent manner, directly targeting aqueous humour trabecular outflow. kinase inhibitors reduce IOP by enhancing aqueous humour drainage through the TM and also lower episcleral venous pressure (EVP) [79,80].

Adenosine receptor agonists increase the conventional aqueous outflow and are under experimental stage for lowering IOP (76-77]. These agents also cause cell shrinkage and secretion of metalloproteases in human trabecular meshwork, resulting in remodeling of the extracellular matrix and reduced outflow resistance [78].

Latrunculin B is another novel agent targeting the trabecular meshwork. Twice daily latrunculin B (0.005%, 0.01%, 0.02%, or 0.05% solution) significantly lowered IOP compared with contralateral, placebo-treated eyes, with few and mild ocular adverse events in patients with ocular hypertension or early POAG. [79].

Neuroprotective agents are being explored for treating glaucoma [80]. Although significant evidence from preclinical studies has suggested a potential role of neuroprotectors (such as brimonidine or memantine) in the prevention of glaucomatous degeneration, clinical research has been inconclusive on the neuroprotective effects of oral and topical medical therapy for glaucoma in adults.

Citicolline is a newer drug used in OAG. OAG patients had an improvement of ganglion cell function and of neural conduction along the visual pathways after intramuscular or oral treatment with citicolline [81-83]. Goldberg [83] suggested that citicoline may have a neuroenhancing effect that could explain the amelioration of the glaucomatous perimetric condition and the reduction of the progression of visual field defects as recently reported in glaucomatous eyes (by using 500 mg of citicoline in oral solution). Topical citicoline inOAG patients may induce an enhancement in the glaucomatous retinal function (PERG improvement) with a consequent better neural conduction along the visual pathways (VEP improvement).

Different drug formulations and delivery methods are also being investigated with a goal to reduce inconvenience associated with topical drug delivery. Some of them include punctal or tear duct plugs, topical ring inserts, subconjunctival injections and inserts, and intraocular inserts.

Surgical Management:

Filtering Surgery: Filtering surgery in glaucoma is indicated when medical treatment and laser therapy are unable to prevent, stop or delay the progression of the disease. The traditional filtering surgery is a challenge, especially in advanced glaucoma because it can be accompanied by complications and failure.

Trabeculectomy is considered the "gold standard" of non-penetrating surgery in glaucoma; it is the surgical technique from which all the others are derived, newer procedures, with better efficacy and safety.

Surgical procedures are based on one of the two mechanisms to reduce IOP:

1. Improving drainage of aqueous humor (AH)

2. Reducing production of AH.

The first technique is the one usually used. There are two types of procedures: ab externo and ab interno.

1.1 non-penetrating anterior filtering techniques:

1.1.1 deep sclerectomy (DS) (simple or assisted by a CO2 laser)

1.1.2 canaloplasty

1.2 penetrating anterior filtering techniques:

1.2.1 trabectome

1.2.2 Fugo blade

1.2.3 Excimer laser assisted trabeculectomy

1.3 penetrating posterior filtering techniques

1.1 **Non-penetrating anterior filtering techniques**

The efficacy of antiglaucoma non-penetrating surgery: Success rate varies between 45% and 69%. The rate of complete success is 34.6% for deep sclerectomy and 63.4% for deep sclerectomy with collagen implant, after 48 months [84]. Qualified success can be up to 69-100%.

Indications for non-penetrating anterior filtering techniques: Primary open angle glaucoma (POAG), pigmentary glaucoma, pseudoexfoliative glaucoma

Contraindications for non-penetrating anterior filtering techniques: Patients with scaring of the Schlemm's canal caused by laser, surgical procedures or corneo-scleral trauma, anomalies of the camerular angle, primary angle-closure, open-angle glaucoma due to ocular trauma

Complications of non-penetrating anterior filtering techniques: Hyphema, early or late elevation of IOP, suture detachment, Descemet detachment, iris prolapse, hypotonia, inflammation, failure of the procedure

1.1.1 Deep sclerectomy

1.1.1.1 Non-penetrating simple deep sclerectomy: In this technique the Schlemm's canal is opened and partial excision of the external and internal walls and of a part of the trabecular meshwork is made.

The most frequently used technique is to make two scleral flaps, one superficially situated with the base at the limbus and another, more profound, as a mark for the opening of Schlemm's canal. The profound flap is excised, eliminating the internal and external walls of the Schlemm's canal. The drainage of the aqueous humor is observed. All the anatomical planes are sutured [85,86].

1.1.1.1 CO2 laser assisted deep sclerectomy (CLASS): Here, the conjunctiva is incised for making a flap with the ab externo base. A rectangular sclera flap is made (1/3 or 1/2 of the sclera's thickness), with the base at the limbus. The CO2 laser is applied, along with the HENE guidance. The CO2 laser will excise the external wall of the Schlemm's canal. An average IOP reduction of 13.1±4.3 mm Hg (45.1%) and 11.5±5.5 mm Hg (39.2%) was seen at 6 months and 12 months in a study conducted on 15 patients. The complete success rate was 45.5% after 12 months, and qualified success was 90.9% [87].

Trabeculectomy versus deep sclerectomy: There are numerous randomized studies that reveal the superiority of non-penetrating surgery concerning safety with fewer complications (84-88); when it comes to efficacy, the success rates are higher in trabeculectomy in some studies (85,88,89) and equal in others(86,90)

1.1.1 Canaloplasty: In this type of non-penetrating surgery, a wire is introduced in the Schlemm's canal, guided by an optic fiber micro catheter. The wire dilates and keeps tension in Schlemm's canal, reestablishing the flow of aqueous humor through the physiological paths. A viscoelastic product is injected for opening the Schlemm's canal. The tension created improves the flow through the trabecular meshwork [91].

Advantages: The 360° controlled opening of Schlemm's canal, the possibility to combine the procedure with deep sclerectomy for better lowering of the IOP

Disadvantages: Expensive device, unknown long term effect of the implant in Schlemm's canal

1.2 **Penetrating anterior filtering techniques:**

1.2.1 Trabectome: The trabectome is a surgical instrument used for controlled partial endoelectro ablation of the trabecular mesh, under gonioscopic guidance. This is an ab interno procedure which dissects the juxtatrabecular region and create a direct flow of the aqueous humor through the Schlemm's canal and the collector channels by eliminating resistance [92].

Indications: POAG, pigmentary and pseudoexfoliative glaucoma, POAG with ineffective filtering.

Contraindications: Angle closure, with or without peripheralsynechiae.

Complications: Hyphema, iridodialysis, Ciclodialysis, the abrupt elevation of the IOP.

Advantages: Creating a large communication between the anterior chamber and the collector channels; lack of adjacent tissue damage, unaffected conjunctival integrity, no filtering bleb.

Disadvantages: The opening of the Schlemm's canal is not circumferential, a limited lowering of the IOP caused by the pressure in the aqueous veins, expensive procedure.

1.2.2 Fugo plasma blade – transciliary filtration: Fugo plasma blade is the first plasma ablation system that can create precise low-energy incisions on the ocular surface without damaging the adjacent elements, with instantaneous hemostasis. The Fugo blade technique can also be ab interno by creating fenestrations in the internal wall of Schlemm's canal, that allow the AH to flow without resistance. The procedure was found to be safe and effective [93].

Advantages: Posterior drainage, no antimetabolites needed, the price is not very high, the short duration of the intervention.

Disadvantages: The risk of a hyperfiltering, hypotonia

1.2.3 Excimer laser assisted trabeculectomy: The procedure is ab interno; it creates small gaps in the trabecular meshwork so that aqueous humor passes through the Schlemm's canal without encountering resistance. An Excimer xenon-chloride laser is used.

Advantages: The ab interno approach keeps the conjunctiva intact, control of the ablation, without alternative tissue damage, can be combined easily with phacoemulsification, short duration of the intervention.

1.3 **Non-penetrating posterior filtering techniques**

Indications: Glaucoma unresponsive to medical treatment, POAG with moderate IOP, early onset POAG, failure of trabeculectomy, pigmentary glaucoma, pseudoexfoliative glaucoma, Sturge-Weber syndrome, aphakic glaucoma.

