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Pediatric viral respiratory infections in Saudi Arabia: Narrative and descriptive revisits for the etiology, epidemiology and clinical phenotypes with diagnostic challenges highlights

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ABSTRACT

Objective: To review, describe and narrate the etiology, epidemiology and clinical phenotypes of pediatric viral respiratory infections (PVRIs) in Saudi Arabia (KSA)

Design: A comprehensive electronic search of the literature for PVRIs in KSA

Setting: An electronic search in PubMed, SCOPUS, Google Scholar and MEDLINE

Subjects: Articles published up till 2019 and those that dealt with the detection of viruses from clinical specimens

Interventions: Retrieved articles were subtly studied. Data obtained included the virus reported, year of publication, diagnostics, region or city, research purpose, the season of infection and hospital of admission (if any).

Main outcome measure(s): The etiology, epidemiological features and clinical phenotypes associated with the PVRIs in each study were recorded and analyzed.

Result(s): The first report for PVRIs in KSA was in 1988. Up to 2019, 35 studies were published in the topic. The highest number of reports was for respiratory syncytial viruses (n=17, 48.6%), while bocaviruses are the least reported viruses (n=3, 8.6%). Clinical presentations reported suggested both upper and lower respiratory tract infections. PVRIs were reported from Riyadh, Al-Qassim, Jazan, Jeddah, Dammam, Najran, Taif and Abha. Immunofluorescence assays, enzyme-linked immunosorbent assay, polymerase chain reaction and virus isolation were employed.

Conclusion(s): In this review communication, we described the etiology, epidemiology and clinical phenotypes of PVRIs in KSA reported from 1988 through 2019. We also showed some challenges associated with the diagnostic protocols employed. Directions for future research in this topic, particularly towards diagnostics and preventive medicine, were also recommended.

INTRODUCTION

It is well-established that respiratory tract infections are major causes of morbidities and mortalities among children worldwide[1]. A recent World Health Organization (WHO) report revealed that 18% of deaths among children under five years are attributable to pneumonia[2,3]. Among the different causes of respiratory infections, viruses were known to constitute the major etiological factor responsible for acute respiratory infections (ARIs) in pediatrics globally[4,5]. In poor and developing countries, these infections resulted in far higher mortality rates in children as compared to those in resource-rich countries. Inadequate data about the public health impacts and economic losses of these infections in developed countries are available[6-8]. These data are always critically essential for the design and development of efficient protective measures and treatment protocols. The viruses which are known to be responsible for ARIIs in infants and children included influenza viruses, human respiratory syncytial virus (HRSV), human metapneumovirus (HMPV), human
coronaviruses (HCoVs), human parainfluenza viruses (HPIVs), human adenoviruses (HAdVs), and human bocaviruses (HBoVs).

Although the burden and public health implications of influenza infections are yet to be known in many parts of the world, particularly in resource-poor countries, it has been shown that influenza is characterized by high incidence rates and hospitalizations in the tropics and subtropics\(^8\). The global incidences and mortalities due to influenza in children less than five years was also estimated and noted to be significantly high in terms of number of deaths, particularly in the developing countries\(^8\). In many epidemiological studies, HMPV were recognized as potential etiologic agents for acute lower respiratory tract infections (ALRTIs), namely bronchopneumonia and bronchiolitis, in children\(^11\). Although the life-threatening effects of HMPV infections in children were known in some cases, the fatalities were usually seen associated with other underlying chronic conditions such as chronic lung disease of prematurity, asthma\(^17\), cancer\(^13\) and immunosuppression\(^19\). Following intensive literature revisits and personal communications, there were no obvious distinctions in the epidemiological and clinical patterns between HRSV and HMPV infections in pediatric patients. Both viruses cause severe and ALRTIs in infants and children, and both represent primary reasons for emergency department visits and hospitalization\(^18,20\). However, HMPV infections were observed to occur in relatively older children, as compared to HRSV\(^17\). HCoVs were also noted, causing numerous seasonal clinical respiratory infections in children since ancient times\(^21\). The epidemiological patterns of these HCoVs-associated diseases were observed undergoing regular changes every time and the respiratory infections attributable to HCoVs were observed not only confined to upper respiratory tract infections (URTIs), but they are also seen to cause pneumonia in infants and children\(^22\). Several reports describing the role of HCoVs in the lower respiratory tract infections (LRTIs) with their clinical presentations and complications in the pediatrics were also published\(^23\). HCoV-severe acute respiratory syndrome (HCoV-SARS) has emerged as the first HCoV identified responsible for severe, acute and fatal respiratory infection in children in many parts of the world\(^26,27\). Recently, HCoV-Middle East Respiratory Syndrome (HCoV-MERS) has also emerged from KSA and proven as a potential etiologic agent for severe URTIs and LRTIs in children and young adults\(^28\). Although HAdVs were primarily recognized to cause mild URT and LRT infections in young children, severe infections of HAdVs during epidemics were also noted in immunocompromised patients\(^29\). Several serotypes of HAdVs were isolated from children suffering from ALRTIs. It has been suggested that the epidemiological parameters of the infections including incidences, prevalences, morbidities and mortalities due to HAdVs are highly virus type dependent\(^30\). HPIVs were also recognized to be associated with URT and LRT illnesses in children with their pathology, symptomatology and epidemiology dependent on the virus serotype, age and season\(^31\). Among the four genotypes of HBoVs known so far, HBoV-1 is the predominant genotype known to infect the respiratory tract of children\(^32,33\). Throughout the years, human rhinoviruses (HRVs), were known as a significant cause of the “common cold” in children and adults worldwide, with considerable economic burdens incurred due to medical visits, schooling and work absenteeism\(^34\). Other viruses causing respiratory infections in children and reported at various points of time include Nipah and Hendra viruses\(^35\).

Taken all together, viral respiratory infections are considered as major health concerns in pediatric practice in many parts of the world, particularly in developing and resource-poor countries. As diagnostic testing is improved, more respiratory viruses are expected to be explored. This review intended to focus on the clinical phenotypes and epidemiological pictures of pediatric viral respiratory infections (PVRIs) in Saudi Arabia (KSA) concerning the previously published reports in that respect. We would also like to cast some light on the diagnostic and medical intervention challenges.

**METHODS**

**Search methodology**

In this study, we performed a comprehensive electronic search of the literature for PVRIs in KSA in PubMed, SCOPUS, Google Scholar and MEDLINE databases. The keywords used in the search include Saudi Arabia, respiratory, children, infants and viruses (the word “virus” was used at times and the virus name was specified at other times). The search considered articles from ancient times up to 2019. The retrieved articles were carefully read to help in further search for additional articles. The only considered and documented studies are those that dealt with the detection and/or isolation of viruses from clinical specimens of the patients and published in peer-reviewed journals.

**Data retrieval and analysis**

The clinical and epidemiological features associated with PVRIs in each study were recorded and analyzed. The elements recorded included the author(s) who conducted the research, year of publication, the virus reported to cause the infection, diagnostic technique employed, region or city of the study, the research purpose, the season of the infection and the hospital...
of patient admission (if any). A narrative description of the situations was then generated in this manuscript using this data.

**LITERATURE REVIEW**

**Epidemiology and clinical phenotypes of PVRIs**

The previous reports for the detection of different respiratory viruses among pediatric patients in KSA from 1988 - 2019 are demonstrated in Table 1. The total number of reports of respiratory viruses in children in different cities of KSA is determined (Fig. 1). The geographical distribution of these infections in the different cities and regions of the country is also retrieved from the data obtained (Fig. 2). Detailed descriptions for the etiology, epidemiology and clinical features of the PVRIs in infants and children in KSA, as retrieved from the previously published research, are made in the following presentations:

**Influenza**

Influenza is a highly contagious disease caused by influenza viruses type A, B and C (IAV, IBV and ICV). These viruses are characterized by segmented RNA genomes and antigenic diversities. They were classified with the family Orthomyxoviridae. IAV causes pandemics and epidemics worldwide; those belonging to group B cause epidemics and outbreaks; while those belonging to group C cause sporadic and mild respiratory infections[36]. In KSA, the first report for influenza was made in 1988, when a cross-sectional epidemiological study was carried out to determine the viral etiology of tonsillitis among children in Riyadh[37].

In another study, a significant percentage of infants and children attending the emergency or pediatric clinics of King Faisal Specialist Hospital (KFSH) in Riyadh also reported positive to influenza viruses in 1998[38]. IAV and IBV were also detected in 2005 in the nasopharyngeal secretions of young children admitted with acute LRTIs to Buraidah Maternity and Pediatric Hospital (BMPH) in Al-Qasim (central province of KSA)[39].

Additionally, during the swine flu global pandemic in 2009, AlMazroa and co-workers published a comprehensive report showing a significant number of cases affected with swine flu virus (A-H1N1) among children aged 1 - 10 years in different regions and localities of KSA. These children included both Saudi nationals and imported cases, and concluded that influenza A-H1N1 constitute a considerable threat to KSA people at the time of the study[40]. In a more recent epidemiological study, six cases of IAV and one case of IBV were also diagnosed using multiplex RT-PCR among children at Najran Maternity and Children Hospital (NMCH) in Najran (southern region of KSA), without adequate description to the clinical and epidemiological patterns of these infections being reported[41]. In a comprehensive surveillance study in Jazan (southwestern region of KSA), IAV and IBV were also detected among pediatric patients without the determination of virus subtypes[42]. In a more recent study, the influenza virus A-H1N1 was isolated from children suspected with HCoV-MERS and presented to John Hopkins Aramco Healthcare facilities in Damman (the eastern region of KSA)[43]. In this study,

<table>
<thead>
<tr>
<th>Virus</th>
<th>No. of reports</th>
<th>Regions of reports</th>
<th>Years of reports</th>
<th>References</th>
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<tr>
<td></td>
<td>Single (%)(^a)</td>
<td>Combined (%)(^b)</td>
<td>Total (%)(^c)</td>
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<tr>
<td>HAdVs</td>
<td>0 (0.0)</td>
<td>8 (100)</td>
<td>8 (22.9)</td>
<td>Riyadh, Abha, Al-Qasim, Najran 1988, 1998, 2005, 2014, 2017</td>
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<tr>
<td>HRVs</td>
<td>0 (0.0)</td>
<td>4 (100)</td>
<td>4 (11.4)</td>
<td>Najran, Riyadh, Jazan 2014, 2017</td>
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<tr>
<td>HBoVs</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>3 (08.6)</td>
<td>Taif, Najran, Dammam 2013, 2014, 2015</td>
</tr>
</tbody>
</table>

HRSV: Human respiratory virus; HMPV: Human metapneumovirus; HCoVs: Human coronaviruses; HAdVs: Human adenoviruses; HPIVs: Human parainfluenza viruses; HRVs: Human rhinoviruses; HBoVs: Human bocaviruses

The presented data are expressed as numbers and percentages (%).

\(^a\) Single report means the study reported only one single virus type; combined report means the study reported more than one virus type.

\(^b\) The percentages of single and combined reports were calculated from the total number of reports for each virus individually.

\(^c\) The percentages of the total reports of each virus were calculated from the total number reports for all viruses noticed in this review (35 reports).

* The reference number as given in the reference list.
Fig 1: Report rates of pediatric respiratory viruses in different cities of KSA Riyadh (central province); Dammam (eastern province); Al-Qasim (northern province); Abha (Asir region, southern province); Jeddah (western province); Najran (Najran region, southern province); Jazan (southwestern region); Taif (western province)

Rates were calculated as percentages from number of reports in each region out of the total number of reports in the kingdom (35 reports)

Fig 2: Geographic distribution of viral respiratory infections in children and infants in Saudi Arabia through 1988-2019

HRSV: human respiratory virus; HMPV: human metapneumovirus; HCoVs: human coronaviruses; HAdVs: human adenoviruses; HPIVs: human parainfluenza viruses; HRVs: human rhinoviruses; HBoVs: human bocaviruses
the authors declared higher incidence among patients came from Ras Tanura city (far eastern region of KSA; Fig. 2).

In total, a considerable number of reports about influenza infections among pediatric patients in KSA was noted in the literature. The majority of the available data were those published during the global “avian flu” pandemic in 2005 - 2006 and the global “swine flu” pandemic in 2009 - 2010. Despite all these reports, we believe that adequate data pertaining to the virology, clinical phenotypes and epidemiological aspects of influenza viruses in KSA, among adult populations in general and children in specific, are still lacking.

**Human respiratory syncytial virus (HRSV)**

HRSV was confirmed in many studies and surveys as the leading cause of respiratory tract infections in infants and young children throughout the world. HRSV is a non-segmented, negative-sense, single-stranded RNA enveloped virus belonging to the family *Pneumoviridae* and the genus *pneumovirus*. As compared to influenza, more studies were conducted to detect HRSV from children in different cities and regions of KSA, namely Riyadh, Najran, Jazan, Al-Qasim and Abha. In all of these studies, no detailed clinical presentations or specific epidemiological patterns for HRSV infections were described; however, bronchopneumonia (BP) and bronchiolitis were reported as the leading cause of morbidities and hospitalization. It was also revealed that the infections of HRSV peak in winters and autumn seasons. Deaths attributable to these infections among infants were also recorded, though dearth. The genetic analysis of HRSV group B (HRSV-B) strains circulating in KSA was also studied in 2014 by Almajhdi and co-researchers. This study helped to cast some light on the circulation pattern and molecular characteristics of HRSV- B strain in the KSA.

Medical intervention of HRSV infectivity among children in KSA remains the most crucial concern to health practitioners and the public. Special attention was particularly directed towards hospitalized RSV-infected premature infants and children suffering from chronic lung disease or congenital heart disease. Palivizumab (Synagis, Medimmune) is a humanized monoclonal antibody, which is a combination of human (95%) and murine (5%) antibody sequences. In KSA, Palivizumab was used for the prevention of severe RSV infections in high-risk groups of children. It was well-documented that Palivizumab is an effective agent for the prevention of RSV mortalities and fatalities. However, the notable possible drawbacks associated with this medication include the expense and extensiveness of use without rationality. Conclusively, the different studies concerning the treatment of children against HRSV using different types of medicines and regimens in KSA were recently reviewed by Alharbi and co-researchers.

**Human metapneumovirus (HMPV)**

HMPV was first recognized and described in Netherlands in 2001 by van den Hoogen and others. It is a negative sense, single-stranded RNA enveloped virus and classified as a member of the *Paramyxoviridae* family, *pneumovirinae* subfamily and *pneumovirus* genus. In KSA, HMPV was first detected in 2011 among Saudi children hospitalized with ARI in Riyadh. Afterward, the virus was also detected among children who presented with ARTIs to NMCH in Najran, with brief explanations of the clinical and epidemiological correlates of the infections. The authors identified the virus in infants in both single viral infections and viral co-infections. HMPV was also isolated during an investigation in a cohort of children suffering severe LRTIs and hospitalized at a tertiary referral center in Riyadh in 2016. The epidemiology and some genetic properties of that isolated virus were also studied. That is considered the first report addressing the HMPV genotypes circulation in the KSA. HMPV was also detected in a retrospective study performed to determine the viral etiological agents causing RTIs among pediatric patients admitted to the Department of Pediatrics, King Abdul-Aziz Medical City (KAMC) in Riyadh. In a recent publication, we reported the incidence of HMPV in the Aseer region (southern provinces of KSA) among children who attended the pediatric emergency rooms and were hospitalized in Aseer Central Hospital with acute bronchiolitis and BP. In that study, we reported for the first time the large population of virus-infected children in the area, particularly in Abha city and the vicinity. In the previously published articles, reverse transcriptase PCR (RT-PCR) and direct fluorescent antibody (DFA) test were employed for the detection of the virus nucleic acid and antigens respectively, in the nasopharyngeal secretions from infected children. Apart from the previously mentioned reports of HMPV infections, the virus was not detected in any other region or city of the Kingdom. The role of HMPV in respiratory infections in pediatric medicine in the western, eastern and northern regions of KSA was not determined yet. The risk factors associated with the severity of HMPV in children in the KSA were not precisely known up to date. In conclusion, meager studies regarding the virus distribution, prevalence, clinical presentations and medical interventions of HMPV in KSA were made so far, and much research work is worthy in these aspects.
Human coronaviruses (HCoVs)

Human coronaviruses (HCoVs) are a well-known cause for URT and LRT infections in all age groups. They are positive-sense, single-stranded RNA viruses classified in the family Coronaviridae\[^{63}\]. Before HCoV-SARS and HCoV-MERS, which cause severe and acute respiratory infections, four other HCoVs were recognized to be responsible for mild respiratory infections in adults and children namely HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1. The first report for HCoVs infections among children in KSA was made by Al-Hajjar and co-workers in 2011\[^{60}\]. In this study, HCoV-NL63 was isolated from children less than 16 years old hospitalized with ART illness during autumn and winter at KFSH in Riyadh. HCoV-NL63 and HCoV-OC43 were also detected among children presenting with acute LRT infections and showing symptoms of bronchiolitis and pneumonia in Najran region of KSA in 2014\[^{41}\]. In another cross-sectional study carried out to determine the prevalence of viruses causing ARTIs among hospitalized children in Riyadh area, a considerable number of them were diagnosed with HCoVs\[^{50}\]. The HCoVs serotypes detected in this study were not specified and were most prevalent in infants less than six months old. Non-MERS HCoVs were also detected in nasopharyngeal swabs collected from asymptomatic outpatients less than 15 years old in Jazan province\[^{42}\]. Despite the wide spread of HCoV-SARS during the global disease pandemic in 2003, no single report about the virus infectivity in children in KSA was made. As the HCoV-MERS originated from Jeddah (western region of KSA) in 2012\[^{28}\], plenty of reports, thereafter, describing the virological, epidemiological and clinical characteristics of the virus were made in KSA at large. Primarily, a single pediatric case (out of 47 sampled patients), laboratory confirmed positive to HCoV-MERS was identified by Assiri and co-workers throughout KSA as a first report, in 2013\[^{84}\]. Consequently, HCoV-MERS was also reported among eleven pediatric patients in Riyadh in 2014\[^{60}\]. In this report, the clinical presentations and outcomes of the patients were adequately described; nine cases were asymptomatic, whereas two cases were admitted to the ICUs suffering severe respiratory infections, with one of whom died. A case report describing a complicated HCoV-MERS infection in a 9-month-old child admitted to the pediatric ICU of Prince Sultan Military Medical City in Riyadh, with infantile nephrotic syndrome that resulted in death, was also published by Thabet and his team in 2015\[^{66}\]. In a comprehensive search in the literature made by Al-Tawfiq and co-researchers in 2016; a conclusion was drawn to indicate that low number of MERS pediatric cases were evident in KSA and the reasons for this low prevalence was unknown\[^{67}\]. In this report, the symptoms, mean age of infection and source of infection among pediatric patients were described to an optimal level. The various scientific elements of HCoV-MERS infectivity for children were also recently reviewed by Al-Sehaibany in 2017, when he concluded that MERS is a disease of adults, where few cases among children were known with different clinical manifestations and lower mortality rates as compared to infection in adults\[^{68}\]. Conclusively, despite the intensive studies for detection of HCoV-MERS among adults in KSA and surrounding countries, a limited number of cases were reported for this virus in children. However, in recent publications, it had been reported that the proportion of asymptomatic cases among pediatric confirmed HCoV-MERS cases was significantly high\[^{69,70}\].

Human adenoviruses (HAdVs)

Human adenoviruses (HAdVs) were known to have a significant contribution in PVRIs. HAdVs infections were observed as mild and indistinguishable from other viral respiratory infections in children on their pathology and clinical grounds\[^{71}\]. However, acute and severe URT and LRT infections attributable to HAdVs were also noted among pediatric patients\[^{71,72}\]. Since 1988 up to date, only nine studies discussing the incidences and other clinical and epidemiological parameters of adenoviral infections in children in KSA were made. In a serological and virological investigation by Hossain et al in 1988, the first report for HAdVs infections in children in KSA was made. They showed that HAdVs were the leading cause of tonsillitis among Saudi children during the study period\[^{37}\]. About ten years later, adenovirus infections were also reported in children who attended the emergency of pediatric wards at KFSH and Research Center in Riyadh\[^{88}\]. In the same year, HAdVs infections were also detected among Saudi children under five years who presented to King Khalid University Hospital (KKUH) in Riyadh with complaints of ARTIs\[^{47}\]. In another prospective study, adenoviruses were also detected in the nasopharyngeal aspirates of children hospitalized due to severe bronchiolitis in Abha city\[^{53}\]. In that study, the clinical features and risk factors of adenovirus-associated bronchiolitis were described to an adequate level. They specified the risk factors including prematurity, chronic lung diseases, atopic dermatitis, pure formula feeding, passive smoking and age. Also, Meqdam and coauthors reported the role of HAdVs in the ALRTIs among infants and young children admitted to BMPH in Al-Qassim\[^{39}\]. Adenoviruses were also identified as a significant cause of respiratory infections in children less than five years in Najran city, and mainly observed to be associated with bronchiolitis and acute wheezing episodes\[^{41}\]. In two recent epidemiological studies, the role of HAdVs
in ARTIs among pediatric patients presenting to the King Fahad City[73] and KAMC[51] in Riyadh was also confirmed.

Human parainfluenza viruses (HPIVs)

HPIVs are genetically and antigenically grouped into four types namely HPIV-1, HPIV-2, HPIV-3 and HPIV-4. They are enveloped viruses with single-stranded, negative-sense RNA genomes and belong to the Paramyxoviridae family, paramyxovirinae subfamily and paramyxovirus genus[74]. HPIV-1, 2 and 3 were first reported in KSA among Saudi children below 15 years of age, who were suffering from acute tonsillitis in Riyadh[37]. HPIV-3 was particularly diagnosed in children presented to KKUH[47], and KFSH and Research Center[38] in Riyadh. HPIVs were also confirmed in another study among children suffering acute LRTIs in Al-Qassim, without specification for the virus type and clinical description of the infection[39]. In Abha city, HPIV-1, HPIV-2 and HPIV-3 were also isolated from children less than two years of age, who were diagnosed with bronchiolitis[53]. The first molecular epidemiological study in KSA was carried out to screen HPVI-3 in nasopharyngeal secretions collected from children hospitalized in Riyadh with acute respiratory diseases using nested RT-PCR[59]. In another similar study, HPIV-2 was also isolated from children in Riyadh[59]. Al-Ayed and co-workers also identified HPIV-1 and HPIV-3 in children less than five years old with ARTIs in Najran[41]. Although HPIVs were widely seen as infectious to URT, in a retrospective study performed at the Departments of Pediatrics, Pathology and Microbiology of KKUH in Riyadh, a small portion of children less than one-year-old were observed as suffering bronchiolitis and pneumonia due to HPIV-1, 2 and 3 infections[77]. In another epidemiological investigation among hospitalized children at a tertiary referral center in Riyadh, HPIVs were also detected in the nasopharyngeal aspirates using monoplex RT-PCR[59]. In that study, HPIVs were seen mostly prevalent in infants less than six months during winter.

In conclusion, HPIV-1 and HPIV-3 were the most commonly observed viruses causing RTIs among children in KSA. There were many factors reported to predispose the children to these infections, such as overcrowding, non-breast feeding and environmental smoke. Symptoms associated with HPIVs have also been correlated with the age of the child and virus type.

Human rhinoviruses (HRVs)

HRVs were first identified in the 1950s and known as the most predominant cause of URTIs. HRVs are non-enveloped viruses, with positive-sense, single-stranded RNA genomes, and classified in the family Picornaviridae and the genus enterovirus[78]. Although HRVs were known since early days to cause respiratory infections among pediatric patients in many parts of the world, they have only recently been identified in KSA. The first report for HRVs was made in 2014 when recognized as one of the viral etiologies of respiratory infections in children in Najran in 2014[41]. Later, three reports were made for HRVs in 2017; two in Riyadh[61,73] and one in Jazan[42]. In all these studies, HRVs had been seen to constitute the primary cause of RTIs among the tested children. Their epidemiological pattern and infectivity was noted to peak in winter, with serious clinical consequences in infants and young children. Dual infections with other viruses such as HRSV, HCoVs, HAdVs, HMPV and influenza were more likely to occur, as retrieved from these studies. In conclusion, a limited number of studies discussing the clinical and epidemiological elements of HPIVs were published in KSA.

Human bocaviruses (HBoVs)

HBoV is a parvovirus first identified in 2005 and known as a causative agent of respiratory tract infections[32]. Four HBoV subtypes were recognized so far, namely HBoV-1, HBoV-2, HBoV-3 and HBoV-4. HBoV-1 was isolated from infants with respiratory manifestations including cough, dyspnea, wheezing and suffering from rhinitis, pharyngitis, pneumonia and otitis media. HBoVs are classified with the family Parvoviridae, subfamily Parvovirinae, genus Bocavirus[79]. Following a systematic search in the literature, only three reports for HBoV infections among pediatric patients in KSA were noticed. The first report for HBoV in KSA was made by Abdel-Moneim and co-workers in 2013 in Taif city (western region of KSA) when they detected the virus in 22% of the tested children with respiratory distress[80]. In that study, the authors confirmed that the circulating HBoV genotype among the tested patient was HBoV-1. They also showed that co-infection with other viruses was seen in the majority of samples. The second report was from Najran in 2014[41], while the third report for HBoV in KSA was made by Bubshait and his group in 2015 among children admitted to King Fahad University Hospital in Dammam. They reported five positive cases for HBoV, with their clinical presentations varying from mild to severe disease[81].

Diagnostic challenges

The PVRIs in KSA have been reported for thirty years. Several methods and techniques were employed for the diagnosis of these infections. Viral antigen detection using DFA, ELISA and virus propagation in cell cultures were the commonly
performed methodologies. However, epidemiological studies for investigations of viral etiologies of respiratory tract infections later relied mainly on the PCR and RT-PCR for detection of DNA and RNA viruses, respectively. These molecular methods were seen to significantly increase the viral detection sensitivities and specificities. A great debate for the reliability of these tests was raised, since positive reactions for asymptomatic patients were observed. The debate was also raised due to positive reactions observed for bronchiolitis cases associated with viruses which were well known to cause URTIs.

One of the great difficulties and challenges associated with the diagnostic concerns in the different regions of KSA was convincing the children, their parents, or representatives with sampling (pharyngeal swabs and aspirates, blood), particularly for research purposes. Another significant concern for health specialists and practitioners is the distribution of diagnostic logistics among the different regions and provinces of the kingdom. More focus and attention, as per the diagnostic facilities, are directed towards the central province of the kingdom (Riyadh area) with limited resources available at the peripheral regions. That had been obvious and affected the screening program during the HCoV-MERS epidemic in 2012 & 2013, when samples for virus detection had to be sent to central laboratories in Riyadh. Challenges associated with the availability of diagnosticians and laboratory technical staff were also raised on many occasions, since the qualified personnel are not available in all regions.

CONCLUSIONS

- A total number of 35 studies were retrieved from the literature that reported the detection of respiratory viruses in infants and children in KSA from 1988 until 2019.
- HRSVs are the most commonly reported virus involved in respiratory infections among pediatric patients in KSA, while HBoVs are the least reported viruses.
- The highest number (68.6%) of reports for PVRIs was observed from Riyadh region (including Riyadh city). This is presumably attributable to the fact that Riyadh, as the capital city of KSA, encompasses a high number of hospitals and medical cities as compared to other regions. Additionally, better diagnostic and research facilities are available in the research centers and university laboratories in Riyadh.

Directions for future research

After careful analysis and subtle investigations in the previously published work in the topic, the following elements should have special emphasis in future research attempts:

- Detailed description of the epidemiological patterns of these viruses among different populations of children should be documented.
- Nationwide surveillance studies to reveal the exact prevalence of these viruses among newborns, infants and children in the country are recommended.
- The exact morbidities and long-term consequences of the early life infection with these viruses, especially among the high-risk groups (e.g., children with chronic lung disease and high risk of pulmonary asthma) should be determined.

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Authors Contribution

AAS: literature search, data extraction and recording, manuscript writing and revision, tables and figures preparation. ASA: literature search, data extraction and recording, manuscript writing and revision. AMH: manuscript writing and revision. AAA: manuscript revision, editorial and language. SMA: manuscript revision, editorial and language.

REFERENCES


Original Article

Evaluation of atrial conduction characteristics in adult patients with asthma

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ABSTRACT

Objective: The electrophysiological properties of the right atrium could be impaired by right ventricular dysfunction, pulmonary hypertension and atrial enlargement in asthma. We aimed to evaluate atrial conduction abnormalities obtained by Doppler tissue imaging and electrocardiogram analysis in adult patients with asthma.

Design: Cross-sectional observational study

Setting: Şanlıurfa Mehmet Akif İnan Training and Research Hospital, Şanlıurfa, Turkey

Subjects: Study consisted of 90 (57 men, 25.7 ± 4.2 years) patients with asthma and 90 (59 men, 25.0 ± 4.0 years) healthy controls

Intervention: Twelve lead surface electrocardiogram, pulmonary function tests and echocardiographic imaging were performed and recorded.

Main outcome measures: Atrial conduction times were measured.

Results: Intra-right atrial conduction time (IRCT-echo) (11.9 ± 2.7 and 8.8 ± 2.4; p < 0.001), inter-atrial conduction time (IACT-echo) (25.7 ± 4.1 and 22.0 ± 3.1; p < 0.001) and P wave dispersion (PWD) (39.8 ± 10.4 and 36.2 ± 6.2; p < 0.001) were significantly increased in patients with asthma than controls. IACT-echo was positively correlated with IRCT-echo and intra-left atrial conduction time (ILCT-echo) (r = 0.687, p < 0.001 and r = 0.660, p < 0.001, respectively).

Conclusions: IRCT-echo, IACT-echo and PWD measurements are higher in asthmatic patients in our study. IACT-echo was significantly correlated with IRCT-echo and ILCT-echo.

INTRODUCTION

Asthma is a chronic disease in which inflammation causes airway obstruction and spasms of bronchi. The prevalence of this disorder is approximately 300 million people[1]. The relationship between asthma and cardiovascular disease has been reported in previous studies[2]. Asthma is also associated with increased risk of cardiac arrhythmias, including atrial fibrillation (AF) [3]. Although the mechanism of the relationship between AF and asthma is not fully understood, inflammation is incriminated in the pathogenesis of both asthma and AF[4]. Structural changes in right atrium induced by increased pulmonary artery pressure is also one of the possible mechanisms leading to AF in asthma[4].

Atrial conduction abnormalities are associated with increased risk of AF development[4]. These abnormalities could be measured by using electrocardiography (ECG) and tissue Doppler imaging (TDI). Atrial electromechanical delay (AED) and P wave dispersion (PWD) measurements could reflect the atrial conduction prolongation, which may trigger AF[5-7].

To the best of our knowledge, this is the first study evaluating the atrial conduction times detected by TDI and ECG in adult patients with asthma.

SUBJECTS AND METHODS

This is a cross-sectional study performed in Mehmet Akif İnan Training and Research Hospital between September 2016 and August 2017. One hundred
patients were enrolled in the study group. They were evaluated at our outpatient pulmonology clinic with dyspnea and diagnosed with bronchial asthma according to Global Initiative for Asthma guidelines at the first time[1]. The control group consisted of 90 age and sex-matched volunteers without any disease. Patients who were diagnosed with asthma were referred to our cardiology outpatient clinic for further medical evaluation including medical history, physical examination, ECG and echocardiography. Diagnosis of asthma depended on clinical symptoms, physical examination and pulmonary function tests. All subjects underwent pulmonary function tests which were performed by the same technician according to the European Respiratory Society consensus standards[8].

Echocardiography

Two-dimensional, M-mode, pulsed and color Doppler echocardiographic imaging was performed using Philips iE33 ultrasound system (Andover, Md., USA) with 2–4 MHz transducer by the same experienced cardiologist, who was blinded to the clinical status of all patients. Single derivation ECG was simultaneously recorded during imaging. Cardiac chamber dimensions and wall thickness were measured from parasternal long axis and apical four-chamber views. Echocardiographic examinations were performed according to the criteria of the American Society of Echocardiography guidelines[9]. Peak systolic velocity (Sm), early diastolic velocity (Em), late diastolic velocity (Am) and isovolumetric relaxation time (IVRT) were measured from the mitral, lateral, septal and tricuspid lateral annuluses. The myocardial performance index (MPI), an index of combined septal and tricuspid lateral annuluses. The myocardial time (IVRT) were measured from the mitral, lateral, diastolic velocity (Am) and isovolumetric relaxation velocity (Sm), early diastolic velocity (Em), late diastolic velocity (Am), left ventricular ejection fraction, left atrial diameter, right atrial diameter, mitral inflow parameters, tricuspid inflow parameters, mitral Sm, mitral Em, mitral Am, LV MPI, LV IVRT and RV Sm were similar between case and control groups. There is no significant difference between asthma and control groups in age (25.7 ± 4.2 and 25.0 ± 4.0; p: 0.29), body mass index (25.3 ± 1.9 and 24.8 ± 2.0; p: 0.12), systolic blood pressure (121.7 ± 6.2 and 120.9 ± 6.5; p: 0.37) and diastolic blood pressure (76.6 ± 6.6 and 75.8 ± 6.0; p: 0.56). The demographic and spirometry results were shown in Table 1.

RESULTS

Baseline demographic features are similar between case and control groups. There is no significant difference between asthma and control groups in age (25.7 ± 4.2 and 25.0 ± 4.0; p: 0.29), body mass index (25.3 ± 1.9 and 24.8 ± 2.0; p: 0.12), systolic blood pressure (121.7 ± 6.2 and 120.9 ± 6.5; p: 0.37) and diastolic blood pressure (76.6 ± 6.6 and 75.8 ± 6.0; p: 0.56). The demographic and spirometry results were shown in Table 1.

All echocardiographic measurements were listed in Table 2. Left ventricle end-diastolic diameter, interventricular septal wall thickness, left ventricular ejection fraction, left atrial diameter, right atrial diameter, mitral inflow parameters, tricuspid inflow parameters, mitral Sm, mitral Em, mitral Am, LV MPI, LV IVRT and RV Sm were similar between case and
control groups. RV Em (11.9 ± 2.0 and 12.9 ± 2.3 cm/s; p < 0.001), RV Am (11.4 ± 1.9 and 12.2 ± 1.9 cm/s; p < 0.001), tricuspid annular plane systolic excursion (TAPSE) (24.9 ± 2.0 and 25.7 ± 2.1 mm; p = 0.01), pulmonary artery acceleration time (PAAT) (130.3 ± 9.8 and 134.5 ± 11.2; p < 0.001*), lateral PA (62.8 ± 5.0 and 56.7 ± 4.0; p < 0.001), septal PA (49.0 ± 4.4 and 43.6 ± 4.4; p < 0.001), RV PA (37.0 ± 4.9 and 34.7 ± 4.0; p < 0.001), IACT-echo (25.7 ± 4.1 and 22.0 ± 3.1; p < 0.001) and IRCT-echo (11.9 ± 2.7 and 8.8 ± 2.4; p < 0.001) were higher in asthmatic patients compared to healthy subjects. P_{max}, P_{min} and ILCT-echo values did not differ between groups.

### DISCUSSION

In our study, we found higher IRCT-echo and IACT-echo measurements in asthmatic adult patients. However, similar ILCT-echo values were observed in these patients. Moreover, higher PWD values were detected in this population. To the best of our knowledge, this is the first study demonstrating an increase in PWD and right atrial conduction time in adult asthmatic population. IACT-echo was significantly correlated with IRCT-echo and ILCT-echo.

It was reported that asthma is associated with an increased risk for AF, although the exact mechanism hasn’t been fully understood[14-11]. Also, the adult asthmatic patients were observed to have more tachycardia and premature ventricular contractions...
than patients without asthma\[3\]. Pathogenesis of asthma is chronic inflammation of airways causing reversible obstruction. Chronic inflammation may be one of the possible explanations for increased arrhythmias in asthma\[4,12\]. Pulmonary hypertension (PHT) is one of the risk factors of AF. In asthma, recurrent hypoxemia and chronic inflammation may lead to pulmonary vasoconstriction, causing the development of pulmonary hypertension. This could result in right heart enlargement and right ventricular hypertrophy\[4,13\]. In later stages of the disease, both systolic and diastolic RV dysfunction occurs and this will impair the left ventricle functions due to increased RV afterload. All these structural and hemodynamic changes may trigger arrhythmias in asthmatic patients\[14\].

In our study, we found that asthma has a negative role in right ventricular functions. TAPSE, an echocardiographic indicator of RV function, and PAAT, an indicator of PHT, were significantly lower in asthmatic patients. Also, TDI parameters such as RV Em and RV Am were significantly decreased; and RV MPI and RV IVRT were significantly increased in subjects with asthma. These findings suggested that subclinical RV functional impairment started in patients with asthma in our study population. Previous study reports support our findings\[15,16\]. RV dysfunction was thought to be a potential risk factor for the development of AF\[17,18\]. This could be one of the underlying mechanisms leading to increased AF incidence in asthmatic patients.

It has been reported that increased AED measurements obtained by TDI were independent predictors of AF occurrence\[5,9,20\]. Atrial stretch due to increased RV afterload causes morphological changes in right atrium. This makes changes in electroanatomical substrate, which leads to delay in electrical conduction and development of re-entrant circuits in the atrium\[21\]. This is one of the possible explanations for AF development. It was shown that right atrial conduction time was increased in pediatric asthmatic patients\[10\]. In adult population, we also observed right atrial conduction delay in our study. The IACT-echo and IRCT-echo measurements were higher in asthmatic patients than control subjects. However, we didn’t see any statistical difference in ILCT-echo. Çiflet et al\[10\] reached similar results as our study in pediatric asthmatic population. We also found a significant correlation between IACT-echo and IRCT-echo and ILCT-echo.

PWD reflects the inhomogeneous and delayed conduction of sinus impulses. Increased PWD is associated with higher risk of AF. Atrial stretch due to increased afterload, electrolyte imbalance and sympathetic activity stimulation are the reasons for increased PWD\[5,6,10\]. In previous studies with pediatric asthmatic patients, no significant change was found in P-wave durations (P_max, P_min) and PWD\[10,22\]. However, in our study, we found higher PWD measurements in asthmatic subjects than controls in adult population. Higher disease duration could be the reason why significantly increased PWD values were observed in adult asthmatics.

Cross-sectional design of the study and lack of follow-up for detecting arrhythmias are the main limitations of this study. Manual evaluation of ECG parameters, lack of intra-rater and inter-rater variability calculation and measurement of conduction intervals without electrophysiological study (the gold standard technique) were the other limitations of our study.

CONCLUSION
IRCT-echo and IACT-echo measurements are prolonged in asthmatic patients in our study. IRCT-echo is associated with subclinical RV dysfunction in patients with asthma. PWD is higher in asthmatic patients. IACT-echo was significantly correlated with IRCT-echo and ILCT-echo. These results may be the underlying mechanisms to explain the impaired atrial electrophysiological properties in patients with asthma which may result in AF development. Longer prospective studies are needed to explain the exact pathophysiology of atrial arrhythmias observed in asthma.

