



KMJ

KUWAIT MEDICAL JOURNAL



The Official Journal of The Kuwait Medical Association

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Editorial

Need a Rebirth of Clinical Medicine

Belle M Hegde

The Journal of the Science of Healing Outcomes, State College, Pennsylvania, USA and Mangalore, India*

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I learnt my medicine at the feet of some of the great teachers in India, the UK and the USA. That was the time when every patient used to have a detailed interview for history taking, and then a thorough clinical examination. Tests were done parsimoniously, only when indicated, to either confirm or refute the bedside diagnosis, and not all tests were done for all patients. What I see today baffles me. Doctors rarely examine patients, but rely on all tests to base their management. The very act of examining a patient could act as placebo therapy.

Every day, I get emails enclosing all kinds of test reports for advice. I get confused. This trend is bad for the patients, even though it is good for business; if medical practice were to be a business. This has to stop and we should get back to clinical medicine. Even senior doctors have got acclimatised to this new environment. A senior doctor in Chennai came to see me. I wanted him to get on to the examination couch. He was surprised! He told me that all his reports are in his file and asked me why he should be examined. I had to explain it to him to convince him. To both of our surprise, his diagnosis was totally different at the end of the day. He was elated and went on to tell his students that he is changing his teaching style. Hippocrates said that if a doctor listens to his/her patients long enough, he/she will know what is wrong with her/him. How very true!

When the first Corporate Hospital came up in a metropolis in India, my former teacher, Late Professor C.R.R. Pillai admitted one of his private patients there with clear cut instructions. To his dismay, the next morning his patient had undergone all the tests the

hospital could offer. He got his patient discharged forthwith and never entered that hospital during his life time again. The hospital has grown from then on to be one of the biggest corporate monstrosities since, making huge profits at patient's misery!

Re-emergence of clinical medicine is going to make medical care very inexpensive from the patient's point of view, and will make for better diagnosis and cheaper treatment also. Many a time, it might make major risky surgeries unnecessary. Even the NHS in the UK feels that over-intervention is not only a bane, but also prohibitively expensive. They have taken a bold decision to cut down on unnecessary and doubtful interventions for NHS patients: "be saved every year by tightening criteria for treatments where "the risks... outweigh the benefits". It said the proposals will ensure procedures, such as those for carpal tunnel, haemorrhoids and varicose veins, will only take place where there is good reason to do so. Alternative treatments such as injections, changes of diet or physiotherapy will be effective in the majority of cases, NHS England said. National medical director Professor Stephen Powis said: "If we want the very best clinical care for our patients, we need to stop putting them through treatments where risks and harms outweigh the benefits. By reducing unnecessary or risky procedures for some patients, we can get better outcomes while reducing waste and targeting resource to where it is most needed." Speaking to the Times, he added this would be the "first stage" in looking at situations where surgery is better avoided. He told the paper: "We shouldn't, at best, inconvenience or disappoint patients by offering treatments that are

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‡Affiliate Professor of Human Health

not effective and, at worst, harming patients." NHS England's board of directors will meet next week to discuss the plans which will then be put out to consultation. Other procedures on the list of 17 include grommets for glue ear and tonsil removal, with the plans drawn up. In consultation with the National Institute for Health and Care Excellence (Nice), four of them will be offered only when a patient makes a specific request, with the other 13 being offered only when specific criteria are met.

If this is the state of affairs in the NHS, one could imagine the status in corporate hospitals, especially in India, where the latter are built to amass wealth at human misery. I am sure the reader will be convinced that if we resurrect clinical medicine as described above, mankind will be happy.

One actual case history will reinforce this point. A middle-aged gentleman had some unusually spicy food one afternoon and had tummy upset with vomiting. The food eaten that night again gave him the same feeling. He slept well. The next morning, the

tummy ache returned with one more bout of vomiting. A good doctor in Mangalore, who was an old student of mine and who practises good clinical medicine, arrived at the right diagnosis of acute gastritis and prescribed correctly. The patient was a very rich man who was not impressed by this. He went to a corporate hospital, where a cardiologist heard three words: vomiting and upper G.I. pain.

He never had any examination at all and was admitted to the ICU with a provisional diagnosis of acute coronary syndrome. A good history alone would have given away the secret. He had to go through the usual drill and ended up with a coronary angiogram. Lo and behold! There was a block which was angioplastied. Now this man gets two blood thinners, both of which are gastric irritants. The angry stomach reacted violently. The tummy ache and the vomiting promptly returned with a vengeance. This is today's corporate medical practice, which netted a few lakhs of rupees to the hospital and the doctor. May clinical bedside medicine return for human good.