Contraindications: Primary angle closure, secondary glaucoma, acute angle-closure, uveitic glaucoma, traumatic glaucoma, neovascular glacoma, iridocorneal endothelial syndrome, active ocular infection, ocular surgery in the last 12 months, active ocular pathologies.

Complications: Blockage of the aqueous humor flow, possible peripheral anterior synechiae, hyphema, hypotonie, supracoroidian hemorrhage, migration of the device, discoloration of the Descemet membrane.

Advantages: Lowered risk of hypotonia, continuous control of filtering, reduced inflammation: no iridectomy needed, fixed and continuous drainage through metallic stent, maintaining the integrity of the conjunctiva, possibility of combined surgery, possibility of modulating the IOP by changing parameters of the devices, low risk of creating a filtering bleb, a permanent communication between the anterior chamber and the supracoroidian space, excellent biocompatibility, a permanent communication between the anterior chamber and the subconvunctival space, no adjacent tissue damage.

Disadvantages: The risk of antimetabolites, the risk of contact with the iris or cornea, the necessity of multiple stents for obtaining a higher flow, the risk of device migration, difficult procedure, expensive device, creating a filtering bleb, the possibility of conjunctival damage, risk of fibrosis.

1.3.1 Ex-Press device: It is an alternative to conventional surgery. Ex-Press stent has better efficacy than trabeculectomy in reducing IOP [94]. Complication rates were similar for the two types of surgery, except development of hyphema in few patients in the Ex-PRESS group [95].

1.1.1 IStent (Glaukos Corp): The IStent shunt is the first micro-bypass ab interno implant for glaucoma treatment. It was designed for reestablishing the physiological flow of the AH, by creating a by-pass through the trabecular meshwork of the Schlemm's canal. The IStent is positioned ab interno in the inferior nasal quadrant, through a small incision in the Schlemm's canal [96].

1.1.1 Gold micro shunt: The Gold micro shunt is a micro gold plaque of 24 karats that contains 19 canals. It is used for creating a communication between the anterior chamber of the eye and the supracoroidian region. The pressure difference between the anterior chamber and the supraciliary space determines flow of the aqueous humor through the micro-canals. It

is the first implant that uses natural pressure gradient for continuous flow of the AH [97,98].

1.3.4 EyePass: EyePass glaucoma implant is a micro tube shaped as a "Y"; it by-passes the trabecular meshwork and make a communication between the Schlemm's canal and the anterior chamber. The procedure is ab externo; both arms of the device have to be placed inside the Schlemm's canal [99].

1.3.4 CyPass Micro-Stent: CyPass Micro- Stent is a polyamide cannula, with a 6.25 mm length and a diameter of 300 μm. It is placed in the supraciliary space so that the aqueous humor will drain through the gaps of this tube [100]. CyPass Micro-Stent implantation resulted in minimal complications and reduced IOP 12 months postoperatively in a study conducted on 142 patients [101].

1.3.6 Hydrus microstent: Hydrus microstent is an "intracanalicular scaffolding". The procedure is done ab interno; it is a micro-by-pass that reestablishes flow through the trabecul-Schlemm's canal, using a direct communication between the anterior chamber and the Schlemm's canal. The device is made of nitinol (nickel-titanium) and has the size of an eyelash; it is very elastic and biocompatible. The two most common complications were transient hyphema and Peripheral Anterior Synechiae (PAS) formation in 15% and 10% of patients respectively [102].

1.3.7 AqueSys: The AqueSys system is described as the first procedure with an ab interno subconjunctival approach for lowering the IOP. It creates a direct link between the anterior chamber and the subconjunctival space. The implant is flexible, with a gel-like structure; its diameter is that of a human strand of hair (65μm) [103].

1.4. Conclusion

Glaucoma causes irreversible damage to the optic nerve, thereby causing damage to the vision and leading to poor quality of life. Early diagnosis and prompt treatment is essential to halt the progression of the disease. Many novel medical and surgical modalities of treatment are available at present. It is the duty of the physician to explain the patient about various modalities of treatment and select the appropriate treatment based on the individual characteristics, their needs and preferences. Regular follow up and adherence to treatment has to be ensured to stop or slow the disease progression, thereby reducing the overall morbidity caused by the disease.

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CORONARY ARTERY BYPASS GRAFTING SURGERY AND COMPLICATIONS

Hüseyin SİCİM - Ertan DEMİRDAŞ

Introduction

James Herrick and pathologist Ludvig Hektoen of Rush Medical College in Chicago in 1912, they published an article entitled Klinik Clinical Indicators of Sudden Obstruction in Coronary Arteries Amerikan in the Journal of the American Medical Association. His papers have led to observations that many researchers, such as Osler, Dock, Hammer and Fothergill, have been making observations for centuries since William Heberden fully described angina pectoris and natural development in 1768. This was the first true and integrative explanation of myocardial ischemia syndrome and its pathological correlation with coronary occlusion.

The history of CAD treatment methods can be divided into many branches that may be associated with CABG, from a modern point of view these interventions can be considered as the best early interventions, such as the worst false onset or treatment options such as transmyocardial revascularization and coronary endarterectomy. As an example, sympathectomy and indirect revascularization methods which can be considered as a first in terms of palliative but surgical intervention pericardial and cardiac powdering, pectoral muscle, omentum, jejunum, skin or spleen myocardial grafting, direct implantation of vessels such as LIMA in myocardium and collateral mammary arteries, coronary sinus and bronchial artery in order to change the direction of circulation interferences involving ligation of structures such as arteries.

Risk factors for perioperative mortality and morbidity after CABG surgery have been extensively studied and can be divided into three categories: patient characteristics, provider characteristics, and postoperative factors. Patient characteristics include older age, female sex, African American race, greater body surface area, and previous myocardial infarction (MI) within one week. Additionally, patient comorbidities associated with increased morbidity and mortality include history of

femoral/popliteal disease, chronic obstructive pulmonary disease, congestive heart failure, calcified ascending aorta, carotid/cerebrovascular disease, aortoiliac disease hepatic failure, renal failure, previous MI, and previous open-heart surgery.

Operation Technique And Graft Options Used In Aortocoronary Bypass Surgery

The age of the patient, the characteristics of the target vessel, the presence of other graft options, the medical history of the patient and the preferences of the surgeon may play a role in the selection of the graft to be used. Other than saphenous vein grafts, other graft options are mentioned by name only. Internal thoracic artery (uni- or bilateral), radial artery, gastropepiploic artery, and inferior epigastric arteries are among the options of arterial grafts. In addition to v.safena magna grafts which are the most commonly used grafts, v.safena parva and cephalic vein grafts are theoretically possible. What is clear today is that anastomosis of at least one pedicular arterial graft to a distal high flow arterial system has a direct effect on reducing early and late mortality of patients.

Conduits

Multiple conduits may be employed to establish cardiac revascularization.The LIMA is the vessel of first choice. IMAs usually are patent for many years postoperatively (10-year patency >90%) because of the fact that <4% of IMAs develop atherosclerosis, and only 1% have atherosclerotic stenoses of hemodynamic significance.

Reversed saphenous vein grafts (SVGs) are commonly used in patients undergoing CABG. Their disadvantage is a declining patency with time: 10% to as many as 25% of them occlude within 1 year of CABG; an additional 1% to 2% occlude each year during the 1 to 5 years after surgery; and 4% to 5% occlude each year between 6 and 10 years postoperatively. Therefore, 10 years after CABG, 50% to 60% of SVGs are patent, only half of which have no angiographic evidence of atherosclerosis.

Other arterial conduits, such as the radial, gastroepiploic, and inferior epigastric arteries, have been used in CABG. Radial artery graft patency is best when used to graft a left-sided coronary artery with high grade stenosis and worst when utilized on the lower pressure right heart. The gastroepiploic artery is most often used to bypass the right coronary artery or its branches, but it is prone to spasm. The 1-, 5-, and 10-year patency rates of the gastroepiploic artery are reportedly 91%, 80%, and 62%, respectively.