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Complications and specimen quality in transrectal ultrasound guided prostate biopsy: Comparison of 16G and 18G needles

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ABSTRACT

Objectives: To evaluate specimen quality, pathological results, complications and pain in transrectal ultrasound (TRUS) guided prostate biopsy using 16 gauge (G) or 18G biopsy needles

Design: Retrospective study

Setting: Türkiye Yüksek İhtisas Training and Research Hospital, Ankara, Turkey

Subjects: Retrospective analysis of 243 TRUS guided prostate biopsies between March 2011 and April 2016

Interventions: Group 1 (n=121) underwent TRUS guided prostate biopsy using a 16 G needle and Group 2 (n=122) underwent TRUS guided prostate biopsy with an 18 G-needle.

Main outcome measures: We compared two biopsy needle sizes (16G vs 18G) in relation to sample quality, prostate cancer detection rate, pain, bleeding and infection rates in 243 patients. Core fragmentation and short specimen length (<10mm) rate were the sample quality criteria. Pain was evaluated using visual analog scale (VAS).

Results: There were no statistically significant differences in mean patient ages, prostate-specific antigen values and prostate volumes between groups 1 and 2. Sixteen gauge needles caused significantly less fragmentation of the biopsy cores when compared to 18G needles (p=0.00), but no statistically significant difference between two groups was recorded for pathological results (p=0.72) and shorter specimen length (p=0.567). Haematuria, rectal bleeding and infection were similar in both groups. Mean VAS score of group 1 was significantly greater than that of group 2 (3.19 vs 2.66;p=0.027).

Conclusion: Though thicker needles provided better sampling quality, the cancer detection rate was not altered by the needle size. Also, even though complication rates were similar for different needle sizes, the 18G needles were better tolerated.

INTRODUCTION

The main method of diagnosing prostate cancer is by performing prostate biopsy (PB). While finger-guided and lesion-focused techniques were used in the past, it has recently become a standard diagnostic method to perform systematic prostate biopsies under the guidance of transrectal ultrasound (TRUS) [1]. Over the years, various biopsy schemes have been proposed to make PB more accurate and to avoid error in diagnosis. Currently, with the opinion that sextant biopsy (the first described method) is inadequate for diagnosis, there is still no consensus about the optimal number of cores and core localization[1,2]. The diagnostic accuracy of PB may be increased by increasing the volume of the tissue and sampling quality[3]. For this purpose, it is recommended to use larger needles that can receive larger volumes of tissue, but it is thought that the risk of complications such as pain and bleeding may increase as a result[4]. Today, 16G and 18G needles are widely used in PB. When compared with 18G needle, 16G biopsy needle can theoretically take larger and better quality samples

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and make more accurate pathologic evaluation due to its larger calibre, but there aren’t enough studies in the literature that compare the two different PB needles.

In this study, we aimed to compare 18G and 16G PB needles in terms of prostate cancer detection rate; morbidities such as pain, bleeding and infection; and sampling quality in TRUS-guided PB.

SUBJECTS AND METHODS
Clinical and pathological data from 243 patients who underwent 16 cores TRUS-guided transrectal PB because of elevated prostate-specific antigen (PSA) level between March 2011 and April 2016 were analyzed retrospectively. Patients with total PSA levels between 4 and 10 ng/ml, who had no history of anticoagulant or antiplatelet drug use, bleeding disorder and prostatic surgery were included in the study. Patients with suspicious lesions detected on rectal examination or TRUS were excluded. One hundred and twenty-one patients underwent PB with 16G needle between March 2011 and February 2013 while 122 underwent PB with 18G needle between March 2013 and April 2016.

Prostatic biopsies were performed by two experienced urologists. All patients were started on ciprofloxacin 500 mg twice daily one day before the procedure for prophylaxis and continued until three days after the procedure. All patients were given detailed information about the PB and signed a consent form. PB was routinely performed in the lateral decubitus position following rectal enema. Periprostatic nerve block was performed by injecting a total of 10 ml 2% prilocaine into the junctional area between seminal vesicles and the prostate, including 5 ml on each side. Prostatic volume was then calculated by the ellipsoid formula using 6.5-Hz ultrasound probe. All patients underwent a total of 10 ml 2% prilocaine into the junctional area between seminal vesicles and the prostate, including 5 ml on each side. Prostatic volume was then calculated by the ellipsoid formula using 6.5-Hz ultrasound probe. All patients underwent a total of 16 cores PB using 25 cm 16G or 18G biopsy needles from both right and left lobes of the prostate including two lateral peripheral (basal, midgland), three far lateral peripheral (basal, midgland apical) and three medial (basal, midgland, apical). Each sample was sent for pathological examination in separate bottles containing 10% formalin.

Severity of pain during prostatic biopsy was graded from 0 to 10 by using the visual analog scale (VAS). Evaluation of morbidity was generally made one week after the procedure. Hematuria and rectal bleeding that requires endoscopic or pharmacological treatment. Fever of 38 °C and above that occurred within 48 hours after the procedure and that required parenteral antibiotic treatment was considered as procedure-induced infection. The following criteria were used to evaluate the sampling quality: having fragmented cores and shorter length of prostatic tissue in non-fragmented cores (core length <10 mm)[4,6].

Data from patients who underwent biopsies with 18G and 16G needles were compared in terms of age, prostatic volume, total and free PSA, treatment induced pain (VAS), the quality of the sampling, detection rate of prostate cancer and morbidity. Since the study is retrospective, there is no ethical committee approval and patient’s consent in our study.

Statistical analysis
Independent sample t-test and chi-square test were used for statistical analysis. All data were analyzed using SPSS (Statistical Package for the Social Sciences, Inc., Chicago, IL, USA) 16.0 for Windows programme.

RESULTS
Data from a total of 243 patients including 121 patients who underwent biopsy with 16G PB needle (Group 1) and 122 patients with 18G PB needle (Group 2) were analyzed. There was no statistically significant difference between the groups in terms of patient age, prostatic volume, total and free PSA values (Table 1).

| Table 1: Age, prostatic volume, total and free PSA values in two groups |
|---------------------------------|----------------|----------------|
| **Baseline demographics**       | **Group 1** (n = 121) | **Group 2** (n = 122) | **p-value** |
| Age (years) | 56.47 ± 20.42 | 56.0 ± 7.94 | 0.33 |
| Range | 48 - 78 | 56 - 76 | |
| Vp (cc) | 15 - 115 | 30 – 150 | 0.228 |
| Mean ± SD | 52.16 ± 22.01 | 56.47 ± 20.42 | |
| Range | 14.1 – 9.89 | 4.06 – 9.96 | 0.441 |
| Total PSA (ng/ml) | 6.90 ± 2.03 | 7.15 ± 1.88 | |
| Mean ± SD | 4.14 – 9.89 | 4.06 – 9.96 | 0.22 |
| Range | 1.37 ± 0.58 | 1.53 ± 0.76 | |
| Free PSA (ng/ml) | 0.16 – 3.19 | 0.26 – 3.04 | |
| Mean ± SD | 51.26 ± 22.01 | 56.47 ± 20.42 | |
| Range | 14.1 – 9.89 | 4.06 – 9.96 | |
| Vp: Prostatic volume; SD: Standard deviation; PSA: Prostate specific antigen |

After pathological evaluation, benign pathology was detected in 140 (57.6%), prostate cancer in 80 (32.9%) and atypical small acinar proliferation (ASAP) in 23 (9.4%). There was no statistically significant difference between the groups in terms of cancer, benign pathology and ASAP detection rates (p = 0.72) (Table 2).

Mean VAS scores for pain were 3.19 ± 1.58 and 2.66 ± 1.23 in Groups 1 and 2, respectively and the difference
Effectiveness of different biopsy schemes have been investigated in order to reach the correct diagnosis. While different PB schemes were identified by increasing the number of cores, there is still no biopsy scheme that is generally standardized and accepted. Scattoni et al. investigated the ideal number of cores in PB for the diagnosis of prostate cancer in their study and they concluded the most ideal core number as between 10 to 16 depending on digital rectal examination findings, prostate size and age. In another study, saturation (20 cores and more) biopsy was concluded to be unnecessary for first time biopsies due to increase in morbidity. Therefore, it is reasonable to perform saturation biopsy in patients with previously negative biopsies and rising or persistent high PSA levels. Although it is not a generally accepted scheme, it is recommended to take biopsies from between 10 and 18 cores as lateral as possible for the first biopsy.

In our own practice, we usually carry out a total of 16 cores sampling including six far lateral peripheral, four lateral peripheral and six medial.

The second way to increase the reliability of prostate biopsy is providing the pathological specimen in adequate quantity and quality. Theoretically, if the needle used for this purpose is longer or larger in caliber, the samples taken in each core would be in larger volume and better quality. Supporting this hypothesis, Dogan et al. reported that tissues obtained in biopsies using longer needles (end cut, 33 mm) were superior in quantity and quality, while cancer detection rate was not different when compared with the needles in the standard size (side notch, 22 mm). However, Özdén et al. concluded that taller needles (end-cut, 33 mm) did not provide any advantage in sampling quality compared with the standard needle.

Recently, standard (side-notch) 16G and 18G biopsy needles are widely used in PB. When compared, 16G and 18G needles are equal in length while 16G needle is thicker and has more volume by up to 1.5 times. Therefore, it can theoretically be expected to obtain larger tissues in quality and volume in biopsies with 16G needle. At the same time, increasing the thickness of the biopsy needle may lead to an increase in complications. Helbich et al. compared 16G and 18G needles in breast biopsies and concluded that 16G needle has reached better sampling quantity and quality. In this topic, there are only a few number of studies in the literature. Inal et al. compared their PB outcomes of 103 patients conducted with 16G needle and 101 patients with 18G needle. They concluded better sampling quality in the first group while prostate cancer detection rates, complications and VAS pain scores were not different from the second group. Cicione et al. investigated the effects of PB with 16G and 18G needles on cancer detection rate, sampling quality and morbidity; no significant differences were reported in any of these three criteria.

### Table 2: Pathology reports of two groups (chi-square test)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Group 1 (n = 121)</th>
<th>Group 2 (n = 122)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>68 (56.1%)</td>
<td>72 (59.01%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>39 (32.2%)</td>
<td>41 (33.6%)</td>
<td></td>
</tr>
<tr>
<td>ASAP</td>
<td>14 (11.5%)</td>
<td>9 (7.37%)</td>
<td></td>
</tr>
</tbody>
</table>

ASAP: atypical small acinar proliferation

was statistically significant (p = 0.027). There was no statistically significant difference between the groups in terms of complications (p = 0.842) (Table 3).

### Table 3: Comparison of the complications in two groups. (chi-square test)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Group 1 (n = 121)</th>
<th>Group 2 (n = 122)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>112 (92.56%)</td>
<td>115 (94.45%)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>9 (7.43%)</td>
<td>7 (5.73%)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td></td>
<td></td>
<td>0.842</td>
</tr>
<tr>
<td>Grade 0</td>
<td>112 (92.56%)</td>
<td>116 (95.08%)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>9 (7.43%)</td>
<td>6 (4.91%)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>2 (1.65%)</td>
<td>2 (1.63%)</td>
<td></td>
</tr>
</tbody>
</table>

When compared to 18G needles, 16G needles were found to cause less fragmentation (p = 0.00), but the difference in sampling rate of <10 mm length was not statistically significant between the groups (p = 0.567) (Table 4).

### Table 4: Comparison of sampling quality of two groups (chi-square test)

<table>
<thead>
<tr>
<th>Sample quality</th>
<th>Group 1 (n = 121)</th>
<th>Group 2 (n = 122)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragmentation</td>
<td></td>
<td></td>
<td>0.00</td>
</tr>
<tr>
<td>1 core</td>
<td>17 (14.04%)</td>
<td>66 (54.09%)</td>
<td></td>
</tr>
<tr>
<td>2 cores</td>
<td>20 (16.52%)</td>
<td>22 (18.03%)</td>
<td></td>
</tr>
<tr>
<td>3 cores</td>
<td>10 (8.26%)</td>
<td>10 (8.19%)</td>
<td></td>
</tr>
<tr>
<td>4 cores</td>
<td>5 (4.13%)</td>
<td>3 (2.45%)</td>
<td></td>
</tr>
<tr>
<td>5 cores</td>
<td>5 (4.13%)</td>
<td>2 (1.63%)</td>
<td></td>
</tr>
<tr>
<td>6 cores</td>
<td>0</td>
<td>2 (1.63%)</td>
<td></td>
</tr>
<tr>
<td>&lt;10 mm sample</td>
<td></td>
<td></td>
<td>0.567</td>
</tr>
<tr>
<td>1 core</td>
<td>46 (38.01%)</td>
<td>36 (29.50%)</td>
<td></td>
</tr>
<tr>
<td>2 cores</td>
<td>19 (15.7%)</td>
<td>17 (13.9%)</td>
<td></td>
</tr>
<tr>
<td>3 cores</td>
<td>5 (4.13%)</td>
<td>10 (8.19%)</td>
<td></td>
</tr>
<tr>
<td>4 cores</td>
<td>0</td>
<td>2 (1.63%)</td>
<td></td>
</tr>
</tbody>
</table>

### DISCUSSION

Today, TRUS-guided PB is the main diagnostic method used in the diagnosis of prostate cancer. In various studies, as the first identified scheme for PB, sextant biopsy has been reported to overlook the existing cancer in up to 30% of the cases. Therefore, the common view is that sextant biopsy is inadequate and outdated in the diagnosis of prostate cancer. Sextant biopsy has been reported to overlook the various studies, as the first identified scheme for PB, method used in the diagnosis of prostate cancer. In (Table 4).
In our study, 16G needle led to less core fragmentation when compared with 18G. However, there were no significant differences between the number of cores containing samples less than 10 mm. Even though sample quality is better with the 16G needle, there was no statistically significant difference between the two groups in terms of prostate cancer and ASAP detection rates.

We also observed that our patients had difficulty in tolerating PB as the needle size increased. VAS pain scores were significantly higher in 16G needle biopsy group. This can be a result of ineffectiveness of peri-prostatic block on rectal mucosa and contact of the thicker needle with the rectal mucosa. Intrarectal pomads and gels with local anesthetics in addition to the peri-prostatic block can be useful in patients during biopsy with thicker needle. Giannarini et al\[14\] concluded less pain scores in patients who underwent PB with peri-prostatic block in combination with intrarectal lidocaine-prilocaine cream, when compared with peri-prostatic block alone.

In our study, complication rates such as hematuria, rectal bleeding and infection were not significantly different between the two groups. Bleeding that required endoscopic or pharmacological treatment (grade 2) were not observed in both groups. Infection that required parenteral antibiotic therapy was observed only in four patients, two in each group. In parallel with our results, previous studies reported no increase in complications in transrectal PB with thicker needles\[6,7,13\]. Giovanni et al\[4\] also reported that increase in needle size did not result in a change in the complication rate of transperineal PB.

CONCLUSION

We conclude that thicker needles did not provide any significant advantage. Though thicker needles provided better sampling quality, the cancer detection rate was not altered by the needle size. Also, even though complication rates were similar for different needle sizes, the 18G needles were better tolerated. Further prospective and randomized trials with larger series are required to determine if 16G needle provides any advantage.

ACKNOWLEDGMENT

Conflicts of interest: The authors declare no conflicts of interest.

REFERENCES

Factors influencing the acceptance of prenatal testing by pregnant women

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2Koc University, School of Nursing and Health Sciences, Istanbul, Turkey
3Department of Genetics, Erciyes University Faculty of Medicine, Kayseri, Turkey

ABSTRACT

Objectives: To analyze the factors influencing the maternal uptake of invasive prenatal testing
Design: Retrospective clinical study
Setting: Erciyes University Obstetric Clinic Perinatology Unit, Turkey
Subjects: A total of 1412 referred patients, of whom 291 were offered invasive prenatal testing (20.6%)
Intervention(s): 143 women (49.1%) opted for invasive testing (group 1) and 148 women (50.9%) declined (group 2).
Main outcome measure(s): We compared the distribution of invasive test uptake relevant to the maternal age, obstetric history, educational level, abnormal screening tests, structural malformations and living area.
Results: We offered an invasive prenatal testing to 291 women out of 1412 patients (20.6%) for various reasons. Among them, 143 women (49.1%) opted for invasive testing and 148 women (50.9%) declined. Abnormal prenatal screening tests were found to have no effect on the uptake of invasive testing by women of advanced maternal age. The only demographic parameter that affects the uptake of invasive testing was the location, and women who were living in the rural areas had a higher rate of uptake (p: 0.026). No statistically significant difference was detected for the uptake of test with respect to age, educational level or previous pregnancy loss (p >0.05).
Conclusions: The uptake of invasive diagnostic tests by pregnant women is determined by the complex network of personal and social factors rather than screening tests and maternal age. Therefore, antenatal screening, and genetic counselling program taking into account these factors should be implemented.

INTRODUCTION

Prenatal screening can identify a high-risk subgroup for chromosomal trisomies within a population of pregnant women, and thus provides an individualized risk estimation of having a child with one of these disorders. In accordance with the local guidelines, screening may be performed in the first or second trimester, and it involves the use of biochemical tests on maternal serum and or ultrasound (US) scanning of the foetus. The subgroup of women with an increased risk can be offered a prenatal diagnostic testing in order to provide a certain diagnosis. Every chromosomal disorder is potentially detectable in utero. Thus, any pregnant woman could undergo an invasive procedure to exclude these conditions, with near 100% certainty. The most common indications that justify prenatal invasive testing are: (1) advanced maternal age; (2) previous pregnancy with autosomal trisomy; (3) parental chromosomal rearrangement; (4) abnormal US findings during the current pregnancy; and (4) increased risk, as calculated from non-invasive screening results, nuchal translucency and maternal serum analyses. The analysis of the foetal chromosomes can be performed using a sample obtained by amniocentesis (AS), chorionic villus sampling (CVS), and cordocentesis, all of which carry a risk of miscarriage reported to be around 0.5% for CVS 1% for AS, respectively[1]. However, for some women, the potential risk of pregnancy loss associated with these diagnostic tests is

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SUBJECTS AND METHODS

This retrospective cohort analysis evaluated pregnant women who had high risk for chromosomal abnormalities in May 2010 - May 2012 at Erciyes University, Obstetrics and Gynecology, Prenatal Diagnosis Unit. Erciyes University is a tertiary referral center providing care to approximately 2,100,000 women in Kayseri and neighbouring cities.

During the study period, the genetic counselling session were performed by two experienced perinatologists (MSK and MTO), who also did the US examinations. Patients signed a written informed consent for examination and we received approval of the study protocol from local institute ethical committee. At the first visit, the patients were asked their age, education, area of living, history of a previous baby with chromosomal abnormality and recurrent fetal loss. The educational level is grouped as uneducated / primary school (low), high school (middle) and university (high). The living areas of the patients were grouped as urban and rural.

The women, who attended our antenatal follow-up clinics during the first three months, are offered first trimester screening that includes nuchal translucency, pregnancy-associated plasma protein-A and free B-hCG. The women who were first seen after the first trimester were routinely offered quadruple or triple test (Alpha Feto Protein, Beta human chorionic gonadotropin, Inhibin A, Estriol). The same screening program was implemented by the local clinics, and no sequential or contingent approach for screening was adopted in our region. A high risk was defined as the combined risk value greater than 1 / 300 at the first trimester screening, and 1 / 270 in the second trimester tests[1-3]. Women of advanced maternal age (AMA) were informed of the fact that screening tests have limited value in detecting chromosomal abnormality in their age groups (> 35 years) and that normal results do not rule out chromosomal disease. Therefore, invasive testing was offered to all women of AMA irrespective of their screening results. Invasive prenatal testing was also offered to all women who had a previous history of a child with chromosomal abnormality, structural malformation or abnormal USG findings/ marker that associated with chromosomal abnormality (nuchal fold thickening, mild ventriculomegaly, nasal bone hypoplasia, echogenic bowel, echogenic focus in the heart).

All invasive diagnostic testing were also performed by the two operators (MSK and MTO). The information regarding the invasive procedure and 1% risk of abortion was also provided before the procedure. Their queries were answered and, if the women opted for the procedure, an informed consent was obtained.

To compare the distributions of invasive test uptake relevant to the maternal age, obstetric history, educational level, abnormal screening tests, structural malformations and living area, chi-square test were used. SPSS 15.0 was used for the analysis of data, and p <0.05 was admitted as statistically significant.

RESULTS

In this study, 1412 women were referred to our tertiary prenatal diagnosis center. The median age of the women who were offered invasive prenatal testing was 32.8 ± 6.67 years (range: 17 - 47 years). Patient characteristics in the study group are shown in Table 1. We offered invasive prenatal testing to 291 women (291/1412, 20.6%) due to the various reasons cited above. Among them, 143 women (49.1%) opted for invasive testing and 148 women (50.9%) declined. The indications for referrals (first trimester screening test risk, second trimester screening test risk, suspicious congenital malformation, isolated AMA and previous pregnancy with autosomal trisomy) are shown in Table 2. Fifty-one women were referred to us with abnormal first trimester screening test results (51/291, 17.5%), 61 with abnormal second trimester screening test results (61/291, 21%), and 76 women
(76/291, 26.1%) were referred for suspicious structural malformations. Seventeen women had a previous child with chromosomal abnormality (17/291, 5.8%). Isolated advanced maternal age was the indication for referral in 86 women (86/291, 29.5%). A total of 148 women, who were over 35 years old, had either structural malformation or abnormal screening tests (148/291, 50.8%). Thirty-four women of AMA also had abnormal screening tests (34/148, 22.9%). The effects of abnormal screening tests on the uptake of invasive testing in the AMA group are shown in Table 3.

### Table 2: Distribution according to maternal age, obstetric history, educational level and living area at presentation and uptake of invasive tests

<table>
<thead>
<tr>
<th>Demographic parameters</th>
<th>Invasive testing done n (%)</th>
<th>Invasive testing rejected n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application reason</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>32 (62.7)</td>
<td>19 (37.3)</td>
<td>0.248</td>
</tr>
<tr>
<td>screening test risk</td>
<td>27 (44.3)</td>
<td>34 (55.7)</td>
<td></td>
</tr>
<tr>
<td>Second trimester</td>
<td>34 (44.7)</td>
<td>42 (55.3)</td>
<td></td>
</tr>
<tr>
<td>screening test risk</td>
<td>43 (50.0)</td>
<td>43 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Isolated advanced</td>
<td>7 (41.2)</td>
<td>10 (58.8)</td>
<td></td>
</tr>
<tr>
<td>maternal age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or more</td>
<td>44 (44.9)</td>
<td>54 (55.1)</td>
<td>0.302</td>
</tr>
<tr>
<td>than one</td>
<td>99 (51.3)</td>
<td>94 (48.7)</td>
<td></td>
</tr>
<tr>
<td>Living area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country side</td>
<td>43 (60.6)</td>
<td>28 (39.4)</td>
<td>0.027</td>
</tr>
<tr>
<td>City centre</td>
<td>100 (45.5)</td>
<td>120 (54.5)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>38 (50.7)</td>
<td>37 (49.3)</td>
<td>0.759</td>
</tr>
<tr>
<td>Multiparous</td>
<td>105 (48.6)</td>
<td>111 (51.4)</td>
<td></td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;35</td>
<td>75 (50.7)</td>
<td>73 (49.3)</td>
<td>0.594</td>
</tr>
<tr>
<td>&lt;35</td>
<td>68 (47.6)</td>
<td>75 (52.4)</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td>0.805</td>
</tr>
<tr>
<td>Low</td>
<td>86 (48.9)</td>
<td>90 (51.1)</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>33 (47.1)</td>
<td>37 (52.9)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>24 (53.3)</td>
<td>21 (46.7)</td>
<td></td>
</tr>
</tbody>
</table>

In the abnormal screening group, women were more inclined for invasive testing when the abnormal screening test was performed in the first trimester than in second trimester; however the difference is not statistically significant (p = 0.248). The only demographic parameter that affects the uptake of invasive testing was location; and women who were living in rural areas had a higher rate of uptake (p = 0.026). No statistically significant difference was detected for the uptake of test with respect to age, educational level and previous pregnancy loss (p >0.05).

### DISCUSSION

The identification of foetal aneuploidy requires the incorporation of various risk factors like maternal age and maternal screening results. The family members’ evaluation of the risk of aneuploidy varies depending on their socioeconomic background and education level, as well as any past experience regarding such tests. Genetic counselling for the expectant mother is crucial on such a sensitive issue. Different families may interpret the risk differently and may react differently to similar situations.

Maternal age is an important factor for determining the risk of having a baby with chromosomal abnormality[6]. The American College of Obstetrics and Gynaecology (ACOG) guidelines recommend offering prenatal diagnostics testing for fetal aneuploidy to all pregnant women who will be aged 35 or older at the time of delivery[7]. In some countries, prenatal screening tests are offered to all women including women of AMA. However, diagnostic sensitivity of the screening tests in these age groups is notoriously low with nearly 20% false positivity[8], so that the invasive tests are the only reliable methods for excluding chromosomal abnormalities. The effect of maternal age on uptake of invasive tests had been studied by Nakata et al in a very large population. Their study showed that average AS and CVS uptake increased with increased maternal age, irrespective of
other factors\(^9\). On the other hand, Sharda S et al did not show a significant correlation between maternal age and invasive test uptake\(^{10}\). Similarly, our results showed no statistical difference between women over and under 35 years of age.

In the past ten years, different methods have been suggested to reduce the need for invasive prenatal tests. Nakata et al surveyed the trend in uptake of invasive tests between 2001-2007 and concluded that implementation of screening tests reduced the invasive procedures, and this trend reversed after 2008, probably due to ACOGs recommendation supporting routine first trimester screening that lead to increased detection of high-risk pregnancies\(^9\). Similarly, Sharda et al reported that the detection of soft markers by the second trimester US was associated with higher acceptance of amniocentesis\(^{10}\). Conversely, Wray et al detected a dramatically decreased uptake of invasive testing after the implementation of first trimester screening\(^{13}\). Since our study covers the last three years, it is not possible to comment on general trends for the uptake of invasive testing. However, the addition of screening tests had no significant effect on the uptake of invasive testing among the women of AMA.

The effects of ethnic, social, religious and cultural factors on the perception of health, health risks, and the medical/surgical intervention have been studied by obstetrics/gynaecology specialists and medical anthropologists\(^{4-12}\). The anthropologists Rayna Rapp and Faye Ginsburg contend that the conceptions of abortion, kinship and disability do not only belong to the cultural realm of beliefs and values, but they are also shaped by concrete economic and social factors, such as the practical logistics of taking care of a child with a disability. Similarly, our study showed that the location of the family is the only significant factor affecting uptake rate. Families who live in rural areas have more financial and social problems in taking care of their disabled children, and can hardly benefit from the special centers for this purpose, which are mostly located in the major cities of Turkey. In contrast, the urban families benefit from a wide array of possibilities, such as regular medical counselling, and governmental and non-governmental organisations for social and medical assistance. Moreover, people in rural areas are much less covered and/or temporarily covered by social security system, which leads them to view having a disabled child as a major financial burden.

The definition of abnormality is also strongly conditioned by social and cultural factors, and the concept of risk is shaped by personal, traditional and religious beliefs, and life experiences. Therefore, the choice of parents in a given population is expected to differ in accordance with their socio-economic profile, religious views, and educational level. For instance, a study conducted by Vergani et al in Italy demonstrated that the uptake was highly related to women’s a priori opinions about testing and the negative ‘a priori’ attitude towards amniocentesis in particular was the single most important determinant of rejecting the invasive test\(^{13}\). Similarly, Kuppermann et al and Baker et al found that African-American women were less likely to undertake the invasive antenatal testing than women of other ethnic groups in their study\(^{14-15}\). In fact, the great majority of studies evaluating maternal attitude towards invasive testing are coming from North America, Europe, China, and Israel\(^{9,13-20}\). Therefore, this is the first medical study evaluating the uptake of the invasive test in a Muslim population (99%). Previously, Muhsen et al determined that the Israeli-Arab Muslim women with AMA were less likely to undergo an invasive test than other Israeli women\(^{21}\). Our results showed that nearly half of all women opted for the invasive test, and this ratio was comparable to other studies. Can Acıksoz, who interviewed the women faced with the decision of undergoing an amniocentesis during their pregnancy in Istanbul, argues that many pregnant women closely follow the foreign and Turkish internet sites, where lay people and medical experts discuss these issues in a less formal manner, and shape their decision accordingly. Acıksoz also notes that the images of “Chernobyl babies”, the malformed foetuses and newborn babies after the Chernobyl nuclear disaster, were displayed quite extensively in the Turkish media since the late 1980s, since Turkey was one of the countries affected by that disaster\(^{22}\). Accordingly, those images shaped the collective memory and created a long-term fear and anxiety of having a baby with a genetic disease. The women viewed the genetic evaluations as nerve-wracking tests to pass or fail, and emphasized that they remained undecided on whether to take those tests for several days. Some of them confessed that they delegated this major responsibility by letting their doctors decide for them, or preferred to tackle the daunting problem of disability after childbirth, if the baby is born disabled.

Our experience showed that counselling about invasive testing is difficult, even for women having multiple risk factors for chromosomal abnormality, as many lay people do not understand the concept of probability\(^{23,10}\). In Turkey, there are no legal restrictions that regulate antenatal screening for chromosomal abnormalities, and the current practise is largely based on expert opinion and institutional practise. Since the combination of screening modalities even in high risk pregnant women does not change the maternal attitude towards invasive testing, it would be reasonable to embrace a less vigorous and more cost-effective screening approach for chromosomal abnormalities.
CONCLUSION
The uptake of invasive diagnostic tests by the future mother is determined by a complex network of personal and social factors, the majority of which could not be revealed here. In order to delineate relationship between these factors, qualitative studies which will be designed to assess the deeper stratum of personal and social issues are needed. The cooperation between perinatologists and social scientists in this area would provide new perspectives, and contribute greatly to the existing literature.

ACKNOWLEDGMENT
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REFERENCES
Original Article

The biofilm formation properties of the 
*S. epidermidis* isolates obtained from conjunctiva and multi-drug resistance

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ABSTRACT

**Objective:** Biofilm was shown on ocular abiotic surfaces such as contact lenses, intra-ocular lenses, glaucoma shunts and corneal sutures. The aim of this study is to compare success of Microtiter plate (MTP) and Congo Red Agar (CRA) methods in showing biofilm formation of *S. epidermidis* isolates that were obtained from conjunctiva regarding presence of icaA gene locus and multi-drug resistance.

**Design:** Interventional

**Setting:** Department of Biology, Faculty of Science, Eskisehir Technical University

**Subjects:** *S. epidermidis* isolates obtained from conjunctivas of healthy patients

**Interventions:** MTP and CRA methods and antibiotic susceptibility tests were done and scanning electron microscopy was performed.

**Main outcome measures:** Biofilm forming capacity, multidrug resistance states and bacterial adhesion of *S. epidermidis*

**Results:** Nine isolates were found as strong biofilm producers with MTP and CRA methods. There were six icaA negative isolates, one of which was not a biofilm producer. From the icaA and icaD positive isolates, 13 were biofilm negative with MTP method and seven were biofilm negative with CRA method. Eighteen isolates were determined as resistant to three or more antibiotics. Ten of 18 isolates were strong biofilm producer with MTP and eight of 18 isolates were strong biofilm producer with CRA. Biofilm producer isolates were found to be resistant to antibiotics.

**Conclusion:** It is noted that biofilm formation capacity of *S. epidermidis* isolates that were obtained from ocular surface were determined and multidrug resistance were estimated more successfully with MTP method. However, there is no method which can successfully detect biofilm formation capacity with 100% accuracy.

KEY WORDS: congo red agar, eye, ica gene, microtiter plate, ocular surface

INTRODUCTION

Staphylococci are opportunistic pathogens for humans and animals, and colonize in various parts of the human body. Slime factor generation and biofilm formation are among the factors of pathogenicity[1]. It was shown that staphylococci were able to hold onto medical devices through these slime properties. *Staphylococcus epidermidis* is frequently isolated during infections associated with medical devices. *S. epidermidis* is part of the normal skin flora and mucous membranes, but can enter into the body while attaching bio-materials or during operation. In recent years, with the increasing use of medical materials such as intravascular catheters, vascular grafts, sutures and orthopaedic devices, *S. epidermidis* has become the most frequently isolated bacteria in nosocomial and biomaterial-based infections[2,3]. As the eye was first shown on ocular abiotic materials such as contact lenses, intraocular lenses, glaucoma shunts, corneal sutures and scleral cerclage bands, biofilm was also associated with some chronic infections such as diffuse lamellar keratitis and infectious crystal keratopathy, as well as ocular abiotic materials such as contact lenses, intraocular lenses, glaucoma shunts, corneal sutures...
and scleral cerclage bands\textsuperscript{[4-7]}. \textit{S. epidermidis} is one of the most frequently isolated microorganisms from acute onset endophthalmitis after cataract surgery\textsuperscript{[7]}. Biofilm formation is one of the most important mechanisms that determine the disease-causing capacity of species. Biofilm-forming microorganisms form the basis of persistent and chronic infections. Biofilm is a colony formed by microorganisms living in a matrix embedded in a polysaccharide matrix, which adheres to a living or inanimate surface. Biofilm is a consortium of various chemical substances, such as exopolysaccharides, proteins, teichoic acids and extracellular DNA, which are formed by bacteria species, strains and environmental conditions (Fig 1). The biofilm-forming bacteria are resistant to antibiotics, disinfectants, phagocytosis and other components of the innate adaptive immune and inflammatory defense system of the host\textsuperscript{[8]}. The production of polysaccharide intercellular adenine (PIA) through enzymes encoding the intercellular adhesion (ica) operon is by far the best-understood mechanism of biofilm development in staphylococci. In particular, icaA and icaD have an important role in the production of \textit{S. epidermidis} for slime production\textsuperscript{[9]}. In recent years, the identification of \textit{S. epidermidis} biofilm formation has gained importance in eye infections\textsuperscript{[3]}. Biofilm production can be accomplished by phenotypic methods such as the microtiter plate (MTP) test developed by Christensen \textit{et al}\textsuperscript{[10]}, by the Congo red agar (CRA) test as described by Freeman \textit{et al}\textsuperscript{[11]}, and by the molecular\textsuperscript{[12]} identification of the ica locus. Our aim in this study was to find the most successful method in determining the biofilm development properties of \textit{S. epidermidis} isolates isolated from the ocular surface, and thus estimating the multiple antibiotic resistance cases. MTP and CRA methods were compared with the presence of the ica gene locus and antibiotic resistance status.

**MATERIALS AND METHODS**

**Materials**

In previous studies, icaA and icaD isolated and identified from the conjunctiva of 42 \textit{S. epidermidis} isolates, whose characteristics were shown in Table 1, was obtained from Eskisehir Technical University Faculty of Science, Department of Biology, Microbiology Laboratory and used in various studies. Only one of the isolates (CA 11.1) was positive for the biofilm associated protein (bap) gene. The \textit{S. epidermidis} ATCC 12228 which does not produce biofilms, and the \textit{S. epidermidis} ATCC 35984 which produces strong biofilms, were used as controls.

**Methods**

The potential of \textit{S. epidermidis} isolates for biofilm formation was determined by MTP and CRA method.

**Determination of biofilm production by MTP method**

Fresh cultures of microorganisms were prepared by incubating them in tryptic soy broth (TSB) at 37°C for 24 hours. These cultures were diluted at the rate of 1:100 with TSB medium containing 2% glucose and transferred to 200 μl of 96 well flat-bottomed ELISA petri. Plates were incubated at 37 °C for 24 hours. At the end of the incubation period, samples were read at 490 nm wavelength with the help of spectrophotometer (Shimadzu, UV-2101PC). After the reading, the nutrient media in the plate was drained and the plate was washed twice with sterile distilled water. 200 μl of 95% ethanol was transferred onto the plate and allowed to stand for 15 minutes. The plate was then evacuated and allowed to air dry for 45 minutes. After the wells were dried, 150 μl of a 1% crystal violet dye solution was added and allowed to stand for five minutes to penetrate into the cells. The dye in the plate was then drained and washed twice with sterile distilled water. Finally, 160 μl of 33% acetic acid was added to the plate and the samples were read with a spectrophotometer (Shimadzu, UV-2101PC) at a wavelength of 570 nm. As a result of the processing, evaluation was made according to changes in color and spectrophotometer values before and after dyeing. According to the results obtained from the MTP method, classification was made in 4 ways\textsuperscript{[13]}:

- Optical Density (OD) ≤ Optical Density Limit (ODc): no biofilm formation (−);
- ODc ≤ OD ≤ 2 x ODc: weak biofilm (+);
- 2 x ODc ≤ OD ≤ 4 x ODc: intermediate biofilm (++);
- 4 x ODc < OD: strong biofilm (+++).

All these tests were repeated three times and the averages were taken.

Fig 1: Biofilm formation stages
Table 1: IcaA and IcaD genes, antibiotic susceptibility and biofilm formation status of S. epidermidis isolates.

<table>
<thead>
<tr>
<th>Isolates</th>
<th>IcaA</th>
<th>IcaD</th>
<th>Ceftazidime</th>
<th>Ciprofloxacin</th>
<th>Gentamicin</th>
<th>Amikacin</th>
<th>Vancomycin*</th>
<th>Cat/Flucloxacillin</th>
<th>Lomafloxacin</th>
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<td>S</td>
<td>7</td>
<td>+</td>
</tr>
<tr>
<td>4-1</td>
<td>+</td>
<td>+</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>I</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>6</td>
<td>+++</td>
</tr>
<tr>
<td>8-1</td>
<td>+</td>
<td>+</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>3</td>
<td>++</td>
</tr>
</tbody>
</table>

*Minimum inhibitory concentration values were used; MTP: Microtiter plate; CRA: Congo Red Agar

Determination of biofilm formation in CRA

Activated *S. epidermidis* cultures in TSB were inoculated into petri dish containing CRA and the plates were incubated at 37 °C for 24 hours. The morphological appearance of the developing colonies at the end of the incubation period was examined. It was evaluated that the black colonies were positive; the pinkish red colonies which did not change color were negative[^1].

Determining the antibiotic sensitivity

Antibiotic resistance status of the 42 *S. epidermidis* strains was investigated using the Kirby-Bauer disk diffusion method and the Mueller Hinton agar (Merck, Turkey) strain in accordance with the recommendations of the Clinical and Laboratory Standards Institute (CLSI)[^2]. In susceptibility tests, cefoxitin (30 μg), ciprofloxacin (5 μg), gentamicin (10 μg), lomefloxacin (10 μg), ceftazidime (30 μg), cefuroxime (30 μg),...
amikacin Moxifloxacin (5μg) antibiotic discs (Bioanalyse, Turkey) were used. Minimum inhibitory concentration (MIC) values of vancomycin (Sigma-Aldrich, Turkey) were determined by microdilution broth method according to CLSI standards. MIC values were interpreted as ≤4: sensitive, ≥32: resistant.