Review Article

The Ubiquitous Invasion of Social Media in Lifelong Learning in Medical Education: Review Article

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ABSTRACT

The field of health care is fairly diverse and rapidly changing. Knowledge and skills attained at the end of formal undergraduate and postgraduate medical education are not sufficient to maintain competence and performance throughout health professionals' entire career. Practitioners are required to be involved in lifelong learning, either through participating in organized continuing education programs, e.g. CME (Continuous Medical Education), CPD (Continuous Professional Development) or through individual learning activities. Social media encourages passive learners to become active learners through an attitude of sharing and interacting, far more than an attitude of retrieving. It is

hypothesized that in spite of the growing use of social media by health professionals, medical education hitherto has not assimilated these tools at all levels in form of CME/CPD credit. Many participants seemingly are maintaining their presence in multiple social media platforms to engage in social and learning activities. Social media has clear potential to contribute to lifelong learning in medical education.

This article examines the recent literature in the use of social media as a learning tool for lifelong learning, followed by a discussion on the emerging role of social media in medical education. The article also explores various factors affecting social media use in medical education.

KEY WORDS: education, internet, medicine, students, teaching

INTRODUCTION

Social media have been defined as "a group of internet-based applications that build on the ideological and technological foundations of Web 2.0, and that allow the creation and exchange of user-generated content"^[1]. In congruence to every other facet of life, higher education institutions view online technology and social media tools as a cost-effective and innovative solution to enhance student performance, learning and satisfaction. This has ensued in the development of online, web-enhanced, blended, and hybrid courses with the use of Web 2.0 tools. Later research has also verified that integrating online technology into the classroom can create a rich and efficient learning environment, which improves student performance and learning^[2]. Facebook, Instagram, Twitter, LinkedIn, YouTube and Google+ are typical examples of social media tools of the Web 2.0.

There is no second opinion in the claim that digital social media in the last few years have completely transformed the scenario of human interaction and the individual's interaction with society. Digital social media provide individuals and communities the opportunities to communicate beyond defined boundaries across the globe in case of humanitarian crises like Haiti or mass mobilizations like Arab Spring^[3].

The European Commission (2002) report defines lifelong learning as "a continuously supportive process that stimulates and empowers individuals to acquire all the knowledge, values, skills, and understanding they will require throughout their lifetimes and to apply them with confidence, creativity, and enjoyment in all roles, circumstances, and environments"^[4,5].

The field of health care is fairly diverse and rapidly changing. The knowledge and skills attained at the end of formal undergraduate and

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postgraduate professional medical education are not sufficient to maintain competence and performance throughout the career. Practitioners are required to be effectively participating in organized continuing education programs such as CMEs (Continuous Medical Education) or CPD (Continuous Professional Development) or through individual learning activities^[6]. The ubiquitous invasion of social media in personal and professional lives also found its way into the toolboxes of students, residents, physicians, and educators all over the world^[7].

In this context, Medicine 2.0 and e-Health are two tools extensively used in the last five years. e-Health primarily involves the computerization of medical services such as remote surgeries by using a surgical robot or provision of digital educational support for students and residents, while Medicine 2.0 has developed a new system of doctor-patient relationship to provide medical information to patients through new web technologies with an aim to promote health education^[8]. However, as the medical profession is notorious for slow take-up of all new technologies^[9], it is hypothesized that in spite of the growing use of social media by health care professionals, medical education hitherto has not assimilated these tools at all levels, especially integrating social media use in form of CME/CPD credit or score.

The purpose of this review is to examine recent literature in the use of social media as a learning tool for lifelong learning, followed by a discussion of the emerging role of social media in medical education. The article also aims to explore various factors affecting the use of social media in medical education.

HISTORY

When the concept of lifelong learning was first developed in the early 1970s, it was propagated by international organizations like The United Nations Educational, Scientific and Cultural Organization (UNESCO), The Organization for Economic Cooperation and Development (OECD), the World Bank and two European regional organizations, first the Council of Europe and then the European Union (EU). In the 1990s, the concept of lifelong learning resurfaced again with emphasis on lifelong learning as a foundation of strong human capital. Unlike the initial phase in the 1970s, this new concept in the 90s was embraced both by governments of the western countries and industries^[10].

The development of modern social media tools has assisted people to learn anywhere, anytime and is currently linked to many useful activities that can assist in learning. Such examples of freely available products that are commonly used and interlinked with

each other include:

- Search tools: Google, Wikipedia, and YouTube
- Network tools: Facebook, LinkedIn and Twitter
- Communication tools: e-mail, Google Wave and Skype
- Sharing resources: Google Calendar and DropBox
- Sharing experiences by blogging or podcasting: Posterous and Audacity.

CME is the term used to provide up-to-date knowledge and skills to physicians about their specialty, subsequently the term CPD was introduced, as it was realized that health professionals needed to learn other skills beyond those related to their field or specialty, namely managerial, personal and social skills^[11]. Social media is perceived to have significant potential to aid educators, physicians and students for enhancing their learning experiences through customization, personalization, and greater opportunities for networking and collaboration^[12].