Complications

Deep sternal wound infection

Wound infection after cardiac surgery, especially mediastinitis, is rare but important because it is life-threatening. The risk of mediastinitis after cardiac surgery varies between 0.4% and 5% (1). The risk of mortality is high in patients who develop mediastinitis and range from 20-40%. Prolongs hospital stay and increases costs. In addition, right ventricular rupture due to mediastinitis, rupture of saphenous vein graft, aortic fistula formation complications may develop or even vertebral osteomyelitis may occur after mediastinitis, retrograde or through tissue penetration with the common venous drainage system between the vertebra and mediastinum.

The reason for the increased risk of DSWI in obese patients can be related to the poor perfusion of subcutaneous adipose layers with low levels of prophylactic antibiotics in this tissue.

Convincing evidence has emerged that the control of blood glucose levels during surgery and the immediate postoperative period with frequent monitoring and protocols for continuous intravenous administration insulin can decrease DSWI rate. A large prospective study of diabetic patients undergoing cardiac surgery demonstrated that hyperglycemia was an independent risk factor for death, length of hospital stay, and infection rates, and found that a continuous insulin infusion reduced these risks.

The patient's carriage of Staphylococcus aureus on skin and nares has been identified as an important risk factor for DSWI. The Society of Thoracic Surgeons practice guidelines upon antimicrobial prophylaxis recommend routine 5-d mupirocin 2% nasal administration for all patients undergoing cardiac surgery in the absence of a documented negative testing for staphylococcal colonization. However, concerns still remain about the extensive use of mupirocin because of lack of efficacy, risk of widespread high-level resistance, and costs[13]. Of note, the only prospective, randomized, and double-blinded trial of mupirocin in cardiac surgery patients did not show benefit: No patients with poststernotomy mediastinitis caused by methicillin-resistant Staphylococcus aureus (MRSA) had identical isolates in preoperative and surgical-site cultures.

Venous Thromboembolism

Venous thromboembolism (VTE) is the general name of all pathological thrombosis occurring in venous circulation. Most commonly in deep veins

of the lower extremities (deep vein thrombosis, DVT); more rarely in the upper extremity, pelvis and other veins. The most important life threatening component of VTE is pulmonary embolism (PE). Venous thromboembolism is generally seen as DVT per year in the general population in 1-2 of every 1000 people. It rises up to 1 in 100 years of age. It is estimated that 2 to 5 out of 100 people will have a VTE at least once in their lifetime. It is estimated that there are approximately 2 million DVT cases and 600000 PE cases in the United States of America (USA). In addition, approximately 200000 people die every year in the US due to PE. This number; AIDS (acquired immune deficiency syndrome), breast cancer and traffic accidents. Venous thromboembolism is a multifactorial disease and the more risk factors can be found together. The more risk factors the patient has, the higher the risk of developing VTE. Three major pathogenetic mechanisms that facilitate the development of venous thromboembolism have been described by Virchow about 150 years ago. These basic pathogenetic mechanisms are still accepted, and with today's technology genetic changes (polymorphisms / mutations) have been added to these mechanisms.

Pulmonary hypertension

Pulmonary hypertension following CABG surgery presents a significant diagnostic and therapeutic challenge, as it is associated with high morbidity and mortality secondary to right ventricular failure, arrhythmias, myocardial ischemia, and intractable hypoxia. While the mechanism for development of pulmonary hypertension is complex, several factors induce pulmonary hypertension in the postoperative setting, including left ventricular dysfunction, underlying pulmonary hypertension, pulmonary inflammation and ischemia, mitral or aortic patient-prosthesis-mismatch, pulmonary emboli, and mechanical compression of the pulmonary vessels[15].

Pericardial effusion and cardiac tamponade

Despite recent improvements in intraoperative management, surgical technique, and postoperative care, pericardial effusions continue to be a significant cause of morbidity after CABG surgery. While these pericardial effusions may delay recovery, they can be life-threatening with tamponade and hemodynamic compromise. Additionally, there has been an increase in the incidence of postoperative pericardial effusions, likely due to the widespread use of chronic anticoagulation and increased complexity of cardiothoracic operations.

Cerebrovascular disease

The presence of neurological abnormalities after CABG is a frightening complication. Its incidence varies from 0.4% to 80% depending on what is defined [19-20]. Neurological deficit after CABG is divided into 2 types: Type 1 deficit is characterized by destructive, focal motor loss, stupor and coma, while Type 2 deficit is characterized by intellectual function and memory disorientation. Roach et al. [10] reported a multicenter prospective study to determine the true incidence of Type 1 (stroke) and Type 2 (encephalopathy) deficits after CABGO. In their study, 2108 patients were operated in 24 centers and were observed neurologically after CABG. 129 patients (6.1%) had cerebral complications; Type 1 (3.1%) and Type 2 (3.0%) rates were found.

Renal dysfunction

Although cardiopulmonary bypass is an indispensable element in the vast majority of open heart surgeries, it is also the cause of undesirable inflammatory responses (7-9). Many factors during the KPB or the material used (blood non-physiological surfaces) or is material-independent (surgical trauma, ischemereperfusion injury of organs, changes in body temperature, release of endotoxins). Complement activation of KPB, cytokine release, leukocyte activation and expression of adhesion molecules, free oxygen radicals, arachidonic acid metabolites, platelet activating factor. It has been shown in previous studies that it causes complex inflammatory response involving the production of various substances including nitric oxide, and endothelin (1,2). This inflammatory cycle may contribute to the development of respiratory insufficiency, renal dysfunction, bleeding disorders, neurological dysfunction, liver dysfunction and ultimately multiple organ dysfunction.

When the factors activating the inflammatory system during CPB are considered, extracorporeal lines constitute only one of these factors; cardiotomy suction blood, blood-air contact, hypothermia, heparin and protamine, can be defined as the manipulation of the aorta and reperfusion injury (10-13).

Based on all this, much effort has been made on measures to reduce the inflammatory response during CPB. The spectrum of renal damage after CPB is broad, ranging from subclinical injury to defined renal failure requiring dialysis. Despite advances in anesthetic techniques and perioperative management of cardiac surgery patients, acute renal failure remains a frequent and serious complication of cardiac surgery. According

to the definition of the incidence of acute renal failure (ARF) and 1-5% (14-16).

Gastrointestinal (GI) Complications

Historically, gastrointestinal (GI) complications have been recognized to cause significant morbidity and mortality after coronary artery bypass grafting (CABG). From the 1980s through 2004, many retrospective and prospective single-institution studies have documented an incidence of 0.6% to 2.4% for GI complications after CABG, with an associated mortality rate of 14% to 63%[20]. These reported GI complications include bleeding (24% to 61%), pancre- atitis (2% to 34%), perforated ulcer (2% to 8%), mesen- teric ischemia (5% to 36%), ileus/obstruction (3% to 21%), cholecystitis (5% to 14%), diverticulitis (2% to 3%), and hepatic failure (5% to 10%)[20]. In addi tion to high mortality, such GI complications have been associated with increased morbidity after CABG, necessitating additional endoscopic and surgical interventions, prolonged ventilation, and ICU and hospital lengths of stay.

Mediastinitis

Mediastinitis after cardiac surgery continues to represent an important complication associated with tremendous morbidity and cost. [20]. The exact mechanism by which mediastinitis develops is unknown and multifactorial. In the present report, a wide variety of preoperative and operative variables are examined with multivariate analysis to determine independent predictors of mediastinitis. A total of 6459 consecutive patients were analyzed; all data were collected prospectively. In an effort to define consensus risk factors for the development of mediastinitis, a comprehensive review of the literature was performed, and results from this analysis were compared with results from previous reports.

Modern management of mediastinitis with early, aggressive debridement followed by delayed closure has been reported to reduce early mortality to less than 20%(21).The effect of mediastinitis and its current treatments on long-term survival has not been investigated; whether long-term sequelae exist in patients who survive acute therapy is unknown. Therefore, we examined whether the rates of mortality up to 2 years after surgery were different for patients who developed mediastinitis than for patients who did not have this complication. Mortality rates in the two groups were adjusted with the use of a Cox proportional hazards model for a number of variables that influenced late survival; this adjustment helped to identify the influence of mediastinitis on long-term survival.