Isolates that were resistant to three or more antibiotics were described as multidrug resistant isolates.

**Scanning Electron Microscopy**

Bacterial adhesion was examined by scanning electron microscopy and by making some changes according to Okajima et al[15]. *S. epidermidis* isolates were incubated in TSB containing 2% glucose at 37 °C for 24 hours. Subsequently, the developing culture was diluted 1:100 and placed in 12 wells of polystyrene plaques. After incubation at 37 °C for 24 hours, the wells were drained and washed three times with sterile PBS. Plates were fixed with 2.5% glutaraldehyde in 0.2M sodium cacodylate buffer (pH 7.2) followed by post-fixation with 1% OsO₄. Washing was repeated 2 - 3 times with cacodylate buffer. Dehydration with alcohol was performed. After the alcohol series, they were immediately dried in the Critical Point Dryer. The samples were then coated with gold for 1 minute at 40 mA and examined by scanning electron microscopy.

**Statistical analysis**

SPSS 22 (IBM) computer program was used for statistical analysis. Fisher’s exact probability test and Pearson’s chi-square test were used to compare the MTP and CRA methods with each other and with the absence of ica gene loci. Multinominal regression analysis was performed on multidrug resistance with the MTP and CRA method and biofilm positivity and icaA gene locus positivity. In the statistical tests, p-value was considered to be significant below 0.05.

**RESULTS**

In our study, *S. epidermidis* isolates isolated from 42 ocular surfaces were evaluated in terms of biofilm formation by isolate using the MTP (Figure 2) and CRA (Figure 3) methods. The biofilm formation status of the isolates obtained in the test is given in Table 2. Thirty-three isolates (21.2%), which were determined to produce biofilm by the CRA method did not produce biofilm by the MTP method. Of the 28 isolates identified as biofilm by the MTP method, no biofilm was detected in 2 of them (7.1%) by the CRA method. This difference was statistically significant (p = 0.003, Fisher’s exact test). It was found that nine isolates (21.4%) produced strong biofilm with both MTP and CRA methods. Scanning electron microscopy also revealed a three-dimensional biofilm structure in the biofilm-positive isolates after twenty-four hours of incubation. It was found that there were unoccupied cells on the surface of the non-biofilm isolates (Figure 4A). It was observed that the bacteria were surrounded by gelatinous material (Figure 4B).

<table>
<thead>
<tr>
<th>Method</th>
<th>Biofilm</th>
<th>MTP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>CRA</td>
<td>26</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>14</td>
<td>42</td>
</tr>
</tbody>
</table>

MTP: microtiter plate; CRA: congo red agar

While one of the negative isolates did not form a biofilm, four of them produced a weaker biofilm and one of them a strong one (Table 1). In the case of isolates that were negative for icaA and negative for icaD, while a weak biofilm formation was detected by the MTP method, strong biofilm formation was detected by the CRA method. It was observed that strong biofilm formation occurred in both methods, in the case of icaA, icaD and bap positive isolates. Thirteen (30.95%) and seven (16.67%) of the isolates

![Fig 2: Biofilm formation in micro-titrate plaque](image)

![Fig 3: Determination of biofilm production by CRA method. A. biofilm negative, B. Mild biofilm, C. Strong biofilm](image)
with icaA and icaD-positive by the MTP method and the CRA method were negative, respectively (Table 1). When evaluated separately for both methods, it was found that the distribution of the isolates, which were positive and negative, was similar in terms of biofilm formation (p ≥0.05).

It was found that 20 isolates were resistant to three or more antibiotics. Thirteen (65%) of these isolates produced strong biofilm by at least one of the methods (MTP or CRA). It was found that 11 isolates were resistant to four or more antibiotics and eight of these isolates produced strong biofilm by at least one of the methods. However, it was found that 22 isolates were resistant to two antibiotics or less and six of them were strong biofilm producer isolates (p = 0.029; Fischer exact test) (Table 3). When we look at antibiotic resistance, it was found that strains that form biofilms in both methods were more resistant to antibiotics. It was found that the biofilm formation by the MTP method was significant (p = 0.012; 0.051% 95 CI 0.005-0.515) when the multinominal regression test for the presence of the icaA gene locus for multidrug resistance (three and over antibiotic resistance) and biofilm development for the MTP and CRA were evaluated.

In both methods, it was observed that resistance to methicillin, ciprofloxacin and lomefloxacin in biofilm-forming strains was similar. Eighteen of the strains (42.86%) were resistant to methicillin and 13 (20.57%) to cefuroxime and lomefloxacin. The resistance of amikacin, vancomycin and gatifloxacin were similar and six (14.28%) strains presented resistance. These strains are the strains in which biofilm formation was

![Fig 4: Scanning electron microscopy photography of biofilm formation. A. Planktonic cells, B. Biofilm formation](image)

Table 3: Relation between multidrug resistance rate and biofilm formation

<table>
<thead>
<tr>
<th>Number of resistant antibiotic</th>
<th>Isolate number</th>
<th>Moderate or strong biofilm producer isolates</th>
<th>By at least one of the methods (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
<td>MTP CRA</td>
<td></td>
</tr>
<tr>
<td>2a*</td>
<td>22</td>
<td>1 6</td>
<td>6 27</td>
</tr>
<tr>
<td>3a*</td>
<td>20</td>
<td>11 7</td>
<td>6 13</td>
</tr>
<tr>
<td>4a</td>
<td>11</td>
<td>8 5</td>
<td>7 65</td>
</tr>
<tr>
<td>5a</td>
<td>8</td>
<td>7 5</td>
<td>7 88</td>
</tr>
<tr>
<td>6a</td>
<td>7</td>
<td>6 4</td>
<td>6 85</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>2 0</td>
<td>2 66</td>
</tr>
</tbody>
</table>

N: number; MTP: microtiter plate; CRA: congo red agar
*aStatistically significant difference (p value=0.029) between 3a and 2a antibiotic resistance
detected by both methods. No gentamicin resistance was detected in the strains. It was found that multiple antibiotic resistance was high in the icaA positive isolates, which was found to produce biofilms by both methods. Lomefloxacin and moxifloxacin-resistant strains produced statistically significant level of biofilms in the MTP (p = 0.049; p = 0.015; Pearson Chi-square test, respectively). No similar result was found for the CRA method.

Multiple antibiotic resistance was detected in an isolate that was icaA negative and did not produce any biofilm. It was found that the biofilm, which was negative for icaA, was positive by the MTP method and the isolate which was negative by the CRA method was resistant to three antibiotics. Two isolates that were icaA negative, but were found as positive by both methods, showed resistance only to amikacin. Resistance to six antibiotics was detected in the isolate which was negative to icaA but found to have strong biofilm by both methods.

**DISCUSSION**

Biofilm is defined as a colony formed by microorganisms that are completely different in terms of genetic structure and protein synthesis embedded in an organic exopolysaccharide matrix adhered to a living or inanimate surface and immobilized on each other, on a solid surface or an interfacial surface (Figure 1). Today, it is accepted that microorganisms are in an environment [16]. Presently, two methods (MTP and CRA) are frequently used to determine whether strains produce biofilms. Christensen *et al* [10] developed the MTP test; in this test, dark colored wells on the microtiter plate indicate strong biofilm formation, while light colored and colorless wells indicate that biofilm formation is either weak or no formation has occurred, respectively (Figure 2). Freeman *et al* described the CRA test; in this test, if the colonies are black, it is considered that biofilm formation is strong (Figures 3 A-C). Congo red is a coloring matter consisting of a combination of benzidine and naphthionic acid. The mechanism of the CRA in the formation of biofilm is not fully explained, but it shows affinity for Congo red polysaccharides. Since the biofilm is composed of the polysaccharide structure, the colonies appear dark when combined with Congo red. In the colonies that do not form biofilm, light color is seen.

In our study, it was found that 66.67% of 42 *S. epidermidis* strains isolated from the ocular surface were positive by the MTP method and 78.57% by the CRA method. Statistically, there was a significant difference between the two methods. It was found that the MTP was a more effective method in determining biofilm and determining multiple drug resistance.

Ju´arez-Verdayes *et al* [27] reported that 66% of the *S. epidermidis* isolates isolated from bacterial conjunctivitis, corneal ulcer and endophthalmitis cases formed biofilms. Cantalanotti *et al* [18] reported that 74% of the *S. epidermidis* isolates isolated from the samples using bilateral conjunctival soft contact lenses were biofilm generators. Arciola *et al* [9] found that nine of the 15 isolates of the *S. epidermidis* isolated from prosthetic infections (60%) were biofilm-positive. Unlike our findings, some researchers reported lower rate of biofilm formation by both methods. Hou *et al* [20] reported that the clinical isolates of *S. epidermidis* had a slime-positive rate of 34.38% with the CRA method and 28.13% with the MTP plaque method. Nayak *et al* [21] reported that while 42.9% of the 382 pathogenic *S. epidermidis* isolates isolated from the corneal ulcers produced slime, 24.1% of 87 *S. epidermidis* isolates which were isolated from healthy eyes also produced slime. Özgüneş *et al* [22] reported that 22% of the 50 coagulase negative isolates they isolated from clinical specimens were slime positive. Scanning electron microscopy images of the biofilm-forming and non-biofilm isolates revealed biofilm structure in bacteria surrounded by the gelatinous material around the biofilm-positive isolates (Figure 4B). The isolates that did not form biofilms were identified to have discrete cells on the surface (Figure 4A).

In a similar study, Hou *et al* [20] also came up with these types of findings. ica ADBC operon and its product PIA are responsible for biofilm formation in staphylococci. The ica ADBC operon is responsible for the synthesis of poly- N-acetyl-beta-1,6-glucosamine oligomers in the PIA formation in the intercellular adhesion portion of the biofilm formation in staphylococci. The ica genes allow for the synthesis of the ß-1-6 glycosaminoglycan chain, a polysaccharide substance in *S. epidermidis*. It was found that the icaA and icaD genes were more important in the biofilm formation of *S. epidermidis*. The task of the icaA and icaD genes is to synthesize the sugar oligomers using UDP-N-acetylglucosamine as substrate. While icaA alone exhibited low N-acetylglucosamine transferase activity, significant increase in enzyme activity in the presence of the icaD gene was observed [24].

In our study, while one of the isolates negative for icaA did not form a biofilm, four formed a weak and one a strong biofilm. While weak biofilm formation was detected by the MTP method in the isolates with icaA positive and icaD negative, strong biofilm formation was detected by the CRA method. The formation of biofilms in the icaA or icaD deficiency can be explained by the formation of different carbohydrate biofilms. It is because the biofilm forming monomers may differ. In the case of icaA, icaD and bap positive isolates, on the other hand, strong biofilm formation was observed.
in both methods. It was found that 13 (30.95%) of the icaA and icaD positive isolates were negative by the MTP method and seven (16.67%) were negative by the CRA method (Table 1). Hou et al[20] reported that eight isolates did not form biofilm despite the presence of the icaA gene. This can be explained by the fact that the presence of genetic biofilm formation capacity of the bacteria does not mean that they will always produce biofilms. While Hou et al[20] reported similar findings, Suzuki et al[25] reported that all of the isolates identified positively by the CRA method were icaA positive. On the other hand, although the isolate Duggirala et al[26] obtained from the corneal scrape was icaA gene negative, it was found that the biofilm was positive with the CRA method. These studies suggest that biofilm has a complex structure that is influenced by many factors.

Bacteria in the biofilm have antibiotic and phagocytosis resistance and have the capacity to maintain their presence. Due to the limited diffusion of antibiotics within the biofilm, different growth rates of bacteria in the biofilm and micro-environmental changes affect the effectiveness of antibiotics[27]. Biofilm infections are usually asymptomatic in the first period. Planktonic (free-form) micro-organisms that periodically detach from the biofilm when host defense resistance drops can lead to acute infection. Protective doses of antibiotics do not affect biofilm, even though they control these microorganisms[28].

In our study, it was found that methicillin, ciprofloxacin, and lomefloxacin resistance were similar in strains that formed the biofilms in both methods. It was found that 18 (42.86%) of the strains were resistant to methicillin 13 (20.57%) to cefuroxime and lomefloxacin. It was revealed that the biofilm-forming isolates had similar amikacin, vancomycin and gatifloxacin resistance, and six (14.28%) strains presented resistance. These strains are the strains in which biofilm formation is identified by both methods. Gentamicin resistance has not been detected in the strains. It was found that 18 isolates were resistant to three or more antibiotics. Ten isolates, on the other hand, it was revealed, were resistant to four or more antibiotics. It was found that 10% of these isolates produced strong biofilm by the MTP method and 8% by the CRA method. On the other hand, 7% and 5% of these isolates produced strong biofilms by the MTP and the CRA methods, respectively. When we examine the antibiotic resistance, it was found that the strains that formed biofilms in both methods were more resistant to antibiotics. Similarly, Bozkurt et al[28] reported that there was higher antibiotic resistance in slime positive strains. In contrast to our findings, in the Staphylococcus strains Yasar et al[20] isolated from the clinical specimens, they found no reduced sensitivity or resistance to glycopeptides. When antibiotic resistance of the slime-positive and negative strains was compared, the expected high resistance was not observed in the positive ones. It was reported that methicillin resistance and overall antibiotic resistance were higher in the slime negative staphylococci. Resistance to four or more antibiotics was detected in the 19.04% of the biofilm-forming isolates and 4.38% of the non-biofilm isolates. Nayak et al[21] on the other hand, reported that they found multiple antibiotic resistance in 39.6% of slime-positive isolates and 22.4% of slime-negative isolates. The microorganisms in biofilm are more resistant to antimicrobial agents in comparison to the planktonic forms. Any microorganism that is not resistant to antimicrobial agents in any way can become resistant by forming a biofilm and become sensitive again when detached from the biofilm. When we look at isolates that did not have the icaA gene available, it was found that biofilm formation was low by both methods.

CONCLUSION

It is clearly seen that biofilm formation plays an important role in the development of resistance to antibiotics in vitro. In the present study, even though it was seen that biofilm formation was more successful with the MTP method and multidrug resistance could be predicted more successfully, no one single method was 100% successful in determining the biofilm forming strain.

ACKNOWLEDGMENT

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REFERENCES


Original Article

Comparison of femoral nerve block and fascia iliaca compartment block for postoperative analgesia following total knee arthroplasty

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ABSTRACT

Objectives: To compare the analgesic efficacy of a femoral nerve block (FNB) and a fascia iliaca compartment block (FICB) in patients undergoing primary unilateral total knee arthroplasty (TKA)

Design: Prospective randomised trial

Setting: Orthopaedic operating rooms and services of Ankara Numune Education and Research Hospital, Turkey

Subjects: Sixty patients of both genders, aged 40 - 70 years, with an American Society of Anaesthesiology physical status of I, II or III undergoing primary unilateral TKA for osteoarthritis, osteonecrosis or rheumatoid arthritis

Interventions: TKA was performed under spinal anaesthesia on all patients with a 25G spinal needle and 3 ml of 0.5% bupivacaine. After surgery, the sealed envelope method was used to randomly assign patients to the FNB (Group 1, n = 30) or FICB (Group 2, n = 30) group, and blocks were performed using ultrasound guidance.

Main outcome measures: The Visual Analog Scale (VAS) from 0 to 10 points measured at 1, 2, 8, 12 and 24 hours postoperatively. Motor and sensory blocks were also evaluated.

Results: At all the measurement intervals, the VAS pain scores were higher in patients who had received FICB. At two and eight hours after surgery, patients in FICB group required additional analgesics at a significantly higher rate than those in the FNB group (p<0.05). The time to ambulation was longer in patients in the FNB group.

Conclusion: In our study, both methods were found to be efficacious in providing satisfactory postoperative analgesia. However, patients who had FICB mobilised earlier and required earlier analgesic administration compared to the FNB group.

KEY WORDS: fascia iliaca compartment block, femoral nerve block, postoperative analgesia, total knee arthroplasty

INTRODUCTION

Total knee arthroplasty (TKA) is a common surgical procedure frequently associated with severe postoperative pain. Effective analgesia plays a vital role in faster and improved recovery. Postoperative pain relief is a vital criterion for patients undergoing major orthopaedic surgeries[1]. Adequate pain relief has a considerable role in patient recovery, enhancing functional recovery, including the timely recovery of knee mobility, and reducing postoperative morbidity. Effective pain relief results in a reduced risk of postoperative complications such as thromboembolism and hospital-acquired infections[2] by facilitating earlier mobilisation. Inadequate analgesia may lead to patient distress, suboptimal knee mobilisation and postoperative complications. These factors may delay rehabilitation and prolong hospital stay[3].

Recently, regional nerve blocks have gained popularity in TKA, as they have the advantage of being able to anaesthetise a large area while being remote from the operative field and spinal cord[4]. Peripheral neural blockade, specifically femoral nerve blockade, has been shown to provide effective analgesia following TKA[5-7]. The knee joint is innervated primarily by the femoral nerve but also receives branches of the obturator and sciatic nerves.

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Direct femoral nerve blocks (FNBs) have a recognised incidence of femoral nerve injury and the potential for injury to the femoral vessels\cite{8,9}. It has been proposed that the fascia iliaca compartment block (FICB) avoids these complications by anaesthetising the femoral nerve at a site remote from important neurovascular structures while still providing adequate analgesia\cite{10}. Ultrasound guidance for peripheral nerve blockades, which is intended to improve the block success rate, is increasingly used.

The aim of this study was to compare the analgesic efficacy of FNB and FICB in patients undergoing primary unilateral TKA.

**SUBJECTS AND METHODS**

This prospective, randomised study was approved by the Institutional Ethics Committee. The study included 60 patients of both genders, 40 - 70 years old, with an American Society of Anaesthesiology (ASA) physical status of I, II or III undergoing primary unilateral TKA for osteoarthritis, osteonecrosis or rheumatoid arthritis.

Exclusion criteria included obese patients where the block might be anatomically difficult to perform; patients undergoing bilateral TKA; patients with infection at the site of the block; patients receiving routine nonsteroidal anti-inflammatory drugs; narcotic users and those with an allergy to any of the drugs used in this study; a higher ASA physical status; neuromuscular disease; sensory disturbances of the legs; severe diabetes; heart failure (American Heart Association Classification N3); renal impairment (estimated glomerular filtration rate <60 ml.min\(^{-1}\) · 1.73 m\(^{-2}\)); liver dysfunction (Child–Pugh Classification Class B or C) or an inability to understand the Visual Analog Scale (VAS).

Informed consent was obtained from all the participants. The patients were randomly allocated using the sealed envelope method to either the FNB (Group 1, n = 30) or FICB (Group 2, n = 30) group. In the operating room, a subarachnoid block was administered to all patients under strict aseptic procedures according to local policy with a 25G spinal needle. After confirming clear cerebrospinal fluid flow, 3 ml of 0.5% bupivacaine was injected. After checking the level of the block, surgery was allowed to commence. The vital signs of the patient were monitored throughout the procedure. At the end of surgery, FNB or FICB was performed under strict aseptic conditions under ultrasound guidance by an experienced anaesthetist when the sensory block regressed to the T12 dermatome.

**FNB**

The patient was placed in the supine position, the skin was disinfected, and sterile draping was applied. A linear US probe (HFL38, 6-13MHz Logiq e, General Electric, USA) was sheathed and placed on the inguinal crest with a slight anterior tilt. The femoral artery and the nerve were identified. A 5 cm needle (21G, Locoplex, Vygon, Ecouen, France) was inserted lateral to the probe and advanced with an in-plane approach towards the femoral nerve. The needle was inserted in-plane from lateral to medial and advanced towards the lateral aspect of the femoral nerve. For all patients, 20 ml of 0.25% bupivacaine was administered to perform the ultrasound-guided FNB.

**FICB**

The patient was placed in the supine position, the skin was disinfected, and sterile draping was applied. The femoral artery and vein, femoral nerve, iliopsoas muscle, iliacus muscle and fascia iliaca were identified using a 6-13 MHz linear ultrasound transducer between the anterior-superior iliac spine and the pubic tubercle. The transducer was moved laterally until the sartorius muscle was identified. When the target injection site was determined, a 21-gauge, 10-cm needle (21G, Locoplex, Vygon, Ecouen, France) was inserted in-plane from lateral to medial at the level of the femoral crease to cross the fascia iliaca at the junction of the sartorius and iliacus muscles. As the needle passed through the fascia iliaca, the fascia was first seen to be indented by the needle. As the needle eventually pierced through the fascia, a pop could be felt, and the fascia appeared to “snap” back on the ultrasound image. After negative aspiration, 2 mL of local anesthetic was injected to confirm the proper injection plane between the fascia and the iliopsoas muscle. Two experienced operators agreed on the needle placement and on the dissemination of local anaesthetic (LA). If the injection resulted in the separation of the fascia iliaca with the LA in the medial-lateral direction from the point of injection, the block was evaluated as successful. When the medial-lateral spread of LA was not achieved with a single injection, additional injections were made.

The primary outcome measure was pain score measured at rest on a VAS from 0 to 10 points at 1, 2, 8, 12 and 24 hours postoperatively. The occurrence of postoperative complications within 48 hours after surgery (new arrhythmia, hypotension with systolic blood pressure <80 mmHg, hypoxia with SpO\(_2\) <95%, nausea, vomiting, dizziness, itching, numbness) were recorded and investigated. If nausea or vomiting occurred after surgery, 10 mg metoclopramide was injected intravenously. Patients were instructed to press a call button when they felt postoperative pain, and the pain onset time was recorded. To investigate the duration of the motor nerve paralysis associated with the anaesthesia or nerve block, the time required for the patient to perform plantar flexion or
dorsiflexion of the ankle after surgery was recorded. Patient satisfaction with postoperative analgesia was evaluated by the patients on the VAS 48 hours postoperatively. All evaluations were performed with both subjects and observers blinded to the method of analgesia. All complications were recorded. Prior to discharge, the patients were asked to assess their satisfaction with their anaesthetic experience on a four-point categorical scale (1 = outstanding; 2 = very good; 3 = satisfactory; 4 = unsatisfactory).

Statistical analysis
Analysis of the study data was made using SPSS 19.0 statistics software. Descriptive statistical methods (number, percentage, mean and standard deviation) were used in the evaluation of the qualitative data; and the Pearson chi-square test in comparisons of the qualitative data. Conformity of the data to normal distribution was tested with the Kolmogorov-Smirnov test. In the evaluation of quantitative data showing normal distribution, the independent samples t-test was used. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS
Table 1 shows that there was no statistically significant difference between the groups in terms of demographic parameters ($p > 0.05$).

### Table 1: Comparison of demographic values

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Femoral (n = 30)</th>
<th>Fascia Iliaca (n = 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.080</td>
</tr>
<tr>
<td>Male</td>
<td>8 (26.7)</td>
<td>2 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22 (73.3)</td>
<td>28 (93.3)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65.0 ± 9.2</td>
<td>63.9 ± 7.4</td>
<td>0.611</td>
</tr>
<tr>
<td>Height</td>
<td>161.3 ± 9.3</td>
<td>159.2 ± 5.6</td>
<td>0.295</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86.0 ± 14.3</td>
<td>81.5 ± 11.3</td>
<td>0.185</td>
</tr>
<tr>
<td>BMI</td>
<td>33.3 ± 6.2</td>
<td>32.2 ± 4.3</td>
<td>0.430</td>
</tr>
<tr>
<td>Operating time</td>
<td>98.8 ± 19.0</td>
<td>96.5 ± 21.1</td>
<td>0.654</td>
</tr>
<tr>
<td>ASA II</td>
<td>26 (86.7)</td>
<td>27 (90.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>III</td>
<td>4 (13.3)</td>
<td>3 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Blood loss</td>
<td>965.0 ± 208.9</td>
<td>918.3 ± 179.8</td>
<td>0.358</td>
</tr>
</tbody>
</table>

BMI: body mass index; ASA: American Society of Anesthesiologists

A statistically significant difference was found between the groups with regards to the VAS pain scores at the 2nd, 8th, 12th and 24th hours after surgery (Table 2; $p < 0.05$). At all the measurement intervals, the VAS pain scores of patients were higher in the FICB group than in the FNB group. No statistically significant differences were found between groups with respect to the VAS pain scores upon recovery and at the 1st hour ($p > 0.05$).

Table 3 shows that a statistically significant difference was determined between the groups in ambulation time ($p < 0.05$). The time to ambulation was longer in the patients who had FNB. No statistically significant difference was determined between the groups with respect to satisfaction, as seen in Table 4 ($p > 0.05$).

### Table 2: Comparison of VAS between the groups

<table>
<thead>
<tr>
<th>VAS</th>
<th>Femoral (n = 30)</th>
<th>Fascia Iliaca (n = 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>1.3 ± 2.4</td>
<td>2.2 ± 2.8</td>
<td>0.155</td>
</tr>
<tr>
<td>1st hour</td>
<td>2.0 ± 2.5</td>
<td>2.6 ± 2.6</td>
<td>0.396</td>
</tr>
<tr>
<td>2nd hour</td>
<td>2.2 ± 2.2</td>
<td>3.4 ± 2.4</td>
<td>0.037</td>
</tr>
<tr>
<td>8th hour</td>
<td>2.9 ± 2.1</td>
<td>4.7 ± 1.9</td>
<td>0.001</td>
</tr>
<tr>
<td>12th hour</td>
<td>2.6 ± 2.0</td>
<td>3.9 ± 2.2</td>
<td>0.020</td>
</tr>
<tr>
<td>24th hour</td>
<td>2.2 ± 2.1</td>
<td>3.5 ± 2.3</td>
<td>0.019</td>
</tr>
</tbody>
</table>

VAS: visual analog scale

### Table 3: Comparison of ambulation time of the patients between the groups

<table>
<thead>
<tr>
<th>Ambulation time</th>
<th>Femoral (n = 30)</th>
<th>Fascia Iliaca (n = 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st hour</td>
<td>44.1 ± 7.0</td>
<td>39.8 ± 9.4</td>
<td>0.028</td>
</tr>
</tbody>
</table>

### Table 4: Comparison of patient and surgeon satisfaction between the groups

<table>
<thead>
<tr>
<th>Evaluation of Satisfaction</th>
<th>Femoral (n = 30)</th>
<th>Fascia Iliaca (n = 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient satisfaction</td>
<td></td>
<td></td>
<td>0.501</td>
</tr>
<tr>
<td>Good</td>
<td>24 80.0</td>
<td>20 66.7</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>4 13.3</td>
<td>7 23.3</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>2 6.7</td>
<td>3 10.0</td>
<td></td>
</tr>
<tr>
<td>Surgeon Satisfaction</td>
<td></td>
<td></td>
<td>0.428</td>
</tr>
<tr>
<td>Good</td>
<td>24 80.0</td>
<td>20 66.7</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>4 13.3</td>
<td>8 26.7</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>2 6.7</td>
<td>2 6.7</td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

The time to ambulation was longer in the patients in the FNB group. At all the measurement times, the VAS pain scores of patients with FICB were higher than those of patients with FNB. In the sensory and motor examinations at all the measurement intervals where a difference was found, the values of the patients with FNB were higher. Analgesic requirements for breakthrough pain were higher in the FICB group.

In our study, demand for additional postoperative analgesia in patients treated by femoral block was less in the FNB group, but the time to ambulation and recovery from the motor and sensory blocks was longer than that in the FICB group.

TKA is one of the most frequently performed major orthopaedic surgical procedures. The majority of the patients suffer from severe postoperative pain if not adequately addressed. To ensure a successful outcome, postoperative pain control is one of the most important factors. Effective postoperative analgesia increases patient satisfaction, facilitates rehabilitation and shortens hospital stay.

Among the various postoperative analgesic techniques in practice to provide effective analgesia following TKA, central and/or peripheral nerve blocks are extremely efficacious. A central neuraxial block provides effective analgesia. The femoral nerve, together with contributions from the sciatic and obturator nerves at the posterior and medial aspects respectively, provides sensory innervation of the knee. These are the three nerves targeted by peripheral nerve block techniques for major knee surgery.

In accordance with the sensory innervation, lumbar plexus and sciatic block will provide effective postoperative analgesia for TKA. However, blocking the plexus and sciatic nerve is a relatively difficult technique, requiring expertise, difficulty in positioning and the potential for complications from use of high doses of local anaesthesia. Combined lumbar plexus and sciatic nerve block can lead to prolonged motor block with delayed mobilisation. Several studies have shown that despite performing a femoral block below the inguinal, it is often associated with blockade of the obturator nerve.

Although the obturator nerve is far more consistently involved with lumbar plexus blocks than with either infra-inguinal technique, it is not clear that obturator block translates into improved patient recovery after TKA. Magnetic resonance imaging studies have suggested that the local anesthetic solution predominantly spreads caudally after ‘3-in-1’ block using a peripheral nerve stimulator, blocking the femoral and lateral femoral cutaneous nerves and the anterior branch of the obturator nerve, although there is some evidence that the latter nerves are more reliably blocked with the more lateral, blind, ‘double-pop’ FICB.

CONCLUSION

In our study, both methods were found to be successful in providing effective postoperative analgesia. However, ambulation in the FICB group occurred earlier than in the FNB group and was associated with faster analgesic needs. In summary, both methods can be performed to provide equally effective analgesia for patients undergoing TKA with comparable safety margins. We found no significant
differences between the two techniques with regard to operability, analgesic effect, and complications in patients undergoing TKA.

REFERENCES

ORIGINAL ARTICLE

Influenza vaccine: Immunization rates, knowledge and attitudes of healthcare workers in Jordan

Lana Alhalaseh, Nada Yasein
Department of Family and Community Medicine, School of Medicine, University of Jordan, Amman, Jordan

Kuwait Medical Journal 2020; 52 (2): 156 - 163

ABSTRACT

Objectives: To determine the rate of influenza vaccination among Jordanian healthcare workers (HCWs) and to study the factors affecting these rates, including their knowledge and attitudes toward influenza infection and immunization.

Design: Cross-sectional study

Setting: Jordan University Hospital, a university-affiliated academic center

Subjects: A convenience sample of 744 HCWs recruited after the 2015/2016 influenza season. They included 322 physicians, 156 other medical staff (nurses, pharmacists, technicians, etc.), and 266 non-medical hospital staff.

Intervention: A personal interview of HCWs by trained research assistants, using a validated questionnaire

Main outcome measures: Demographic characteristics, vaccination rates, knowledge and attitudes of participants, and perceived barriers to vaccination were analyzed.

Results: The overall one-year immunization rate was 30.8% (95% CI: 27.5% - 34.2%) with no significant differences across different job categories. Vaccinated participants achieved a higher mean knowledge score (±SD) compared to their unvaccinated counterparts (5.86 ± 1.15 vs 5.32 ± 1.38 out of 7; p <0.001). The majority of HCWs knew about the importance of receiving the influenza vaccine to protect themselves (89%) and their patients (83%). They cited their job as HCWs and direct contact with severely ill patients as the main reasons for getting vaccinated. The most common barrier to getting vaccinated was having a “strong immune system”.

Conclusions: This is the first study in Jordan addressing influenza vaccine among HCWs. It is found that despite having sufficient knowledge on influenza infection and vaccination, and the availability of free vaccine, influenza vaccine coverage remains low among HCWs due to inconsistencies between knowledge and practice.

KEY WORDS: attitude, healthcare workers, immunization rate, influenza vaccine, knowledge

INTRODUCTION

Influenza is a highly contagious upper respiratory tract disease with high rates of morbidity and mortality, causing up to 500,000 deaths per year worldwide, especially among high-risk groups such as the elderly, immunocompromised, and critically ill patients in healthcare settings\[1\]. The influenza vaccine has been reported to prevent influenza-related respiratory tract infection, pneumonia, hospitalizations, and mortality by 56%, 53%, 50%, and 68%, respectively\[2\].

Multiple studies have shown that healthcare workers (HCWs), i.e., persons who provide services, work, volunteer, or train in a healthcare setting, are at increased risk of contracting influenza, and when infected, they can transmit it to their vulnerable patients\[3\]. Annual vaccination has been shown to decrease the incidence of influenza infection among HCWs and their patients\[4,5\]. The World Health Organization, along with other major healthcare organizations worldwide, recommend annual influenza vaccination for all HCWs\[3,6-8\]. Notably, vaccination of 80% of HCWs may be necessary to achieve herd immunity\[8,10\]. Despite these longstanding recommendations, the overall rate of influenza vaccination among HCWs remains below the recommended targets throughout pandemic and non-pandemic influenza seasons.

Barriers to immunization range from fear of needles to misconceptions about the influenza vaccine\[11,12\]. Extensive studies regarding influenza vaccination...
among HCWs have been conducted in Western countries, whereas only a few studies have been conducted in Middle Eastern countries, including Saudi Arabia, Oman, Emirates, Kuwait, Turkey, and Lebanon\cite{13-18}. In Jordan, only two studies have been conducted that included the general population and did not specifically target HCWs\cite{19,20}.

This study aimed to determine: (1) the rate of voluntary immunization with the influenza vaccine among HCWs at Jordan University Hospital; (2) the knowledge and attitudes of HCWs regarding the benefits and risks of influenza vaccination; (3) the reasons identified by HCWs for electing or declining immunization; and (4) the appropriate policies to promote acceptable vaccine use.

SUBJECTS AND METHODS
Study design and participants
This cross-sectional study was carried out at Jordan University Hospital, a 550-bed university-affiliated teaching hospital and a tertiary referral center with 2500 employees including, among other staff, 630 physicians, 731 nurses, and 64 pharmacists\cite{21}. Four research assistants, trained by the principal investigator to collect the data through personal interviews, were available during the working hours of the months of March and April, 2016. The hospital floors were divided among the research assistants to prevent duplication of information. The sample size necessary to reach the study objectives was estimated considering a type one error of 0.05, a confidence level of 0.95, a 33% vaccination rate based on our pilot study, and a 0.05 precision level. This showed that a minimum of 340 workers would need to be surveyed. Given that reports suggest a 30% response rate to surveys, it was considered necessary to approach 1500 employees\cite{22}. Of those, 744 eligible HCWs consented to participate in the study with a response rate of 49.6%. Employees who were away during the working hours of these months, those who refused to participate, and those with a contraindication to the influenza vaccine were excluded from the study. Study participants were stratified into three categories: physicians, medical staff, and non-medical staff. The physician group included interns, residents, fellows, specialists, and consultants. The medical staff group included nurses, pharmacists, laboratory and radiology technicians, physiotherapists, and occupational therapists, while the non-medical staff group included accountants, porters, and housekeeping and administrative staff. The study protocol was approved by the Institutional Review Board committee at Jordan University Hospital. All collected data were treated as confidential, and the questionnaires were kept in the principal investigator’s office.

Study instrument
The questionnaire was developed after reviewing the scientific literature on the subject. In particular, the questionnaire was based on that used in the study by Khazaipour et al\cite{23}. The questions were modified by the principal investigator to satisfy the study objectives, and they were tested for validity by three family practice consultants on three separate occasions. Each time, minor changes were made in the layout and the Arabic phrasing of the questions to ensure better understanding. A pilot study was conducted on 50 participants who were not included in the main study. The overall internal reliability (Cronbach’s alpha) was measured at $\alpha = 0.7$ and was considered acceptable.

The questionnaire had three parts. The first part included questions regarding demographic characteristics, including age, sex, marital status, smoking status, level of education, and questions regarding the frequency of availed immunization in the past three years. The second part included Likert-type questions assessing the HCWs’ knowledge of influenza infection and vaccination, including the risk and severity of influenza infection among HCWs and the efficacy of the influenza vaccine and its side effects and complications. The third part of the questionnaire assessed the attitudes of the respondents toward the vaccine in terms of reasons to get vaccinated and barriers that prevented them from getting vaccinated.

Statistical analysis
Data were analyzed using SPSS version 23 (SPSS Inc., Chicago, IL). P-values less than 0.05 were considered significant. Descriptive statistics were used to describe sample characteristics and variables of the study. All Likert-type questions were grouped into two categories: agree and disagree. The total knowledge score then was calculated by summing the total number of correct answers. It ranged between 0 and 7.

Because the data were not normally distributed (Shapiro-Wilk, $p = 0.001$), the association of demographic variables with the median knowledge score was assessed using Wilcoxon-Mann Whitney-U test for dichotomous variables (gender, marital, smoking and vaccination), whereas Kruskal-Wallis test was used for the polychotomous variables (age groups, levels of education, and job groups). While the Mann-Whitney-U test looks for significance in the difference between medians, we have presented means instead of medians because the knowledge score had only seven whole numbers. Thus, the medians for even significantly different groups were often the same. Presenting the means provides more information, in this case, than presenting the medians. On the other hand, studying the association between vaccination status in relation to the following variables: demographic variables,
item-specific knowledge questions, reasons to get vaccinated and barriers to vaccination, was performed using cross-tabulation, where Chi square test was reported for dichotomous variables and Chi square for linear trend was used for polychotomous variables. When the results of the analyses using the above-mentioned tests showed differences, pair-wise post-hoc comparisons were performed using the Bonferroni procedure.

**RESULTS**

**Subject characteristics**

A total of 744 HCWs included 43% physicians, 21% medical staff, and 36% non-medical staff agreed to participate in the study. Of those, 59% were men and 41% were women (Table 1).

**Vaccination uptake**

A total of 386 (52%, 95% confidence interval (CI): 48.5% - 55.5%) HCWs had availed of the influenza vaccine in the previous three years, whereas 229 (30.8%, 95% CI: 27.5% - 34.5%) availed of the vaccine during the 2015/2016 influenza season.

There were no significant differences in vaccination rates across different job categories (p = 0.874), age groups (p = 0.274), or levels of education (p = 0.850), as shown in Table 1.

**Knowledge and attitudes of participants**

The mean (±SD) knowledge score was 5.49 ± 1.34 out of 7. Vaccinated participants achieved significantly higher mean knowledge scores compared to unvaccinated counterparts (5.86 ± 1.15 vs. 5.32 ± 1.38, p < 0.001). No significant differences were noted in the mean knowledge scores between the physician and medical staff groups (p = 1.00), but both groups scored significantly higher than the non-medical staff group (p <0.001 and p = 0.002, respectively). Moreover, mean knowledge scores were significantly higher in females, unmarried and non-smokers (Table 1).