Due to the wide range of social media applications, it is not possible to present an exhaustive list, however a few samples of applications of social media from different perspectives are:

- Educational and research resources: *e.g.* PatientsLikeMe and Medpedia
- Evolving technologies: *e.g.* mobile applications for monitoring of vital signs and chronic conditions, portable ultrasound and smart glucometers
- Bio-statistical applications: *e.g.* medical research analysis, tracking health information, consulting charts, statistical data or even electronic health records
- Social networking: *e.g.* Doctors hangout, LinkedIn, instagram, twitter and research gate

Those are currently used not only to interact with the public to promote health, but also connect researchers and educators with ease to share and advance their research and access knowledge and expertise.

The utilization of social media has generated concerns, *e.g.*, in Wikipedia, content is posted without undergoing rigorous academic peer review, and the sheer abundance of the shared content results in information overload. Uses of social networks and Web 2.0 technology have also raised issues pertaining to medical professionalism, with reports published on incidents of posting unprofessional content online^[13].

LITERATURE REVIEW

A search was conducted using the electronic databases of British Education Index (BEI), MEDLINE, CENTRAL, ERIC, PubMed, CINAHL Plus Full Text, Academic Search Complete, Alt Health Watch, Health Source, Communication and Mass Media Complete, Web of Knowledge, ProQuest, Web of Science and

Google Scholar. Articles were identified using the terms 'lifelong learning', 'informal education', 'social media', 'medical education', 'continuous medical education' and combination of key words such as 'social media' AND 'lifelong learning', 'social media' AND 'medical education'. Key words in combination with variations of the terms such as 'social network', 'Facebook', 'Web 2.0', 'Weblog', 'blog', 'Twitter', 'podcast', and 'Webcast' were also used.

Lifelong learning

European Observatory on Health Systems and Policies (2010) report stated that lifelong learning can include a formal system; where learners have little or no control over the objectives or means of learning, an informal system where learners have no control over the means and learning is incidental, and a self-directed system of learning where learners have complete control over both the objectives and means of learning. The boundaries between the three systems are not well demarcated and often overlap, but there is a general consensus that learners learn best when matched with appropriate learning methods^[6,14].

Lifelong learning can be explained on the basis of its six essential aspects: (1) it is continuous and supportive; (2) it is motivating and empowering; (3) it integrates knowledge, values, skills; (4) it spans a lifetime and is applied (practically relevant to personal and professional lives and not just for knowledge's sake); (5) it encompasses confidence, creativity and enjoyment; and (6) it applies to all roles, circumstances, and environments^[15].

Social media and medical education

Lifelong learning in medicine is part of the Physician Charter endorsed by more than 120 national and international organizations^[16,17].

In addition, documentation of self-directed lifelong learning is now a requirement for residency training, board certification, and maintenance of certification in many countries. Medical schools have introduced problem-based and self-directed learning as a part of lifelong learning in medicine^[18,19].

Access to effective public relation (PR) has been received as current wisdom within medical education. The relationship between social media, PR and learning is indeed a fundamental one. This is due to the fact that significant information about medical research from the academic sectors can be disseminated to health care professionals and the public through various PR educational techniques. In one study, a series of in-depth interviews were conducted with public relations educators to explore their perceptions of mentoring and to understand the choices they make

regarding the use of social media tools. The results showed that PR educators thought that use of social media helps to enhance their mentoring relationships by instantaneous and informal communication, and sharing resources. Challenges in the use of social media were identified as, need for time investment, opposition by people towards change, and the inability to demarcate personal and professional use^[20].

Research has revealed that YouTube content plays a significant role in e-learning, community formation and informal peer learning. There are currently numerous educational videos on Youtube on various medical topics, lectures, physical examination, surgical procedures and training courses^[21].

In a pilot study conducted on 4th year students at Penn State College of Medicine, integration of new social media tools into the curricula of two graduate-level medical humanities electives was evaluated. Social media, *e.g.* Twitter, YouTube, blogging and Skype demonstrated augmented learning opportunities and real-time communication outside the classroom. It also showed better connection with medical experts, creativity enhancement, and helped students acquire problem-solving skills and collaboration^[22].

At least 60% of medical students in the USA and over 70% in the UK use Facebook^[23,24]. They use Facebook groups for exam preparation, sharing online content, discussing clinical cases and exchange information on clerkships. In a systemic review of 16 articles on how Facebook has been integrated into medical education, the result demonstrates easy accessibility of Facebook by students and that it has been used to prepare for exams, share online material, discuss clinical cases, organize face-to-face sessions and exchange information on clerkships. However, the analysis showed that, successful learning groups seemed to be determined by pre-existent social connections and academic guidance, and studies did not use quantitative measures to correlate Facebook-based learning with scores in high-stakes exams or clinical competency^[25]. In a survey conducted on 142 students to identify health professional students' use and behaviors with social media, Facebook and YouTube were utilized for educational purposes by 97% and 60% of participants respectively; and 85% believed that social media could benefit their learning activities^[26].