Low Cardiac Output Syndrome

Low cardiac output syndrome (LCOS) refers to reduction in cardiac output due to transient myocardial dysfunction. LCOS has been defined as the need for postoperative IABP or inotropic support for longer than 30 min to maintain a systolic blood pressure of 90 mmHg or cardiac index of 2.2 L/min per square meter. LCOS is a serious complication of CABG surgery. Mortality rates from this condition can be as high as 38 %, and LCOS is considered the largest cause of mortality in patients following CABG surgery(21). The sequela of this syndrome is that the blood flow is insufficient for the body to maintain its metabolic needs resulting in end-organ dysfunction, e.g., renal dysfunction associated with low urine output, if untreated leading to renal failure. The factors responsible for low cardiac output include hypovolemia, cardiac tamponade, electrolyte abnormalities, arrhythmias, poor ventricular contractility due to myocardial ischemia, and hypoxemia. The management of this condition includes mild inotropy and reduction of afterload often by means of IABP to reduce the workload of the heart.

Mediastinal Bleeding

Mediastinal bleeding is a serious complication of CABG surgery. Acceptable drain output after a standard CABG operation can be 400/200 ml in 24 h. In patients with preoperative dual antiplatelet therapy, this amount can reach as much as 1,200 ml in 24 h. The amount of bleeding is usually greatest in the first 6 h and starts to tail off in the subsequent 6–12 h. Acute severe bleeding may warrant the use of allogeneic blood product transfusion and/or performing sternal reopening and re-exploration, both of which are independent risk factors for in-hospital mortality. Acute bleeding occurs in 3–5 % of patients post-CABG surgery(22). In 1–3 % of patients sternal reopening and exploration is warranted in the operating theater/intensive therapy unit. Postoperative bleeding can be categorized into surgical or medical. However, etiology of bleeding in the postoperative period is most often complex and multifactorial. Significant bleeding after an uneventful operation should be assumed to be from a surgical cause. Common surgical sites of bleeding are from the anastomotic suture lines, side branches of the arterial or venous conduits, and substernal and periosteal regions of the sternum.

Mediastinal bleeding should be anticipated preoperatively in any patient undergoing CABG surgery. Coagulation markers such as prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count should be measured preoperatively, and any preexisting derangements

should be corrected. In patients on oral anticoagulation, warfarin should be withheld 4 days prior to surgery. Antiplatelet therapy with aspirin and/or clopidogrel should ideally be withheld 5–7 days prior to operation to minimize the risk of bleeding. Antiplatelet therapy is continued in cases of urgent CABG surgery in patients with acute coronary syndrome (ACS) up to the day of surgery; higher than average bleeding risk should be anticipated in these cases. Alternatively glycoprotein IIb/IIIa inhibitor agents such as Eptifibatide can be utilized to bridge patients with ACS up to 2 h prior to CABG surgery to minimize progression of disease prior to surgery and reduce the risk of bleeding due to their shorter half-life. Meticulous surgical technique and surgical hemostasis are perhaps the most important aspect in the prevention of major postoperative hemorrhage. Rewarming the patient to normothermia prior to termination of cardiopulmonary bypass would improve coagulation system function and reduce the risk of postoperative bleeding.

In postoperative patients, in whom bleeding is suspected, any hemodynamic instability should be addressed immediately. Chest drain output should be meticulously measured, and drain patency should be verified at all times. Patients should be warmed if hypothermic to improve the coagulation system function. Coagulation studies should urgently be performed, and any derangements should be corrected with the use of appropriate blood products. Transesophageal/thoracic echocardiography (TEE/TTE) should be performed to identify any signs of cardiac tamponade. Sternal reopening should be performed if life-threatening mediastinal bleeding is suspected.

Arrhythmias

Arrhythmias are common phenomenon after CABG surgery. Atrial fibrillation (AF) is usually of benign nature and is said to occur in about 25 % of patients postoperatively after CABG. Although the etiology of postoperative AF is still unclear, it can lead to devastating complications such as stroke. Ventricular arrhythmias on the other hand occur rarely after CABG surgery but are likely to signify more sinister causes such as myocardial injury and should trigger further investigations by means of bedside TTE, CT angiography scan, and/or coronary angiography.

Conduction abnormalities occur commonly post-CABG surgery[23]. 25 % of patients develop transient conduction abnormalities, which generally resolve in 24–48 h and are associated with the use of cold cardioplegia solution. Persistent conduction abnormalities do not influence the long-term outcome after CABG surgery. The prevalence of more serious conduction

abnormalities such as atrioventricular block (AV) (Mobitz type II) and complete AV block is very low after CABG surgery. The risk of developing AV block post-CABG surgery increases with the higher number of coronary vessels bypassed, longer CPB time, and longer cross-clamp times.

Potassium channel blockers (e.g., amiodarone) are used very commonly for rhythm control in patients with postoperative AF. In refractory AF rate control can be achieved with digoxin, nondihydro-pyridine calcium channel blockers (e.g., diltiazem), or beta-blockers (e.g., metoprolol). Anticoagulation with heparin and warfarin should be considered if arrhythmias persist for >48 h. Bradyarrhythmias are often encountered after CABG surgery. Epicardial pacing by means of epicardial pacing wires should be commenced to maintain hemodynamic stability. In cases where no epicardial pacing wires have been inserted at the time of surgery, transcutaneous/transvenous cadiac pacing is an alternative. As per management of tachyarrhythmias, electrolyte disturbances should also be addressed in bradyarrhythmias. In patients with unresolved bradyarrhythmias, insertion of a permanent pacemaker should be considered.

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VETERINARY MEDICINE

HEALTH MONITORING

Buğra GENÇ*

Science, like other activities in human life, is globalizing. With the globalization of science, the number of research is increasing and the negative effects of regional and cultural differences on research are decreasing. In order to make the results obtained in the biomedical researches more reliable, in vivo methods using live animal models are increasingly preferred. Among these methods, the creation of laboratory animal models is one of the most reliable options. In order to reach the most accurate and realistic result, it is of utmost importance that the most appropriate model is formed and the continuity of the model characteristics is achieved.

The health status of the animals to be used in the research has the potential to directly affect the results of the research (Sellers et al., 2012; Treuting et al., 2012). Even the possibility of infectious agents present at the breeding line or at any critical point in the study raises the need for microbiological quality monitoring of the animals. (Mansfield et al., 2010). For these reasons, the use of animals with known biological properties in scientific studies using animal models is important to ensure repeatability of experimental results. The point of these findings is to harmonize health monitoring programs (such as design, sampling, monitoring, reporting and interpretation) that help to meet scientific, legal and animal welfare requirements and provide information on the microbiological quality information of animals used in research (Mahler et al., 2014).

Laboratory animals are threatened by a wide variety of microorganisms that can cause infection. Many of these microorganisms can cause infection without clinical symptoms. Therefore, it is not enough to try to perform health monitoring by observing clinical symptoms. Latent form and invisible symptoms may affect the outcome of the research. Symptomatic and non-symptomatic infections may lead to complex results in the research and may increase the number of animals used due to their negative effects. Presence of tumors and other tissues, cell lines, serum, embryos and gametes may be the cause of a latent infection. (Nicklas et al., 1993, Mahabir et al., 2008). It should be kept in mind that infective agents that may be present in laboratory animals may have zoonotic character. This not only affects animal health and research quality in a negative way, but it can also reach dimensions that threaten public health. For these and other reasons, it is important that all centers and affiliated units working with the

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laboratory animal establish a laboratory animal health monitoring program to cover every critical point and as an integrated part of any quality assurance system. At this point, the cost of preventive measures and health monitoring program requirements may seem high, but is very low in relation to the total cost of the research project and the continuity in the organization (Nicklas et al., 2002). The fact that the costs of health surveillance are salvage against a possible loss requires that the cost be ignored (Newcomer & Fox, 2007).