### Table 1: Demographic characteristics of the study participants according to knowledge score and vaccination status

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Subgroup</th>
<th>Mean knowledge score (± SD)</th>
<th>p-value</th>
<th>Proportion vaccinated n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>270 (36)</td>
<td>5.60 (1.30)</td>
<td>0.089</td>
<td>73 (27.0)</td>
<td>0.274</td>
</tr>
<tr>
<td>30-39</td>
<td>224 (30)</td>
<td>5.52 (1.34)</td>
<td></td>
<td>75 (33.5)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>180 (24)</td>
<td>5.33 (1.41)</td>
<td></td>
<td>60 (33.3)</td>
<td></td>
</tr>
<tr>
<td>+50</td>
<td>70 (10)</td>
<td>5.31 (1.23)</td>
<td></td>
<td>21 (30.0)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>442 (59.4)</td>
<td>5.38 (1.35)</td>
<td>0.003*</td>
<td>136 (30.8)</td>
<td>0.760</td>
</tr>
<tr>
<td>Female</td>
<td>302 (40.6)</td>
<td>5.64 (1.32)</td>
<td></td>
<td>89 (29.5)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>544 (73)</td>
<td>5.40 (1.40)</td>
<td>0.013*</td>
<td>182 (33.5)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Single/other</td>
<td>200 (27)</td>
<td>5.72 (1.12)</td>
<td></td>
<td>47 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
<td></td>
<td>0.055</td>
</tr>
<tr>
<td>Yes</td>
<td>217 (29)</td>
<td>5.17 (1.40)</td>
<td></td>
<td>77 (35.5)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>527 (71)</td>
<td>5.61 (1.29)</td>
<td></td>
<td>151 (28.7)</td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School</td>
<td>97 (13)</td>
<td>5.24 (1.24)</td>
<td>0.001*</td>
<td>31 (32.0)</td>
<td>0.850</td>
</tr>
<tr>
<td>College</td>
<td>140 (18.8)</td>
<td>5.17 (1.50)</td>
<td></td>
<td>45 (32.1)</td>
<td></td>
</tr>
<tr>
<td>Bachelor degree</td>
<td>304 (40.9)</td>
<td>5.62 (1.27)</td>
<td></td>
<td>84 (27.6)</td>
<td></td>
</tr>
<tr>
<td>Higher education</td>
<td>203 (27.3)</td>
<td>5.63 (1.33)</td>
<td></td>
<td>69 (34.0)</td>
<td></td>
</tr>
<tr>
<td>Job category</td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
<td></td>
<td>0.874</td>
</tr>
<tr>
<td>Physicians</td>
<td>322 (43.3)</td>
<td>5.68 (1.23)</td>
<td></td>
<td>95 (29.5)</td>
<td></td>
</tr>
<tr>
<td>Medical house staff</td>
<td>156 (20.9)</td>
<td>5.62 (1.30)</td>
<td></td>
<td>58 (37.2)</td>
<td></td>
</tr>
<tr>
<td>Non-medical staff</td>
<td>266 (35.8)</td>
<td>5.17 (1.43)</td>
<td></td>
<td>76 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Vaccinated in 2015-2016</td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>229 (30.8)</td>
<td>5.86 (1.15)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No</td>
<td>515 (69.2)</td>
<td>5.32 (1.38)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* p-value <0.05
to the increased risk of contracting influenza among HCWs than among the medical staff group (p = 0.0001) who, in turn, was more likely to agree than the non-medical group (p = 0.02). In the question about the prevalence of systemic side effects, the medical staff group were more likely to believe that side effects of the vaccine were very common, compared to the physician (p = 0.002) and non-medical staff groups (p = 0.03).

Figure 1 shows the participants’ attitudes towards the influenza vaccine. The most common reasons to avail of the vaccine were: direct contact with critically-ill patients (88.2%), and working as a HCW (83.6%). Compared to unvaccinated participants, vaccinated counterparts were significantly more likely to avail of the vaccine due to the following reasons: working as a HCW (p = 0.0001), being in direct contact with critically ill patients (p = 0.0001), recommended in the guidelines (p = 0.001), a personal history of a bad flu (p = 0.0001), prevention of absenteeism from work (p = 0.001), and the presence of reported death due to influenza (p = 0.0004).

Physicians were more likely, compared to non-medical staff, to list “working as a health care professional” as a reason to avail of the vaccine (p = 0.007).

### Perceived barriers to vaccination

Barriers to getting vaccinated are detailed in Table 3. The most common barriers to availing the influenza vaccine were having a “strong immune system” and “infrequently contracting the flu”. Compared with the physician group, medical staff were more likely to elicit both barriers as reasons for declining vaccination (p <0.0001 and 0.01; respectively). They were also more likely to enlist their concern about the side effects of the vaccine (p = 0.007) as a barrier to vaccination.

Around 55% of the participants considered vaccine availability a barrier to vaccination, especially

### Table 2: Basic knowledge of influenza infection and influenza vaccine among healthcare workers according to vaccination status

<table>
<thead>
<tr>
<th>Knowledge questions</th>
<th>Correct answers Total (%)</th>
<th>Proportion vaccinated n (%)</th>
<th>Proportion unvaccinated n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza and its complications are very serious among high-risk patients</td>
<td>658 (88.4)</td>
<td>214 (93.4)</td>
<td>444 (86.2)</td>
<td>0.004*</td>
</tr>
<tr>
<td>HCWs’ risk of contracting influenza is higher than the general population’s</td>
<td>610 (82.0)</td>
<td>202 (88.2)</td>
<td>408 (79.2)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Influenza vaccine is effective in preventing seasonal influenza infection</td>
<td>686 (92.2)</td>
<td>217 (94.8)</td>
<td>469 (91.1)</td>
<td>0.083</td>
</tr>
<tr>
<td>Influenza vaccine is effective in preventing the 2009 H1N1 infection</td>
<td>336 (45.2)</td>
<td>119 (52.0)</td>
<td>217 (42.1)</td>
<td>0.013*</td>
</tr>
<tr>
<td>HCWs should receive the influenza vaccine to protect themselves</td>
<td>663 (89.1)</td>
<td>220 (96.1)</td>
<td>443 (86.0)</td>
<td>0.001*</td>
</tr>
<tr>
<td>HCWs should receive the influenza vaccine to protect their patients</td>
<td>616 (82.8)</td>
<td>203 (88.6)</td>
<td>413 (80.2)</td>
<td>0.009*</td>
</tr>
<tr>
<td>The percentage of vaccine recipients experiencing systemic side effects is uncommon</td>
<td>512 (68.8)</td>
<td>168 (73.4)</td>
<td>344 (66.8)</td>
<td>0.074*</td>
</tr>
</tbody>
</table>

* p-value <0.05

---

Fig 1: Reasons to avail of the vaccine
vaccination rate remained low (30.8%) among all Arabia (50.7%), whereas similar rates were found in Saudi Oman (46.4%), Kuwait (67.2%), Iran (67%) and Spain (72%)

lower rates have been reported in the USA (72%),

higher rates have been reported in the USA (72%),

and, at the same time, 58% elicited their concern about these side effects as a barrier to vaccination. This discrepancy could be due to a perceived seriousness of these “uncommon” side effects. It also suggests that although education on the influenza vaccine is important, it does not always result in vaccination[29]. To further support this notion, note that significantly more of those who had been vaccinated gave a correct answer to almost all the knowledge questions compared to those who had not been vaccinated. A reverse causality could be present in this association, by which those who are vaccinated receive education about the vaccine at the time of vaccination. This shows the need to have other measures undertaken to promote vaccine uptake in an organized institutional system, such as providing modeling and support for influenza vaccination by institutional leaders.

Moreover, concerns regarding vaccine efficacy were prevalent in only 22% of our cohort, particularly among unvaccinated HCWs, who addressed this concern as a barrier that impeded vaccination. Specifically, almost 55% of the HCWs believed that the seasonal influenza vaccine distributed during the 2015/2016 season did not have a protective benefit against the 2009 H1N1 strain. This knowledge gap is particularly alarming considering the high rate of influenza A (H1N1)pdm09 in Jordan in 2009, and knowing that the (H1N1)pdm09 virus continues to circulate as a seasonal influenza virus that causes illness and death worldwide every year[38]. These hesitant attitudes toward vaccine safety and efficacy are also corroborated by other studies worldwide[4,25,32,39] and it has been shown that addressing such issues, rather than focusing on the vaccine rejection rates, will help in understanding the main reasons behind HCWs

### Table 3: Barriers to availing of the influenza vaccine as listed by vaccine recipients and vaccine non-recipients

<table>
<thead>
<tr>
<th>Most commonly listed barriers</th>
<th>Total n (%)</th>
<th>Proportion vaccinated n (%)</th>
<th>Proportion unvaccinated n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Having a “strong immune system”</td>
<td>572 (76.9)</td>
<td>175 (76.4)</td>
<td>397 (77.8)</td>
<td>0.669</td>
</tr>
<tr>
<td>Do not usually contract influenza</td>
<td>564 (75.8)</td>
<td>166 (73.1)</td>
<td>398 (78.0)</td>
<td>0.146</td>
</tr>
<tr>
<td>Concern about side effects</td>
<td>429 (57.7)</td>
<td>127 (55.9)</td>
<td>302 (58.9)</td>
<td>0.458</td>
</tr>
<tr>
<td>Availability of vaccine</td>
<td>407 (54.7)</td>
<td>139 (60.7)</td>
<td>268 (52.3)</td>
<td>0.035*</td>
</tr>
<tr>
<td>Cost</td>
<td>283 (38.0)</td>
<td>84 (36.7)</td>
<td>199 (38.7)</td>
<td>0.598</td>
</tr>
<tr>
<td>Don’t like needles</td>
<td>255 (34.3)</td>
<td>77 (33.9)</td>
<td>178 (34.8)</td>
<td>0.810</td>
</tr>
<tr>
<td>Lack of benefit</td>
<td>166 (22.3)</td>
<td>33 (14.5)</td>
<td>133 (25.9)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

* p-value <0.05

vaccinated HCWs (p = 0.035). Interestingly, physicians were more likely to elicit this factor as a barrier compared to the medical staff (p = 0.048).

Regarding the cost of the vaccine as a barrier to vaccination, there was no statistically significant difference between vaccine recipients and non-recipients. Noteworthy, 48.2% (n=110) of the vaccinated HCWs were vaccinated for free through the hospital’s Infection Prevention and Control Department, whose personnel administer the vaccine to HCWs for free throughout the flu season. Another 40.4% (n = 92) had the cost partially covered by their medical insurance. Only 11.4% (n = 26) of the employees paid for the vaccine themselves.

**DISCUSSION**

Influenza vaccination of HCWs is an evidence-based intervention that has been suggested as an effective strategy to lower the rates of nosocomial transmission of influenza to patients at high risk of complications[24]. This paper offers the first insight into HCWs’ knowledge and attitude toward the influenza vaccine in Jordan.

The results of this study show that the total vaccination rate remained low (30.8%) among all categories of HCWs during the 2015/2016 influenza season. The rate of HCWs availing of the influenza vaccine varies among different countries, ranging from 7.5% to 63%[25]. Compared with that in Jordan, higher rates have been reported in the USA (72%), Oman (46.4%), Kuwait (67.2%), Iran (67%) and Spain (50.7%), whereas similar rates were found in Saudi Arabia[9,13-15,22,23]. Meanwhile, lower rates were noted in the UAE (24.7%), Qatar (19.4%), Turkey (12.7–23%), Italy (16.7–24%), Israel (16.4%), and Greece (17%)[15,17,26-31].

The low rates of vaccination in our institution might be explained by several reasons related to knowledge and attitude gaps that were apparently affecting our HCWs’ decision to decline the vaccine, despite having a good total knowledge score and the availability of free vaccine through the hospital. The most common misconceptions seen in our study were a perceived “strong” immune system and the rarity of contracting the influenza infection. Similar knowledge gaps have also been illustrated in different studies[2,32-36]. Indeed, HCWs were found to have altruistic views of vaccination where they tend not to consider themselves as needing vaccination, seeing themselves as strong and healthy compared to their patients[37].

Other misconceptions regarding vaccine’s safety and, to a lesser extent efficacy, were also seen in our study. For example, 69% knew that side effects of the vaccine are uncommon, and, at the same time, 58% elicited their concern about these side effects as a barrier to vaccination. This discrepancy could be due to a perceived seriousness of these “uncommon” side effects. It also suggests that although education on the influenza vaccine is important, it does not always result in vaccination[29]. To further support this notion, note that significantly more of those who had been vaccinated gave a correct answer to almost all the knowledge questions compared to those who had not been vaccinated. A reverse causality could be present in this association, by which those who are vaccinated receive education about the vaccine at the time of vaccination. This shows the need to have other measures undertaken to promote vaccine uptake in an organized institutional system, such as providing modeling and support for influenza vaccination by institutional leaders.
declining vaccination, and lead to the development of appropriate strategies to encourage vaccination and maintain optimal coverage[37].

Furthermore, availability of the vaccine was a major barrier to immunization among our HCWs, especially among physicians, while cost of the vaccine was not, despite the fact that less than half of the vaccinated employees got their vaccine for free. Research has indicated that cost and availability of the influenza vaccine are the most common barriers to influenza vaccination, especially among busy physicians; hence, providing free and accessible vaccines is the most important reason for availing the influenza vaccine[7,13,15,18,40]. In particular, the Advisory Committee on Immunization Practices has recommended measures to improve the rates of vaccination among HCWs with busy schedules, such as the use of a mobile cart to vaccinate HCWs in the workplace, and increased availability of vaccinating personnel after regular daytime working hours. Since these measures have proven effective in increasing the rates of vaccination among HCWs, they should be considered by our local policy makers[7].

As such, we propose that an effective program, carried out throughout the influenza season, to increase the rate of influenza vaccination among HCWs must: (I) provide annual targeted education addressing the knowledge gaps specific to each HCWs subgroup; (II) provide free vaccines at convenient times and locations, including the cafeteria and hallways, and during physicians’ rounds; (III) recommend that HCWs who decline the vaccination must sign declination statements; and (IV) implement surveillance measures to estimate the impact of local vaccination programs.

The following are the strengths and limitations of this study. The study was conducted in the largest academic hospital in Jordan, serving more than 500,000 patients a year. On the other hand, the possibility of selection bias and other unknown differences between respondents and non-respondents cannot be excluded from this cross-sectional survey. However, considering that a total of 744 HCWs were recruited in this study, we believe that we have captured a wide range of opinions that may reflect real differences between vaccinated and unvaccinated HCWs.

Our findings may be of a limited generalisation because we sampled HCWs working at a single healthcare institution, and we cannot be certain these results are applicable to other groups of HCWs throughout the country.

CONCLUSION

This is the first study in Jordan that addresses the influenza vaccine uptake among healthcare workers and highlights the different factors affecting these rates in the first and largest academic institution in Jordan. The rates of influenza vaccination among Jordanian HCWs remain low despite having a good total knowledge score and the availability of free vaccine. To improve the number of HCWs receiving influenza vaccine, enforcement of knowledge and dispelling myths about the vaccine should be undertaken by physicians and decision makers. Furthermore, inconsistencies between knowledge and practice should be acted upon, and different barriers to immunization peculiar to each specific category of HCWs should be addressed in a way pertinent to that particular group of HCWs in order to improve vaccine uptake across all categories of HCWs, especially those with the closest contact with patients.

In fact, these results should not be limited to Jordan University Hospital and they should be taken into consideration by the Ministry of Health when framing policies at the national level, as the hospital serves half a million patients yearly coming from both urban and rural areas throughout the country, in addition to international patients coming from all over the Arab World, especially the neighboring countries. In addition, these results could be of particular significance to HCWs from other countries with similar risks of acquiring and transmitting infectious diseases, particularly influenza. Thus, further studies are needed at the national level to corroborate our study and help outline local and regional preventive health strategies.

ACKNOWLEDGMENTS

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REFERENCES


Original Article

Can serum NSE and S100-β protein levels predict central nervous system injury in patients with carbon dioxide retention?

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Kuwait Medical Journal 2020; 52 (2): 164 - 168

ABSTRACT

Objectives: To evaluate whether serum neuron specific enolase (NSE) or S100-β protein levels are helpful in predicting central nervous system (CNS) injury in patients with carbon dioxide (CO₂) retention

Design: A case-control study

Setting: This study was performed in the Emergency Department of a University Hospital which functions as the only tertiary center in the city.

Subjects: One hundred patients who were admitted to the emergency department and seen to have an arterial partial carbon dioxide pressure above 45 mmHg were included as the study group and 48 healthy volunteers as the control group.

Interventions: None

Main outcome measures: Possible elevations in serum NSE and/or S100-β protein levels in the study group were main outcome measures. The levels of these markers were measured using enzyme-linked immunoassay kits, and mean values of these parameters were compared between the study and the control groups.

Results: Mean NSE level was found to be 69.45 ± 36.39 ng/ml, and mean S100-β level was 160.57 ± 54.05 pg/ml in the study group. Mean NSE and S100-β levels of the control group were 30.99 ± 20.04 ng/ml and 129.31 ± 415.17 pg/ml, respectively. Mean NSE levels differed significantly between the study and control groups; however, mean S100-β levels did not.

Conclusions: The results of the present study suggest that NSE can be used to predict CNS injury in patients with CO₂ retention, but S100-β protein cannot. New studies including larger number of patients are needed to obtain more accurate results on this topic.

KEY WORDS: carbon dioxide retention, central nervous system injury, hypercapnia, neuron-specific enolase, S100-β

INTRODUCTION

Carbon dioxide (CO₂) retention may be defined as decreased removal of CO₂ through the lung due to some pathologic conditions[1]. CO₂ retention may be seen in acute or chronic diseases of various organ systems, of which the respiratory system is the most significant one[2,3]. It was shown that CO₂ retention together with hypoxia, which is generally present concurrently, leads to central nervous system (CNS) injury. This effect of hypercapnia is thought to be associated with enhanced apoptosis secondary to mitochondrial dysfunction, increased generation of reactive oxygen species and resultant higher level of oxidative stress[4-6]. Some biomarkers which can help physicians to predict CNS injury in patients with CO₂ retention are needed. Several proteins like glial fibrillary astrocytic protein, N-methyl-D-aspartate receptor, nucleoside diphosphate kinase A and S100-β have been studied to predict neuronal injury in patients with hemorrhagic stroke, and neuron-specific enolase (NSE) is considered to be a biochemical marker of brain injury in cerebral infarction[7,8]. NSE and S100-β protein are two of the potentially useful biomarkers which may have some role in estimation of CNS injury related to hypercapnia. NSE is an enzyme dimer which serves as a gamma-gamma enolase in glucose metabolism of the brain[9]. It has been shown that NSE levels increase in the case of ischemic stroke,
meningoencephalitis, status epilepticus and head trauma. Besides, serum NSE levels were found to be correlated with the level of brain injury\cite{10}. S100-β is an intracellular calcium-binding protein dimer\cite{11}. The level of this biomarker was shown to be elevated in patients with meningoencephalitis and head trauma, and CNS tumors like glioma, melanoma and schwannoma\cite{12,13}. However, as far as we know, there are no studies in the literature evaluating usefulness of the serum levels of either NSE or S100-β in patients with CO₂ retention. Hence, we aimed in the current study to investigate whether serum levels of these two markers can be used to predict CNS injury associated with hypercapnia.

**SUBJECTS AND METHODS**

One hundred patients having an arterial partial CO₂ pressure (PaCO₂) above 45 mmHg on admission to the emergency department were included in this case-control study as the study group, and 48 healthy volunteers were included as the control group. All subjects were above 18 years of age. Local Clinical Trials Ethics Committee approved the study. All participants gave informed consent for the study. Demographic features including age, sex and past medical history; Glasgow coma scale score (GCS) on admission and arterial blood gas analysis parameters including PaCO₂, pH, partial oxygen pressure and oxygen saturation were recorded for each patient.

Patients included in the study group were divided into three subgroups according to their PaCO₂ levels:

- **Group I:** 45 mmHg < PaCO₂ < 60 mmHg
- **Group II:** 60 mmHg ≤ PaCO₂ < 80 mmHg
- **Group III:** 80 mmHg ≤ PaCO₂

Six ml of venous blood was taken from each patient upon seeing his/her PaCO₂ is above 45 mmHg, and also from the participants in the control group for measurement of NSE and S100-β protein levels. Blood samples were centrifuged at 4000 rpm for 10 minutes in NF 048 Microliter and Hematocrit Centrifuge Machine (Nüve Industrial Equipments Manufacturing and Trade Inc., Ankara, Turkey, 2008) after waiting for two hours, and stored at -20 °C until assayed. Enzyme-linked immunoassay kits were used in the measurement of NSE and S100-β protein levels (h-NSE ELISA for measurement of NSE levels, DiaMetra srl Unipersonale Management and Coordination: Immunodiagnostic Systems [IDS] Ltd, Perugia, Italy, production date: March 2013; and S100-β ELISA for measurement of S100-β levels, DiaMetra srl Unipersonale Management and Coordination: Immunodiagnostic Systems (IDS) Ltd, Perugia, Italy, production date: March 2013). Epoch Microplate Spectrophotometer device (BioTek Instruments Inc., Winooski, USA, 2009) was used in the measurement of NSE and S100-β protein levels, and the data was transferred to digital media by using Gen5 Data Analysis Software, which belongs to the same company.

**Statistical analysis**

The data derived from the study was analyzed using Statistical Package for the Social Science for Windows v21.0 (SPSS Inc., New York, USA). Kolmogorov-Smirnov test was used to investigate whether NSE and S100-β levels were distributed normally. Since NSE and S100-β levels were not distributed normally, the significance of the difference between the study and the control groups was investigated using Mann-Whitney U test, and the difference between the three sub-groups of the study group with Kruskal-Wallis one way analysis of variance. Possible relationships between PaCO₂, NSE, S100-β levels and GCS were evaluated using Spearman’s rho correlation. The categorical variables were evaluated using Pearson’s chi-square (Fischer’s exact chi-square) test; a p-value of <0.05 was considered to be statistically significant.

**RESULTS**

The mean age of the participants in the study group and the control group was 72.65 ± 10.48 years and 45.38 ± 12.63 years, respectively. Most of the participants were male in both the study group and the control group (62% and 62.5%, respectively). The study group and the control group were similar regarding gender distribution (p>0.05). Most of the patients included in the study group had a history of chronic obstructive pulmonary disease (67%), coronary artery disease (62.5%), hypertension (58.3%) and diabetes mellitus (56%). Demographic features of the study group and the control group are given in Table 1.

Mean NSE level was found to be 69.45 ± 36.39 ng/ml, and mean S100-β level was 160.57 ± 54.05 pg/ml.

**Table 1:** Demographic features of the study and the control groups

<table>
<thead>
<tr>
<th>Feature</th>
<th>Study Group (n = 100)</th>
<th>Control Group (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>72.65 ± 10.48 (min:45, max:96)</td>
<td>45.38 ± 12.63 (min:19, max:63)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62%</td>
<td>62.5%</td>
</tr>
<tr>
<td>Female</td>
<td>38%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>COPD</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>62.5%</td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td>58.3%</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>29.2%</td>
<td></td>
</tr>
<tr>
<td>CRF</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>14%</td>
<td></td>
</tr>
</tbody>
</table>

min: minimum; max: maximum; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; HT: hypertension; DM: diabetes mellitus; CHF: congestive heart failure; CRF: chronic renal failure; CVD: cerebrovascular disease.
ml in the study group. Mean NSE and S100-β levels of the control group were 30.99 ± 20.04 ng/ml and 129.31 ± 415.17 pg/ml, respectively. For mean NSE levels, the difference between the study group and the control group was significant (p <0.001). However, the difference between mean S100-β levels of the study and the control groups was not significant (p = 0.118, Figure 1).

![Figure 1: NSE and S100-β levels of the study group and the control group. Mean NSE levels of the study group was found to be significantly higher than that of the control group, but mean S100-β levels did not differ significantly between the groups.](image)

<table>
<thead>
<tr>
<th>Subgroups of the study group</th>
<th>NSE (ng/ml)</th>
<th>p-value</th>
<th>S100-β (pg/ml)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (min-max)</td>
<td>SEM</td>
<td>Median (min-max)</td>
<td>S.E.M.</td>
</tr>
<tr>
<td>Group I (n = 50)</td>
<td>9.23 (0.19-1390)</td>
<td>31.18</td>
<td>NS</td>
<td>0 (0-3453.08)</td>
</tr>
<tr>
<td>Group II (n = 33)</td>
<td>6.02 (0-3320)</td>
<td>100.25</td>
<td>NS</td>
<td>0 (0-2319.19)</td>
</tr>
<tr>
<td>Group III (n = 17)</td>
<td>15.73 (1.51-43.94)</td>
<td>2.86</td>
<td>NS</td>
<td>11.12 (0-3028.82)</td>
</tr>
</tbody>
</table>

Table 2: NSE and S100-β levels of subgroups of the study group

NSE: neuron specific enolase; min: minimum; max: maximum; SEM: standard error of mean; NS: no significance

DISCUSSION

CO₂ is an end-product of cellular respiration which is needed by nearly all living organisms to produce energy. Normal range of PaCO₂ in humans is 35 to 45 mmHg[14]. CO₂ retention is a result of physiopathologic processes leading to decreased removal of CO₂ through the lung. PaCO₂ level is one of the major determinants of respiratory functions regulated by various organ systems, of which CNS is the most significant one[15]. However, CNS cannot trigger an appropriate regulator response when PaCO₂ reaches extreme levels, and a cascade of harmful events begins, which eventually results in neuronal death in the CNS. Findings suggesting CNS injury like neuronal swelling, disruption of cytoplasmic organelles, signs of accelerated apoptosis and increase in water content of the cells were observed in rats exposed to a hypoxic and hyper-carbic environment[5].

Intracellular proteins pass to cerebrospinal fluid (CSF), and then to the blood stream, when CNS injury and cellular death occur. NSE and S100-β are two of the potentially useful biomarkers which have been evaluated for use in the prediction of CNS injury in such conditions. Levels of these proteins in the CNS tissue of rats exposed to chronic hypoxia and hypercapnia were found to be decreased in a study by Yu et al[6]. Although CNS injury was found to be correlated with not only NSE but also S100-β levels in that study, a relationship between CNS injury and NSE levels was only found in the current study. However, we measured serum levels of these markers, while their levels were directly measured in the CNS.
tissue in the subject study. Additionally, the study by Yu et al investigated effects of chronic hypoxia and hypercarbia on the CNS, whereas we took blood samples in the acute period and investigated short-term effects. We suggest that the difference between the findings of these two studies may be attributed to these methodological differences.

There are several studies investigating NSE and S100-β levels in various conditions \[16-20\]. There are also several studies showing that cerebral ischemia elevates NSE and S100-β levels \[17,19,21\]. NSE was found to be significantly correlated with infarct volume in patients with cerebral infarction \[21\]. It was suggested that significantly elevated levels of NSE can be demonstrated as a consequence of ischemia-induced cytoplasmic loss of NSE in CNS neurons \[21\]. Kaca-Oryńska et al \[16\] found significantly higher NSE and S100-β levels in ischemic stroke patients. The current study also showed significantly higher levels of NSE in patients with CO\(_2\) retention compared to those measured in the control group; however, a similar elevation in S100-β levels could not be demonstrated. Some possible explanations for that situation may include the following:

S100-β, which is an intracellular calcium-binding protein, needs to enter the blood stream by passing through the blood brain barrier (BBB) after passing to CSF to have a measurable increase in its serum levels. Our patients were brought to the emergency department due to a respiratory or cardiac pathology just after PaCO\(_2\) levels begin to elevate, and venous blood samples were taken a few minutes after admission. So, serum S100-β level might not have started to increase yet when the blood sample was taken. The reason for that delay may be the BBB which S100-β molecules should pass through to enter the blood stream. Our patients did not have serious inflammatory problems like meningitis, encephalitis and brain abscess which may affect permeability of BBB. Molecular weight of the biggest molecule which can directly pass BBB by membrane diffusion was found to be 7.800 daltons \[22\], whereas the molecular weight of S100-β is 21,000 daltons \[23\]. Hence, it has to use an active transport mechanism to pass the BBB, and elevation of its serum level may be delayed due to saturation of transport mechanisms, even if its concentration in CSF reaches a considerably high level. Serena et al \[24\] reported that they took blood samples approximately 6.3 hours after stroke due to delay in elevation of serum levels caused by BBB. Hardemark et al \[17\] saw a relatively slower increase in S100-β and NSE levels in CSF after middle cerebral artery occlusion (MCA) compared to that seen after trauma, and a peak was observed after 2 to 4 days in an experimental model. Besides, NSE concentration was slightly higher than S100-β level after MCA occlusion. It was seen that NSE level was above the normal value in 93.5% of stroke patients; however, the level of S100-β protein was elevated in only 63.1% of them in the study by Kaca-Oryńska et al \[16\], who took venous blood samples on the 4th day after admission. NSE levels were found to be elevated more prominently in our study, similar to the results of Hardemark et al \[17\] and Kaca-Oryńska et al \[16\].

In the present study, in which patients were divided into subgroups with respect to their PaCO\(_2\) levels, no significant correlations were found between PaCO\(_2\) values and NSE or S100-β levels of each subgroup. An increase in NSE and S100-β levels was notable as PaCO\(_2\) elevated, but this increase did not reach statistical significance. Thus, we can state that a thoroughly remarkable relationship was present between CO\(_2\) retention and both NSE and S100-β levels, but a linear correlation does not exist. Similarly, NSE and S100-β levels do not have a linear correlation; group III had the highest median NSE and S100-β levels but group I and group II had a median S100-β level of zero, which may be attributed to possible factors leading to delayed elevation of serum S100-β levels mentioned above (e.g. effect of BBB). Besides, group I had a higher median NSE than group II. This finding seems a bit strange at first glance, but there may be some explanation of this situation. When the PaCO\(_2\) values begin to rise and CNS injury ensues, the body may activate some protective mechanisms to restrict the damage. A lower median NSE level observed in group II compared to that observed in group I may occur as a result of these protective mechanisms. As it was mentioned above, the highest value of median NSE was observed in group III, which was the group with the highest PaCO\(_2\). When the protective mechanisms of the body begin to fail due to significantly elevated PaCO\(_2\) levels, a rapid increase in the development of CNS injury causing the highest NSE levels in group III may occur.

Our study has some limitations. The first is the timing of venous blood sampling. S100-β levels might be not elevated yet in some patients because blood samples were taken within a few minutes after admission. More accurate results might be obtained if blood samples were taken at a later point in time. We could not follow such a strategy because our patients did not stay in the emergency department for more than a few hours; they had been admitted to a ward, critical care unit or intensive care unit or referred to another medical facility in a few hours. The second limitation is the small number of subjects included in the study and the control groups. The third one is the presence of several co-morbid diseases each patient included in the study group had, which made it impossible to create a pure CO\(_2\) retention group.
CONCLUSION
The results of the present study suggest that NSE can be used to predict CNS injury in patients with CO₂ retention, but S100-β cannot. New studies including larger number of patients are needed to obtain more accurate results on this topic.

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REFERENCES
Original Article

Retrospective analysis of anesthetic management in the cerebral aneurysm treatment: Issues in the course of endovascular versus surgical treatment

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Kuwait Medical Journal 2020; 52 (2): 169 - 174

ABSTRACT

Objective: To compare endovascular and surgical treatments for intracranial aneurysm in terms of anesthetic management, length of stay in the intensive care unit (ICU), morbidity, and mortality

Design: Retrospective study

Setting: Interventional radiology and neurosurgery operation theatre, Ankara Numune Education and Research Hospital, Ankara, Turkey

Subjects: We included 143 patients who underwent endovascular or surgical management for intracranial aneurysms between January 2013 and December 2013.

Interventions: Information taken from anesthesiology department database records

Main outcome measures: Anesthetic agents, duration of anesthesia, controlled hypotension, invasive monitoring methods, length of stay in the post-anesthetic care unit or ICU, complications, and time to discharge were evaluated.

Results: Of all patients, 54.5% (n = 78) underwent an elective procedure and the remainder 45.5% (n = 65) had emergency treatment. In most patients with subarachnoid bleeding (n = 67), surgery was performed in the early phase (n = 36; 53.7%) rather than the late phase (n = 31; 46.3%; p < 0.001). Although there was no significance between the treatment groups in terms of the occurrence of vasospasm, hydrocephalus was more frequently present in the endovascular group than in the surgery group (p = 0.018). There was significant difference between the groups in terms of the time to discharge, the length of stay in the ICU, and the duration of anesthesia (p < 0.05). Although more complications occurred in the surgical group patients, there was no significant difference between groups in mortality.

Conclusions: In these patients, advances in endovascular techniques will enable less invasive monitoring, fewer surgical traumas and postoperative complications, and a shorter period of anesthesia.

KEYWORDS: Anesthesia, aneurysm, endovascular treatment, interventional neuroradiology, neurosurgical

INTRODUCTION

Endovascular and surgical procedures are commonly applied to treat intracranial aneurysms. The assessment of the effectiveness of these treatment modalities shows that each method has its own advantages and disadvantages, and sometimes, they may complement each other[1,2]. The advantages of surgical treatment include the elimination of bleeding risk by protecting the main vessel and its branches during clamping of the aneurysm, as well as the elimination of the balloon-like mass of the aneurysm. In addition, during surgery, blood in the subarachnoid area can be drained to reduce vasospasm and hydrocephalus. However, a disadvantage of surgical treatment is that it requires craniotomy and brain retraction. The main advantages of the endovascular technique are that it is a rapid and less invasive procedure. It is more appropriate for patients who have concomitant diseases, and provides better results for aneurysms located on the posterior side, which are difficult to reach via the surgical approach. However, about 10% of patients undergoing endovascular treatment using
coils may require additional endovascular or surgical treatment sometime in the future\[9].

It is considered that the treatment of aneurysms by the endovascular technique can be performed under local anesthesia and sedation or under general anesthesia; however, it is preferred that the anesthetic technique provides deep anesthesia, immobility, physiological stability, and the ability to perform the procedure without complications\[8]. The depth of anesthesia emergence should also be considered in terms of post-procedural neurological examination.

The present study aims to provide a retrospective comparison of endovascular and surgical methods used to treat intracranial aneurysms with regard to the duration of anesthesia, the length of stay in the intensive care unit (ICU), and postoperative morbidity and mortality.

**SUBJECTS AND METHODS**

This retrospective study investigated the data of patients who received endovascular or surgical treatment for intracranial aneurysms performed between 1 January, 2013 and 31 December, 2013 in the department of Anesthesiology and Reanimation at the Ankara Numune Education and Research Hospital. The study protocol was approved by the local ethics committee.

The data were derived from the patients’ preoperative and intraoperative forms and hospital files. Demographic data, as well as information on American Society of Anesthesiology (ASA) classification, preoperative Glasgow Coma Scale, World Federation of Neurological Surgeons Grading System for Subarachnoid Hemorrhage Scale (WFNS), medical history, and emergence from the procedure were retrieved from the hospital files. Results of preoperative digital subtraction angiography and computerized tomography were evaluated for the presence of vasospasm and hydrocephalus, respectively.

Details on the anesthetic agent used, duration of anesthesia, agents used to control hypotension, colloidal solutions used during the procedures, and invasive monitoring methods (central venous catheterization and arterial catheterization) were recorded. In the postoperative period, we examined the length of stay in the post-anesthetic care unit (PACU) or ICU, complications (motor and sensory dysfunctions, hematoma, respiratory failure, brain death and death), and the time to discharge. The number of intubated patients arriving at the PACU or ICU was also recorded. Operations performed during the first 72 hours and after the seventh day were categorized as early and late surgery, respectively.

| Table 1: Demographic data, ASA classification, and preoperative and postoperative characteristics of the two treatment groups (N = 143) |
|-------------------------------------------------|-------------------------------|-------------------------------|
| Characteristics                                 | Endovascular treatment (n = 73) | Surgical treatment (n = 70)   |
| Age (years)                                     | 57 (± 45.6)                   | 47 (± 12.12)                  |
| Gender (males/females) n(%)                     | 37/36(50.6%/49.3)             | 49/37(57%/43%)               |
| ASA I/II/III/IV n(%)                            | 2/43/25/3                    | 1/43/22/4                    |
| (2.7/58.9/34.2/4.1%)                           | (1.4/61.4/31.4/5.7%)          |
| Additional diseases n (%)                       | 54(73.9%)                    | 55(78.5%)                    |
| GCS                                             | 15 (8-15)                    | 14 (4-15)                    |
| Preoperative                                    | 14 (3-15)                    | 14 (3-15)                    |
| Cerebral vasospasm, n(%)                        | 13 (18%)                     | 18 (26%)                     |
| Hydrocephalus, n(%)                             | 9 (12.3%)                    | 1 (1.43%) p=0.018*           |
| Re-operation, n (%)                             | 8 (11%)                      | 22 (31.4%)                   |
| Postoperative complications, n (%)              | 14 (19.2%)                   | 24 (34.3%)†                  |
| Length of stay in intensive care unit, days (min-max) | 3.6 (1-33)                    | 4.9 (1-72) *                 |
| Mortality n (%)                                 | 8 (11%)                      | 3 (4.3%)                     |

Data are mean + standard deviation, n (%), (minimum-maximum).
\*p <0.001; †p <0.05 between groups; ASA: American Society of Anesthesiology; GCS: Glasgow Coma Scale
Statistical analysis

Statistical analysis was performed using SPSS for Windows version 16. The number and percentage are presented to describe quantitative variables. Mean and standard deviation values are presented for quantitative variables with a normal distribution, and median values (min-max, interquartile ranges) are presented for quantitative variables without a normal distribution. For group comparisons, the Chi-square test was used for quantitative data, the Kruskal-Wallis test for non-parametric data, and the Mann-Whitney U-test was used for comparisons. A p-value <0.05 was considered statistically significant.

RESULTS

This retrospective study evaluated 143 patients. Table 1 presents the demographic data, the information on ASA classifications, and the preoperative/postoperative evaluations. Of all patients, 56 (39%) were female, 87 (61%) were male (F/M ratio: 0.6); mean age was 48 years, and 109 patients had other concomitant diseases. Subarachnoid bleeding was present in 53.5% of the female and 42.5% of the male patients. Although 54.5% (n = 78) of the patients underwent an elective procedure, 45.5% (n = 65) underwent emergency treatment (p <0.001) (Table 1). In most patients with subarachnoid bleeding, surgery was performed in the early phase (n = 36; 53.7%) rather than the late phase (n = 31; 46.3%). Although there was no significant difference between the groups in terms of the presence of vasospasm, more hydrocephalus was present in patients undergoing the endovascular approach compared to those undergoing surgery (p = 0.018) (Table 1). There was no significant difference between the treatment groups (or between early vs. late surgery) in terms of mortality, the time to discharge, and the length of stay in the ICU (p >0.05). Of all patients, 73 (51%) had endovascular treatment and 70 (49%) had surgical treatment. Posterior cerebral artery aneurysms were significantly prevalent in the endovascular group than in the surgery group (n = 29 and n = 4 respectively, p <0.001), whereas middle cerebral artery aneurysms were prevalent in the surgery group (n = 40 and n = 16 respectively, p <0.001). There was no significant difference between treatment groups in the WFN scale. Although the average age was higher in the endovascular group than in the surgery group, the difference was not significant. For both treatment groups, the anesthetic technique applied was general anesthesia with endotracheal intubation. The duration of anesthesia was significantly shorter in the endovascular group (192 min) than in the surgical group (363 min) (p <0.001). Details on the anesthetic method used for both groups are presented in Table 2. Body temperature was not routinely monitored in either group; after surgery, patients were passively warmed in their hospital bed. Total intravenous anesthesia (TIVA) was applied to three patients in the surgical group, but not to any patient in the endovascular group. These latter patients also received Bispectral Index monitoring and somatosensory evoked potential monitoring.