Twitter is a microblogging that seems popular for learning purposes. In 2009, 65 million individuals used Twitter around the world, a 14-fold increase compared to the 2008 ComScore^[27]. Twitter's continuous rise is mainly among those less than 34 years old^[28], and currently there are 288 million monthly active users, 80% of them are on mobile devices and 77% of them from

outside the USA^[29]. Individuals can post comments, pictures, and links to sites, articles and videos. Twitter has the advantage to interlink with other social media platforms such as Facebook, LinkedIn, Instagram, YouTube and others. In a study aimed to demonstrate a supplement to a curriculum using educational “push technology” in mobile devices, a curriculum consisting of high-yield ultrasound concepts was developed on Twitter @EDUultrasound daily. Followers received tweets “pushed” directly to their mobile devices. After the end of the year, a majority of followers (55.6%) were first time Twitter users. The majority of participants (88.9%) found Twitter user-friendly, while most (81.5%) found the information useful^[30].

In 2013, Cheston and colleagues reviewed various strategies for incorporating social media in medical education. Seventy-one percent of included studies used social media tools for learner engagement, while 57% used it for feedback and 36% for collaboration and personal development. The most commonly quoted challenges were technical issues (43% of studies), variable learner participation (43% of studies), and privacy concerns (29% of studies)^[7,13].

Hamm and colleagues reviewed 96 studies in social media use by health professionals and trainees. Discussion forums were the most commonly studied aspect (44.8%). Facebook, YouTube and Twitter were the preferred and commonly used platforms (23/96, 24%). Seventy percent (66/96) of the studies were in education rather than health practice, and nearly all interventions were on students or residents. In 61.5% (59/96), the purpose of the studies were to facilitate communication, 42.7% (41/96) were to evaluate knowledge, and 20.8% (19/96) were in skills. Moreover, quantitative studies represented 56.3% (54/96) whereas qualitative represented 21.9% (21/96) of the studies. Of note, the review found only 13 effectiveness studies, where social media tool was used as one component of a complex intervention. Similarly, only half of the effectiveness studies reported statistically significant findings^[31]. Another recent advancement is its increasing use during health conferences. A research revealed that of the 212 speakers at the International Conference on Emergency Medicine (ICEM) 2012, 41.5% possessed a LinkedIn account while 15.6% were on Twitter. More than 400 people tweeted about the conference, yet only 34% of them were physically present at the conference. Of the tweets produced, 74.4% were related to the clinical and research material of the conference^[32]. A similar study on using Twitter at the 2013 Canadian Conference on Medical Education (CCME) showed that Twitter was mostly used to facilitate discussions and dissemination of useful information^[33].

It is clear that using live feed hashtags (#) during conference events, Twitter facilitates sharing ideas and learning even with individuals that are not present. It also enables discussion for even months after the event. Different articles tweeted by attendees can be accessed directly by professionals in education, medicine, public health *etc.*, and needless to say patients.

Another dynamic use of social media is in facilitating medical and public health professionals to respond to disasters in a better way^[34]. Immediately after the 2010 Haiti earthquake disaster, social media was the main source of information for people around the globe, and texting through mobile phones raised \$5 million for the American Red Cross in the first 2 days. Google Maps, My Space and Facebook proved to be the main sources to share information, donate money, and offer comfort and support^[35].

DISCUSSION

There is a consensus in literature that social media is increasingly used both for formal and informal lifelong learning in general and in medical education. Traditionally, professionals learn about published works in the literature and share research at meetings. Social media has revolutionized this in essence, as members of the public, researchers and scholars are currently able to share knowledge and interact without meeting or prior engagement. Many organizations, regulatory health professional bodies, associations, and journals are participating in social media and helping students and professionals to remain updated and keep abreast of new advances.

Facebook and Twitter both have reached more than 1 billion users worldwide^[36,37]. Such a rise in the use of social media heralds the fact that the current structures of education could undergo significant transformation over the next decade. Social media tools also appear to have a potential role to empower students and healthcare professionals with a large pool of learning materials, mobilize educational resources and enhance learning experience, particularly in poorly resourced areas.

On the other spectrum, social media is not the panacea for all obstacles accompanying lifelong learning in medical education. Students and residents should remember that the most important learning experience in a physicians’ life takes place not only behind the screen, but also in practical and clinical settings.

Ministries of health have shown efforts at using Twitter and Facebook for public health promotion^[38,39]. It has also been used for sexual health education programs^[40], emergency preparation^[34], and sharing reliable sources of information and responding to

public concerns during outbreaks^[41]. Therefore, educators and students can effectively utilize social media tools to collaborate with local and global organizations in their efforts.