Health monitoring is a complex issue, and the training and competence of the person to install this system will directly affect the success of the system and should be performed by an expert and equipped with full authority. The existence of a culture of communication among all those involved in the animal care and use program is inevitable in order to ensure good health monitoring and accurate interpretation of the results. (Koszdin & Di Giacomo, 2002).

Unit Concept in Health Monitoring

According to health monitoring programs, animal facilities should be structured and organized on a microbiological basis (microbiological unit). A microbiological unit is defined as a stand-alone concept with separate space and traffic for animals, personnel and supplies. According to this definition, places where personnel, equipment and animals move freely or where animals are kept in open cages, a barrier facility, an isolator, micro isolation cage and IVC cage, can be named as microbiological unit. The identification of the microbiological units is a critical an done of the most important steps should be considered carefully in the design of the health monitoring program as it will affect the sampling program, the quality and frequency of tests, and the interpretation of the results. For example, since the risk factors and consequences of microbiological contamination may vary between experimental units, the design of the health monitoring program should be based on this diversity. Strict rules to be applied within the facility are also required for the implementation of health monitoring. The most important of these rules is to ensure that the access within the facility is under control and to ensure access to the minimum number of authorized persons, traffic order at the material and animal exits and the order so as not to cause controlled and cross-contamination. In addition, the use of technologically superior material can be an aid to program effectiveness. The use of IVC (individually ventilated cages), which has become rapidly widespread recently, provides a great advantage over conventional open cages in preventing potential contamination among animals. With the use of these units, transmission of not only infectious agents but also allergen agents commonly seen in laboratory animals will be minimized.

In general, a health monitoring program should be established taking into account the microbiological unit, animal species, number and immunological status, monitoring frequency, sample material diversity to be collected and frequency of sampling, and specific conditions for that facility. If there are more than one species in the microbiological unit, separate surveillance of the animals belonging to these species should be ensured.

Risky conditions that may lead to the introduction of unwanted factors in an animal unit are examined in two groups. Including multiple animals per month, physical proximity of different microbiological units, animal entry from different colonies, postoperation animal movements, insects and wild rodent presence, facility serves multi-purpose research, mobility of staff into the unit very often, common use non-disinfectable material are considered high risky activations and situations. Inbreeding, occasional staff mobility into the unit and a limited variety of studies constitute a low risk group (Mahler et al., 2014).

Contamination

Some microorganisms are specific to one species or a very limited number of more than one species, while others may be active in a large number of different species. Some microorganisms are even known as zoonoses having animal-human transmission characteristics. In addition to the aforementioned traffic, animal-human interaction, material-borne and environmental-related contamination, the transmission of these factors is also possible during the use of biological material applied by the research protocol. Currently, humanized immunosuppressed animals are used for studies of human immune system, xenotransplantation and infection models. Together with the transplants, these animals can also transfer HIV, the human-acquired AIDS disease virüs (Berges & Rowan, 2011). For this reason, it is necessary to check the cell lines that are intended to be used in animals under the health monitoring protocol.

Many microorganisms that do not cause clinical symptoms may cause diseases in animals whose immune system is suppressed and whose resistance is reduced due to disease or medication used for research purposes. As a matter of fact, genetically modified rodents constitute the group with unexpected cases and findings. In these species, it is possible to see diseases caused by organisms already known or commensally present in animals, as well as the emergence of unplanned phenotypes that may be considered important for the disease. (Treuting et al., 2012; Franklin, 2006).

Based on current literature knowledge, it is not possible to list all opportunistic microorganisms separately for all species and strains, but periodic controls should be performed at the discretion of the facility

management and research team for possible opportunistic and rarely seen microorganisms. In the table below, the factors that need to be investigated in microbiological tests to be performed in a laboratory animal facility at certain periods are classified according to animal species.

Table I: Microorganisms that should be controlled in three months (A) and yearly (B) periods according to animal species.

Mus musculus			*Rattus novergicus*			*Cavia porcellus*			*Mesocricetus auratus*			*Oryctolagus cuniculus*		
	A	*B*		*A*	*B*		*A*	*B*		*A*	*B*		*A*	*B*
Mouse hepatitis virus			*Kilham rat virus*			*Guinea pig adenovirus*			*Lymphocytic choriomeningitis virus*			*Rabbit haemorrhagic disease virus (RHDV)*		
Mouse rotavirus			*Rat minute virus*			*Guinea pig parainfluenza virus 3/Caviid parainfluenza virus 3*			*Sendai virus*			*Rabbit rotavirus*		
Murine norovirus			*Rat parvovirus*			*Sendai virus*			*Pasteurella pneumotropica*			*Bordetella bronchiseptica*		
Minute virus (Parvo)			*Toolan's H-1 virus*			*Guinea pig cytomegalovirus*			*Clostridium piliforme*			*Clostridium piliforme*		
Mouse parvovirus			*Pneumonia virus of mice*			*Bordetella bronchiseptica*			*Corynebacterium kutscheri*			*Encephalitozoon cuniculi*		
Theiler's murine encephalomyelitis virus			*Rat coronavirus/ Sialodacryoadenitis virus*			*Corynebacterium kutscheri*			*Helicobacter spp.*			*Pasteurella multocida*		
Lymphocytic choriomeningitis virus			*Rat theilovirus*			*Streptococci β-haemolytic (except*			*Salmonella spp.*			*Cilia-associated respiratory bacillus*		

						group D)								
Mouse adenovirus type 1 (FL)			*Hantaviruses*			*Streptococcus pneumoniae*			*Endo- and ectoparasites*			*Salmonella spp.*		
Mouse adenovirus type 2 (K87)			*Mouse adenovirus type 1 (FL)*			*Clostridium piliforme*			*Hamster polyomavirus*	*	*	*Endo- and ectoparasites*		
Mouse pox (ectromelia) virus			*Mouse adenovirus type 2 (K87)*			*Encephalitozoon cuniculi*			*Pneumonia virus of mice*	*	*	*Adenovirus*	*	*
Pneumonia virus of mice			*Reovirus type 3*			*Salmonella spp*			*Encephalitozoon cuniculi*	*	*	*Coronavirus*	*	*
Reovirus type 3			*Sendai virus*			*Streptobacillus moniliformis*			*Lawsonia intracellularis*	*	*	*Myxomatosis virus*	*	*
Sendai virus			*Clostridium piliforme*											
Helicobacter hepaticus			*Helicobacter bilis*			*Endo- and ectoparasites*						*Clostridium spp.*	*	*
Helicobacter bilis			*Mycoplasma pulmonis*			*Chlamydophila caviae*	*	*				*Dermatophytes*	*	*
Helicobacter typhlonius			*Pasteurella pneumotropica*			*Cilia-associated respiratory bacillus*	*	*				*Escherichia coli (enteropathogenic strains)*	*	*
Pasteurella pneumotropica			*Streptococci β-haemolytic (except group D)*			*Dermatophytes*	*	*				*Pneumocystis oryctolagi*	*	*
Streptococci β-haemolytic (except group D)			*Streptococcus pneumoniae*			*Pasteurellaceae*	*	*				*Staphylococcus aureus*	*	*
Streptococcus			*Cilia-associated*			*Pseudomonas*	*	*				*Treponema*	*	*

pneumoniae			*respiratory bacillus*			*aeruginosa*						*paraluiscuniculi*		
Citrobacter rodentium			*Pneumocystis spp.*			*Staphylococcus aureus*	*	*						
Clostridium piliforme			*Salmonella spp.*			*Yersinia pseudotuberculosis*	*	*						
Corynebacterium kutscheri			*Streptobacillus moniliformis*											
Mycoplasma pulmonis			*Endo- and ectoparasites*											
Salmonella spp.			*Bordetella bronchiseptica*	*	*									
Streptobacillus monilif ormis			*Corynebacterium kutscheri*	*	*									
Endo- and ectoparasites			*Encephalitozoon cuniculi*	*	*									
Hanta viruses	*	*	*Klebsiella oxytoca,*	*	*									
Herpes viruses (mouse cytomegalovirus, mouse thymic virus)	*	*	*Klebsiella pneumoniae*	*	*									
Lactate-dehydrogenase elevating virus	*	*	*Pseudomonas aeruginosa*	*	*									
Polyomaviruses (mouse polyomaviru	*	*	*Staphylococcus aureus*	*	*									

s, K virus)														
Cilia-associated respiratory bacillus	*	*												
Klebsiella oxytoca,	*	*												
Klebsiella pneumoniae	*	*												
Pneumocystis murina	*	*												
Pseudomonas aeruginosa	*	*												
Staphylococcus aureus	*	*												

The table is compiled from Mahler et al. (2014).