Table 2: Details of anesthetic methods used during endovascular and surgical procedures

<table>
<thead>
<tr>
<th>Details of anesthesia</th>
<th>Endovascular treatment</th>
<th>Surgical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalational agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>73 (100%)</td>
<td>56 (80%)</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>0</td>
<td>8 (11.43%)</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0</td>
<td>3 (4.29%)</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>0</td>
<td>50 (71.4%)</td>
</tr>
<tr>
<td>Total intravenous anesthesia</td>
<td>0</td>
<td>3 (4.29%)</td>
</tr>
<tr>
<td>Induction agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>62 (84.9%)</td>
<td>50 (71.4%)</td>
</tr>
<tr>
<td>Thiopental</td>
<td>11 (15.1%)</td>
<td>20 (28.6%)</td>
</tr>
<tr>
<td>Central venous catheterization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subclavian vein</td>
<td>0</td>
<td>67 (95.7%)</td>
</tr>
<tr>
<td>Internal jugular vein</td>
<td>1 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Femoral vein</td>
<td>0</td>
<td>3 (4.3%)</td>
</tr>
<tr>
<td>Arterial catheterization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial artery</td>
<td>68 (93.2%)</td>
<td>59 (84.3%)</td>
</tr>
<tr>
<td>Dorsalis pedis artery</td>
<td>2 (2.7%)</td>
<td>4 (5.7%)</td>
</tr>
<tr>
<td>Brachial artery</td>
<td>1 (1.4%)</td>
<td>4 (5.7%)</td>
</tr>
<tr>
<td>Drug infusions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remifentanly</td>
<td>0</td>
<td>28 (40%)</td>
</tr>
<tr>
<td>Esmolol</td>
<td>1 (1.4%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>2 (2.7%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2 (2.7%)</td>
<td>2 (2.9%)</td>
</tr>
</tbody>
</table>

Data are numbers of patients (%)

Table 3: Patients admitted to the intensive care unit and intubated postoperatively

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of patients</th>
<th>Preoperative subarachnoid bleeding</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endovascular</td>
<td>(n = 73)</td>
<td>2(2.7%)</td>
<td>0/1</td>
</tr>
<tr>
<td>Surgical</td>
<td>(n = 70)</td>
<td>2(2.9%)</td>
<td>0/1</td>
</tr>
</tbody>
</table>

Invasive arterial monitoring was applied in 71 patients (97.2%) in the endovascular group and in 67 patients (95.7%) in the surgical group (Table 2). Central vein catheterization was not performed in the endovascular group, with the exception of one patient who earlier had internal jugular vein catheterization. No complications related to arterial or venous catheterization were encountered in this study period. In the endovascular treatment group, 35 patients received intra-arterial nimodipine. Fifty-nine patients in the surgical group and no patient in the endovascular group had infusion of colloidal fluid (p <0.001).
All patients undergoing endovascular treatment were administered heparin empirically without measuring the activated coagulation time (ACT). After the procedure, protamine sulfate was administered to three patients after measuring the ACT.

Four patients (two in the endovascular and two in the surgical group) were admitted to the ICU after the procedures (Table 3). Table 4 presents data on the patients re-operated at our center. There was a significant difference between the treatment groups in terms of postoperative complications and the length of stay in the ICU. More postoperative complications were encountered in the surgical treatment group, and the length of stay in the ICU was longer in patients treated surgically than in those treated with the endovascular approach. However, there was no significant difference between the groups in mortality. The time to discharge from hospital was significantly shorter in the surgical treatment group (10.4 days; range: 3 - 37) than in the endovascular group (10.9 days; range: 1 – 120; p <0.05).

**Table 4: Patients undergoing a second operation in the first 30 days postoperatively**

<table>
<thead>
<tr>
<th>Second treatment group</th>
<th>Endovascular treatment</th>
<th>Surgical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second endovascular treatment</td>
<td>7 (46.7%)</td>
<td>7 (53.9%)</td>
</tr>
<tr>
<td>Second surgical treatment</td>
<td>8 (53.3%)</td>
<td>6 (46.1%)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Currently, intracranial aneurysms are treated either surgically or endovascularly using coils. However, few studies have compared the anesthetic method used for intracranial aneurysms treated either surgically or endovascularly.

In the present study, differences in anesthetic management were found between the two treatment groups. Although the ratio for emergency operation was significantly higher in the endovascular group than in the surgery group, there was no significant difference in the incidence of subarachnoid hemorrhage between the two groups. The duration of anesthesia was shorter in the endovascular group but the length of stay in the ICU was longer. However, postoperative complications were observed in significantly fewer patients in the endovascular treatment group than in the surgery group. Application of invasive monitoring and the use of intraoperative colloidal fluids were higher in the surgical group.

Liu et al compared endovascular coiling and microsurgical clipping in patients with ruptured intracranial aneurysms (133 patients; 39% female, 61% male) in their study, surgical clipping was applied to 62.7% of the patients and endovascular coiling to 37.3% of the patients. In the present study, 68 patients (38% female, 62% male) had a ruptured aneurysm, and 48.5% of these patients were treated surgically while 51.5% were treated with the endovascular approach.

The anesthetic method chosen for endovascular treatment varies between institutions. Generally, the neuroradiologist’s opinion is followed. In our hospital, during the study period investigated, general anesthesia was preferred for the endovascular procedure. As an induction agent, propofol was used in 85% of the endovascular procedures, and thiopental was used in 87% of the surgical procedures. In addition, thiopental was routinely used during temporary clipping of aneurysms. Propofol was preferred for the endovascular treatment probably because this procedure takes less time than a surgery and because of its ready to use nature. Sevoflurane was used as the inhalation agent in all endovascular procedures. For all the surgical cases, sevoflurane (80%), isoflurane (11.4%), and desflurane (4.3%) were used. In addition, 4.3% of the surgical patients received TIVA (a combination of propofol and remifentanil). Although the application of general anesthesia with both TIVA and inhalation anesthetics is recommended, there is no consensus on the superior method of the two. However, nitrous oxide should be avoided, as it can cause micro-emboli formation.

Isoflurane, sevoflurane, and desflurane are less likely to increase cerebral blood flow than other anesthetic agents. However, desflurane can disturb cerebral autoregulation.

In the present study, induced hypertension was not applied in any of the surgically treated patients. It has been suggested that brain perfusion pressure should be normal (or even above normal) after acute central nervous system damage and during neurosurgical procedures. This suggestion is probably related to the fact that cerebral blood flow decreases in some areas of the brain, especially following head injury and subarachnoid hemorrhage. Hypertension may be used to increase cerebral blood flow during temporary artery occlusion. In the present study, more vasoactive agents were used in the endovascular treatment group than in the surgical group. The main reason for this is the use of intra-arterial nimodipine by the neuroradiologists during the procedure.

Normovolemic hemodilution using colloidal solutions reportedly improves blood flow to brain regions that are less well perfused by reducing blood viscosity. Also, normovolemic hemodilution reportedly ameliorates cerebral blood flow and reduces the infarcted area. In the present study, patients who received starch solutions had more postoperative complications and a longer stay in the ICU than patients who did not receive starch solutions.
Postoperative complications were motor and sensory dysfunctions, intracranial hematoma, respiratory failure, and brain death.

The application of central venous catheterization during surgical treatment of cerebral aneurysms depends on medical history, localization and the number of aneurysms, the use of inotropic agents, and the anesthetist’s preference. If peripheral catheterization is adequate, there is no need to place a central catheter for neurosurgical procedures. We found that central venous catheterization was preferred in our center for the surgical treatment group (n = 67; 95.7%) with no associated complications. However, bleeding complications and pneumothorax can occur with jugular venous catheterization and subclavian venous catheterization, respectively. Routine arterial catheterization is advised during surgical or endovascular treatment of intracranial aneurysms.

The main goals of arterial pressure control during neuroradiologic procedures are to achieve adequate brain perfusion pressure, prevent vessel rupture, avoid cerebral edema, and help the neuroradiologist perform the procedure by controlling hemodynamic parameters.

Most of the randomized prospective studies comparing endovascular and surgical treatment were performed in the International Subarachnoid Aneurysm Trial. That study concluded that although the microsurgical technique had advantages over the endovascular approach by providing exact occlusion and reducing the incidence of re-bleeding, ischemic attacks occurred more often with this technique. The re-bleeding incidence was higher in patients having undergone endovascular embolization. However, there was no significant difference between the two groups in terms of mortality rate due to re-bleeding.

In our study, the length of stay in the ICU was significantly longer in patients who had endovascular embolization than in patients who underwent surgical treatment. Recently, studies have compared the length of stay in the ICU. One of them compared coil embolization to surgical clipping. The total time of the procedure (in ruptured aneurysm coiling procedure: 145 min vs. clipping procedure: 203 min) and the length of stay in the ICU (coiling procedure: 5.3 days vs. clipping procedure: 6 days) were significantly shorter in patients treated with endovascular embolization than in those treated with surgical clipping. In addition, the length of stay in hospital was significantly shorter with the coiling procedure (in ruptured aneurysms coiling: 21.4 days, clipping: 26.8 days; in unruptured aneurysms coiling: 9.2 days, clipping: 17.5 days).

We found no significant difference between patients who had early surgical procedure and patients who had late surgical procedure in terms of mortality, time to hospital discharge, and the length of stay in the ICU. However, the incidence to apply early surgical procedure was significantly higher in patients with subarachnoid bleeding. In our study, there were fewer postoperative complications in patients who underwent endovascular procedures. This may be due to the shorter period of anesthesia and fewer surgical traumas in patients undergoing endovascular treatment.

Limitations of the present study are that owing to the retrospective design of the study, only recorded complications were investigated, and some complications may have been missed.

CONCLUSIONS
This study indicates that advances in the endovascular procedure technique will allow for less invasive monitoring, shorter anesthesia duration, fewer surgical traumas, fewer postoperative complications, and a reduced need for intensive care.

ACKNOWLEDGMENTS
Conflict of interest and financial support
The authors declare to have no conflicts of interest. No financial support was received for this study.

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Finite element analysis of biomechanical variation of subchondral bone in osteoarthritis

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ABSTRACT

Objective: This study aimed to investigate the changes in mechanical properties of subchondral bone in the early stage of knee instability and the intervention effects of diphosphate.

Design: Control experiment

Setting: Department of Orthopedics, The Second Hospital Affiliated to Soochow University, Suzhou, China

Subjects: Sixty healthy male New Zealand white rabbits were divided into model, diphosphate, and control groups.

Intervention: Statistical analysis and comparison

Main outcome measures: The obtained 2D image files were then used for the finite element analysis.

Results: Several parameters of the 12- and 4-week groups were compared. Results showed that bone volume fraction, bone density, elastic modulus, reaction force, and von Mises stress were all increased (p <0.01). In the early stage of knee instability, the elastic modulus significantly decreased. The diphosphate could significantly improve the elastic modulus of the subchondral bone by preventing bone resorption.

Conclusions: The changes in the mechanical properties of the subchondral bone showed a significant role in the occurrence and development of osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is a common disease in older people [1]. It is characterized by joint pain and dysfunction [2]. However, its pathogenesis remains unclear, and many factors are involved. Biological and mechanical factors are considered to be the two major risk factors [3]. In recent years, the role of mechanical factors in OA have received increasing attention. Moreover, several studies about the effects of cell biomechanics [4], material biomechanics [5], and subchondral bone biomechanics in OA have been conducted [6-8], and research methods have been constantly updated [9]. OA can lead to anatomical variations of subchondral trabecular bone in the femoral head and changes of trabecular 3D structure, which affect the mechanical properties of the subchondral bone [10]. By establishing a rabbit OA model, the author used micro-CT to perform the 3D reconstruction of subchondral bone. Subsequently, the finite element calculation was conducted, and the mechanical changes of the subchondral bone were observed. Meanwhile, bisphosphonate (Bis) intervention was also applied to investigate the effects of mechanical changes in the subchondral bone on OA progress.

MATERIALS AND METHODS

Experimental animals and grouping

Sixty healthy male New Zealand white rabbits (provided by the Animal Center, School of Medicine of Suzhou University) weighing 2.71 ± 0.29 kg were placed in individual cages. The rabbits were provided granulated diet and free access to drinking water. The ambient temperature was 22 ± 1 °C, with alternate natural light-dark cycles every 12 hours. The rabbits were divided into model (n = 24), Bis (n = 24), and control groups (n = 12) by using a table of random digits. This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National

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Institutes of Health. The animal use protocol has been reviewed and approved by the Institutional Animal Care and Use Committee of Soochow University.

Model duplication and specimen collection
All animals underwent knee-skin preparation one day before the modeling and were weighed before the surgery. About 20 g/L sodium pentobarbital (Sigma Co., San Francisco, USA) was injected through an ear vein at a dose of 30 mg/kg to induce anesthesia. The animal was then disinfected and covered with an operation sheet. A medial patellar incision was made to expose the joint cavity. Joint cavity incision was conducted on the model and Bis groups. Subsequently, the anterior cruciate ligament was cut (confirmed by the drawer test). About 5 mm of the ligament was cut off from the middle segment, and the incision was sutured layer by layer. The same joint cavity incision was performed on the control group, except that the anterior cruciate ligament was only exposed instead of cut, and the incision was sutured layer by layer. The rabbits were intraperitoneally injected with cefazolin sodium (500 mg/d) (Shandong Lukang Pharmaceutical Group Co., Ltd., Shandong, China) for five days postoperatively to prevent infection. The injured limb was not fixed, and the animals were bred separately and allowed free movement. The Bis group was subcutaneously injected daily with 0.01 mg/kg Bis (risedronate sodium; LKT Laboratories Co., Minnesota, USA), whereas the model and control groups were subcutaneously injected with equal volume of isotonic saline. The rabbits were then killed at each predetermined time point (4th, 8th, and 12th weeks after the surgery) by air embolism. The surgical side of the knee (2 cm above and below the reserved knee plane) was cut following the removal of the soft tissues. The knee was cryopreserved at −20 °C for 48 hours and then examined using micro-CT (GE Healthcare, London Ontario, Canada).

Gross scoring and Mankin scoring
Gross morphological evaluation was performed on the intra- and extra-lateral condyle cartilages of femurs. The evaluation was classified into 5 grades according to the OA standard: grade 1 (0 point): the surface was normal and smooth, without damage; grade 2 (1 point): the articular cartilage was rough, gray colored, with small cracks; grade 3 (2 points): the articular surface was erosive, with large cracks, and the cartilage defects reached the middle layer of cartilage surface; grade 4 (3 points): the ulcers and defects of articular cartilage reached the deep layer of cartilage; and grade 5 (4 points): the cartilage exfoliated, and the subchondral bone was exposed. The tissue samples were stained with hematoxylin and eosin (HE) and then observed under a microscope. Scoring was conducted referring to the Mankin scoring criteria.

Micro-CT examination and finite element analysis
The joint sample of the rabbit knee was evenly placed in the examination slot of the micro-CT system and then bundled to prevent movement. The scan was performed along the long axis of the specimen, with a scanning protocol of 45 μm, 24R, and 18 minutes. The scanning parameters were as follows: scan resolution, 45 μm; rotation angle, 360°; rotation angle increment, 0.5°; interlayer spacing, 20 μm; tube voltage, 80 kV; tube current, 450 μA; exposure time, 2960 ms; and scanning time, 18 minutes. Five hundred different sectional images (1024×1024 pixels) of the same sample were obtained, and the segmentation value was set at 1000 to complete the image binarization. The complete bone tissue of the sample was set as the region of interest (ROI) for further 3D reconstruction. 3D visualization was then performed on the selected ROI intra-bone. Micview V2.1.2 3D reconstruction processing software and ABA special bone analysis software were used for quantitative analysis.

The specific measurement parameters were as follows: bone volume fraction (BVF), namely, the division of bone volume by the total volume, and expressed as %; and volumetric bone mineral density (vBMD), namely, the apparent density of porous trabecular bone, reflecting the overall bone mineral density in the region, and expressed as mg/mm3. 2D images in DICOM format were obtained from micro-CT and then imported into Mimics V10.01 software for fitting and threshold setting. The grid redraw module was used to generate the grid, and the Mimics main interface generated the surface mesh model, which was then transmitted into Ansys V10 for the body mesh processing. The obtained body mesh model was finally materialized in Mimics. A total of 10 types of materials were selected, with each representing the material properties of each section. Geomagic Studio 11.0 software was used to repair and optimize the generated models. The Homminga et al. formula is as follows:

\[ E_{\text{element}} = E_{\text{tissued}} \left( \frac{\text{GV}_{\text{element}}}{\text{GV}_{\text{tissue}}} \right) \gamma, \]

where \( E_{\text{element}} \) is the relative gray value based on each finite element (GV element); the normal range is from 0 (bone marrow) to 1 (bone). This formula was used to convert the elastic modulus (EM) into the tissue’s elasticity modulus. The normal gray value was 1754 mgHA/cm3 (equivalent to 12000 CT). Given that the femoral condyle is composed of dense and cancellous pine mass, the dense mass is anisotropic and the cancellous mass is isotropic. Therefore, the simplified material model was unified to the isotropic linear materials. The elastic modulus (\( E_{\text{tissued}} \)) and index (\( \gamma \)) were determined based on the image resolution and structure size; according to literature, \( E_{\text{tissued}} \) was set at 15 GPa, \( \gamma = 1.7^{[12]} \). The apparent EM was reversely calculated using a computer, with a Poisson’s ratio of 0.3.
of 0.3. The boundary condition was set as the stress applied, which made the femoral condyle realize 1% longitudinal compression. Thus, the reaction force (RF) and average von Mises stress, which could induce 1% deformation, were obtained.

Statistical analysis
The data were expressed as x ± s. SPSS 13.0 statistical software was used for all statistical analyses. ANOVA was performed for intergroup comparison. A p-value <0.05 was considered statistically significant.

RESULTS
General observation and OA scoring of cartilages
The knee joint cavity of the control group had no joint effusion. The joint fluid was small and clear, and the joint exhibited no swelling and synovial hyperplasia. In addition, no osteophyte formation was observed. The articular cartilages of the femoral condyle and tibial plateau were blue and white, and bright and smooth, respectively. At the 4th week, joint effusion and synovial hyperplasia appeared in two cases of the model group, and the articular surface was erosive and rough. At the 12th week, the synovium exhibited nodular hyperplasia, and the synovial fluid was cloudy. The surface of the two femoral articular condyle exhibited large cracks and ulcers. The cartilage damages of the Bis group were significantly reduced than those of the model group at the 4th and 12th weeks, as shown in Table 1.

Table 1: OA scores of the three groups (±s)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Postoperative 4th week</th>
<th>Postoperative 12th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>12</td>
<td>0.88 ± 0.6409a</td>
<td>3.25 ± 0.7071ab</td>
</tr>
<tr>
<td>Bis</td>
<td>12</td>
<td>0.38 ± 0.5176b</td>
<td>1.63 ± 0.7440c</td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>0.13 ± 0.3536</td>
<td>0.38 ± 0.5176</td>
</tr>
</tbody>
</table>

Bis: bisphosphonate

Compared with the control group, a p <0.01; compared with the model group, b p <0.05, c p <0.01; compared with the 4th week, d p <0.01

Mankin scoring of articular cartilage injury
The tissue samples were stained with HE and then observed under a microscope. Scoring was performed referring to the Mankin scoring criteria, as shown in Table 2. The control side exhibited normal articular cartilage at the 4th and 12th weeks, and the Mankin scores were 0 - 1 point. HE staining showed that the chondrocytes were uniformly distributed, with clear layers and neat arrangements. The tidal line was intact. Moreover, the toluidine blue staining was uniform, and no staining loss was observed. At the 4th week, the model group exhibited a non-flat cartilage surface. The chondrocytes showed compensatory proliferation and were disorganized; some even appeared in clusters.

Table 2: Mankin scores of the three groups (±s)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Postoperative 4th week</th>
<th>Postoperative 12th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>12</td>
<td>4.53 ± 0.1444a</td>
<td>8.56 ± 1.6832ab</td>
</tr>
<tr>
<td>Bis</td>
<td>12</td>
<td>1.98 ± 0.1931b</td>
<td>2.50 ± 0.1581c</td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>1.41 ± 0.0207</td>
<td>1.40 ± 0.1681</td>
</tr>
</tbody>
</table>

Bis: bisphosphonate

Compared with the control group, a p <0.01; compared with the model group, b p <0.05, c p <0.01; compared with the 4th week, d p <0.01

The chondrocytes with larger volume exhibited a tendency to migrate toward the cartilage surface. Mild loss of toluidine blue staining was observed. At the 12th week, the damages of the articular cartilage were severe, and the tidal line disappeared. Pathological changes, such as disappearance of cartilage and exposure of subchondral bone, were found. Osteophyte formation also occurred. The toluidine blue staining disappeared. Compared with the Bis and control groups, the model group showed cartilage degeneration (p <0.01), which further aggravated at the 12th week (p <0.01). The degeneration at the 12th week was significantly worse than that at the 4th week, (p <0.01). The Bis group exhibited less degeneration than the model group at the 4th and 12th weeks (p <0.01) and showed no statistical significance with the control group.

Structures and mechanical parameters
The BVF, bone trabecular number (Tb.N), bone trabecular thickness (Tb.Th), bone trabecular separation (Tb.Sp), and bone density of the 60 specimens were obtained through micro-CT examination. The finite element software was used to calculate the EM, RF, and average von Mises stress. At postoperative 4th week, the BVF, EM, RF, and average von Mises stress of the model group were decreased when compared with those of the Bis and control groups; the model group was significantly lower than the Bis and control groups (p <0.01). These parameters were also decreased in the Bis group when compared with those of the control group, but the difference was not statistically significant. The bone density of the model group was significantly lower than that of the control and Bis groups (p <0.01). However, the comparison between the Bis and control groups exhibited no statistically significant difference (Table 3). At the 12th week, the BVF and BMD of the model group was significantly increased than those of the control and Bis groups (p <0.01), whereas the EM, RF, and von Mises stress were decreased (p <0.05) (Table 4). The Bis group was also lower than the control group, but the difference was not statistically significant. The BVF, BMD, EM, RF, and von Mises stress at the 12th week were increased when compared with those at the 4th week (p <0.01)
Correlation comparison

At postoperative 4th week, the EM of the model group was negatively correlated with Mankin scores ($r = -0.835$, $p < 0.01$), but positively correlated with BMD ($r = 0.848$, $p < 0.01$) and volume fraction ($r = 0.893$, $p < 0.01$). At postoperative 12th week, the EM of the model group was negatively correlated with Mankin scores ($r = -0.883$, $p < 0.01$), but positively correlated with BMD ($r = 0.861$, $p < 0.01$) and volume fraction ($r = 0.817$, $p < 0.01$).

**DISCUSSION**

Because of its special structure, the subchondral bone has special functions in joint movements. This bone absorbs the stress placed on the articular surface and then distributes it to the backbone and its surrounding tissues, thus buffering the shocks from the joints and protecting the articular cartilage and other vital organs. Meanwhile, the subchondral bone maintains the unique shapes of different joints, making it easier to perform their functions. All these functions require the subchondral bone to have sufficient strength (i.e., the ability to resist damages when bearing the loadings) and stiffness (i.e., the ability to resist deformation under the extra loadings).

Numerous measurement methods and mechanical property studies of knee subchondral bone are available. A bone density detection instrument was commonly used to detect subchondral bone density. Through this evaluation, the relationships between the subchondral bone density and articular cartilage damage were investigated. Mckinley et al. used high-resolution digital imaging and built-in software to measure the sclerotic model of subchondral bone of human cadavers. They found that the stress on the

**Table 3**: Comparison of distal femoral microstructures and mechanical parameters of the three groups on the postoperative 4th week (±s)

<table>
<thead>
<tr>
<th>VM (MPa)</th>
<th>Animal number</th>
<th>The postoperative 4th week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BVF (%)</td>
</tr>
<tr>
<td>Model</td>
<td>12</td>
<td>26.44 ± 1.81</td>
</tr>
<tr>
<td>Bis</td>
<td>12</td>
<td>30.03 ± 2.42</td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>34.10 ± 1.78</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>$&lt; 0.05^a$</td>
</tr>
</tbody>
</table>

**Table 4**: Comparison of distal femoral microstructures and mechanical parameters of the three groups on the postoperative 12th week (±s)

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal number</th>
<th>The postoperative 12th week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BVF (%)</td>
</tr>
<tr>
<td>Model</td>
<td>12</td>
<td>41.21 ± 2.21</td>
</tr>
<tr>
<td>Bis</td>
<td>12</td>
<td>36.13 ± 2.16</td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>35.00 ± 2.86</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>$&lt; 0.01^a$</td>
</tr>
</tbody>
</table>

**Table 5**: Comparison of distal femoral microstructures and mechanical parameters of the model group between the postoperative 4th and 12th week (±s)

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal number</th>
<th>The postoperative 12th week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BVF (%)</td>
</tr>
<tr>
<td>The postoperative 4th week</td>
<td>12</td>
<td>26.44 ± 1.81</td>
</tr>
<tr>
<td>The postoperative 12th week</td>
<td>12</td>
<td>41.21 ± 2.21</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>$&lt; 0.01$</td>
</tr>
</tbody>
</table>

Bis: bisphosphonate; BVF: bone volume fraction; vBMD: volumetric bone mineral density; EM: elastic modulus; RF: reaction force; VM: von Mises stress

Note: Among the p-values, $^a$: comparison between the model group and the bis group; $^b$: comparison between the model group and the control group; $^c$: comparison between the bis group and the control group.
Fig 1: 3D reconstruction figures of knee at different times. A: 2D DICOM and 3D reconstruction images of knee joint of the control group. A1: 2D DICOM; A2: Normal position; A3: Right side. B: 2D DICOM and 3D reconstruction images of knee joint of the model group. B1: Osteophyte in 2D DICOM; B2: Osteophyte in normal position; B3: Osteophyte exhibited in lateral position. C: 2D DICOM and 3D reconstruction images of knee joint of the Bis group. C1: Osteophyte in 2D DICOM; C2: Osteophyte in normal position; C3: Osteophyte in lateral position.
peri-joint trabecular bone is increased because of the sclerosis of the subchondral bone, exhibiting weakened cushioning and protective effects on the articular cartilage. This phenomenon indirectly results in cartilage destruction. A hydraulic mechanical material testing machine was used to prepare a special stainless steel cylindrical indenter and load the oppression on the experimental zone of subchondral bone of the rabbit tibial plateau. The results indicated that the stiffness and strength of rabbit knee in the entire procedure changed from low to high in the early stage of instability. Meanwhile, he studied the correlations between the EM changes and articular cartilage damages. With the development and application of non-invasive and higher resolution equipment, such as CT and MRI, as well as the continuous innovation of computer software, the 3D finite element method is widely applied in biomechanical studies. Previously, this method was used in spine research and then gradually applied to mechanical studies of the skull, pelvis, and limb joints. The development of micro-CT, which is suitable for small animal studies, such as bone anatomy, including teeth, and bone specimens, as well as the limb bones of live animals, greatly contributes to research about bone structures and mechanical properties for clinical and basic needs.[15-17].

In this experiment, an unstable model of the rabbit knee was first established. The femoral distal articular bone was then intercepted, and micro-CT scanning was conducted. Mimics software fitting was used for the images obtained to initially form the 3D model, which was then imported into the Geomagic software for refinement and formation of the 3D solid model that could be recognized by the finite element analysis software. This 3D solid model of bone tissues was then calculated using Ansys software. Subsequently, reverse engineering was performed to calculate the relevant data. Through fixing the nodes, the restraints were loaded to observe the experimental indicators. The results indicated that in the early stage of knee instability (4 weeks after the surgery), the comparison between the model and Bis groups revealed that BVF and BMD, which could reflect the bone mass, were significantly reduced (p <0.01). The EM, RF, and von Mises stress were also significantly reduced; the Bis group was also lower than the control group, indicating that more bone mass indicates better bone structure and mechanical properties and reflects the changes in OA.

The exact mechanism of mechanical property changes of subchondral bone is not completely elucidated. Fazzalari et al.[17-20] believed that abnormal stress causes subchondral bone micro-fractures. These micro-fractures result in bone remodeling, as well as simultaneous activation of osteoblasts and osteoclasts and secretion of various proteases and cytokines, which lead to subchondral bone resorption, bone mass destruction, and trabecular bone fracture. Thus, abnormal stress inevitably causes the reduction of mechanical properties. Meanwhile, bone repair begins, but the destruction and repair are uneven. Calcium deposition is not sufficient, thus decreasing bone density. With the development of disease, repair and calcium deposition are increased, resulting in accelerated subchondral bone remodeling and evident reconstruction, which leads to bone sclerosis. At this time, the EM, bone density, and stress intensity are increased. However, because of excessive subchondral bone sclerosis, its capacity of buffering the joint also drops, so that its stress reverse reaction on the articular cartilage increases, which further promotes articular cartilage destruction. In this study, the general observations were consistent with the aforementioned findings. Regarding the sequence of these changes, namely, whether the cartilage changes first, then affects the subchondral bone, or the subchondral bone changes first, then affects the cartilage, or these two change at the same time, remains unclear.[21-23] However, studies reported that the changes of subchondral bone are observed prior to the cartilage in the OA animal models of primates and the spontaneous OA model of guinea pigs[24].

In this study, it was also observed that the structural characteristics and mechanical indexes of subchondral bone in the bisphosphonates group were significantly higher than those in the model group, indicating that
Bisphosphonates can significantly protect the structure and mechanical properties of subchondral bone. As the third generation of bisphosphonates, sodium rizonium is a synthetic pyrophosphate analogue. The difference in the chemical structure between bisphosphonates and pyrophosphate lies in the substitution of P - O - P bond for P - C - P bond. This substitution makes it resistant to the action of the hydrolase without biodegradation, and its hydroxyl group and 2 phosphate groups make it highly compatible to the bone matrix. The author believed that osteoclasts are target cells of bisphosphonates, which can significantly inhibit the bone resorption of osteoclasts, promote the apoptosis of osteoclasts and inhibit the formation of osteoclasts. Our results also showed that bisphosphonates can effectively inhibit bone destruction, protect the mechanical properties of subchondral bone, reduce bone remodeling and protect articular cartilage. Our previous study[25] showed that the BVF of bone trabecula, Tb.N and Tb.Th of the subchondral bone in rabbit gonarthrosis model at postoperative 4 weeks were significantly reduced as compared with those of the control group, while the Tb.Sp was increased and the vBMD decreased, which indicated that there is abnormal force on articular surface caused by various pathogenic factors in early stage of OA. The bone trabecula of subchondral bone is damaged by repeated overload pressure, and then causes edema, hemorrhage and necrosis of bone marrow locally. The repeated microdamage of the subchondral bone and calcified cartilage initiate the process of bone remodeling, activate osteoclast, decompose a variety of osseous enzymes, promote local osteolysis and destroy the structure of the trabecular bone. At the same time, the neovascularization and the activated osteoblasts promote the formation of new bone and the production of osteoid, but the calcification is not enough, presenting as the decrease of the volume fraction, trabecular bone volume, thickness and bone mineral density. Since the bone density of the subchondral bone is reduced and the structure is destroyed, the mechanical properties will inevitably decrease. The buffer capacity of subchondral bone is not enough for the force from the cartilage, so that the articular cartilage cannot be well protected. The microstructural parameters of the bisphosphonates group were statistically different from that of the model group, indicating the protective effect of bisphosphonates on the destruction of subchondral bone tissue. Meanwhile, we compared bone mineral density and bone trabecular structure between 4 and 12 weeks, and found that BVF, Tb.N, Tb.Th and vBMD were increased significantly at 12 weeks (p <0.05), while the bone trabecular space was decreased (p <0.01). There was no significant difference between the bisphosphonates group and the control group, suggesting an obvious bone destruction in early OA and an accelerated bone formation in the later stage. Early OA showed accelerated bone remodeling with insufficient calcification, destroyed bone trabecular structure and reduced mechanical properties. However, with the repair and reconstruction of subchondral bone in the later stage, the subchondral bone was hardened, resulting in increased hardness of subchondral bone. The uneven hardness of the subchondral bone changed the stress balance of articular cartilage and aggravated the cartilage damage. However, there was a significant difference in various parameters between the bisphosphonates group and the model group, indicating that bisphosphonates could protect the subchondral bone tissue which had been damaged. The general observation of the articular cartilage of the bisphosphonates group in the same period was obviously better than that of the model group, also proving that bisphosphonates can be used as a potential therapeutic drug for OA. The mechanism of sodium rizonium protecting the subchondral bone may be that bisphosphonates can inhibit the enzymolytic effect of a variety of matrix metalloproteinase, cathepsin K and other proteases produced by osteoclasts on the subchondral bone. In addition, bisphosphonates can promote the apoptosis of macrophages, inhibit bone remodeling of subchondral bone, and reduce the destruction of subchondral bone, thereby reducing the occurrence of subchondral osteosclerosis.

The accuracy of the finite element analysis mainly depends on two aspects: the coincidence degree of model and actual tissue and the choice of loading constraints. In the present study, high-resolution micro-CT was used to examine the rabbit knee joint. This technique could reflect the trabecular bone structure from the microstructural aspect. The loading conditions should be in line with the actual situation as much as possible. Although the muscles around the joint are neglected in the finite element analysis, and the complexity of the actual joint movement is not completely considered, this method possesses evident advantages. It can overcome the effects of conventional experiment objects, design methods, and other factors on the results, as well as exclude errors due to different experimental conditions. In this method, one or several parameters can be changed to observe their effects on the entire system. In addition, calculation can be repeated, which is cost-efficient. In this study, the parameters were designed according to the reported standard[28]. This could ensure the accuracy and versatility of the model, establishing a good foundation for further studies.

CONCLUSION

The changes in the mechanical properties of the subchondral bone showed a significant role in the occurrence and development of osteoarthritis.
ACKNOWLEDGMENT

Conflict of interest: All authors have no conflict of interest regarding this paper.

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Original Article

Caesarean section: Sixteen-years’ trend, risk factors and attitudes of females delivered at King Abdulaziz University Hospital, Jeddah, Saudi Arabia

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ABSTRACT

Objective: To determine sixteen-years’ trend of cesarean section (CS), risk factors and attitudes towards it among females delivered at King Abdulaziz University Hospital (KAUH), Jeddah

Design: Two study designs were conducted during 2016. A retrospective study was done through reviewing of delivery records (2000-2015). The second design was a matched case-control study.

Setting: Obstetrics & Gynecology Department of KAUH

Subjects: For the retrospective study, females delivered during the 16 years were scrutinized. For the case-control study, 300 postpartum randomly selected females were recruited (150 cases delivered by CS, and an equal number of controls with vaginal delivery) matched by age and parity.

Intervention: Reviewing delivery records, an interviewing questionnaire with females, and clinical record abstraction forms. Descriptive and inferential statistics were done.

Main outcome measures: Trend, risk factors and attitudes towards CS

Results: An increasing CS trend was obvious (129.5% increase); from 13.86% (2000) to 31.81% (2015). CS delivery was significantly associated with high income, increased weight, smoking, gestational diabetes mellitus, and previous CS(s). Non-cephalic (breech and shoulder) presentation, multiple pregnancies, preterm delivery, fetal distress and low Bishop Score were important risk factors of CS. The most frequent CS indications were history of previous CS, fetal distress and maternal emergencies. CS was done according to mother’s opinion for 3.7%. Regarding attitudes, females delivered by CS perceived it as a safer and more convenient delivery than controls.

Conclusion: Increasing rates of CS prevailed at KAUH. Females with high risk factors require adequate antenatal follow-up. Implementation of programs such as labor induction in low-risk pregnancies is recommended. Increased awareness about CS complicity and advantage of vaginal delivery is needed.

KEY WORDS: attitudes, cesarean section, risk factors, trend

INTRODUCTION

The increasing rates of cesarean section (CS) represents a worldwide escalating epidemic\(^1,2\). The number of babies delivered by CS is rapidly growing both in developed and the developing countries. The rate of CS ranged from 12% - 86% in the industrialized countries\(^3\). In the developing nations, CS rates ranged between 2 - 39%\(^3\). The countries with the highest CS rates as reported in 2016 were Brazil (55.6%) and Dominican Republic (56.4%) from South America and the Caribbean, Egypt (51.8%) from Africa, Iran and Turkey from Asia (47.9% and 47.5%, respectively), Italy (38.1%) from Europe, United States (32.8%) from Northern America, and New Zealand (33.4%) from Oceania\(^4\). CS is a common obstetric procedure\(^5\) and the reasons behind its continuous increasing rates appeared to be multiple, complex and, may be in many cases, specific to the country\(^1,2\). The increasing trend

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of CS may be attributed to maternal, foetal, obstetric and organizational factors\textsuperscript{[6,7]}. In some cases, women may request cesarean delivery without medical need\textsuperscript{[8]}.

There are many concerns regarding the escalating rise in CS rates due to potential maternal and perinatal risks, the probability of obstetric complications in upcoming pregnancies and financial issues\textsuperscript{[9]}. The increased rates of CS lead to increased scar pregnancies, which can have lethal consequences and may affect infant immune system\textsuperscript{[2]}. Females previously delivered by CS may be more liable to postpartum haemorrhage and retained placenta. Uterine rupture and placenta previa are well-known and potentially life-threatening complications of previous CS, but are fortunately still rare conditions\textsuperscript{[10]}.

The World Health Organization has stated that maximum CS percentage should be 15%, and that no region in the world is justified with having a caesarean rate greater than 10% to 15%\textsuperscript{[9]}. Although the rate of CS is escalating, no adequate studies were done about the trend, risk factors and attitudes of mothers towards CS in university hospitals in Jeddah, Saudi Arabia. Therefore, such a study is needed.

The study was done to determine the 16 years’ trend of CS (2000 - 2015), and to identify the risk factors and attitudes towards CS among females who delivered by both CS and vaginal delivery (VD) in the University Hospital from Jeddah.

**SUBJECTS AND METHODS**

Two study designs were conducted:

1. A retrospective record review study (16-years’ trend of CS): All records of deliveries done in the Obstetrics & Gynaecology Department of the University Hospital during a 16 year period (2000 - 2015) were reviewed.

   Data was collected through a pre-constructed clinical data abstraction sheet. It was used to collect information about the numbers and methods of deliveries (CS or VD). The types of CS such as upper segment, transverse and lower segment CS (LSCS) were also recorded. Similarly, the types of VD such as spontaneous VD (SVD), breach and assisted deliveries (ventouse and forceps) were also noted.

2. A matched case-control study: Eligibility criteria for enrolment in this part of the study included all females in the reproductive age, who attended the Gynaecology and Obstetrics Department of the University Hospital for labour during the year 2016, mentally sound, who were willing to participate in the study, and to write the informed written consent.