Goktalay showed that faculty members having less experience with social media showed much higher self-concerns. A similar situation exists in medical education: current trainees and medical students born after 1980 are considered as digital natives, as they grew up in a world where using technology, computers, the Internet, text messaging, blogging, and SMS text messaging was a norm^[2]. In contrast, older faculty trained before 1980 are considered digital immigrants, because they experience a challenge in adapting to the demands of the digital age^[42].

Communication in and out of the medical profession can promote lifelong learning, research, advocacy and patients care. Information dissemination is considered a vital characteristic and function of social media. Social media tools such as Twitter can effectively be used for rapid retention and dissemination of information.

Research studies reviewed for this paper showed an escalating use of social media tools by students and health professionals, but this usage has yet to be properly integrated to the current existing frame work for CME/CPD. Most of the studies incorporated in this review have utilized qualitative measures and only limited rigorous quantitative studies measuring the effect of social media tools on learning. Similarly, the number of social media studies is limited to continuing education and professional development. The same observation applies on social media use, vis-à-vis confidentiality and professionalism.

The overwhelming expansion of online resources demands scrutiny of the quality, appropriateness of the content and professional conduct. In this regard, several organizations have published guidelines on professionalism in the use of social media for students and professionals^[43-45]. Nevertheless, social media like any other online technology should be perceived as a tool that is neither inherently good nor bad^[24].

CONCLUSION

Social media tools encourage passive learners to become active learners through an attitude of sharing and interacting far more than an attitude of retrieving. Research suggests that adult and young learners tend to approach social media and information and communication technology use differently. This calls for setting up appropriate education programs utilizing social media tools, both for formal and informal lifelong learning. Participation in these kinds of learning activities positively affects professional development, and social networks may provide

different types of social capital for professionals, as social media channels are increasingly becoming another venue in which educators can communicate with their students. Therefore, steps should be taken to increase online literacy and train educators on how to use various tools such as Twitter, Facebook, LinkedIn, and YouTube.

CME/CPD initiatives must endeavor to integrate innovations like social media as its core component. We need rigorous, quantitative evidence about how health professionals and students in different clinical contexts actually use social media in their everyday practice. What types of professional-patient communication are evolving online? Studies providing evidence about the effectiveness of using social media to engage the public, provide service, and disseminate useful information are also required. One future direction may be the use of data from Twitter and Facebook for research.

At the heart of the social media in lifelong learning is the evolving interconnected relationship between different social media platforms, *e.g.* Facebook, Instagram, Twitter and YouTube *etc.* despite each social network platform undoubtedly encompassing its own particulars. Many participants and users seemingly are maintaining their presence in multiple social media platforms to engage in social and learning activities. In this context, more robust studies are required to objectively assess if different aspects of identity and learning activity are exposed on different social media platforms.

The evidence presented shows how social media has clear potential to contribute in lifelong learning and medical education, and there is a need to give recognition both to how social media technology can support learning as well as participation in a workplace.

Practice Points

- There is a consensus in literature that social media is increasingly used both for formal and informal lifelong learning in general and in medical education.
- The escalating use by students and health professionals has yet to be properly integrated to the existing framework of CME/CPD.
- The number of social media studies is limited to continuing education, professional development, confidentiality and professionalism.
- Many participants are maintaining their presence in multiple social media platforms to engage in social and learning activities. Robust studies are required to assess if different aspects of identity and learning activity are exposed on different social media platforms.

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Original Article

Gingival Squamous Cell Carcinoma and Khat (*Catha edulis* Forsk) Chewing

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ABSTRACT

Objective: To investigate the relation between chewing khat and gingival squamous cell carcinoma invasion and grade

Design: Retrospective study

Setting: Ibn Sina laboratory database records between 2010 and 2014 in Aden Governorate

Subjects: Seventy-seven adult patients diagnosed with gingival squamous cell carcinoma

Intervention: Gingival mucosal biopsy

Main outcome measure(s): Sex, age, squamous cell invasion, grade and khat chewing

Results: Seventy-seven patients with squamous cell carcinoma of gingiva, consisting of 58 males (75%) and 19 females (25%) were studied. The percentage of men who chewed khat (n = 51, 66%) was higher than females. There was a significant relationship between chewing khat and gender of patients (p < 0.001). The mean age of the patients was 57 years (range: 28 – 80 years). The patients older than

50 years were predominantly affected (n = 47, 61%) and the patients least frequently affected with squamous cell carcinoma were less than 30 years old (n = 3, 3.9%). There was no significant relationship between age groups and khat chewing (p-value = 0.5).

Squamous cell carcinoma was predominant among patients who chewed khat (n = 69, 90%). There was a significant difference between chewing khat and invasion of the squamous carcinoma (p-value = 0.013). Grade II squamous cell carcinoma was most frequent (n = 46, 60%). There was no significant difference between chewing khat and grade of squamous cell carcinoma (p-value = 0.66).