*: When necessary, microorganisms that need to be examined

Animal health, research quality, animal species, prevalence, local factors, zoonotic characteristics, prevalence, microbiological and immunological status of the unit and animal and the targeted results play an important role in the selection of the sources of infection to be monitored in a health monitoring program. Differences can be made in the list of the causative agents according to the status of these variables. Therefore, it may be that the order of importance of the diseases changes, falls off the list or enters the list. In case of the existence of an unlisted factor that is not included in the program during the surveillance applications process, program change is not required. This factor is tried to be neutralized like the other factors in the list and it is tried to take precautions in the future.

Animal Selection in Health Monitoring

Animal selection for the tests to be performed within the scope of the health monitoring program may affect the quality of the program and the results of the research. It is essential that a certain number of animals determined from within the colony be subjected to examinations and inspections at regular intervals. The presence of clinical signs and / or harmful microorganisms in an animal in the examinations and tests

performed within the scope of the program necessitates the same treatment in other animals in the colony. Therefore, the observations and operations are based on the logic that a sample within the whole cluster represents the whole cluster. It is assumed that an agent not detected in selected sample animals is not present in other animals in the colony. In this regard, despite this factor, no treatment and administration is required. Room, cage, building structure, size, barrier systems and protection systems for animals can be used as a facilitator for the identification of microbiological presence and increase the workload as they constitute more control points. In case of increased workload, the details of health monitoring practices (number of animals, etc.) are at the discretion of the staff and may vary.

Number of Animals in Health Monitoring Program

In animal researches, it is very important that the number of animals to be used is sufficient in terms of ensuring animal welfare as well as scientific reality. The same importance appears within the health monitoring program. Colony size, physiological, microbiological, genetic and individual characteristics of animals, and research details are key parameters in determining the number of animals to be allocated for monitoring. In this system, the health status of the colony can be observed by the selected animals, the importance of the number and quality of the animals under monitoring is revealed.

It is important for the accuracy and reliability of the reports to be given by the production centers to make the applications performed using laboratory animals within a certain standardization. For this reason, the implementation of the health monitoring protocol prepared by the Federation of European Laboratory Animal Science Associations (FELASA) is considered to be the most appropriate of the existing systems. (Nicklas et al., 2002). On the basis of this protocol, additions which are not specified in the protocol but may also be made. For this reason, criteria such as the number of animals to be selected and methods of examination can be determined in accordance with the quality of the research and not by systems that contain strict internationally accepted rules. With this approach, health monitoring program can become healthier.

Number of animals to be selected for health monitoring and formulas for some values are given by Hansen (2003).

Number of samples for colonies of more than 1000 animals: S

$$\mathbf{S \geq \log C / \log (1-(p*N1))}$$

Number of samples for colonies less than 1000 animals: S

$$\mathbf{S \geq (1 - C^{1/D}) * (T - ((D-1)/2))}$$

Nosografic sensitivity: N1

N1 = Number of infected animals reacting in the study/ Number of infected animals reacting or not in the study.

Estimated prevalence in colony = p

p = Number of infected animals /Number of total animals

Risk of false negative results in an infected colony: C

C = Number of infected colonies tested with negative results / Total number of animals in infected colonies tested

D= Number of infected animals T= Total number of animals

Use of Sentinel Animal

In some studies, it is not possible to select animals from trial groups for health monitoring. In such cases, an animal with the same genetic and physiological characteristics other than the trial is kept in the trial environment and health surveillance is carried out on that animal. The animal used for this purpose is called sentinel animal (Hansen & Jensen, 1995). It is important for the disease course and detection that an animal designated as a lookout is exactly the same as the animals in the other trial. The age and genetic characteristics of sentinel animals should be considered specifically for the infections to be monitored and should not create an unfavorable situation (Hansen et al., 1994) .

As a general practice in the cages where the animals are located, the sentinels are located on the bottom shelves, and the contaminated bedding materials of other animals are added to their bedding materials by mixing. Dirty bedding materials are effective to accelerate the spread and detection of a possible infection. There are cases where this method cannot be safe. This method is not suitable for Sendai virus (Artwohl et al., 1994), ascarids and other directly diagnosed fecal infections. In addition, it should not be forgotten that not every infection can be transmitted from the stool and urine.

Method Selection

Some factors can be easily isolated from animals, while others can be obtained depending on very specific techniques and conditions. *Spirillum minus*, a rodent agent, cannot be produced *in vitro*, but many endo and ectoparasites can be easily isolated and observed under a microscope (Hansen, 2003). In order to obtain accurate results in a short time, first of all, signs of illness should be sought by observation, if necessary, more detailed tests should be carried out so that economies can be provided in time and in financial terms, and animal discomfort can be minimized within the framework of 3R rules.

Cultivation is a method in which microorganisms (bacteria and fungi) can be grown in artificial environments. Samples from organs for bacteriological examination can be detected using selective or non-selective media. More specific methods are needed to obtain the agent in its purest form. FELASA recommends that some serology tests (immunofluorescence assay (IFA), enzymelinked immunosorbent assay (ELISA) and western immunoblotting) be performed for microorganisms that cannot be cultured easily (Nicklas et al., 2002). Molecular detection methods can be used for factors that cannot be detected by serological and/or culture methods. Today, the most modern molecular methods (PCR, qPCR, in situ hybridization, FISH) can detect DNA, RNA and fractions of microorganisms.

Reporting

The health monitoring report is not considered a laboratory test result report. The health monitoring report provides more detailed information than any laboratory test result report. This report must be prepared by a qualified and authorized personnel. If an agent is detected in one or more animals, it must be reported in the health monitoring report. After reporting an agent in the unit, tests must be repeated at certain time intervals until the agent is eradicated. (Mahler et al. 2014).

Appendix 3, published by FELASA, provides a uniform health monitoring report. In this appendix, possible disease factors are given, as well as examples of data that should be included in the health surveillance report, such as test name, method, last test date, findings from previous tests, findings based on inspection, and laboratory where the test was performed (Nicklas et al., 2002). The results of all tests and observations should be recorded in a timely and complete manner and should be clearly shared with all other concerned. In report document, characteristics describing the animal should be specified and agents must be recorded in alphabetic order. Testing laboratory, test frequency, results in current test and last previous tests are other important datas should be given in report (Table II). In this way, data that may be very important in future studies will be widely available.

Table II. A sample health monitoring report document.

Health Monitoring Report
Center /Laboratory

Animal: **Date:**
Race:
Breeding and housing type:
Sex:
Physiological condition:
Center/laboratory:

Agents	**Testing laboratory**	**Test frequency**	**Results**	**Previous test date**	**Previous results**
Bacteria and Fungi (in alphabetic order)					
Viruses (in alphabetic order)					
Parasites (in alphabetic order)					
Anatomopathology					

Comments:

Laboratory personel (name and signature)
Responsible personel for laboratory monitoring (name and signature)

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ALTERNATIVE APPROACHES TO TREATMENT OF MASTITIS INSTEAD OF TRADITIONAL METHODS

Hande GÜRLER

Introduction

Mastitis, which decreases in milk quantity and quality, is a major problem in dairy animals such as cattle, buffalo, ewe and goat. It is also a health condition that affects human health by causing changes in milk composition. Bovine mastitis plays a decisive role in the conventional and organic dairy industry (Kanbur and Gürbulak, 2017; Krömker and Leimbach, 2017).