   Cases: Females who fulfilled the eligibility criteria and delivered by CS.

   Controls: Females who fulfilled eligibility criteria and had a VD.

   A systemic random sample method was used. Every 7\textsuperscript{th} file of the postpartum females, who fulfilled the eligibility criteria were included. For each selected...
female delivered by CS (case), one female delivered by VD (control) was taken and matched by age and parity.

The sample size for the case-control part was calculated through EpiTools epidemiological calculators[11].

It was assumed that expected proportion of exposure among the control group was 60%, odds ratio (OR) was 2, the power of the sampling equals 80%. At 1.96 confidence level, the calculated sample size was 300, divided into 150 in each group.

A data collection sheet was used for the case-control study and it contained:

- An interviewing questionnaire: A validated, anonymous, interviewing questionnaire with females was used. Two experts examined the face and content validity. The internal constituency reliability was assessed by Cronbach’s α test and was 0.82.

- Post-partum females from both the case and control groups were asked about the personal and socio-demographic information. History of chronic diseases was taken. Gynecological, obstetric history and history of the current pregnancy were determined. In addition, the attitudes of all females towards delivery by CS were assessed.

- Clinical record abstraction form: It was fulfilled through reviewing the hospital files of the selected females for collecting data about the weight, height, gestational age (GA), presence of gestational diabetes mellitus (GDM) and hypertension. The types of CS or VD were taken. Data about the presentation and child’s Apgar score (after one minute) was also collected. Bishop Score was recorded (if data was present). It is based on the consistency, effacement, dilation, and position of cervix. It assessed also the foetal station (how far up the birth canal the baby’s head is)[12].

### Statistical analysis

Data was analysed using SPSS 20 (SPSS Inc., Chicago, IL). The rate of CS was calculated as the number of caesarean births divided by total live births. Bishop score[12] was calculated and categorized into those having a score of ≥6 (labour is likely to start without induction), and those who obtained a score ≤5 (labour is unlikely to start without induction).

Apgar score was categorized. Descriptive and inferential statistics were done. Body mass index was calculated. Chi square, OR and 95% confidence intervals (CIs) were calculated. All p-values <0.05 was considered significant.

### RESULTS

For the retrospective study, the sixteen years’ trend of all deliveries is presented in Table 1 and Figure 1. The total cumulative numbers of deliveries done during the period was 66,000. The rate of VD decreased from 86.14% during 2000 to 68.19% in 2015. On the other hand, the rate of CS increased from 13.86% to 31.81% during the same years, respectively (129.5% increase). CS accounted for 21.2%, and SVD with cephalic presentation represented 75.42% of all deliveries done during the 16-year period. SVD with babies in breach presentation accounted for 1.2%. Assisted VDs were done by ventouse and forceps for 2.1% and 0.08% of females, respectively.

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### Table 1: Sixteen-year trend of types of deliveries between females delivered at the University Hospital (2000 to 2015)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total deliveries</th>
<th>Vaginal deliveries</th>
<th>CS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SVD %</td>
<td>Ventouse %</td>
</tr>
<tr>
<td>2000</td>
<td>3145</td>
<td>2625</td>
<td>83.46</td>
</tr>
<tr>
<td>2001</td>
<td>3790</td>
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<tr>
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<td>4165</td>
<td>3337</td>
<td>80.12</td>
</tr>
<tr>
<td>2003</td>
<td>4027</td>
<td>3963</td>
<td>80.37</td>
</tr>
<tr>
<td>2004</td>
<td>4717</td>
<td>3225</td>
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<td>4243</td>
<td>3165</td>
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<td>2010</td>
<td>4238</td>
<td>3108</td>
<td>73.34</td>
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<tr>
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<tr>
<td>2015</td>
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<td>2146</td>
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<tr>
<td>Total</td>
<td>66,000</td>
<td>49779</td>
<td>75.42</td>
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</tbody>
</table>
Regarding case-control part of the study, the mean age of all 300 females was 30.09 ± 5.16 years. Based on matching criteria, there is no statistical significant difference between cases and controls regarding age or parity (p >0.05). Regarding types, LSCS was the most common type of CS (97.3%). Only two cases (1.3%) were delivered through transverse CS incision, and one case (0.7%) had complication and delivered by emergency caesarean hysterectomy.

Results revealed that all cases of placenta previa (8 cases), preeclampsia (5 cases), cord prolapse and placenta abortion were delivered by CS (4 cases for each). It was found that 18.3% of females were primigravida. The cephalic presentation represented 88%, while non-cephalic (breech and shoulder) accounted for 12% of all presentations. GDM occurred among 8.3% of all females from both groups.

Table 2 illustrates that there is no statistically significant association between the type of delivery and each females' occupation and education (p >0.05). However, females who had enough income delivered more frequently by CS compared to others, with a statistically significant difference (p <0.05). Overweight and obese mothers were 2.25 times more prone to CS delivery compared to others (OR = 2.25; 95% CI: 1.23 - 4.10). Smokers had higher rates of CS compared to others, with statistically significant difference (p <0.05). Shorter GA at birth (≤ 32 weeks) was associated with more CS delivery (p <0.05).

Table 3 revealed that females who delivered by previous CS had an increased risk of delivery by the same method in the current pregnancy (X² = 116.15, p <0.001). Furthermore, mothers who suffered from GDM in the current pregnancy were about three times more at risk of having CS delivery (current) compared to others (OR = 2.79; 95% CI: 1.13 - 6.88). Hypertensive females had a higher rate of delivery by CS compared to others (p <0.05).

Regarding foetal presentation, CS was done for 97.2% of women who had their foetus in the non-cephalic presentations compared to only 43.6% for females whose foetus was in the cephalic presentation (OR = 45.35; 95% CI: 6.12 - 335.95). Mothers who delivered twins were about eight times more liable to CS delivery (OR = 8.22; 95% CI: 1.85 - 36.62). Those who delivered a distressed baby (confirmed by first minute Apgar score ≤ 6) had higher rate of CS compared to others. Females who had a pre-term delivery (GA ≤32 weeks) had a higher susceptibility to CS compared to others (p <0.05).
The most common indications for CS (Table 4) were having a history of previous CS (26%), foetal distress (24.7%) and mother’s emergency (22.3%). Furthermore, opinions of doctors and mothers accounted for 14% and 3.7%, respectively.

Table 5 demonstrates the attitudes of females in both case and control groups towards CS. A higher percentage of females who delivered by CS agreed that CS is a safer method of giving birth than others ($X^2 = 13.79, p < 0.01$). Similarly, there is a statistically significant difference between opinions of both groups concerning CS as a more convenient method of delivery ($p < 0.05$).

**DISCUSSION**

CS is one of the most frequently performed surgical obstetric operations\(^ {13}\). Results of the retrospective part of our study showed an increasing CS trend overtime. The rate was 13.86% during 2000 and increased to 31.81% in 2015 (129.5% increase).
Similarly, several other studies have reported increasing CS trends. On the other hand, Costa et al. conducted a retrospective study at a teaching hospital from Portugal and revealed decreasing CS rates overtime; from 30.9% in 2005 to 27.6% in 2011. The cause behind this discrepancy may be attributed to their implementation of departmental policies as external fetal version program, labor induction after the 41 gestational weeks in pregnancy with low-risk, etc.

In the current study, the cumulative 16-years CS rate was 21.2%, which agrees with 16-years rate (1997-2012) of Lurie et al. In the current work, CS rate increased among female smokers. Our results showed that females with shorter GA (preterm labour) were significantly at an increased risk for CS, which agrees with the results of Patel et al from UK. Furthermore, most of the cases with multiple-pregnancies (twins) in our study were delivered by CS, which coincides with other researches.

Concerning child presentation, our results found that mothers whose babies were in the non-cephalic presentation were about 45 times more prone to CS delivery compared to others, which agrees with two UK studies.

Results of the current study showed that overweight and obese mothers had higher susceptibility to CS delivery. It was found from results of a meta-analysis from 2014 that obese women are more likely to have macrosomic babies, and therefore more likely to have CS. This finding may be because obesity can be associated with other pregnancy problems such as pre-eclampsia, diabetes mellitus and GDM. Similar findings were reported from Peru, Oman and China. Furthermore, our findings illustrated that mothers with GDM had about a threefold increase in risk of CS delivery compared to others. Similar results were obtained from the studies of Oman, UK and Portugal. Hypertension was also associated with CS in our study, which coincides with the Omani study.

In the current work, CS rate increased among smokers compared to non-smokers, which coincides with the results of another study done by Lurie et al. They concluded that foetal compromise can occur during labour, leading to increased rates of operative delivery among female smokers.

Our results revealed presence of significant association between low Bishops score and CS, which agrees with results from Iran and Turkey.
Low Apgar score (≤ 6) was significantly associated with CS delivery in our study, which coincides with results from another study done by Gasim in Al-Khobar, KSA, which indicated that CS was conducted more in foetal distress[23].

Regarding attitudes, a higher percentage of females delivered by CS in our study agreed that CS is an easier, safer and more convenient way of giving birth compared to the control group. Women who preferred CS from another Saudi study done by Gari et al[30], and those from an Iranian ethnographic study reported that they preferred CS as it is less painful[31]. Ashimi et al found that a majority of their Nigerian pregnant females are willing to undergo and repeat CS if it is indicated[32]. However, a study of Adageba et al from Ghana showed that the majority of women in their study preferred VD unless CS is necessary[33].

CONCLUSION

An increasing trend of CS prevailed among females delivered at the University Hospital during the 16 years (2000 to 2015). CS was associated with females who had enough income, smokers, with higher body mass index, GDM and hypertension. It was also associated with preterm delivery, non-cephalic presentation, multiple pregnancies, foetal distress, and with low Bishop Score. The most frequent CS indications were previous CS, foetal distress and maternal emergencies. Opinion of doctors and mothers accounted for 14% and 3.7% of CS, respectively. Regarding attitudes, females in CS group perceived it as a safer and more convenient way of delivery compared to those in the control group. Preventing the escalating trend of CS is needed through sound provision of antenatal care. Females with high risk factors require adequate follow-up. Implementation of programs such as external fetal version program and labor induction in low-risk pregnancies is recommended. Providing sound, detailed educational CS messages is needed for both physicians and females.

ACKNOWLEDGMENT

We would like to thank all the participants in the study, all the students who helped in data collection, and all administrators who facilitated it.

Conflict of interests: None

REFERENCES


Incidence of malnutrition in patients with maintenance hemodialysis – a single centre experience

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Department of Nephrology, St. John’s Medical College Hospital, Bengaluru, Karnataka, India

ABSTRACT

Objective: Malnutrition embarks as a significant criterion to portray patients on hemodialysis. The main aim was to find out the incidence of malnutrition among maintenance hemodialysis patients using a panel of nutritional markers.

Design: A retrospective study on maintenance hemodialysis patients for one year on interval of three month follow-up basis.

Setting: Department of Nephrology, St. John’s Medical College Hospital, Bengaluru, India

Subjects: Adult patients (aged ≥18 and ≤65 years) who were on regular hemodialysis (n=90).

Interventions: The samples were assessed for anthropometry, haematochemical parameters, dietary pattern, appetite status and subjective global assessment.

Main outcome measure: Assessment of nutritional status among hemodialysis patients

Results: The mean age was 49.67±13.17 years and 68% were males. Each anthropometric measure was nearly similar at each time point indicative of non-detriment in body composition, which symbolizes good nutritional status. Body mass index was within the ideal range all through study duration. Based on biochemical investigational parameters, there was significant change over time from baseline to end of study for serum albumin, serum calcium, serum phosphorus and urea reduction ratio towards improvement phase. Other biochemical parameters showed no statistical significance, with means being consistent over the time during the study period, suggesting continuance of health status and adherence to 3 D’s of therapy. Appetite status assessment scoring showed improvement from baseline to end of study, hence good eating ability was supported with improved overall nutritional status.

Conclusion: With adequate dietary intake, there was maintenance of nutritional status blended with effective periodic educational programs.

KEY WORDS: counselling, hemodialysis, nutritional, status

INTRODUCTION

Nutritional status determines the nutritional health of an individual, describing the wellness of nutrients that are being met in the form of food. It is not only influenced by living situation, availability of food and their choices, but also the state of health of that individual depicting the body’s absorption and utilization of nutrients. A complete evaluation of nutritional status involves a combination of anthropometric, biochemical, clinical and dietary measurements[1]. Chronic kidney disease (CKD) is a public health problem. The incidence and prevalence of end stage renal disease has become more evident in this era of modern medicine. Malnutrition is a significant co-morbidity of CKD, including patients on hemodialysis (HD) or peritoneal dialysis therapy[2,3]. Malnutrition is a frequent complication affecting quality of life since it is associated with increased risk of morbidity and mortality among maintenance hemodialysis (MHD) patients[4]. There is paucity of Indian dialysis patients’ data on quality of life and associated survival related to poor nutrition and dialysis noncompliance[5]. Periodic evaluation and monitoring of nutritional status is found to be the vital component of nutrition care in patients with kidney disease. To ascertain nutritional status, the nutrition care plan involves an array of indexes, each representing a specific data category measured.
independently and evaluated collectively\cite{2,3}. As per the definition of protein energy malnutrition (PEM), there is a lack in supply of sufficient energy or protein to meet the body’s metabolic demands as a result of either an inadequate dietary intake of protein, intake of poor quality dietary protein, increased demands due to disease condition or increased nutrient losses. Many studies have reported the presence of PEM at the initiation of dialysis therapy due to change in body composition at pre-dialysis CKD stages\cite{6}. There are many contributing factors for protein energy wasting among dialysis populace, but those of concern are inadequate food intake and abnormal nutrient metabolism, which may be associated with underlying psychological distress, barriers and burden of illness\cite{7}.

Hence, a one year retrospective study was conducted to assess the incidence of malnutrition among MHD patients.

**SUBJECTS AND METHODS**

**Sample selection**

One-hundred patients regularly visiting the dialysis center at St. John’s Medical College Hospital were enrolled in the study. They were studied prospectively for one year on an interval of three monthly follow-up basis, i.e., initial month (baseline), third month, sixth month, ninth month and twelfth month (end of study (EOS)). The study samples were undergoing regular twice/thrice weekly HD sessions. By the end of the study period, ten subjects could not complete the research program due to unavoidable reasons like change in dialysis centre, lost to follow up, change in dialysis modality and death. Finally, the study sample size was minimized to 90 subjects who successfully accomplished the requirements of research protocol.

Institutional Ethical Committee approval was obtained for the conduct of the study. A one to one interview schedule method was used for data collection to obtain accurate and appropriate information. A window period of ±7 days was employed at each scheduled visit for each individual after their enrollment into the study.

The criterion considered for patient selection included:

**Inclusion criteria**

1. Subjects with CKD stage V on MHD of either gender with ≥18 to ≤65 years of age
2. Subjects who have undergone ≥3 months of HD and permanent dialysis access AV fistula / AV graft
3. Subjects who were willing to undergo regular tests
4. Subjects who were voluntarily willing to participate in the research program and signed informed consent.

**Exclusion criteria**

1. Those subjects suffering from severe cardiac and liver failure
2. Subjects who were retroviral positive
3. Subjects diagnosed to have tuberculosis or malignancy
4. Those planned for renal transplantation in near future

**General observations**

The basic information was collected as per the following:

**Socio-Demographics** data along with details of dialysis modality

**Anthropometric status**

One of the methods of assessing nutritional status was by physical examination and was performed after one hour of post dialysis session on non-vascular side. Anthropometric assessment status included measurements and recordings of subjects at baseline visit and at each follow-up visit until end of the study visit. Anthropometric status of both male and female subjects were included as mentioned below:

- Primary anthropometric measurements –
  1. Weight (kg)
  2. Height (cm)
  3. Mid arm Circumference (MAC-cm)
  4. Four sites of skin fold thickness (mm) at biceps, triceps, subscapular and suprailiac

- Derived from primary anthropometric measurement details –
  1. Body mass index (BMI - kg/m²)
  2. Arm muscle area (AMA – cm²)
  3. Total body percent fat
  4. Fat free mass (FFM-kg)
  5. Fat mass (FM-kg).

Body composition parameters were analyzed using bioelectrical impedance and skinfold calipers and the inference values were considered as per actuals. Body fat was analyzed using Holtain skin fold calipers and body composition using Multivariate Maltron BioScan 920-2 Bioelectrical impedance. Body composition techniques were used to diagnose protein depletion and to monitor efficacy of nutritional therapies using KDOQI guidelines for anthropometry\cite{8}.

**Biochemical investigation status**

The biochemical laboratory tests were performed on a sub-sample of the study population (n = 30) during each study visit. Adequacy of dialysis was calculated using urea reduction ratio (URR) at every study visit.

**Dietary pattern**

Detailed information about the eating pattern was obtained.
Appetite assessment
A detailed profile on barriers and facilitators of adequate food consumption for the past one week duration was assessed.

The subjects were exposed to intervention program of education modules developed through lecture method, individual and group (patient and care givers) counselling sessions, visual aids, interaction sessions, demonstrations and group discussions.

Subjective Global Assessment (SGA)
A short form 36 scoring was considered for nutritional status assessment for all study patients every six months.

Statistical methods
Data are presented in continuous variables as mean ± standard deviation for the normally distributed variables; otherwise median and inter-quartile range was used. Categorical variables were reported using number and percentages. Repeated measures ANOVA, which analyzes the equality of means, was carried out to assess the time effect and interaction effect of outcome which was applied to analyze anthropometry, biochemical investigations and total dietary and appetite scoring. Cochran’s Q test was used to analyze SGA. A p-value ≤0.05 was considered for statistical significance. All the analysis was done using SPSS version 18.0.

RESULTS
The data in Table 1 provides the demographic profile of the respondents. Nearly two-thirds (45%) of the study population were in the age group of 56 to 65 years and 68% of the study population belonged to the male gender. The mean age was found to be 49.67 ± 13.17 years.

The anthropometric indices mentioned in Table 2 depicted that there was no significant change in the mean measurements of MAC, BMI, AMA, FFM, FM and total body percent fat over the study period. The mean value of each anthropometric parameter was nearly similar at each time point, indicative of non-detritment in body composition. BMI of the study group were in the ideal range as per Asia Pacific standard all through the study duration.

Table 3 highlights the biochemical findings which reveals that there was a significant change over time from baseline to EOS in haematochemical parameters like serum calcium, phosphorus, serum albumin and URR. Serum calcium and phosphorus stores were in sufficient parametric data to predict bone health status. Though there was not much variation in the means of albumin, calcium and phosphorus levels, their statistical significance posed good control of essential indices. Other biochemical parameters showed no significance and the means were consistent over time during study period. All biochemical indices were in the required reference range, which reflected their good nutritional status and adherence to 3D’s of therapy (diet, drug and dialysis) during the study period and was attained by regular interaction.

It was evident from Table 4 that the dynamics of dietary pattern and the subjects’ food habits reflected on their food intake along with dialysis regimen. Majority

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Respondents (N = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group (years)</td>
<td></td>
</tr>
<tr>
<td>18 - 30</td>
<td>11</td>
</tr>
<tr>
<td>31 – 45</td>
<td>17</td>
</tr>
<tr>
<td>46 – 55</td>
<td>22</td>
</tr>
<tr>
<td>56 - 65</td>
<td>40</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 1: Sociodemographic profile

Table 2: Body composition of the subjects

<table>
<thead>
<tr>
<th>Category</th>
<th>0 Month</th>
<th>3 Month</th>
<th>6 Month</th>
<th>9 Month</th>
<th>12 Month</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid Arm Circumference(cm)</td>
<td>25.25 (3.95)</td>
<td>25.28 (4.01)</td>
<td>25.26 (3.96)</td>
<td>25.26 (4.01)</td>
<td>25.28 (3.99)</td>
<td>0.32 NS</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>21.25 (3.97)</td>
<td>21.29 (3.96)</td>
<td>21.30 (3.96)</td>
<td>21.32 (3.96)</td>
<td>21.34 (3.93)</td>
<td>0.55 NS</td>
</tr>
<tr>
<td>Arm Muscle Area (cm²)</td>
<td>30.56 (11.66)</td>
<td>30.69 (11.91)</td>
<td>31.81 (14.89)</td>
<td>30.73 (11.99)</td>
<td>30.80 (11.98)</td>
<td>0.33 NS</td>
</tr>
<tr>
<td>Skin fold Calipers</td>
<td>41.68 (7.84)</td>
<td>41.76 (7.94)</td>
<td>41.67 (8.18)</td>
<td>41.73 (8.22)</td>
<td>41.89 (7.94)</td>
<td>0.43 NS</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>14.30 (7.31)</td>
<td>14.34 (7.18)</td>
<td>14.33 (7.17)</td>
<td>14.34 (7.17)</td>
<td>14.36 (7.17)</td>
<td>0.79 NS</td>
</tr>
<tr>
<td>Percentage of body fat</td>
<td>23.94 (7.37)</td>
<td>23.94 (7.38)</td>
<td>23.93 (7.33)</td>
<td>23.92 (7.34)</td>
<td>23.83 (7.32)</td>
<td>0.45 NS</td>
</tr>
<tr>
<td>Bioelectrical Impedance Analysis</td>
<td>47.35 (9.03)</td>
<td>47.38 (9.30)</td>
<td>47.56 (8.83)</td>
<td>47.64 (8.88)</td>
<td>47.55 (9.06)</td>
<td>0.46 NS</td>
</tr>
<tr>
<td>Fat Free Mass (kg)</td>
<td>8.78 (5.68)</td>
<td>8.63 (5.65)</td>
<td>8.65 (5.50)</td>
<td>8.52 (5.42)</td>
<td>8.68 (5.54)</td>
<td>0.35 NS</td>
</tr>
<tr>
<td>Percentage of body fat</td>
<td>18.99 (7.24)</td>
<td>18.94 (7.24)</td>
<td>18.97 (7.22)</td>
<td>18.99 (7.24)</td>
<td>18.89 (7.19)</td>
<td>0.75 NS</td>
</tr>
</tbody>
</table>

NS: Non-significant
of the respondents were non-vegetarians, had better food intake post dialysis and preferred to liberalise their dietary restrictions at pre-dialysis session. Most of them felt taste was a predominant factor for their non-adherence to renal diet prescription and they preferred hot platter.

Table 5 concentrated mainly on the appetite pattern of the samples which included feeling full of a meal, hunger, food taste, meal pattern, nausea and mood swings. There was a statistical mean significance in total appetite assessment scoring which showed an increasing trend over the time, projecting improvement of appetite status [Baseline = 21.66 ± 3.62; 6\textsuperscript{th} month = 23.42 ± 2.35; EOS = 24.66 ± 0.93]. There was a good response for appetite which showed improvement from poor to average, and then to good criteria, with statistical significance. It was also seen that there was a higher number of cases who reported no weight change over time during every study visit; hence, the respondents were maintaining their health status during the study period. A trend of three meal pattern with acceptable food taste was observed among a majority of the study population. Improvement in appetite status was found beneficial with counselling rendered at every study visit. Irrespective of the cause of native kidney disease, our samples exhibited same kind of dietary and appetite pattern.

There was a shift in the nutritional status from severely malnourished to mildly to moderately malnourished and then to well-nourished group among the study population depicting gradual improvement during study duration (Fig. 1).

Significant outcome was obtained between SGA and serum albumin levels and frequency of dialysis pattern. Irrespective of the cause of native kidney disease, our respondents were maintaining their health status during the study period. A trend of three meal pattern with acceptable food taste was observed among a majority of the study population. Improvement in appetite status was found beneficial with counselling rendered at every study visit. Irrespective of the cause of native kidney disease, our samples exhibited same kind of dietary and appetite pattern.

<table>
<thead>
<tr>
<th>Category</th>
<th>0 Month Mean (SD)</th>
<th>3 Month Mean (SD)</th>
<th>6 Month Mean (SD)</th>
<th>9 Month Mean (SD)</th>
<th>12 Month Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>009.25 (01.52)</td>
<td>009.04 (01.58)</td>
<td>009.16 (01.50)</td>
<td>009.29 (01.33)</td>
<td>009.44 (01.35)</td>
<td>0.17 NS</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>008.17 (00.77)</td>
<td>008.28 (00.65)</td>
<td>008.36 (00.57)</td>
<td>008.40 (00.64)</td>
<td>008.53 (00.64)</td>
<td>0.02 S</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>004.48 (01.31)</td>
<td>004.52 (01.44)</td>
<td>004.64 (01.41)</td>
<td>004.42 (01.31)</td>
<td>004.16 (01.26)</td>
<td>0.01 S</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>003.49 (00.44)</td>
<td>003.49 (00.35)</td>
<td>003.41 (00.34)</td>
<td>003.47 (00.32)</td>
<td>003.57 (00.38)</td>
<td>0.005 S</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>005.49 (00.71)</td>
<td>005.53 (00.74)</td>
<td>005.49 (00.69)</td>
<td>005.55 (00.60)</td>
<td>005.62 (00.64)</td>
<td>0.02 S</td>
</tr>
<tr>
<td>Urea Reduction Ratio</td>
<td>066.52 (09.30)</td>
<td>066.20 (08.48)</td>
<td>069.59 (08.64)</td>
<td>068.86 (08.51)</td>
<td>069.99 (08.06)</td>
<td>0.02 S</td>
</tr>
</tbody>
</table>

Table 3: Biochemical parameters of the subjects

<table>
<thead>
<tr>
<th>NS: Non-significant, S: Significant</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Category</th>
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<th>6 Month Mean (SD)</th>
<th>9 Month Mean (SD)</th>
<th>12 Month Mean (SD)</th>
<th>p-value</th>
</tr>
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<td>009.29 (01.33)</td>
<td>009.44 (01.35)</td>
<td>0.17 NS</td>
</tr>
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<td>008.36 (00.57)</td>
<td>008.40 (00.64)</td>
<td>008.53 (00.64)</td>
<td>0.02 S</td>
</tr>
<tr>
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<td>004.48 (01.31)</td>
<td>004.52 (01.44)</td>
<td>004.64 (01.41)</td>
<td>004.42 (01.31)</td>
<td>004.16 (01.26)</td>
<td>0.01 S</td>
</tr>
<tr>
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<td>003.49 (00.35)</td>
<td>003.41 (00.34)</td>
<td>003.47 (00.32)</td>
<td>003.57 (00.38)</td>
<td>0.005 S</td>
</tr>
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<td>005.55 (00.60)</td>
<td>005.62 (00.64)</td>
<td>0.02 S</td>
</tr>
<tr>
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<td>066.20 (08.48)</td>
<td>069.59 (08.64)</td>
<td>068.86 (08.51)</td>
<td>069.99 (08.06)</td>
<td>0.02 S</td>
</tr>
</tbody>
</table>
Table 5: Assessment of appetite status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline (0 Month)</th>
<th>3rd Month Followup</th>
<th>6th Month Followup</th>
<th>9th Month Followup</th>
<th>12th Month (EOS)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Appetite in past 4 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Poor</td>
<td>06</td>
<td>07</td>
<td>02</td>
<td>02</td>
<td>02</td>
<td>02</td>
</tr>
<tr>
<td>Average</td>
<td>32</td>
<td>36</td>
<td>30</td>
<td>33</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Good</td>
<td>52</td>
<td>57</td>
<td>58</td>
<td>65</td>
<td>63</td>
<td>70</td>
</tr>
<tr>
<td>Change in appetite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
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<td>19</td>
<td>28</td>
<td>31</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>Decreased</td>
<td>11</td>
<td>12</td>
<td>12</td>
<td>13</td>
<td>08</td>
<td>09</td>
</tr>
<tr>
<td>No change</td>
<td>62</td>
<td>69</td>
<td>50</td>
<td>56</td>
<td>58</td>
<td>64</td>
</tr>
<tr>
<td>Weight Change in last 3 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain</td>
<td>31</td>
<td>35</td>
<td>29</td>
<td>32</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Loss</td>
<td>29</td>
<td>32</td>
<td>20</td>
<td>22</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>No change</td>
<td>30</td>
<td>33</td>
<td>41</td>
<td>46</td>
<td>45</td>
<td>50</td>
</tr>
</tbody>
</table>

NS: Non-significant, S: Significant

Fig.1: Subjective Global Assessment scoring

status of the study population. With the increase in serum albumin status which determines the visceral protein status, there was rise in well nourished status [AOR=4.62, (1.74, 12.4]. However there was a trend towards BMI for well nourished group, though not statistically significant. There was no statistical significance for AMA, gender and age indicating that there was no difference in their outcome between the well nourished and malnourished group during the study period.

DISCUSSION

We analysed the impact of inter-related components of malnutrition to assess its rate of incidence among Indian subset of population in South India, Karnataka over a one-year period in a retrospective study.

Table 6: Estimation of SGA with other nutritional parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>B</th>
<th>Std. Error</th>
<th>Wald Chi-Square</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95% Wald Confidence Interval for Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Albumin level</td>
<td>1.535</td>
<td>0.5013</td>
<td>23.612</td>
<td>1</td>
<td>0.002</td>
<td>S</td>
<td>4.642</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.738 [12.400]</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.107</td>
<td>0.0667</td>
<td>09.379</td>
<td>1</td>
<td>0.108</td>
<td></td>
<td>1.113</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.977 [1.268]</td>
</tr>
<tr>
<td>Arm muscle area</td>
<td>0.012</td>
<td>0.0185</td>
<td>02.579</td>
<td>1</td>
<td>0.504</td>
<td></td>
<td>1.012</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.976 [1.050]</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.713</td>
<td>0.4950</td>
<td>00.303</td>
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<td>Age (yrs)</td>
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<td>0.0165</td>
<td>0.839</td>
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<td></td>
<td>0.971</td>
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<td></td>
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<td>1.036</td>
</tr>
</tbody>
</table>

Dependent Variable: SGA; Model: Serum Albumin level, BMI, AMA, Gender, Age (yrs), Frequency of dialysis; S:Significant
The prevalence of malnutrition in HD patients was found to be widely between 20% and 60%\[9\]. However, in our study population, there was maintenance of nutritional status. Testa et al reported in their study that nearly 45% of the study samples were steadily on a high interdialytic weight gain (IDWG)\[10\]. Hence, high IDWG was associated with better nutritional status, which attributed to intake of fluid and sodium overload, which was on par with the present study. The samples were undergoing hemodialysis for one year and 66% of them were on a twice-weekly dialysis regimen. Majority of our subjects were in the IDWG between 3 and 4 kg, with no significant change in means over time during study period (Fig. 2).

Studies conducted by Girija et al and Tayyem et al\[11,12\] revealed similar anthropometric indices to those of the present study. The BMI classification (Asia-Pacific standard) was illustrated by Roy et al and showed their samples to be in normal BMI range (22%)\[13\], as against majority of samples from the present study. Present study conferred anthropometric parameters being consistent throughout the study period, which revealed maintenance of nutritional status among the subjects. Clinically, dialysis subjects are considered as chronically ill, but there seemed to be no sign of deterioration among the study populace, which discloses condensed interaction with them in continuance of maintaining health status during the study period.

Similar and concurrent studies’ reported findings which were on par with the present study, showing all biochemical parameters being in the normal range\[12\]. Present study depicted majority of study samples to be in 3.5 mg/dl as against 39% by a study conducted by Girija et al\[11\].

Appetite status was evaluated by Radha et al, who showed from their study that majority of their study samples had normal appetite and they attained early satiety when food was consumed\[14\], which was against the present study showing a majority of subjects having normal appetite but attained slow satiety. Gastrointestinal symptoms like vomiting/nausea were not found to be a barrier for food intake among our study population as against the aforementioned study subjects who had affected food intake leading to malnutrition. The present study revealed better appetite pattern of the study populace, enabling the subjects to consume adequate diet, eventually resulting in good nourishment status supported with better SGA scoring.

CONCLUSIONS

Nutritional outcomes over the study duration of one year showed the health status of the study population being consistent, which exhibited continuance of their nutritional status. Underlying barriers and burdens of the illness were overcome with effective counselling to improve their overall health status. A strong family, social and health care support can frame a backbone to enhance longevity with secured quality of life.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

Original Article

Effect of positive end-expiratory pressure on right heart function in mechanically ventilated patients: An ultrasonography based study

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Kuwait Medical Journal 2020; 52 (2): 198 - 203

ABSTRACT

Objective: To investigate the effect of positive end-expiratory pressure (PEEP) on right heart function in mechanically ventilated patients using bedside ultrasonography

Design: Retrospective study

Setting: Department of Emergency Medicine, the First Affiliated Hospital of Anhui Medical University, Hefei, China

Subjects: Eighteen patients who received mechanical ventilation between December 2014 and May 2016

Interventions: Different levels of PEEP were applied to patients to achieve appropriate PaO2 levels.

Main outcome measures: Indices of right heart function was assessed at three different PEEP levels, ≤5 cm H2O, 5-10 cm H2O or ≥10 cm H2O. Indices included preload assessment by measurement of the area of the right atrium (RA), the diameter of the inferior vena cava (IVC) and measurement of the central venous pressure (CVP); afterload was assessed by estimation of the pulmonary vessel resistance (PVR); right ventricular systolic function was assessed by tricuspid annular plane systolic excursion (TAPSE).

Results: The IVC diameter and the CVP increased as PEEP levels increased (14.5±2.2 vs. 16.9±1.4 vs. 22.6±2.4; 7.1±1.1 vs. 7.9±1.3 vs. 13.2±2.0); the RA area decreased at the same time (36.6±2.9 vs. 32.1±2.0 vs. 25.3±3.8). These changes were statistically significant. PVR and TAPSE changed significantly at higher levels of PEEP (p<0.05). PEEP levels positively correlated with the IVC diameter and the PVR, and negatively correlated with TAPSE; coefficients of determination were 0.644, 0.759, and 0.628, respectively.

Conclusions: The application of PEEP decreased the preload and increased the afterload of the right heart. Right ventricular contractility decreased significantly at higher levels of PEEP.

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INTRODUCTION

It is important to stabilize cardiopulmonary function in critically ill patients. Cardiopulmonary interactions may be influenced by intermittent positive pressure ventilation through alterations in intrathoracic pressure[1]. The effect of tide volume variation on intrathoracic pressure and cardiac function has been previously reported[3]. However, there are few reports on the effect of positive end-expiratory pressure (PEEP) on cardiac function, especially that of the right heart. PEEP is widely used during mechanical ventilation (MV). Historically, the effect of PEEP on left heart function has been studied more than its effect on right heart function. The pathophysiology of right ventricular failure includes increased afterload and reduced right ventricular contractility[3,4]. The venous return may decrease due to high intrathoracic pressures generated during positive pressure ventilation, leading to a fall in right ventricular output[5,6]. The application of PEEP may further reduce preload; however, it leads to an increase in the pulmonary vascular resistance (PVR) and increases afterload. Hence, it is important to assess the effect of PEEP on right heart function.

Ultrasound plays a key role in the evaluation of cardiac function. Historically, invasive techniques including the Swan-Ganz catheter were the main...
monitoring tools used to detect cardiac function in critically ill patients[7]. However, being invasive, it carries potential risks, and cannot be applied in all critically ill patients. Recently, bedside-ultrasonography has been widely used in the assessment of critically ill patients, especially to evaluate cardiac function[8,9]. Previous studies have demonstrated the accuracy of bedside-ultrasonography and shown good correlation with invasive monitoring[10,11].

There are few studies that focus on the effect of PEEP on right heart function. We aimed to assess the influence of different levels of PEEP on right heart function by bedside ultrasonographic evaluation.

SUBJECTS AND METHODS
Patients
We included 18 patients who received MV in our unit between December 2014 and May 2016. Twelve patients were diagnosed with acute respiratory distress syndrome (ARDS) according to the Berlin definition[12]. The other six patients had respiratory failure due to poisoning with anticholinesterase insecticide. All patients had acute respiratory failure with no previous history of cardiovascular or pulmonary disease and required MV because of severe hypoxemia. Midazolam, sufentanil, and etomidate were administered for tracheal intubation and to attain ventilator synchrony as required. During the course of this study, all patients remained hemodynamically stable and did not need vasopressors. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Anhui Medical University. Written informed consent was obtained from all participants or their guardians.

Ventilator settings
MV was carried out in the synchronized intermittent mandatory ventilation mode initially using standard ventilators (Puritan Bennett 760, Covidien, USA); all patients were in the weaning phase.

We used PEEP with every mode, at a baseline level of 5 cm H\textsubscript{2}O or less. For sustained oxygen saturation greater than 90%, the level of PEEP was increased step by step from a low (5 cm H\textsubscript{2}O) to a sufficient level. The fractional inspired oxygen concentration (FiO\textsubscript{2}), and the PEEP levels were selected according to a PEEP-FiO\textsubscript{2} table (Table 1). Depending on the response, the PEEP level was increased gradually, to a maximum limit of 15 cm H\textsubscript{2}O. The PEEP level was classified as ≤5 cm H\textsubscript{2}O, 5 - 10 cm H\textsubscript{2}O or ≥10 cm H\textsubscript{2}O.

Ultrasonographic assessment
Echocardiographic evaluation was carried out in all patients prior to the initiation of MV and at different levels of PEEP using a Sonosite MAXX machine (Sonosite, Seattle, USA) equipped with 2.5- and 3.5-MHz transducers. Studies were carried out with the patient in the supine position. We evaluated right heart function based on three types of indices.

The preload indexes: The area of the right atrium (RA) was measured by echocardiographic imaging at end-diastole in the apical view. The diameter of inferior vena cava (IVC) was measured in the subcostal view to estimate RA pressure.

The afterload indexes: The PVR was estimated from the peak tricuspid regurgitant velocity (TRV) and the right ventricular outflow tract time-velocity integral (TVI\textsubscript{RVOT}) in accordance with published guidelines[13], using the equation, PVR = (TRV/TVI\textsubscript{RVOT}) × 10\textsuperscript{0.16}. Color-flow Doppler examination was used to screen for the presence of valvular regurgitation in apical windows.

The index of right heart systolic function: We estimated tricuspid annular plane systolic excursion (TAPSE) in real time. On M-mode, the cursor was passed through the lateral tricuspid annulus in the apical 4-chamber view. TAPSE was estimated by measurement of the extent of longitudinal motion of the lateral tricuspid annulus at peak systole[14].

Statistical analysis
Statistical analyses were performed by using the SPSS 16.0 statistical software. Data are expressed as means ± SD, unless otherwise specified. Repeated measure analysis at different PEEP levels was done using the one-way ANOVA. The correlation of different PEEP levels with IVC, PVR and TAPSE are shown as scatter plots. The coefficients of determination were analyzed. A p-value <0.05 was considered as statistically significant.