Conclusion: The chewing of khat was associated with a majority of patients diagnosed with gingival squamous cell carcinoma. Males were predominantly affected. Invasive squamous cell carcinoma and grade II were the most common types.

KEY WORDS: grade, invasion, khat, sex, squamous cell carcinoma

INTRODUCTION

Khat is a shrub or small to medium sized evergreen tree that belongs to the Celastraceae family^[1]. Khat leaves (*Catha edulis* Forsk) have a natural psychoactive substance and has been chewed for many years in Ethiopia, East Africa, and the southern Arabian Peninsula^[2]. The leaves have an aromatic odor. The taste is astringent and slightly sweet. The plant is seedless and hardy, growing in a variety of climates and soils. Khat can be grown in droughts where other crops have failed and also at high altitudes. Khat is harvested throughout the year^[3].

In Yemen, up to 82% of adult males are estimated to chew khat^[2]. In the past, the habit of chewing khat was

socially normalized among adult Yemeni males only. However, a recent study for the World Bank estimated that 73% of women in Yemen chew the khat leaf more or less frequently. Meanwhile, a staggering 15 – 20% of children under the age of 12 are also daily consumers^[4].

Fresh leaves and shoots of the khat plant contain alkaloids. Its active ingredients comprise cathinone, cathine, and norephedrine, which are analogous to amphetamine^[5]. Therefore, people chew khat to get psycho-stimulation effect in the form of euphoria and excitement^[6]. During chewing sessions, large amounts of khat leaves, shoots, and barks are placed in the oral cavity in close contact with the buccal mucosa in the lower distal mucobuccal fold, and usually chewed for

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several hours^[7] to release the active components in the juice, which is then swallowed with saliva^[3].

The mucosa of the oral cavity is considered to be the first absorption segment, where the major proportion of the alkaloids is absorbed^[8]. Therefore, oral tissues, especially the oral mucosa, are exposed to high doses of khat constituents while chewing khat, rendering them susceptible to its potentially toxic effects^[7]. Khat has been associated with oral keratotic white lesions which occur in the same region within the vestibule or buccal mucosa where the khat bolus is placed while chewing^[9]. It was also found to be a risk factor for developing cellular atypia^[3] in addition to abnormal keratinization of the superficial cell layer and showed increased epithelial thickness affecting all layers^[7].

The aim of this study was to find the relation between chewing Khat and squamous cell carcinoma of the gingiva invasion and grade.

MATERIALS AND METHODS

This study is a descriptive, retrospective study of all patients who were diagnosed with gingival mucosal carcinoma in biopsy specimens. The clinical data including sex, age and presence of khat chewing habit were collected from the request forms. Histopathology data of squamous cell carcinoma, invasion and grading using Anneroth's classification (multifactor grading system)^[10] were collected from the reports found in the archives of Ibn Sina laboratory in Aden governorate during a period of 5 years (2010 – 2014).

Data processing and data analysis were done using the Statistical Package for the Social Sciences (SPSS-20). Percentage was calculated. Chi-Square test was applied to identify any significant relationship between the study variables with a significant level of p -value < 0.05.

RESULTS

This study was conducted on 77 patients with squamous cell carcinoma in the gingiva. The male to female ratio is 3:1. Males were predominantly ($n = 58$, 75%) affected with squamous cell carcinoma. Male khat chewers represented 66% ($n = 51$) of the total cases and only 7 (9%) did not chew khat. Of the 19 females included in the study, only 6 (8%) chewed khat and 13 (17%) did not chew khat. There was a significant relationship between chewing of khat and the gender of patients (p -value < 0.001, Table 1).

The age of the patients ranged from 28 - 80 years and the mean age was 57 years. The patients older than 50 years were predominantly affected ($n = 47$, 61%) and 33 (42.9%) were khat chewers. The patients who were aged between 30 - 50 years were the second

Table 1: Khat (*Catha edulis*) chewing and gender of patients with squamous cell carcinoma

Gender*	Khat (<i>Catha edulis</i>)		Total n (%)
	Non-chewers n (%)	Chewers n (%)	
Male	7 (9)	51 (66)	58 (75)
Female	13 (17)	6 (8)	19 (25)
Total	20 (26)	57 (74)	77 (100)

* p -value < 0.001

most affected ($n = 27$, 35.1%), of which 22 (28.6%) were khat chewers.

Even though the patients least frequently affected with squamous cell carcinoma were less than 30 years old ($n = 3$, 3.9%), khat chewers were predominant than non-chewers in this age group also. There was no significant relationship between age groups and khat chewing (p -value = 0.5, Table 2).