Mastitis is a disease that is difficult to control due to the complex multifactorial etiopathology. The traditional treatment of mastitis is antibiotics (Grave et al., 1999). However, antibiotic treatment is moderately effective in an established mammary infection. Because of the drainage of the drug due to lactation, inflammation of the glandular cells, immunosuppressive effect, the development of new concomitant infections often fail the effectiveness of antibiotics (Sandholm et al, 1990). Conventional treatment of mastitis using antibiotics has led to the emergence of antimicrobial resistance (AMR) against most of the commonly used antibacterial agents (Alekish et al., 2018). AMR is a serious threat to global public health and food security. According to O'Neil et al. (2014), 700,000 people die each year from infections caused by multiresistant bacteria.

It also increases animal suffering and production losses in animals. In addition, the passage of drug residues in humans through milk and milk products, the development of resistance to these drugs and the high cost are increasing the interest in alternative treatment interventions (Krömker and Leimbach, 2017; Reshi et al.,2017).

It is thought that mastitis is a disease that needs to be protected rather than treated. It is reported that in modern herd health management, the implementation of preventive mastitis programmes against contagious pathogens resulted in an increase of clinical mastitis cases caused by environmental pathogens like *Streptococcus uberis*, *Escherichia coli* and minor pathogens. It should be noted that the effectiveness of the therapy used is critical for udder health status at the farm level (Werner et al., 2010).

For these reasons, alternative methods for antibiotic therapy such as phytotheraphy and homeopathic treatment, acupuncture, clay treatment, oxygen therapy, vaccination, bacteriophage teraphy, nanoparticles treatment, cytokine application, photodynamic therapy, probiotic and vitamin adminastration are being studied. In this article, we will give an overview of alternative methods and give information about the current situation.

Phytotheraphy and Homeopathic Treatment

Plants or herbal extracts can be administered orally, intramammary or topically in the form of gel in the treatment of mastitis. There are also commercial mammary preparations containing herbal ingredients.

Traditional Chinese medicine (TCM) for the treatment of bovine mastitis is commonly prepared from Taraxacum mongolicum (Pu Gong Ying), Lonicera japonica Thunb. (Jin Yin Hua), Viola patrinu (Zi Hua Di Ding) and Folium isatidis (Da Qing Ye), based on oral heat-cleaning, detoxification, anti-inflammatory and antibacterial effects (Yang et al., 2019) Many other TCM plants have similar pharmacological factors, such as Angelica dahurica (Bai Zhi), Coptis chinensis (Huang Lian), Phellodendron amurense (Huang Bo), Rheum o cinale (Da Huang), and Scutellaria baicalensis (Huang Qin) (Cai et al., 2004, Muluye et al., 2014) According to TCM concept, ese herbs, which are “cold (寒, hán) ve and can clean the internal heat and are generally used as antibiotic and antipyretic agents, are considered as anti-inflammatory and antimicrobial agents and have been reported to be effective in the treatment of inflammatory diseases and microbial infections (Yang et al, 2019).

Kher et al., (2019) reported that they could be used as an alternative treatment to antibiotics in bovine subclinical mastitis as a result of their study with *Terminalia chebula*. Terminalia chebula (T. chebula, Combretaceae) is one of the most versatile medicinal plants with great biological activities. T. chebula is called “Wonder Medicine Ay in Ayurveda and King Medicine King Tib in Tibet and is always at the top of the list in Ayurveda Materia Medica because of its extraordinary healing power (21). This is one of the main components of the well-known Ayurvedic medicine known as “Triphala Powder.The fruits, roots and bark of this plant are used in the preparation of herbal medicines. It has been reported to be used to treat a variety of conditions such as fever, cough, diarrhea, gastroenteritis, skin diseases, candidiasis, urinary tract infection and wound infections.

Medicinal plants such as Calendula officinalis, Ocimum sanctum, Aloe vera, Houttuynia cordata, Persicaria senegalense, Panax ginseng, *Minthostachys verticillata* and many others have been reported to reduce somatic cell count with anti-inflammatory effects, improve milk quality

and reduce the incidence of mastitis. (Cerioli et al, 2018; Kanbur and Gürbulak, 2017; Shafi et al., 2016). However, WHO has recommended to all member countries to actively promote native medicines of their respective country and initiate steps to conserve medicinal plants. Reshi et al. reported that the herbal medicines has some advantages such as non-toxic, efficacious, cultural acceptability, lesser side effects (Kamboj opcit), and act selectively enhancing body resistance (Reshi et al., 2017). Research shows that most of the plants used to prepare native medicines contain valuable active ingredients, but more studies are needed in this area.

Homeopathy is a method used both in the prevention of mastitis and in the treatment of mastitis. Homeopathy has been reported to be useful in the prevention and treatment of mastitis (Kanbur and Gürbulak, 2017).

Werner et al. reported that a therapeutic effect in mild homeopathic therapies in cases of mild or moderate clinical mastitis caused by environmental pathogens (2010).

Because of the interest in the veterinary practices of native wild plants, the spread of this traditional knowledge to new generations can lead to a revaluation of local plant resources, which promotes the conservation of medicinal vegetation and regional biodiversity in the study area. In this sense, it emphasizes that it is important to recover and record the use of medicinal plants used in veterinary medicine in a scientific context as discussed in this study (Martínez and Luján, 2011).

Bacteriophage Therapy

Bacteriophage therapy is a method that uses pathogen specific bacteriophages in the treatment of a bacterial infection. Bacteriophages are viruses that can infect and kill bacteria. Phages have been identified as novel antimicrobial agents for veterinary applications. Phage K in infections caused by *S. aureus* has been used as a prophylactic measure (O'flaherty and Coffey 2005).

In a study (Gill et al., 2006) also tested the efficacy of phage K against *S. aureus*. The phage has various limitations, such as milk and its constituents (whey proteins) and its degradation and consequently inactivation by the immune system. Kwiatek et al. (2012) isolated a new virulent phage (MSA6) from a mastitis cow, presenting a broad lytic spectrum against bovine staphylococcus strains. This invaluable nature of MSA6 is crucial for its potential use as a universal anti-staphylococcal agent. Furthermore, given the various features presented by MSA6, this phage can be used in many staphylococcal infections, including bovine mastitis. Fenton et al. (2013) bacteriophage-derived peptidase was tested; $CHAP_K$ against *S. aureus* isolated from mastitis infected cows. This study demonstrated the potential use of $CHAP_K$ as prophylactic and therapeutic

measures for mastitis infections. $CHAP_K$ was effective against biological filters by preventing biofilm formation or by breaking down established biofilms of staphylococcus strains due to bovine mastitis. Dias et al. (2013) isolated that bacteriophages can infect S. aureus from mastitis positive cows. These phages exhibit a wide range of properties critical to their use as phage therapy, such as a wide range of hosts, high lytic activity and thermostability. Basdew and Laing (2014) tested some phage sensitivities to some simulation stresses. Sabp-P1, Sabp-P2 and Sabp-P3 are less susceptible to stresses tested in vitro and are therefore the future favorites in in vivo experiments and their future use as therapeutic strategy for the treatment of mastitis-infected cows has been demonstrated. Although there are some limitations, bacteriophage treatment in general seems to be a serious candidate for antibiotic alternatives to be used in the future control and treatment of bovine mastitis. However, additional further research is required to explore the therapeutic potential of bacteriophages to treat clinical and subclinical mastitis associated bacterial infections.

Acupuncture

Acupuncture is a traditional Chinese medicine has been used for analgesia and therapy in humans for more than 4,000 years. It is performed by stimulating predetermined points in the body that are fully connected to the central nervous system and cause a certain physiological effect (Schoen, 1994). Acupuncture has been used successfully to treat many disorders including mastitis in dairy cattle. However, most of the procedures used expensive equipment such as lasers and electrostimulators and various acupuncture points (Daga et al., 2013).