RESULTS
Baseline patient characteristics
We enrolled 18 patients in this study. Twelve patients underwent mechanical ventilation for ARDS secondary to pneumonia, severe acute pancreatitis, or

<table>
<thead>
<tr>
<th>PEPE (cmH\textsubscript{2}O)</th>
<th>5</th>
<th>5</th>
<th>8</th>
<th>8</th>
<th>10</th>
<th>10</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>14</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>18-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO\textsubscript{2}</td>
<td>0.3</td>
<td>0.4</td>
<td>0.4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Note: 1 cm H\textsubscript{2}O = 0.098kPa
severe sepsis. The other six patients were diagnosed with acute pulmonary edema or acute respiratory failure secondary to organophosphorus pesticide poisoning. The highest levels of PEEP ranged from 12 to 15 cm H₂O (13.1 ± 1.3). The duration of ventilation ranged from 6 to 20 days (9.8 ± 4.5). The Apache II scores ranged from 20 to 36 (26.1 ± 5.1). Table 2 shows baseline patient characteristics.

Arterial blood gas analysis and pulmonary mechanics

All patients had severe hypoxemia with a low PaO₂/FiO₂ ratio at baseline. The PaO₂ and PaO₂/FiO₂ ratios improved with increasing levels of PEEP. However, the peak inspiratory pressure (PIP) and the plateau pressure (Pplat) also increased as the PEEP levels increased (25.3 ± 8.2 vs. 28.9 ± 6.3 vs. 33.2 ± 5.6; 7.1 ± 1.1 vs. 7.9 ± 1.3 vs. 13.2 ± 2.0). The change in IVC diameter and the RA area were statistically significant (p <0.05).

Preload indexes

The IVC diameter and the central venous pressure (CVP) increased with increasing PEEP levels (14.5 ± 2.2 vs. 16.9 ± 1.4 vs. 22.6 ± 2.4; 7.1 ± 1.1 vs. 7.9 ± 1.3 vs. 13.2 ± 2.0). The RA area decreased with increasing PEEP (36.6 ± 2.9 vs. 32.1 ± 2.0 vs. 25.3 ± 3.8). The change in IVC diameter and the RA area were statistically significant (p <0.05).

**Table 2: Baseline patient characteristics**

<table>
<thead>
<tr>
<th>Gender / age</th>
<th>Diagnosis/reason for intubation</th>
<th>Highest level of PEEP (cm H₂O)</th>
<th>Time of MV</th>
<th>Apache II score</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/56</td>
<td>Pneumonia/ARDS</td>
<td>12</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>M/32</td>
<td>Pneumonia/ARDS</td>
<td>12</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>F/30</td>
<td>SAP/ARDS</td>
<td>15</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>M/45</td>
<td>Pneumonia/ARDS</td>
<td>14</td>
<td>9</td>
<td>25</td>
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<tr>
<td>F/28</td>
<td>SAP/ARDS</td>
<td>12</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>M/50</td>
<td>Severe sepsis/ARDS</td>
<td>12</td>
<td>7</td>
<td>36</td>
</tr>
<tr>
<td>F/62</td>
<td>Pneumonia/ARDS</td>
<td>15</td>
<td>20</td>
<td>30</td>
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<tr>
<td>M/48</td>
<td>SAP/ARDS</td>
<td>15</td>
<td>7</td>
<td>25</td>
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<td>F/54</td>
<td>Pneumonia/ARDS</td>
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<td>7</td>
<td>28</td>
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<tr>
<td>M/60</td>
<td>Severe sepsis/ARDS</td>
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<td>10</td>
<td>32</td>
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<td>F/40</td>
<td>SAP/ARDS</td>
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<td>15</td>
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<tr>
<td>F/32</td>
<td>AOPP/acute pulmonary edema</td>
<td>12</td>
<td>6</td>
<td>22</td>
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<tr>
<td>F/40</td>
<td>AOPP/acute pulmonary edema</td>
<td>14</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>F/32</td>
<td>AOPP/acute pulmonary edema</td>
<td>14</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>M/38</td>
<td>AOPP/acute respiratory failure</td>
<td>12</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>F/35</td>
<td>AOPP/acute respiratory failure</td>
<td>12</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>M/50</td>
<td>AOPP/acute pulmonary edema</td>
<td>12</td>
<td>6</td>
<td>20</td>
</tr>
</tbody>
</table>

SAP: severe acute pancreatitis; AOPP: acute organophosphorus pesticide poisoning; ARDS: acute respiratory distress syndrome

**Table 3: Arterial blood gas and pulmonary mechanics at different PEEP levels (cmH₂O)**

<table>
<thead>
<tr>
<th>Patients indexes</th>
<th>PEEP≤5</th>
<th>5&lt;PEEP≤10</th>
<th>10&lt;PEEP≤15</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂ (mmHg)</td>
<td>47 ± 12</td>
<td>55 ± 10*</td>
<td>66 ± 13#</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>42 ± 11</td>
<td>40 ± 12</td>
<td>41 ± 11</td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>76 ± 10</td>
<td>112 ± 13*</td>
<td>180 ± 18#</td>
</tr>
<tr>
<td>PIP (cmH₂O)</td>
<td>25.3 ± 8.2</td>
<td>28.9 ± 6.3*</td>
<td>33.2 ± 5.6#</td>
</tr>
<tr>
<td>Pplat (cmH₂O)</td>
<td>20.1 ± 3.8</td>
<td>25.4 ± 4.3*</td>
<td>29.7 ± 4.6#</td>
</tr>
</tbody>
</table>

Compared with PEEP≤5, *p <0.05; #p <0.01.
PIP: peak inspiratory pressure; Pplat: plateau pressure

**Table 4: Right heart function at different PEEP levels (cmH₂O)**

<table>
<thead>
<tr>
<th>Right heart indexes</th>
<th>PEEP≤5</th>
<th>5&lt;PEEP≤10</th>
<th>10&lt;PEEP≤15</th>
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</thead>
<tbody>
<tr>
<td>RA area (cm)</td>
<td>36.6 ± 2.9</td>
<td>32.1 ± 2.0*</td>
<td>25.3 ± 3.8#</td>
</tr>
<tr>
<td>IVC (mm)</td>
<td>14.5 ± 2.2</td>
<td>16.9 ± 1.4*</td>
<td>22.6 ± 2.4#</td>
</tr>
<tr>
<td>CVP (cmH₂O)</td>
<td>7.1 ± 1.1</td>
<td>7.9 ± 1.3*</td>
<td>13.2 ± 2.0#</td>
</tr>
<tr>
<td>PVR</td>
<td>2.4 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td>3.7 ± 0.3*</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>17.2 ± 2.5</td>
<td>16.3 ± 2.5</td>
<td>11.1 ± 1.6*</td>
</tr>
</tbody>
</table>

RA: right atrium; IVC: the diameter of inferior vena cava; CVP: center vessel pressure; PVR: pulmonary vessel pressure; TAPSE: tricuspid annular plane systolic excursion. Compared with PEEP≤5, *p <0.05; #p <0.01

**Right ventricular function**

TAPSE decreased with increasing levels of PEEP; however, there was no significant difference between baseline (PEEP ≤5 cmH₂O) and lower levels of PEEP (5–10 cmH₂O). TAPSE decreased significantly at PEEP levels of >10 cmH₂O (17.2 ± 2.5 vs. 16.3 ± 2.5 vs. 11.1 ± 1.6), (p <0.01) (Table 4).
Correlation analysis

The correlation between IVC, PVR, TAPSE, and PEEP levels are shown as scatter plots. PEEP levels showed a positive correlation with IVC and PVR and a negative correlation with TAPSE. The central line in the scatter plot is the regression line; the two lines on either side of the regression line are 95% CI of individual predicted values. The coefficients of determination were 0.644, 0.759, and 0.628 (Figure 1).

DISCUSSION

The patients in our study had ARDS and acute lung edema secondary to underlying disease. PEEP can prevent cyclic opening and collapse of alveoli by maintaining the alveolar pressure at end expiration[15]. PEEP may influence cardiac output, especially that of the left ventricle, through changes in intrathoracic pressure[16]. Due to its anatomical characteristics, right ventricular changes during positive pressure ventilation are less noticed compared with those of the left ventricle. As the output from the right ventricle flows into the pulmonary arteries, changes in intrathoracic pressure may influence right ventricular output through alterations in preload, afterload, and right ventricular systolic function. We used ultrasonography to verify this hypothesis.

Our patients were on MV for variable periods of time. The duration of ventilation in patients with poisoning was shorter than that in ARDS patients. There were more female patients with poisoning, which may be peculiar to China. PaO₂ and PaO₂/FiO₂ ratios were significantly lower than normal in all patients. PIP and Pplat increased as the PEEP level increased, leading to high ventilation pressures.

CVP denotes the pressure within the RA, besides reflecting the volume status. A change in the CVP level can influence the diameter of the IVC[17]. In previous studies[18,19], the prognostic value of the IVC diameter was similar to that of RA pressure. In our study, the CVP levels and the IVC diameter were significantly different in groups with different PEEP levels. The increase in IVC diameter showed a positive correlation with the PEEP level. The mechanism of this phenomenon may be as reported by Jellinek et al[20]. They demonstrated that positive airway pressure equally increases the mean systemic filling pressure and the RA pressure in humans, and alters venous return without changes in the pressure gradient. In our opinion, the reduction in RA area may reduce the preload to the right heart. PEEP may increase the intrathoracic pressure, leading to compression of the RA and reduction of its area. The reduction in RA area was more obvious in the high PEEP group (>10 cm H₂O). As reported previously[21], we noted a decrease in atrial volumes in systole and diastole with positive pressure ventilation, with atrial volumes decreasing relatively more than ventricular volumes. The absolute and relative decrease in RA volumes was higher compared to left atrium volumes. Therefore, the influence of PEEP on RA preload may be significant.

PVR is considered to constitute the right ventricular afterload. It is a concept that relates to the pressure needed to drive blood across the lungs to the pulmonary circulation. The resistances of large and small arteries, the pulmonary microcirculation, and the veins are the main contributors to PVR. Several factors can contribute to changes in PVR. In ARDS, PVR is elevated due to hypoxic vasoconstriction and tortuosity of the medium and large intrapulmonary blood vessels[22]. PEEP affects PVR by compression of intra-alveolar capillaries by over expanded alveoli[23]. The reservoir-wave model suggested that there was a small increase in microcirculatory resistance with the application of PEEP[24]. The present study demonstrated that PVR increased significantly at PEEP levels of >10 cm H₂O. However, the difference in PVR between PEEP levels of ≤5 cm H₂O and 5 - 10 cm H₂O was not significant. These results may indicate that compression of intra-alveolar capillaries and increase in microcirculatory resistance became significant at PEEP levels of >10 cm H₂O.

The change in right ventricular function or contractility was less compared to preload and afterload changes of the right heart during mechanical ventilation...
ventilation. The right ventricular perfusion is dependent on the gradient between aortic pressure and the right ventricular systolic pressure; it is also influenced by the intrathoracic pressure. High levels of PEEP can worsen right ventricular ischemia. A previous study demonstrated that the right ventricular free wall showed dysynchronous contraction at the highest PEEP level reached on assessment by speckle tracking echocardiography. TAPSE is a better, non-invasive index of right ventricular function. It provides information not only on the emptying of the right ventricle, but also on the driving force which acts on the systemic venous column because systolic shortening of the right ventricle occurs from base to apex. In our study, TAPSE decreased significantly at PEEP levels of >10 cm H₂O. The scatter plot revealed that the decrease in TAPSE correlated with increasing PEEP levels. This suggests that right ventricular contractility may be influenced by higher levels of PEEP.

Limitations
There are several limitations to our study. First, our study was limited to two main disease processes. Previous studies have shown that PVR may be higher than normal in the early stage of ARDS. Besides, organophosphorus pesticide poisoning could result in myocardial injury. These two factors could have contributed to the variability observed in the results. However, a clear correlation was observed between right heart function and the level of PEEP. A larger sample size is required to confirm our findings. Second, although bedside ultrasound is a convenient, non-invasive technique of hemodynamic assessment in critically ill patients, it has some limitations. A reliable ultrasonographic assessment depends on several factors including patient condition, the use of MV, and individual proficiency in carrying out the examination.

CONCLUSIONS
We demonstrated in our study that right heart function could be reliably assessed by bed-side ultrasonography. The application of PEEP decreased the preload and increased the afterload of the right heart. Right ventricular contractility decreased significantly at higher levels of PEEP.

ACKNOWLEDGMENT
Conflict of interest: The authors declare no conflict of interest.

REFERENCES
Case Report

Humeral biepicondylar fracture in a child without elbow dislocation: A rare case and review of literature

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1Department of Orthopaedics and Traumatology, Erciyes University Medical Faculty, Kayseri, Turkey
2Department of Orthopaedics and Traumatology, Training and Research Hospital, Kayseri, Turkey

Kuwait Medical Journal 2020; 52 (2): 204 - 206

ABSTRACT

In children, humeral biepicondylar fracture is extremely rare among traumas involving elbow region. The main goal should be to provide elbow stability in these patients. Thus, open reduction plus internal fixation should be performed in these cases. Here, we aimed to present an 11-year-old patient with biepicondylar humeral fracture without elbow dislocation, which is rarely seen among pediatric elbow traumas.

KEY WORDS: child, elbow, epicondyle, humerus

INTRODUCTION

The upper extremity fractures are commonly seen in children and a majority of these injuries occur at elbow region. Distal humerus fractures comprise approximately 90% of fractures at elbow region[1]. The most common fracture is supracondylar humerus fracture, while medial epicondylar fractures are the third most common fractures at elbow region[2]. However, biepicondylar fractures are extremely rare, and PubMed search of the term “biepicondylar fracture” revealed 6 case reports in the literature[3-7]. Thus, the case reported here will be seventh case in the literature. Mechanism of injury generally involves fall on outstretched hand. Medial epicondylar fractures occur due to traction by flexor, pronator and ulnar collateral ligament, while lateral epicondylar fractures occur due to traction force by extensor muscles associated to varus force. One-half of medial epicondylar fractures are accompanied by elbow dislocation while no elbow dislocation is seen in remaining half[8].

Here, we aimed to present an 11-year-old patient who had biepicondylar humeral fracture without elbow dislocation.

CASE REPORT

An 11-year-old presented to the emergency department with fall on outstretched hand while playing at the park. He was assessed due to swelling and deformity at left elbow and ecchymosis at lateral epicondylar region. No additional neurovascular abnormality was detected, but there were fractures at medial and lateral epicondyles in anteroposterior and lateral direct radiographs (Figure 1). The patient underwent surgery under general anesthesia due to displaced fragments. In surgery, medial and lateral epicondyles were fixed by K-wire following open reduction (Figure 2). After surgery, long-arm splint was applied for 4 weeks. At the end of week 4, splint was removed and rehabilitation was started. At week 6, K-wires were removed. At 6th month after surgery, full elbow extension and flexion were achieved and Maya elbow score was estimated to be 100 (Figure 3). On radiographs, it was seen that union was achieved on medial epicondyly but opacities suggesting heterotopic ossification were observed at distal to medial epicondyle. The lateral epicondyle underwent lysis due to complete avascular necrosis (Figure 4).
DISCUSSION

In the literature, there are only a few pediatric cases with biepicondylar humerus fracture. Assessment and management of childhood elbow trauma is challenging due to complex anatomy of elbow and differing ossification timing of growth plates.

Primary and secondary stabilizers play different roles in elbow stability during joint movement. Primary stabilizer structure is humeroulnar joint and coronoid process is the most important component of this structure. Thus, it is recommended to assess coronoid process and to ensure integrity in elbow fractures. In our case, it was seen that coronoid process was intact. Flexor, pronator, extensor muscles and ulnar collateral ligaments surrounding elbow act as secondary stabilizers. The secondary stabilizers are also involved in the etiology of biepicondylar fractures. Medial epicondylar fractures generally occur due to traction of flexor-pronator muscles and ulnar collateral ligament following valgus trauma after fall on outstretched hand. On the other hand, lateral epicondylar fractures often occur due to traction of extensor muscles as well as varus and internal rotation trauma of forearm. Our patient was also exposed to a similar trauma after fall on outstretched hand when he was playing at the park. If a similar trauma occurs in an adult age; terrible triad and posterior elbow dislocation are likely to be seen. It can also be assumed that supracondylar humerus fractures may develop due to low bone quality in older ages.

Elbow dislocation can be seen in one-half of medial epicondylar fractures. Elbow dislocation accompanied the fracture in all six cases of biepicondylar fracture reported in the literature. However, elbow dislocation accompanying fracture was lacking in our case, contrary to cases in the literature.

Elbow instability is the major problem in biepicondylar fractures. Thus, one should aim to ensure elbow stability in these cases. Sufficient biomechanical stability couldn’t be achieved following closed reduction in general. Thus, open reduction plus internal fixation should be preferred in order to ensure stability. We also performed open reduction and fixation by K-wire in our case.

Given the complex anatomy and differential timing...
of ossification in growth plates, several problems can be encountered in the assessment of pediatric patients with elbow trauma. Either imaging of intact extremity or advanced imaging modalities such as CT scan or MRI should be used to avoid misdiagnosis\(^\text{[13]}\). In our case, comparative radiographs were sufficient to establish diagnosis.

One should beware the neurological injuries associated to biepicondylar fractures. Radial and ulnar nerve injuries have been shown in biepicondylar fractures with elbow dislocation\(^\text{[4,14]}\). In our case, no neurological injury was present. We think that this was due to lack of accompanying elbow dislocation. If there is a concomitant nerve injury, exploration must be done at the time of the surgery and if necessary, microsurgical nerve repair must be done\(^\text{[4]}\).

**CONCLUSION**

Biepicondylar elbow fractures are instable injuries which may be accompanied by elbow dislocation and neurological injuries. Open reduction plus internal fixation should be performed in order to ensure elbow stability.

**REFERENCES**

Case Report

Traumatic isolated dislocation of the trapeziometacarpal joint: A rare case report

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ABSTRACT

Isolated dislocation of trapeziometacarpal (TMC) joint is a rarely seen entity among hand injuries. It often develops after axial loading on thumb at partial flexion. It may eventually result in TMC arthritis, pain and dysfunction in thumb due to TMC joint instability if treated inadequately or left untreated. Here, we aimed to present successful outcome in a case who presented with acute instable dislocation of TMC joint and underwent dorsoradial carpal and volar oblique ligament repair after two years of follow-up.

KEY WORDS: carpometacarpal joint, dorsoradial ligament, thumb, volar oblique ligament

INTRODUCTION

Isolated dislocation of trapeziometacarpal (TMC) joint is a rarely seen entity among hand injuries[1]. It often develops after axial loading on thumb at partial flexion[2]. Although reduction is easy, instability is commonly seen following reduction[1]. It may eventually result in TMC arthritis, pain and dysfunction in thumb due to TMC joint instability if treated inadequately or left untreated[3]. Despite the presence of four stabilizer structures, dorsoradial carpal ligament is considered as the primary stabilizer in TMC joint[4]. Dorsoradial carpal ligament is accepted as the primary structure that prevents dorsal dislocation of TMC joint. In addition, it is known that volar oblique ligament is involved in the anterior stabilization of TMC joint[5]. The management is still controversial in dislocation of TMC joint with no optimal treatment method established in acute cases[3]. Primarily, three therapeutic modalities are employed for management of TMC joint dislocations: closed reduction plus cast; close or open reduction plus pinning; and ligament repair plus capsulorrhaphy[1,6,7]. However, ligament repair is considered as the only treatment option in instable dislocation[3]. Here, we aimed to present successful outcome in a case who presented with acute instable dislocation of TMC joint and underwent dorsoradial carpal and volar oblique ligament repair after two years of follow-up.

CASE REPORT

A 22-year-old patient who crashed into an abiding object while riding a bike was examined at the Emergency Department. In physical examination, it was found that the thumb of the right hand was deformed and that there was swelling and tenderness at carpometacarpal joint level (Figure 1). In radiological assessment, it was seen that TMC joint was partially dislocated (Figure 2). Reduction in TMC joint was performed in the Emergency Department but the TMC joint was found to be unstable in Torque test. Thus, the patient underwent surgery under general anesthesia. The joint was exposed via Wagner approach and it was seen that TMC joint was displaced and that subluxation was relapsed after reduction. In addition, it was seen that dorsoradial carpal ligament was avulsed from base of metacarpal bone whereas oblique ligament was avulsed over trapezium (Figure 3). After reduction, both ligaments were repaired at avulsion site by 2.0

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Anchor sutures. Then, capsulorrhaphy was performed and TMC joint was stabilized by two K-wires. The surgery was completed by closing the surgery site using the appropriate technique. The short-arm splint was applied for thumb. Postoperative radiological assessment revealed successful reduction in TMC joint (Figure 4). The K-wires were removed at week 3, while splint was removed at week 6 after surgery. Rehabilitation program was initiated thereafter. On control visit at year 2, it was observed that TMC joint was stable without degenerative changes (Figure 5) and that VAS pain score was “0” and range of motion was comparable to contralateral side.

DISCUSSION

Several mechanisms regarding trauma exposed have been defined in dislocation of TMC joint. Among these, the most common mechanism is dislocation caused by axial loading during mild flexion of thumb\(^2\), while the second most common mechanism is shearing force on first web\(^8\). In our case, dislocation occurred due to latter mechanism of injury. The injury occurred due to shearing force applied on first web by handlebar when the patient crashed into an abiding object with a bike.
In the dislocation of TMC joint, the diagnosis is generally made by radiographs, which also show avulsion fractures that may accompany the dislocation. Besides, instability should be assessed at clinical assessment. Torque test is widely used for this purpose[9]. Magnetic resonance imaging (MRI) can be used in acute cases, if diagnosis couldn’t be established by radiographs or those with delayed presentation[10]. The MRI will help to define injuries of capsule and ligaments that may accompany the dislocation, and it might be useful in very limited cases. In our case, radiography was sufficient to establish diagnosis. The dislocation was established and no avulsion fracture was observed on radiographs. The torque test after closed reduction showed presence of instability. No advanced imaging modality such as MRI was needed as radiographs established diagnosis. Also, computed tomography would be more helpful for diagnosis if a fracture occurred with the dislocation.

In these cases, one should be careful and may need to use different therapeutic modalities in order to achieve stable and functional joint due to anatomy of TMC joint[11]. Capsule and ligament damages can be present at varying rates in acute unstable dislocations of TMC[10]. Thus, early repair of ligaments is recommended in instable dislocations[6]. However, closed reduction plus casting or pinning can be preferred in the absence of instability[12]. We preferred open reduction and repair in dorsoradial carpal, and volar oblique ligaments as well as capsule due to instability following closed reduction. End-to-end repair is possible in primary cases, while anchor suturing provides better outcome if ligament damage occurs via avulsion injury[7]. In our case, both ligaments were repaired at avulsion site by 2.0 Anchor sutures; dorsoradial carpal ligament was avulsed from base of metacarp whereas oblique ligament was avulsed over trapezium. In addition, temporary fixation by K-wire is recommended if there is doubt in ensuring stability after ligament and capsule repair. In order to enhance stability, we also performed fixation by two K-wires, which were removed at week 3 after surgery. Ligament reconstruction will be warranted in cases with delayed presentation, failed conservative treatment or those with instability, since primary ligament repair is impossible[13]. Ligament reconstruction is a more invasive and challenging surgical technique. Thus, one should attempt to ensure stable joint in acute cases. In the literature, there are a lot of controversies about management such as closed reduction and casting, closed reduction and pinning or open reduction and ligament reconstruction. The surgeon must decide on the treatment based on the instability of the joint and the level of injury (acute or chronic).

Prognosis will be better in cases with dislocation of TMC joint when acute treatment is provided. However, secondary arthritis development seems inevitable in cases with instability and ongoing subluxation despite treatment[8]. In our case, no arthritic change was observed after two-year follow-up, as joint stability was achieved.

CONCLUSION

Acute dislocation of TMC joint is a rare entity and they are often unstable injuries. A stable and functional joint should be aimed due to anatomy of TMC joint. Thus, ligament repair and capsulorrhaphy should be preferred in acute instable TMC dislocation, which will provide better prognosis.

REFERENCES


Case Report

Stone formation on a surgical tack migrated to the bladder 7 years after laparoscopic incontinence surgery

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ABSTRACT

A 53-year-old woman admitted to our outpatient urology clinic with complaints of dysuria, urgency and recurrent urinary tract infection (UTI). She had undergone an unknown laparoscopic incontinence surgery seven years ago that we considered being burch colposuspension. She had recurrent UTI for more than one year. Plain radiography showed multiple radiopaque helical materials and semi-opacity in bony pelvis. Cystoscopic evaluation revealed a 3 cm stone fixed at the dome of the urinary bladder. Stone was fragmented endoscopically using pneumatic lithotripter. After fragmentation of the stone, three tacks became apparent. The adhered tack was removed with the aid of grasping forceps by a rotation maneuver. It was not possible to remove the embedded tacks and the operation was ended. One month later, the patient underwent cystoscopy. The bladder mucosa was exactly intact and no tack was visible. Migration of tacks into the bladder after laparoscopic incontinence surgery must be kept in mind, especially in patients with recurrent UTI and lower urinary system symptoms post-surgery. Endoscopic approach by means of a cystoscopy should be the preferred technique because of adhesion at the previous operation side. A rotation maneuver could be used to remove embedded tacks.

KEY WORDS: bladder stone, colposuspension, incontinence, surgical tack

INTRODUCTION

Burch colposuspension has been utilized in the treatment of stress urinary incontinence for many years. Several modified techniques have been described and materials used since the description of the procedure by Burch JC\textsuperscript{[1-3]}. Various complications have been reported related to materials used to fix the paravaginal tissues to the Cooper’s ligament. Herein, we present a patient who developed a large bladder stone due to migrated surgical tack seven years after laparoscopic (L/S) colposuspension.

CASE REPORT

A 53-year-old woman admitted to our outpatient urology clinic with complaints of dysuria, urgency and recurrent urinary tract infection. She had a medical history of type 2 diabetes mellitus and asthma. She was on medication with insulin and inhaler corticosteroid. She had undergone laparoscopic burch colposuspension seven years ago at another institution. She also had recurrent urinary tract infection for more than one year and had taken several courses of various antibiotics. Physical examination and routine blood parameters did not reveal any abnormality. Urine culture yielded >100,000 CFU/mL \textit{Escherichia coli}. After ten days of antibiotic therapy, there was no evidence of infection in either urinalysis or urine culture. Kidney-ureter-bladder radiography showed multiple radiopaque helical materials and semi-opacity in bony pelvis (Figure 1a). Abdominal ultrasonography revealed a 25 mm hyperecogenity suspicious of urinary bladder stone. Non-contrast abdominal computed tomography revealed 2.5 x 2.9 cm opacity consistent with urinary bladder stone and multiple opacities in millimeter size close to symphisis pubis (Figure 1b-1c). The patient was scheduled for cystoscopy and synchronous required intervention. Cystoscopic evaluation revealed a 3 cm stone fixed at the dome of the urinary bladder. Stone was fragmented endoscopically using pneumatic lithotripter. After fragmentation of the stone, three tacks became apparent. Among the three tacks, two were almost embedded into bladder mucosa and one was adhered to the bladder from one edge (Figure 2). The adhered
tack was removed with the aid of grasping forceps by a rotation maneuver. It was not possible to remove the embedded tacks, and the operation was ended. The situation was discussed with the patient. The patient was scheduled for cystoscopy and informed about the possible need of an open surgical removal of the tacks. One month later, the patient underwent cystoscopy. The bladder mucosa was exactly intact and no tack was visible. Her urine analysis was also normal and she had no complaints.

Fig 1: (a) Multiple helical tacks and semi-opacitly close to symhisis pubis on Kidney-Ureter-Bladder radiography; (b) Multiple echogenicities in millimeter size at anterosuperior of the urinary bladder on computed tomography; (c) A 3 cm stone seen in urinary bladder in CT.

DISCUSSION

The Burch colposuspension, described by John C. Burch in 1961, had been the preferred choice of treatment of stress urinary incontinence in women for many years. The main principle of the operation is fixation of perivaginal tissues to the Cooper’s ligament to restore the normal anatomy of the bladder neck[1]. Over the decades, several modifications on the procedure have been made in terms of type of surgery (open/laparoscopic) and materials used[2-4]. In early 1990’s, L/S colcosuspension emerged as a minimal invasive technique with shorter convalescence and smaller incisions compared to open surgery. Despite its advantages, it has been related to more surgical complications and poorer outcomes[5]. One of the main difficulties encountered in L/S colcosuspension, especially by inexperienced surgeons, is placing sutures in a restricted area. Using a hernia mesh and tacker was considered to overcome the suturing difficulty[6]. Various complications have been reported in using mesh, suture or tack including migration of tack into the bladder, stone formation in the bladder, and suture, mesh and tack erosion[7-10]. Foreign bodies like sutures and tacks can act as a nidus in the urinary tract for stone formation. There are a few reports in the literature describing stone formation on sutures and tacks[7,8,10]. Arunkalaivanan[10] reported a stone 1 cm in diameter on a suture after L/S colpususpension which was removed by forceps cystoscopically. Salvareci et al[7] also reported a small stone in the bladder surrounding a tack utilized in L/S Burch colposuspension, which was extracted by means of a forceps endoscopically. In the present case, we have reported the largest stone in dimension that has ever been reported in the literature. Moreover, the stone was fragmented with a lithotripter, which made three tacks visible. A rotation maneuver was used to remove the tack embedded to the urothelium.

CONCLUSION

Migrations of tacks into the bladder after L/S incontinence surgery must be keep in mind, especially in patients with recurrent urinary tract infection and lower urinary system symptoms post-surgery. Endoscopic approach by means of a cystoscope should be the preferred technique because of the cohesion at the previous operation side. A rotation maneuver could be used to remove embedded tacks. When cystoscopic intervention fails, the surgeon may repeat cystoscopy 4 - 6 weeks later to avoid unnecessary re-operation, in case of urothelium covering the almost embedded tackers.

Fig 2: Cystoscopic view of helical tack adhered to bladder wall and embedded tack nearby, which could be seen after stone fragmentation
ACKNOWLEDGMENT
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REFERENCES

COVID-19 infection is a new emerging coronavirus infection[1]. It started in China and has already caused problems in more than 50 countries in Asia, Europe, Africa, America and Australia. Typically, the new infection presents with acute febrile illness. The patient usually has respiratory problems, and severe respiratory distress might occur[2-4]. Regarding basic laboratory investigation, lymphopenia is a hematological finding from complete blood count[2-4]. Here, the authors reappraised clinical data published to summarize the frequency of lymphopenia and expected range of lymphocyte count. Based on available data of 278 cases with COVID[2-4], lymphopenia occurred in 158 cases, giving a summative frequency of lymphopenia as 56.83% (95% confidence interval: 51.3% - 62.97%). The expected range (mean ± 2 SD) of lymphocyte count is 0.84 ± 0.14 x 10^9/L (expected range: 0.70 – 0.98 x 10^9/L). It can be seen that lymphopenia might not occur in all cases (since it is usually used as a local criteria for further working up for diagnosis of COVID-19), and if the criteria of lymphopenia is used for primary recruiting for suspicious COVID-19 cases, missed diagnosis is likely to occur.

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Conflict of Interest: None

REFERENCES

Rhinoconjunctivitis among Adolescents in Kuwait and Associated Risk Factors: A Cross-Sectional Study

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Rhinoconjunctivitis is a public health problem that causes major illness and disability worldwide. Epidemiological studies intended to determine the burden of rhinoconjunctivitis in Kuwait are limited. Hence, this study sought to estimate the prevalence of rhinoconjunctivitis among adolescents in Kuwait and explore its association with different risk factors. Schoolchildren aged 11-14 years (n = 3,864) were enrolled in a cross-sectional study. Parents completed questionnaires regarding their children’s clinical history and symptoms of rhinoconjunctivitis and relevant exposures. Associations were assessed using Poisson regression with robust variance estimation, and adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) were estimated. The 12-month (current) prevalence estimates of rhinitis, rhinoconjunctivitis, and severe rhinoconjunctivitis were 28.6% (1,040/3,643), 13.5% (497/3,689), and 1.2% (44/3,689), respectively. The prevalence of current rhinoconjunctivitis symptoms was higher in boys compared to girls (aPR = 1.19, 95% CI: 1.01-1.41). Parental history of rhinitis and asthma showed positive associations with rhinoconjunctivitis in offspring. Trend analyses showed that rhinoconjunctivitis prevalence decreased with increasing numbers of total siblings (aPR = 0.92, \( P_{\text{trend}} < 0.001 \)) and older siblings (aPR = 0.90, \( P_{\text{trend}} < 0.001 \)). Rhinoconjunctivitis is common among adolescents in Kuwait and its epidemiology is similar to that found in western countries.

Elevated concentrations of bromate in drinking water and groundwater from Kuwait and associated exposure and health risks

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Drinking water is an important source of human exposure to bromate, an ubiquitous environmental contaminant and a suspect human carcinogen. Nevertheless, little is known with regard to bromate
exposure from water produced by thermal desalination of seawater. The purpose of this study was to determine the occurrence of bromate in desalinated drinking water and groundwater from Kuwait and estimate associated exposure and health risks to consumers. In this study, 194 tap and ground water samples collected from Kuwait were analyzed for the presence of bromate and bromide (reduced form of bromine). Bromate was found in almost all tap water samples with a mean concentration of 19.6 μg/L, which is higher than the maximum acceptable contaminant level (MCL) of 10 μg/L. The mean concentration of bromide in tap water samples was 46.2 μg/L. In bottled water, lower mean bromate concentration was found (2.89 μg/L) with mean bromide levels at 76.1 μg/L. Saline brackish water had bromate concentration at 9.48 μg/L while bromate was not detected in saline groundwater/well water samples. The mean estimated daily intake (EDI) of bromate by the Kuwaiti population through tap water and commonly consumed bottled water was 21.7 μg/d and 3.21 μg/d, respectively. Among the five age groups, 3 to 5-year-old children had the highest EDI of bromate at 15.4 μg/d. The excess cancer risk due to ingestion of bromate in tap water was estimated to be 3.92 × 10⁻⁴, which is approximately one order of magnitude higher than the maximum acceptable level of risk (2 × 10⁻⁵). This study highlights the significance of desalinated water as a source of bromate exposure.

Physical Therapists with Work-Related Musculoskeletal Disorders in the State of Kuwait: A Comparison across Countries and Health Care Professions

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BACKGROUND
In the US, as the demands for rehabilitation services increase, work-related musculoskeletal disorders (WMSDs) have increased among rehabilitation practitioners. This trend has been noticed among physical therapists (PTs) in the State of Kuwait.

OBJECTIVE
The purpose of this study was to determine the prevalence and risk factors associated with WMSDs among PTs in Kuwait over a 12-month period. In addition, the result compared across countries and health care professions.

METHODS
A descriptive cross-sectional design was used in this study. A self-administered questionnaire was distributed to the PT departments at Kuwait government hospitals and schools. A total of 312 returned questionnaires (69.3% response rate) were received.

RESULTS
Results showed that 149 (48%) PT respondents experienced WMSDs. The lower back and muscle spasm were the most common area of the body injured and type of injury, respectively. Manual therapy techniques and patient transfers were most common activities associated with injuries.