Table 2: Khat chewing and age group in patients with squamous cell carcinoma of the gingiva

Age groups (years)	Non-chewers n (%)	Chewers n (%)	Total n (%)
Less than 30	1 (1.3)	2 (2.6)	3 (3.9)
30 - 50	5 (6.5)	22 (28.6)	27 (35.1)
Above 50	14 (18.2)	33 (42.9)	47 (61)
Total	20 (26)	57 (74)	77 (100)

p -value: 0.543

The majority of the patients had invasive carcinoma ($n = 69$, 89.6%) and was more common among patients who chewed khat ($n = 54$, 70.1%), while the non-chewers represented 19.5% of the patients ($n = 15$). There were only 8 (10.4%) cases of carcinoma insitu, and it was more frequent in patients who did not chew khat ($n = 5$, 6.5%) than in khat chewers ($n = 3$, 3.9%). There was a significant difference between chewing of khat and invasion of the squamous carcinoma (p -value = 0.013, Table 3).

Khat chewers affected with gingival squamous cell carcinoma according to Anneroth's classification (multifactor grading system) were predominant in

Table 3: Association of invasion of gingival squamous cell carcinoma and khat

Khat	Carcinoma in situ n (%)	Invasive carcinoma n (%)	Total n (%)
Non-chewers	5 (6.5)	15 (19.5)	20 (26)
Chewers	3 (3.9)	54 (70.1)	57 (74)
Total	8 (10.4)	69 (89.6)	77 (100)

p -value: 0.013

grade I, II and III (well differentiated squamous cell carcinoma, moderately differentiated and poorly differentiated squamous cell carcinoma, respectively). In grade I gingival squamous cell carcinoma, the squamous cell carcinoma was well-delineated infiltrating borders in 27 (35.1%) cases, there were 8 patients with carcinoma insitu and 69 in invasive stage in the lamina propria. Grade II was the most frequent (n = 46, 59.7%) where the pattern of invasion was solid cords, and grade III was the least frequent with only 4 cases (5.2%) where the infiltration was in small groups and was present only in patients chewing khat. All patients with grade II and grade III were in invasive stage in the lamina propria.

We did not have a single case in grade IV (undifferentiated carcinoma) with the pattern of invasion was widespread cellular dissemination in single cells.

There was no significant difference between chewing khat and the grade of squamous cell carcinoma (p-value = 0.66, Table 4).

Table 4: Relation of histological grade of gingival squamous cell carcinoma and khat

Khat	Grade I n (%)	Grade II n (%)	Grade III n (%)	Total n (%)
Non-chewers	11 (14.3)	9 (11.7)	0 (0)	20 (26)
Chewers	16 (20.8)	37 (48.1)	4 (5.2)	57 (74)
Total	27 (35.1)	46 (59.7)	4 (5.2)	77 (100)

p-value: 0.66

DISCUSSION

Oral cancer is a major problem in oral health^[11]. Oral squamous cell carcinoma (OSCC) is the most frequent^[12], accounting for more than 90% of malignant tumours of this anatomic region, and it often arises from precursor lesions^[13]. It has been reported that approximately 10% of all malignant tumors of the oral cavity occur on the gingiva^[12]. The etiology of OSCC remains unknown, but many predisposing factors such as smoking associated with heavy alcohol use are well known^[14]. From the literature, there are findings that khat use contributes to the occurrence of cytological atypia that might develop to oral precancerous or cancerous lesions^[15]. Nasr *et al* reported that patients of OSCC were addicted to khat chewing from childhood, which may be considered as an important contributing factor^[16]. Seventy-four percent of khat chewers in this study were affected with squamous cell carcinoma in the gingiva. In a study done by Makki, 90% of her patients were also khat addicts and she correlated that most of the OSCC were in buccal mucosa and lateral sides of the tongue which comes directly in contact

with the khat^[17]. Nasr *et al* reported 47% of tumours were localized to the oral cavity and the most common presenting complaint was mass in the tongue^[16]. Oral cancers in the Asir region of Saudi Arabia have been observed to occur mostly among patients who have been long-term khat users over a period of 25 years or longer^[18].

The male to female ratio in our patients was 3:1. Similarly, it has been observed that males are affected more than females in the Arab world^[19]. The literature shows more male khat chewers have OSCC^[16] and this was in accordance with our study.

The overall mean age of gingival carcinoma was 57, similar to the results of Al Amad *et al* in Jordan^[20] and less than previously published by Halboub *et al* in Yemen^[21] and Al-Rajhi *et al* in Saudia^[22], but higher than the report of Ibrahim *et al* in Egypt^[23].