There are different methods of stimulating acupuncture points traditional and modern. Traditional methods include conventional white needle acupuncture (CWNA), aquapuncture, moxibustion, cupping, pneumopuncture, embedding, fire needling, hemoacupuncture and auriculoacupuncture. Aquapuncture is known to be the most common technique of acupoint stimulation by injection. It is performed by injecting the solution into the acupuncture points by using an appropriate size needle and sterile syringe. Aquapuncture utilizes different solutions including homeopathic remedies, antibiotics, vitamins, hormones, sterile saline, herbal extracts and the patient's own blood (Daga et al., 2013). Daga et al., (2013) have injected 1% chilli pepper boil at acupuncture points and reported that it is effective in reducing the incidence of mastitis and increasing milk production. However they recommend longer-term studies. The length of the treatment period and the insufficient of veterinary acupuncturists constitute the disadvantages of this application (Duval, 1997; Kendall,1988).

Clay Treatment

Clay has been used in the treatment of mastitis due to its high absorption properties. For this purpose, the mixture of clay and water and oil is applied to the breast with mastitis 2-3 times a day after milking and the breast is wrapped with cloth. By adding a few drops of pine or peppermint oil into this mixture, the effectiveness of the clay can be increased. With this application, it can be seen in 2-3 hours in acute mastitis and in 2-3 days in chronic mastitis industry (Kanbur and Gürbulak, 2017).

Oxygen Therapy

Oxygen therapy can be used to treat diseases in humans and animals; Glyroxilide, given as an intramuscular single dose, two doses or rarely 3 doses, has been reported to give good results in the treatment of mastitis, but in some studies it has not been shown to be effective enough (Duval, 1997).

Vaccination

Mastitis vaccines have been formulated with the hope of reducing the incidence mastitis in dairy farming and promoting the profit of industry. Some vaccines were developed against *S. aureus* mastitis but all presented limited efficacy. The improper immunization schedules, ineffective adjuvant formulation, and the limited range of protection are some of the causes of their ineffectiveness It is clear that a single vaccine will not prevent mastitis caused by the plethora of pathogens and their different mechanisms of pathogenesis (Bannerman and Wall, 2005). Coliform vaccines can decrease the prevalence, severity and length of infections in both milking cows and heifers (Gomes and Henriques, 2016). There are no vaccines available to prevent mastitis caused by *K. pneumonia* (Tiwari et al., 2013). The research in this area continues.

Nanoparticles Treatment

Nanotechnology is a rapidly growing field. The surface area volume ratio of nanoscale materials is high. Antimicrobial agents have unique chemical and physical properties thanks to nanotechnology. NPs are manufactured and used in a wide variety of commercial products such as silver nanoparticles (AgNPs), electronics, bio-detection, clothing, food production, dyes, sunscreens, cosmetics, and the medical field. However, opinions about the toxicity of NPs differ among scientists; For example, the type or size of NPs may be related to various factors such as the synthesis method or conditions (Ahamed et al, 2010; Albrechtet al., 2006; Morones et al., 2005; Kim et al., 2007).

Sankar (2016) has reported in a study that ZnO nanoparticles inhibit the growth of bacteria, molds and yeasts that cause superficial or deep infections and even toxicities, and can be used successfully as bacteria and

fungicides in the treatment of microbial diseases in human area and veterinary medicine. In the study, ZnO can be applied as a food additive to advanced areas and will be preferred more to improve animal and human health in the near future.

Nanoparticles are seen as a potential for the treatment of bovine mastitis when used as phagocytes. For example, silver nanoparticles exhibited inhibitory activity against *S. aureus* isolated from subclinical mastitis (Dehkordi et al., 2011) and are excellent for a great economic antimicrobial solution. Alexander et al. (2019), in their study reported that copper and silver NPs will be used in the preparation of disinfectants that can be used in dairy cows the milking routine. In addition, antibiotics have now been incorporated into most of the nanoparticle delivery system to combat microorganisms. Amoxicillin added to nanoparticles exhibited biodynamic against S. aureus, E. coli and S. agalactiae (Yang et al., 2009) The most important challenge seems to be that they are getting plenty of antibiotic loading into these delivery systems.

Cytokine Application

Cytokines are very small proteins (less than 50 kDa) that act as intercellular communication signals mediate the exchange of autocrine, paracrine or endocrine signals in hematopoiesis, stress, inflammation, immune and tissue repair (Belardelli and Ferrantini, 2002; Rouveix, 1997). Identification of a large number of cytokines and blocking of cytokine production, stimulation of inhibiting pathways, inhibition of circulation, inhibition of binding, inhibition of receptors and signaling mechanisms have led to progress in diagnosis and treatment.Cytokines are signals that dictate immune responses in normal and mastitis breasts. Therefore, subtle changes in the cytokine network of the mammary gland in health and disease may help in detecting early infection and monitoring the effectiveness of treatment. However, the cytokine network in the bovine mammary gland has not yet been fully investigated and needs to be identified at different stages of lactation and lactation. Techniques based on real-time PCR or microarray may be reliable, but are not yet suitable for daily control of breast health. Practical application cytokines as a diagnostic tool in bovine mastitis require the automation of procedures for detection and monitoring of cytokines (Alluwaimi, 2004).

Numerous cytokines like complement component, interleukins (IL) -1, -2, -6 and -8, and tumor necrosis factor alpha (TNF-α) have been recognized as key actors during the acute-phase reaction. They have chemotactic activity responsible for leukocyte uptake and activation and may also increase the bactericidal activity of phagocytes. Numerous experimental works point out that use of cytokines with or without antibiotics signi cantly improved the cure rate in *S. aureus* infected

mastitis. Cytokines therapy appears to be a promising method; however, advanced research has to be done to accept therapeutic attention (Hossain et al., 2017).

Photodynamic Therapy

The use of non-toxic dyes or photosensitizers (PS) in combination with harmless visible light that is known as photodynamic therapy (Costano, 2004). Photodynamic Therapy (PDT) is alternative treatment for microbial resistance and promising strategy for the eradication of Gram-positive, Gram negative, yeast and fungal bacteria (F Sperandio, 2013).

The mechanism of PDT is the activation of a non-toxic photosensitizer that through appropriate exposure to light at a convenient wavelength and energy density generates reactive oxygen species, including free radicals and singlet oxygen which, when in contact with the microorganisms, can modify bacterial DNA and cell membrane, leading to microbial death (Costano, 2013; Hamblin and Hasan, 2004).

Phenothiazinium dyes, such as methyleneblue (MB), are used as photosensitizers (PS) for both gram-positive and negative bacteria exhibiting effective eradication. In fact, MB is used as a lead compound because of its low toxicity in the human patient. Another advantage of this cationic PS is its affinity for targeting microorganisms rather than host cells. Therefore, short-term irradiation treatment with MB shows minimal antimicrobial activity while minimally damaging host cells (Sellera et al., 2016).

Researchers report that intermolecular interactions between PS and milk components should be considered in order to optimize clinical protocols and that appropriate light delivery systems should reach deeper udder tissue because pathogens normally colonize the entire mammary gland. Therefore, they report that research on different light distribution systems can optimize clinical protocols and facilitate the use of PDT in the dairy industry (Riberio et al, 2018).

It is reported that PDT is the effective treatment of subclinical mastitis in cows in vivo, without the need to remove the animal from production. However, because mastitis has a multifactorial etiology, further studies are needed to develop other therapeutic protocols (Sellera et al., 2016; Moreira et al., 2018).

Probiotic and Vitamin Adminastration

Probiotics are often used for multiple purposes and most of the applications are performed both in humans and in different animals productivity (Nader-Macías et al., 2008). Nader-Macías et al., (2008) have isolated lactic acid bacteria (LAB) from natural bovine ecosystems because of their probiotic potential. The useful probiotic LAB was isolated from

the vaginal tracts of newborn calves and the mammary glands of adult heifers, faeces and oral cavity. They could improve the health of the animal and promote their productivity. Bacterial strains and their numbers varied for each tract examined. Several strains reported that they were able to produce bacteriocin and were isolated only from mammary gland and faeces. At the end of the study it was reported that some strains can prevent mastitis by applying to the mammary gland and can also promote colonization of the newborn intestinal system (Nader-Macías et al., 2008).

In a study conducted with vitamin B2 injection in clinical mastitis caused by *S.aureus*, it has been reported that VB2 injection reduces the number of somatic cells both by activating neutrophil function and by increasing and / or regulating cytokine production (Sato et al., 1999).

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