CONCLUSIONS
The prevalence of PTs with WMSDs in Kuwait was high and similar to other studies of PTs with WMSDs working in other countries. The performance of work activities was the leading risk factor for WMSDs, and WMSDs were prevalent among industrialized, industrially developing, and underdeveloped countries. Education of PTs regarding ergonomic and biomechanical principles as well as hands-on training of patient handling are the key tools to help prevent WMSDs.
Forthcoming Conferences and Meetings

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Vineetha Elizabeth Mammen

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23rd Global Summit on Paediatrics, Neonatology and Primary Care
Jun 12 - 13, 2020
Turkey / Istanbul
Email: paediatrics@memeetings.com

13th International Conference on Anaesthesiology and Critical care
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Email: anaesthesiology@memeetings.com

24th Annual Congress on Paediatrics and Neonatology
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Email: pediatriccare@asiapacificmeets.com

16th International Conference on Digestive Disorders and Gastroenterology
Jun 08 - 09, 2020
Thailand / Bangkok
Email: gi@expert-meetings.com

24th World Congress on Neonatology and Perinatology
Jun 08 - 09, 2020
Thailand / Bangkok
Email: neonatologycongress@asia-meetings.com

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Germany / Frankfurt
Email: eurovaccines@brainstormingmeetings.com

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Thailand / Bangkok
Email: diabetessummit@asia-meetings.com

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Email: neonatalcongress@asiameets.com

7th Asia Pacific Gynecology and Obstetrics Congress
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Singapore / Singapore
Email: gynecology@asiameets.com

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Jun 15 - 16, 2020
Spain / Barcelona
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35th International Conference on Dental and Oral Health
Jun 15 - 16, 2020
United Arab Emirates / Abu Dhabi
Email: dentalmanagement@memeetings.com

29th International Conference on Insights in Ophthalmology
Jun 17 - 18, 2020
United Kingdom / London
Email: ophthalmologysummit@europeannualconference.com

17th International Conference on Paediatrics and Pediatric Cardiology
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France / Paris
Email: pediatriccardiology@europemeet.com

31st European Heart and Heart Failure Congress
Jun 18 - 19, 2020
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Email: heartfailure@europemeet.com

2nd International Conference on Gynecology and Obstetrics
Jun 18 - 19, 2020
Switzerland / Geneva
Email: gynecology@europemeet.com
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Email: eurohypertension@europemeet.com

16th World Conference on Cosmetic Dermatology and Aesthetic Medicine
Jun 22 - 23, 2020
France / Paris
Email: cosmetology@europemeet.com

11th World Conference on Gynecology, Obstetrics and Women Health
Jun 22 - 23, 2020
Czech Republic / Prague
Email: gynecology@globalannualsummit.com

30th International Conference on Paediatrics, Neonatology and Pediatric Nursing
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Czech Republic / Prague
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World Congress on Pediatric Neurology and Neuropathology
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Email: meevents@memeetings.com

5th World Kidney Congress
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United Arab Emirates / Abu Dhabi
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3rd Middle East Obesity, Bariatric Surgery and Endocrinology Congress
Jun 22 - 23, 2020
United Arab Emirates / Abu Dhabi
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3rd International Conference on Advances in Neonatal and Pediatric Nutrition
Jun 22 - 23, 2020
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26th International Conference on Human Metabolic Health-Diabetes, Obesity & Endocrinology
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16th International Conference on Nephrology and Hypertension
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United Arab Emirates / Abu Dhabi
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27th International Conference and Exhibition on Cardiology and Cardiovascular Medicine
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Email: cardiomeet@expert-meetings.com

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Jun 23 - 24, 2020
Japan / Tokyo
Email: hypertension@asiaconvention.com

International Conference on Cardiology and Heart Failure
Jun 23 - 24, 2020
Malaysia / Kuala Lampur
Email: heartfailure@asiameets.com

3rd International Conference on Vaccines, Immunology and Clinical Trials
Jun 24 - 25, 2020
Netherlands / Amsterdam
Email: vaccineresearch@europemeet.com

15th Euro-Global Gastroenterology Conference
Jun 24 - 25, 2020
Italy / Rome
Email: gastrocongress@brainstormingmeetings.com

22nd World Dermatology and Aesthetic Congress
Jun 25 - 26, 2020
United Arab Emirates / Abu Dhabi
Email: aestheticmeet@memeetings.com

World Congress on Pediatric and Neonatal Nursing
Jun 25 - 26, 2020
Indonesia / Bali
Email: pediatricnursing@asiameets.com
Forthcoming Conferences and Meetings June 2020

Asian Cardiology Congress
Jun 25 - 26, 2020
Japan / Osaka
Email: asiancardiology@asia-meetings.com

3rd World Congress on Surgeons
Jun 25 - 26, 2020
United Arab Emirates / Abu Dhabi
Email: surgeons@memeetings.com

2nd World Cardiology and Cardiac Rehabilitation Meeting
Jul 01 - 02, 2020
Greece / Athens
Email: cardiology@europemeet.com

2nd World Congress on Advancements in Tuberculosis and Lung Diseases
Jul 02 - 03, 2020
Netherlands / Amsterdam
Email: tuberculosis@asiameets.com

2nd International Conference on Womens Health, Gynecology and Obstetrics
Jul 06 - 07, 2020
Australia / Sydney
Email: womenhealth@asia-meetings.com

5th Annual Meet on Obesity and Diet
Jul 09 - 10, 2020
Austria / Vienna
Email: obesity@insightmeet.com

Euro Ophthalmology and Eye Surgery Conference
Jul 13 - 14, 2020
Finland / Helsinki
Email: eyesurgery@mehealthmeetings.com

International Conference on Hepatitis and Liver Diseases
Jul 13 - 14, 2020
Australia / Sydney
Email: hepatitisasia@asia-meetings.com

2nd International Conference on Dermatology and Allergic Diseases
Jul 13 - 14, 2020
Finland / Helsinki
Email: allergicdiseases@memeetings.com

22nd World Congress on Toxicology and Pharmacology
Jul 14 - 15, 2020
Japan / Kyoto
Email: toxicology@globalconferences.net

16th International Conference on Surgical Pathology and Cancer Diagnosis
Jul 15 - 16, 2020
United Kingdom / London
Email: surgicalpathology@surgeryconventions.com

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Malaysia / Kuala Lampur
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9th International Conference on Sports Medicine, Physical Rehabilitation and Physiotherapy
Jul 15, 2020
United Kingdom / London
Email: michaelsmith@conferenceseries.com

13th International Conference on Orthopaedics, Arthroplasty and Rheumatology
Jul 17 - 18, 2020
Austria / Vienna
Email: orthopaedics@sciencesummits.com

20th World Gastroenterologists Summit
Jul 20 - 21, 2020
Japan / Osaka
Email: gastroenterologists@asia-meetings.com

9th Annual Congress on Primary Healthcare, Nursing and Neonatal Screening
Jul 20 - 21, 2020
Canada / Vancouver
Email: primaryhealthcare@americameetings.com

Annual Summit on Cardiology and Heart Diseases
Jul 20 - 21, 2020
Canada / Montreal
Email: cardiology@annualamericacongress.org

29th International Conference on Clinical and Experimental Cardiology Research
Jul 20 - 21, 2020
Canada / Montreal
Email: clinicalcardiology@eventsupporting.org

19th Annual World Congress on Neonatology
Jul 20 - 21, 2020
Canada / Vancouver
Email: neonatal@pediatricsconferences.com

2nd International Conference on Pediatric Pharmacology and Therapeutics
Jul 20 - 21, 2020
Canada / Vancouver
Email: pediatricpharma@eventsupporting.org
International Conference on Paediatrics, Child Health and Emergency Care
Jul 22 - 23, 2020
Italy / Florence
Email: pediatricshealth@contactexperts.org

32nd European Paediatrics Congress
Jul 22 - 23, 2020
Italy / Florence
Email: europediatrics@europemeet.com

International Congress on Reproductive Health and Medicine
Jul 23 - 24, 2020
Netherlands / Amsterdam
Email: reproductivehealth@asiameets.com

33rd World Congress on Cardiology and Heart Diseases
Jul 27 - 28, 2020
Czech Republic / Prague
Email: cardiology@globalannualmeet.com

4th International Conference on Ophthalmology
Aug 07 - 08, 2020
Japan / Osaka
Email: worldophthalmology@asia-meetings.com

5th International Anesthesia and Pain Medicine Conference
Aug 10 - 11, 2020
United Arab Emirates / Dubai
Email: anesthesiamaeetings.com

30th International Cardiology and Healthcare
Aug 10 - 11, 2020
United Arab Emirates / Dubai
Email: cardiology@memeeetings.com

3rd International Dermatology Conference: Skin and Body
Aug 13 - 14, 2020
United Arab Emirates / Dubai
Email: skincares@memeeetings.com

5th Global Meeting on Plastic, Aesthetic and Reconstructive Surgery
Aug 17 - 18, 2020
United Kingdom / London
Email: plasticsurgery@medicalscienceconference.com

10th International Conference on COPD and Lungs
Aug 17 - 18, 2020
Czech Republic / Prague
Email: earthscience@conferenceseries.org

20th World Conference on Environmental Toxicology and Pharmacology
Aug 19 - 20, 2020
Japan / Tokyo
Email: envitoxsummit@globalconferences.net

29th World Congress on Neonatology and Perinatology
Aug 20 - 21, 2020
Prague / Czech Republic
Email: neonatologymeet@asiameets.com

34th International Conference on Neonatology and Perinatology
Aug 20 - 21, 2020
France / Paris
Email: neonatology@brainstormingmeetings.com

18th Global Conference on Diabetes, Endocrinology and Primary Healthcare
Aug 21 - 22, 2020
Switzerland / Geneva
Email: globaldiabetes@europemeet.com

2nd European Cardiology Congress
Aug 21 - 22, 2020
Italy / Florence
Email: eurocardiology@europemeet.com

4th International Conference on Craniofacial Surgery
Aug 24 - 25, 2020
Spain / Barcelona
Email: craniofacial@sciencesummits.com

World Congress on Ophthalmology & Optometry
Aug 24 - 25, 2020
United Kingdom / London
Email: neuroophthalmology@medicalscienceconference.com

4th Global Summit on Surgery and Anaesthesia
Aug 24 - 25, 2020
Ireland / Dublin
Email: surgeryconference@insightmeet.com

Asia Orthopedics Congress
Aug 26 - 27, 2020
Singapore / Singapore
Email: orthopedics@asiaconvention.com

4th World Congress on Diabetes and Endocrine Disorders
Aug 27 - 28, 2020
Czech Republic / Prague
Email: worlddiabetes@insightmeet.com
30th International Congress on Vision Science and Eye
Aug 28 - 29, 2020
Spain / Barcelona
Email: visionscience@brainstormingmeetings.com

International Conference and Expo on Heart Ailments
Sep 07 - 08, 2020
Czech Republic / Prague
Email: cardiologycongress@expert-meetings.com

22nd World Nephrologists Summit
Sep 07 - 08, 2020
Japan / Tokyo
Email: nephrologists@theexpertsmeet.com

Global summit on Maternal, Infant and Child Health
Sep 09 - 10, 2020
Netherlands / Amsterdam
Email: maternal@asiameets.com

International Conference on Aesthetic science and plastic surgery
Sep 10 - 11, 2020
Netherlands / Amsterdam
Email: aestheticmedicine@theexpertsmeet.com

2nd World Congress on Pain Medicine and Management
Sep 14 - 15, 2020
Japan / Tokyo
Email: painmedicine@asiameets.com

11th International Congress on Clinical and Medical Case Reports
Sep 14 - 15, 2020
Austria / Vienna
Email: casereport@europemeet.com

30th International Conference on Pediatrics & Primary Care
Sep 16 - 17, 2020
Italy / Rome
Email: pediatricprimarycare@brainstormingmeetings.com

Asia Pacific conference on Dermatology and Cosmetology
Sep 16 - 17, 2020
Malaysia / Kuala Lumpur
Email: dermatologymeet@asiaconvention.com

5th World Congress on Nephrology and Renal Care
Sep 16 - 17, 2020
Spain / Barcelona
Email: nephrology@insightmeet.com

International Conference on Cardiac Imaging and Diagnostics
Sep 18 - 19, 2020
United Arab Emirates / Dubai
Email: meevents@memeetings.com

2nd International Conference on Cell Metabolism
Sep 18 - 19, 2020
United Arab Emirates / Dubai
Email: cellmetabolism@meconferences.org

2nd Annual Conference on Vascular Medicine
Sep 18 - 19, 2020
United Arab Emirates / Dubai
Email: meeevents@memeetings.com

9th World Congress on Addictive Disorders & Addiction Therapy
Sep 21 - 22, 2020
Italy / Rome
Email: info@conferencesint.com

14th International Conference on Orthopedics, Arthroplasty and Rheumatology
Sep 21 - 22, 2020
Italy / Rome
Email: orthopedics@brainstormingmeetings.com

2nd World Cardiology Experts Meeting
Sep 21 - 22, 2020
Spain / Valencia
Email: worldcardiology@asiapacificmeets.com

30th International Conference on Pediatrics, Neonatology and Pediatric Nursing
Sep 21 - 22, 2020
Germany / Berlin
Email: pediatrics@europeannualconference.com

International Conference on Heart Surgery
Sep 21 - 22, 2020
Scotland / Edinburgh
Email: heartsurgery@euroannualmeetings.com

6th World Heart Congress
Sep 21 - 23, 2020
France / Paris
Email: heartcongress@cardiologymeeting.com

2nd Asia Pacific Endocrinology Congress
Sep 22 - 23, 2020
Singapore / Singapore
Email: asiaendocrinology@asiaconvention.com
International Conference on Dialysis
Sep 22 - 23, 2020
United Arab Emirates / Dubai
Email: dialysis@mhealthmeetings.com

31st International Congress on Prevention of Diabetes and Complications
Sep 23 - 24, 2020
Italy / Rome
Email: diabetesmeetings@europeannualconference.com

19th International Conference on Gastroenterology and Digestive Disorders
Sep 24 – 25, 2020
United Arab Emirates / Dubai
Email: gastro@memeetings.com

5th International Conference on Cardiovascular Medicine and Cardiac Surgery
Sep 23 - 24, 2020
Germany / Berlin
Email: cardiovascular@brainstormingmeetings.com

20th International Conference on Gastroenterology and Hepatology
Sep 24 - 25, 2020
United Arab Emirates / Dubai
Email: gastrocongress@memeetings.com

International Conference on Orthopedics and Sports Medicine
Sep 24 - 25, 2020
United Arab Emirates / Dubai
Email: orthosportsmeet@memeetings.com

6th Annual Congress on Traditional and Alternative Medicine
Sep 24 - 25, 2020
France / Paris
Email: alternativemedicine@sciencesummits.com

International Conference on Orthodontics
Sep 25 - 26, 2020
United Arab Emirates / Dubai
Email: meevents@memeetings.com

27th International Conference & Exhibition on Cardiovascular and Thoracic Surgery
Sep 28 - 29, 2020
China / Beijing
Email: cardiovascular@asia-meetings.com

4th Global Congress on Bacteriology and Infectious Diseases
Sep 28 - 29, 2020
Czech Republic / Prague
Email: reachus@conferencesmeet.com
WHO-Facts Sheet

1. COVID-19
2. Depression
3. Musculoskeletal Conditions
4. Onchocerciasis

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1. COVID-19

What is a coronavirus?
Coronaviruses are a large family of viruses which may cause illness in animals or humans. In humans, several coronaviruses are known to cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The most recently discovered coronavirus causes coronavirus disease COVID-19.

What is COVID-19?
COVID-19 is the infectious disease caused by the most recently discovered coronavirus. This new virus and disease were unknown before the outbreak began in Wuhan, China, in December 2019. COVID-19 is now a pandemic affecting many countries globally.

What are the symptoms of COVID-19?
The most common symptoms of COVID-19 are fever, dry cough, and tiredness. Other symptoms that are less common and may affect some patients include aches and pains, nasal congestion, headache, conjunctivitis, sore throat, diarrhea, loss of taste or smell or a rash on skin or discoloration of fingers or toes. These symptoms are usually mild and begin gradually. Some people become infected but only have very mild symptoms.

Most people (about 80%) recover from the disease without needing hospital treatment. Around 1 out of every 5 people who gets COVID-19 becomes seriously ill and develops difficulty breathing. Older people, and those with underlying medical problems like high blood pressure, heart and lung problems, diabetes, or cancer, are at higher risk of developing serious illness. However, anyone can catch COVID-19 and become seriously ill. People of all ages who experience fever and/or cough associated with difficulty breathing/shortness of breath, chest pain/pressure, or loss of speech or movement should seek medical attention immediately. If possible, it is recommended to call the health care provider or facility first, so the patient can be directed to the right clinic.

What should I do if I have COVID-19 symptoms and when should I seek medical care?

If you have minor symptoms, such as a slight cough or a mild fever, there is generally no need to seek medical care. Stay at home, self-isolate and monitor your symptoms. Follow national guidance on self-isolation.

However, if you live in an area with malaria or dengue fever it is important that you do not ignore symptoms of fever. Seek medical help. When you attend the health facility wear a mask if possible, keep at least 1 metre distance from other people and do not touch surfaces with your hands. If it is a child who is sick help the child stick to this advice.

Seek immediate medical care if you have difficulty breathing or pain/pressure in the chest. If possible, call your health care provider in advance, so he/she can direct you to the right health facility.

How does COVID-19 spread?
People can catch COVID-19 from others who have the virus. The disease spreads primarily from person to person through small droplets from the nose or mouth, which are expelled when a person with COVID-19 coughs, sneezes, or speaks. These droplets are relatively heavy, do not travel far and quickly sink to the ground. People can catch COVID-19 if they breathe in these droplets from a person infected with the virus. This is why it is important to stay at least 1 meter away from others. These droplets can land...
on objects and surfaces around the person such as tables, doorknobs and handrails. People can become infected by touching these objects or surfaces, then touching their eyes, nose or mouth. This is why it is important to wash your hands regularly with soap and water or clean with alcohol-based hand rub.

WHO is assessing ongoing research on the ways that COVID-19 is spread and will continue to share updated findings.

Can COVID-19 be caught from a person who has no symptoms?

COVID-19 is mainly spread through respiratory droplets expelled by someone who is coughing or has other symptoms such as fever or tiredness. Many people with COVID-19 experience only mild symptoms. This is particularly true in the early stages of the disease. It is possible to catch COVID-19 from someone who has just a mild cough and does not feel ill.

Some reports have indicated that people with no symptoms can transmit the virus. It is not yet known how often it happens. WHO is assessing ongoing research on the topic and will continue to share updated findings.

Protecting yourself and others from the spread of COVID-19

You can reduce your chances of being infected or spreading COVID-19 by taking some simple precautions:

• Regularly and thoroughly clean your hands with an alcohol-based hand rub or wash them with soap and water. Why? Washing your hands with soap and water or using alcohol-based hand rub kills viruses that may be on your hands.

• Maintain at least 1 metre (3 feet) distance between yourself and others. Why? When someone coughs, sneezes, or speaks they spray small liquid droplets from their nose or mouth which may contain virus. If you are too close, you can breathe in the droplets, including the COVID-19 virus if the person has the disease.

• Avoid going to crowded places. Why? Where people come together in crowds, you are more likely to come into close contact with someone that has COVID-19 and it is more difficult to maintain physical distance of 1 metre (3 feet).

• Avoid touching eyes, nose and mouth. Why? Hands touch many surfaces and can pick up viruses. Once contaminated, hands can transfer the virus to your eyes, nose or mouth. From there, the virus can enter your body and infect you.

• Make sure you, and the people around you, follow good respiratory hygiene. This means covering your mouth and nose with your bent elbow or tissue when you cough or sneeze. Then dispose of the used tissue immediately and wash your hands. Why? Droplets spread virus. By following good respiratory hygiene, you protect the people around you from viruses such as cold, flu and COVID-19.

• Stay home and self-isolate even with minor symptoms such as cough, headache, mild fever, until you recover. Have someone bring you supplies. If you need to leave your house, wear a mask to avoid infecting others. Why? Avoiding contact with others will protect them from possible COVID-19 and other viruses.

• If you have a fever, cough and difficulty breathing, seek medical attention, but call by telephone in advance if possible and follow the directions of your local health authority. Why? National and local authorities will have the most up to date information on the situation in your area. Calling in advance will allow your health care provider to quickly direct you to the right health facility. This will also protect you and help prevent spread of viruses and other infections.

• Keep up to date on the latest information from trusted sources, such as WHO or your local and national health authorities. Why? Local and national authorities are best placed to advise on what people in your area should be doing to protect themselves.

Advice on the safe use of alcohol-based hand sanitizers

To protect yourself and others against COVID-19, clean your hands frequently and thoroughly. Use alcohol-based hand sanitizer or wash your hands with soap and water. If you use an alcohol-based hand sanitizer, make sure you use and store it carefully.

- Keep alcohol-based hand sanitizers out of children’s reach. Teach them how to apply the sanitizer and monitor its use.
- Apply a coin-sized amount on your hands. There is no need to use a large amount of the product.
- Avoid touching your eyes, mouth and nose immediately after using an alcohol-based hand sanitizer, as it can cause irritation.
- Hand sanitizers recommended to protect against COVID-19 are alcohol-based and therefore can be flammable. Do not use before handling fire or cooking.
- Under no circumstance, drink or let children swallow an alcohol-based hand sanitizer. It can be poisonous.
Remember that washing your hands with soap and water is also effective against COVID-19.

**When and how to use masks**

- Before putting on a mask, clean hands with alcohol-based hand rub or soap and water.
- Cover mouth and nose with mask and make sure there are no gaps between your face and the mask.
- Avoid touching the mask while using it; if you do, clean your hands with alcohol-based hand rub or soap and water.
- Replace the mask with a new one as soon as it is damp and do not re-use single-use masks.
- To remove the mask: remove it from behind (do not touch the front of mask); discard immediately in a closed bin; clean hands with alcohol-based hand rub or soap and water.
- If you are healthy, you only need to wear a mask if you are taking care of a person with COVID-19.
- Wear a mask if you are coughing or sneezing.
- Masks are effective only when used in combination with frequent hand-cleaning with alcohol-based hand rub or soap and water.

**MYTH BUSTERS**

1. **There are currently no drugs licensed for the treatment or prevention of COVID-19**

   While several drug trials are ongoing, there is currently no proof that hydroxychloroquine or any other drug can cure or prevent COVID-19. The misuse of hydroxychloroquine can cause serious side effects and illness and even lead to death. WHO is coordinating efforts to develop and evaluate medicines to treat COVID-19

2. **Adding pepper to your soup or other meals DOES NOT prevent or cure COVID-19**

   Hot peppers in your food, though very tasty, cannot prevent or cure COVID-19. The best way to protect yourself against the new coronavirus is to keep at least 1 metre away from others and to wash your hands frequently and thoroughly. It is also beneficial for your general health to maintain a balanced diet, stay well hydrated, exercise regularly and sleep well.

3. **COVID-19 IS NOT transmitted through houseflies**

   To date, there is no evidence or information to suggest that the COVID-19 virus transmitted through houseflies. The virus that cause COVID-19 spreads primarily through droplets generated when an infected person coughs, sneezes or speaks. You can also become infected by touching a contaminated surface and then touching your eyes, nose or mouth before washing your hands. To protect yourself, keep at least 1-metre distance from others and disinfect frequently-touched surfaces. Clean your hands thoroughly and often and avoid touching your eyes, mouth and nose.

4. **Spraying and introducing bleach or another disinfectant into your body WILL NOT protect you against COVID-19 and can be dangerous**

   Do not under any circumstance spray or introduce bleach or any other disinfectant into your body. These substances can be poisonous if ingested and cause irritation and damage to your skin and eyes.

   Bleach and disinfectant should be used carefully to disinfect surfaces only. Remember to keep chlorine (bleach) and other disinfectants out of reach of children.

5. **Drinking methanol, ethanol or bleach DOES NOT prevent or cure COVID-19 and can be extremely dangerous**

   Methanol, ethanol, and bleach are poisons. Drinking them can lead to disability and death. Methanol, ethanol, and bleach are sometimes used in cleaning products to kill the virus on surfaces – however you should never drink them. They will not kill the virus in your body and they will harm your internal organs.

   To protect yourself against COVID-19, disinfect objects and surfaces, especially the ones you touch regularly. You can use diluted bleach or alcohol for that. Make sure you clean your hands frequently and thoroughly and avoid touching your eyes, mouth and nose.

6. **Exposing yourself to the sun or to temperatures higher than 25C degrees DOES NOT prevent the coronavirus disease (COVID-19)**

   You can catch COVID-19, no matter how sunny or hot the weather is. Countries with hot weather have reported cases of COVID-19. To protect yourself, make sure you clean your hands frequently and thoroughly and avoid touching your eyes, mouth and nose.

7. **Do vaccines against pneumonia protect you against the new coronavirus?**

   No. Vaccines against pneumonia, such as pneumococcal vaccine and Haemophilus influenza type B (Hib) vaccine, do not provide protection against the new coronavirus.

   The virus is so new and different that it needs its own vaccine. Researchers are trying to develop a vaccine against 2019-nCoV, and WHO is supporting their efforts.

   Although these vaccines are not effective against 2019-nCoV, vaccination against respiratory illnesses is highly recommended to protect your health.
8. Can regularly rinsing your nose with saline help prevent infection with the new coronavirus?

No. There is no evidence that regularly rinsing the nose with saline has protected people from infection with the new coronavirus.

There is some limited evidence that regularly rinsing nose with saline can help people recover more quickly from the common cold. However, regularly rinsing the nose has not been shown to prevent respiratory infections.

9. Can eating garlic help prevent infection with the new coronavirus?

Garlic is a healthy food that may have some antimicrobial properties. However, there is no evidence from the current outbreak that eating garlic has protected people from the new coronavirus.

10. Does the new coronavirus affect older people, or are younger people also susceptible?

People of all ages can be infected by the new coronavirus (2019-nCoV). Older people, and people with pre-existing medical conditions (such as asthma, diabetes, heart disease) appear to be more vulnerable to becoming severely ill with the virus.

WHO advises people of all ages to take steps to protect themselves from the virus, for example by following good hand hygiene and good respiratory hygiene.

11. Are antibiotics effective in preventing and treating the new coronavirus?

No, antibiotics do not work against viruses, only bacteria.

The new coronavirus (2019-nCoV) is a virus and, therefore, antibiotics should not be used as a means of prevention or treatment.

However, if you are hospitalized for the 2019-nCoV, you may receive antibiotics because bacterial co-infection is possible.

12. Are there any specific medicines to prevent or treat the new coronavirus?

To date, there is no specific medicine recommended to prevent or treat the new coronavirus (2019-nCoV).

However, those infected with the virus should receive appropriate care to relieve and treat symptoms, and those with severe illness should receive optimized supportive care. Some specific treatments are under investigation, and will be tested through clinical trials. WHO is helping to accelerate research and development efforts with a range of partners.

2. DEPRESSION

KEY FACTS

- Depression is a common mental disorder. Globally, more than 264 million people of all ages suffer from depression.
- Depression is a leading cause of disability worldwide and is a major contributor to the overall global burden of disease.
- More women are affected by depression than men.
- Depression can lead to suicide.
- There are effective psychological and pharmacological treatments for moderate and severe depression.

Overview

Depression is a common illness worldwide, with more than 264 million people affected(1). Depression is different from usual mood fluctuations and short-lived emotional responses to challenges in everyday life. Especially when long-lasting and with moderate or severe intensity, depression may become a serious health condition. It can cause the affected person to suffer greatly and function poorly at work, at school and in the family. At its worst, depression can lead to suicide. Close to 800 000 people die due to suicide every year. Suicide is the second leading cause of death in 15-29-year-olds.

Although there are known, effective treatments for mental disorders, between 76% and 85% of people in low- and middle-income countries receive no treatment for their disorder(2). Barriers to effective care include a lack of resources, lack of trained health-care providers and social stigma associated with mental disorders. Another barrier to effective care is inaccurate assessment. In countries of all income levels, people who are depressed are often not correctly diagnosed, and others who do not have the disorder are too often misdiagnosed and prescribed antidepressants.

The burden of depression and other mental health conditions is on the rise globally. A World Health Assembly resolution passed in May 2013 has called for a comprehensive, coordinated response to mental disorders at the country level.

Types and symptoms

Depending on the number and severity of symptoms, a depressive episode can be categorized as mild, moderate or severe.

A key distinction is also made between depression in people who have or do not have a history of manic episodes. Both types of depression can be chronic (i.e. over an extended period) with relapses, especially if they go untreated.
Recurrent depressive disorder: this disorder involves repeated depressive episodes. During these episodes, the person experiences depressed mood, loss of interest and enjoyment, and reduced energy leading to diminished activity for at least two weeks. Many people with depression also suffer from anxiety symptoms, disturbed sleep and appetite, and may have feelings of guilt or low self-worth, poor concentration and even symptoms that cannot be explained by a medical diagnosis.

Depending on the number and severity of symptoms, a depressive episode can be categorized as mild, moderate or severe. An individual with a mild depressive episode will have some difficulty in continuing with ordinary work and social activities but will probably not cease to function completely. During a severe depressive episode, it is unlikely that the sufferer will be able to continue with social, work or domestic activities, except to a limited extent.

Bipolar affective disorder: this type of depression typically consists of both manic and depressive episodes separated by periods of normal mood. Manic episodes involve elevated or irritable mood, over-activity, pressure of speech, inflated self-esteem and a decreased need for sleep.

Contributing factors and prevention
Depression results from a complex interaction of social, psychological and biological factors. People who have gone through adverse life events (unemployment, bereavement, psychological trauma) are more likely to develop depression. Depression can, in turn, lead to more stress and dysfunction and worsen the affected person’s life situation and depression itself.

There are interrelationships between depression and physical health. For example, cardiovascular disease can lead to depression and vice versa.

Prevention programmes have been shown to reduce depression. Effective community approaches to prevent depression include school-based programmes to enhance a pattern of positive thinking in children and adolescents. Interventions for parents of children with behavioural problems may reduce parental depressive symptoms and improve outcomes for their children. Exercise programmes for the elderly can also be effective in depression prevention.

Diagnosis and treatment
There are effective treatments for moderate and severe depression. Health-care providers may offer psychological treatments such as behavioural activation, cognitive behavioural therapy (CBT) and interpersonal psychotherapy (IPT), or antidepressant medication such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Health-care providers should keep in mind the possible adverse effects associated with antidepressant medication, the ability to deliver either intervention (in terms of expertise, and/or treatment availability), and individual preferences. Different psychological treatment formats for consideration include individual and/or group face-to-face psychological treatments delivered by professionals and supervised lay therapists.

Psychosocial treatments are also effective for mild depression. Antidepressants can be an effective form of treatment for moderate-severe depression but are not the first line of treatment for cases of mild depression. They should not be used for treating depression in children and are not the first line of treatment in adolescents, among whom they should be used with extra caution.

WHO response
Depression is one of the priority conditions covered by WHO’s mental health Gap Action Programme (mhGAP). The Programme aims to help countries increase services for people with mental, neurological and substance use disorders through care provided by health workers who are not specialists in mental health. WHO has developed brief psychological intervention manuals for depression that may be delivered by lay workers. An example is Problem Management Plus, which describes the use of behavioural activation, relaxation training, problem solving treatment and strengthening social support. Moreover, the manual Group Interpersonal Therapy (IPT) for Depression describes group treatment of depression. Finally, Thinking Healthy covers the use of cognitive-behavioural therapy for perinatal depression.

REFERENCES
3. MUSCULOSKELETAL CONDITIONS

KEY FACTS

- Musculoskeletal conditions are the leading contributor to disability worldwide, with low back pain being the single leading cause of disability globally.
- Musculoskeletal conditions and injuries are not just conditions of older age; they are prevalent across the life-course. Between one in three and one in five people (including children) live with a musculoskeletal pain condition.
- Musculoskeletal conditions significantly limit mobility and dexterity, leading to early retirement from work, reduced accumulated wealth and reduced ability to participate in social roles.
- The greatest proportion of non-cancer persistent pain conditions is accounted for by musculoskeletal conditions.
- Highly prevalent among multi-morbidity health states, musculoskeletal conditions are prevalent in one third to one-half of multi-morbidity presentations, particularly in older people.
- Musculoskeletal conditions are commonly linked with depression and increase the risk of developing other chronic health conditions.

Introduction

Musculoskeletal conditions comprise more than 150 diagnoses that affect the locomotor system; that is, muscles, bones, joints and associated tissues such as tendons and ligaments, as listed in the International Classification of Diseases. They range from those that arise suddenly and are short-lived, such as fractures, sprains and strains, to lifelong conditions associated with ongoing pain and disability.

Musculoskeletal conditions are typically characterised by pain (often persistent) and limitations in mobility, dexterity and functional ability, reducing people’s ability to work and participate in social roles with associated impacts on mental wellbeing, and at a broader level impacts on the prosperity of communities. The most common and disabling musculoskeletal conditions are osteoarthritis, back and neck pain, fractures associated with bone fragility, injuries and systemic inflammatory conditions such as rheumatoid arthritis.

Musculoskeletal conditions include conditions that affect:

- the spine, such as back and neck pain;
- multiple body areas or systems, such as regional and widespread pain disorders and inflammatory diseases such as connective tissue diseases and vasculitis that have musculoskeletal manifestations, for example systemic lupus erythematosus.

Musculoskeletal conditions are prevalent across the life-course and most commonly affect people from adolescence through to older age. The prevalence and impact of musculoskeletal conditions is predicted to rise as the global population ages and the prevalence of risk factors for noncommunicable diseases increases, particularly in low- and middle-income settings. Musculoskeletal conditions occur commonly with other noncommunicable diseases in multimorbidity health states.

Scope of the health issue

Musculoskeletal conditions affect people across the life-course in all regions of the world. Musculoskeletal conditions were the leading cause of disability in four of the six WHO regions in 2017 (ranked second in the East Mediterranean Region and third in the African Region). While the prevalence of musculoskeletal conditions increases with age, younger people are also affected, often during their peak income-earning years.

The Global Burden of Disease (GBD) study provides evidence of the impact of musculoskeletal conditions, highlighting the significant disability burden associated with these conditions. In the 2017 GBD study, musculoskeletal conditions were the highest contributor to global disability (accounting for 16% of all years lived with disability), and lower back pain remained the single leading cause of disability since it was first measured in 1990 (1). While the prevalence of musculoskeletal conditions varies by age and diagnosis, between 20%–33% of people across the globe live with a painful musculoskeletal condition.

A recent report from the United States of America suggests that one in two adult Americans live with a musculoskeletal condition – the same number as those with cardiovascular or chronic respiratory diseases combined (2).

Analysis of data from WHO's Study on global AGEing and adult health (SAGE) point to the high prevalence of arthritis in low- and middle-income settings, particularly among those in a lower socioeconomic position (3).

- WHO Study on global AGEing and adult health (SAGE)

Signs and symptoms

Pain and restricted mobility are the unifying features of the range of musculoskeletal conditions.
Pain is typically persistent for long-term conditions. In some conditions, joint deformity may occur, where early diagnosis and treatment are not available.

**Prevention and management**

Musculoskeletal conditions share some similar risk factors to other noncommunicable diseases, such as inadequate physical activity, obesity, smoking and poor nutrition. While management of some musculoskeletal conditions may require specialist and/or surgical care, many musculoskeletal conditions can be managed in primary care through a combination of core non-pharmacologic interventions such as exercise, weight management, psychological therapies and pharmacologic therapies.

**Social and economic implications**

The health and broader social cost of musculoskeletal conditions are significant. Spending on musculoskeletal conditions is challenging to measure due to the vast array of musculoskeletal conditions and limitations in health surveillance systems. Orthopaedic surgery procedures, for example total joint replacement, account for one of the greatest hospital expenditures. Data are particularly scarce in low- and middle-income areas. Musculoskeletal conditions account for the greatest proportion of lost productivity in the workplace. In 2011, musculoskeletal conditions cost US$ 213 billion – 1.4% of Gross Domestic Product (2).

**WHO response**

WHO recognises that musculoskeletal health conditions contribute greatly to disability across the life-course in all regions of the world. In particular, WHO recognises that musculoskeletal conditions significantly impact functional ability. In this context, WHO is responding through the Integrated Care for Older People (ICOPE) approach, which identifies the need to improve musculoskeletal function through a range of interventions, with multimodal exercise as a key component.

**Integrated Care for Older People**

The need to address impairments in musculoskeletal health is also identified in WHO’s Global Programme of Work on rehabilitation, in order to improve peoples’ performance. Prevention of musculoskeletal trauma is addressed in WHO’s Global Programme of Work on road traffic injuries.

**REFERENCES**


4. ONCHOCERCIASIS

**KEY FACTS**

- Onchocerciasis, commonly known as “river blindness”, is caused by the parasitic worm Onchocerca volvulus.
- It is transmitted to humans through exposure to repeated bites of infected blackflies of the genus Simulium
- Symptoms include severe itching, disfiguring skin conditions, and visual impairment, including permanent blindness.
- More than 99% of infected people live in 31 African countries. The disease also exists in some foci in Latin America and Yemen.
- The Global Burden of Disease Study estimated in 2017 that there were 20.9 million prevalent O. volvulus infections worldwide: 14.6 million of the infected people had skin disease and 1.15 million had vision loss.
- Community-directed treatment with ivermectin is the core strategy to eliminate onchocerciasis in Africa. In the Americas the strategy is biannual large-scale treatment with ivermectin.
- Four countries have been verified by WHO as free of onchocerciasis after successfully implementing elimination activities for decades: Colombia, Ecuador, Mexico, and Guatemala.
- By the end of 2017, three additional countries had stopped mass drug administration and completed 3 years of post-treatment surveillance in at least one transmission area: Bolivarian Republic of Venezuela, Uganda, and Sudan.
- 1.8 million people live in areas that no longer require mass drug administration for onchocerciasis.
Onchocerciasis – or “river blindness” – is a parasitic disease caused by the filarial worm *Onchocerca volvulus* transmitted by repeated bites of infected blackflies (*Simulium* spp.). These blackflies breed along fast-flowing rivers and streams, close to remote villages located near fertile land where people rely on agriculture.

In the human body, the adult worms produce embryonic larvae (microfilariae) that migrate to the skin, eyes and other organs. When a female blackfly bites an infected person during a blood meal, it also ingests microfilariae which develop further in the blackfly and are then transmitted to the next human host during subsequent bites.

**Signs and symptoms**

Onchocerciasis is an eye and skin disease. Symptoms are caused by the microfilariae, which move around the human body in the subcutaneous tissue and induce intense inflammatory responses when they die. Infected people may show symptoms such as severe itching and various skin changes. Some infected people develop eye lesions which can lead to visual impairment and permanent blindness. In most cases, nodules under the skin form around the adult worms.

**Geographical distribution 2017**


Onchocerciasis is also transmitted in Brazil, Venezuela (Bolivarian Republic of) and Yemen.

**Prevention, control and elimination programmes**

There is no vaccine or medication to prevent infection with *O. volvulus*.

Between 1974 and 2002, disease caused by onchocerciasis was brought under control in West Africa through the work of the Onchocerciasis Control Programme (OCP), using mainly the spraying of insecticides against blackfly larvae (vector control) by helicopters and airplanes. This has been supplemented by large-scale distribution of ivermectin since 1989.

The OCP relieved 40 million people from infection, prevented blindness in 600 000 people, and ensured that 18 million children were born free from the threat of the disease and blindness. In addition, 25 million hectares of abandoned arable land were reclaimed for settlement and agricultural production, capable of feeding 17 million people annually.

The African Programme for Onchocerciasis Control (APOC) was launched in 1995 with the objective of controlling onchocerciasis in the remaining endemic countries in Africa and closed at the end of 2015 after beginning the transition to onchocerciasis elimination. Its main strategy has been the establishment of sustainable community-directed treatment with ivermectin (CDTI) and vector control with environmentally-safe methods where appropriate. In APOC’s final year, more than 119 million people were treated with ivermectin, and many countries had greatly decreased the morbidity associated with onchocerciasis. More than 800,000 people in Uganda and 120,000 people in Sudan no longer required ivermectin by the time that APOC closed.

In 2017, more than 145 million people were treated in Africa where the strategy of CDTI was implemented, representing more than 70% coverage of the number of people who require treatment globally. The Expanded Special Project for the Elimination of Neglected Tropical Diseases in Africa (ESPEN), set up to cover the five preventive chemotherapy NTDs, has 4 core objectives: 1. Scale up treatments towards the achievement of 100% geographic coverage, 2. Scale down: stopping treatments once transmission has been interrupted or control achieved, 3. Strengthen information systems for evidence-based action, and 4. Improve the effective use of donated medicines through enhance supply chain management. ESPEN is housed in the WHO Regional Office for Africa.

The Onchocerciasis Elimination Program of the Americas (OEPA) began in 1992 with the objective of eliminating ocular morbidity and interruption of transmission throughout the Americas by 2015 through biannual large-scale treatment with ivermectin. All 13 foci in this region achieved coverage of more than 85% in 2006, and transmission was interrupted in 11 of the 13 foci so far in 2017. Elimination efforts are now focused on the Yanomami people living in Brazil and Venezuela (Bolivarian Republic of).

On 5 April 2013, the Director-General of WHO issued an official letter confirming that Colombia has achieved elimination of onchocerciasis. Colombia was the first country in the world to be verified and declared free of onchocerciasis by WHO. This has been followed by Ecuador in September 2014, Mexico in July 2015, and Guatemala in July 2016. More than 500 000 people no longer need ivermectin in the Americas.
Treatment

WHO recommends treating onchocerciasis with ivermectin at least once yearly for between 10 to 15 years. Where O. volvulus co-exists with Loa loa, treatment strategies have to be adjusted. Loa loa is a parasitic filarial worm that is endemic in Cameroon, the Central African Republic, Congo, the Democratic Republic of the Congo, Nigeria and South Sudan. Treatment of individuals with high levels of L. loa in the blood can sometimes result in severe adverse events. In affected countries, it is recommended to follow the Mectizan Expert Committee (MEC)/APOC recommendations for the management of severe adverse events.

WHO response

WHO headquarters provides administrative, technical and operational research support to three regions where onchocerciasis is transmitted.

The Onchocerciasis Technical Advisory Subgroup (OTS) was organized by WHO in 2017 to provide recommendations to WHO about future policy and guideline development and priorities for research required to help programme achieve their elimination objectives. Reports from the OTS meetings can be found here.

The WHO Regional Office for Africa, which had an overall supervisory role for OCP from 1975 to 2002 and APOC from 1995 to 2015, currently supervises ESPEN which coordinates PC-NTD control and elimination activities in that region.

Through the OEPA partnership, WHO collaborates with endemic countries and international partners in the WHO Region of the Americas. Although there is no official programme to coordinate activities in the WHO Eastern Mediterranean Region, the two countries in the region collaborate on elimination activities.