The greatest challenge is that oral cancer is not detected early enough for successful treatment, despite the fact that oral cancer is mostly a visible lesion^[19]. Carcinoma of the gingiva is an insidious disease that is usually painless^[12]. These tumors are misdiagnosed as benign tumors or other inflammatory responses^[24], which may lead to delay in treatment. Prognostic evaluation for OSCC is mainly based on clinical TNM classification^[25]. It should be noted that TNM staging alone cannot predict prognosis. Other tumor characteristics, particularly histologic parameters, must be utilized to identify the prognosis and select favorable treatment^[26]. Here in Aden, investigating with more advanced parameters like molecular marker^[27] is not possible and the specimen received in the laboratory was an incisional biopsy and not neck dissection. The Anneroth's classification used in this study could be taken as a valuable diagnostic factor^[25], as histologically invasive areas may be primarily responsible for the clinical behavior of the tumor, and this may be important for the therapy of choice for oral squamous cell carcinoma and have high prognostic value^[28]. In the present study, 89.6% of patients had invasive carcinoma and khat chewers were a majority. This is consistent with studies that revealed cases of oral cancer lesions were diagnosed at later stages in Yemen^[19, 29]. Grades I to III of malignancy were present among khat chewers and grade II was the most common, contrary to the reports of Nasr *et al*^[16] and Halboub *et al*^[21, 29], where grade I (well differentiated) is more common.

CONCLUSION

Khat was associated with a majority of gingival squamous carcinoma cases. Males were affected more than females, and invasive squamous cell carcinoma grade II was the most common type.

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Original Article

Age-related Differences in the Efficacy of Dexamethasone for Postoperative Analgesia in Patients undergoing Laparoscopic Cholecystectomy: A randomised controlled study

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ABSTRACT

Objective: This study aimed to investigate age-related differences in the effects of dexamethasone pre-treatment on pain intensity and morphine consumption in patients undergoing laparoscopic cholecystectomy.

Design: Randomized, prospective study

Setting: Operating room of a Wonkwang university hospital, South Korea

Subjects: Three hundred and eighty-eight patients undergoing laparoscopic cholecystectomy, 194 from a younger age group (18 - 45 years) and 194 from an older age group (≥ 65 years).

Intervention: The patients within each group were randomly allocated into younger (normal saline/dexamethasone: 97/97) and older (97/97) groups. They received either intravenous dexamethasone 0.1 mg/kg or normal saline 1 hour before anaesthesia induction.

Main outcome measures: The effect of dexamethasone on cumulative morphine-containing patient-controlled analgesia consumption, visual analogue scale scores for pain at 1, 2, 6, 12, and 24 hours after surgery, mean morphine consumption, and time to first rescue analgesia

Results: When dexamethasone was administered, both age groups had significantly less cumulative patient-controlled analgesia consumption, mean morphine consumption, and longer time to first rescue analgesia. These effects were of greater magnitude in the older than in the younger group. Visual analogue scales for pain at 1, 6, and 12 hours after surgery was significantly higher in the younger group.

Conclusion: The effects of dexamethasone on clinically relevant pain were greater in the older group, who experienced less post-operative pain. Further investigation regarding this association is warranted.

KEY WORDS: age, analgesia, dexamethasone, pain

INTRODUCTION

The evaluation and management of pain in elderly patients is a significant challenge for healthcare providers^[1]. Evidence has shown that older patients report less pain after surgery and other interventional procedures^[1,2]. The threshold for pain tends to be higher in older patients when the exposure to stimuli is brief, of lesser spatial extent, and at peripheral, cutaneous or visceral sites. Age-related increase in pain may be more apparent when stimuli are very intense and/or persist for longer periods^[2,3].

Age and disease-related changes in physiology, diminished physiological reserves, and concurrent

medications may alter the pharmacokinetics and pharmacodynamics of some analgesic medications and the techniques used in acute pain management. Functional, structural, and biochemical changes in nociceptive pathway have been reported in peripheral and central nervous systems in healthy older adults^[4,5].

The anti-inflammatory effects of dexamethasone contribute to pain relief and amelioration of nausea and vomiting. However, it remains to be determined whether the efficacy of dexamethasone for reducing pain intensity and opioid consumption is affected by age-related differences^[6,7]. This study aimed to investigate age-related differences in the effects of

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dexamethasone pre-treatment on pain intensity and analgesic consumption in patients undergoing laparoscopic cholecystectomy.

SUBJECTS AND METHODS

Ethical approval for this study (Registration No. 003549) was provided by the Institutional Review Board (IRB) of Wonkwang University Hospital, Iksan, Republic of Korea (Chairperson: Prof KH Yun) in January 2013. Written informed consent was obtained from all participants. The study was performed at Wonkwang University Hospital from February 2013 to December 2015. The study included 388 patients categorized into class I–II according to the American Society of Anesthesiologist (ASA) physical status; of these, 194 were younger (aged 18 - 45 years) and 194 were older (≥ 65 years) patients scheduled for laparoscopic cholecystectomy. Patients with hepatic and renal insufficiency, history of corticosteroid hypersensitivity, diabetes mellitus, previous gastric ulcers, cognitive impairment, or those receiving corticosteroids or immunosuppressive drugs and chronic opioids or other analgesics were excluded.

The patients were randomly allocated (sealed envelope) into a normal saline or dexamethasone group within each age group. There were 97 younger and 97 older patients each in normal saline and dexamethasone group. Patients in both groups received intravenous dexamethasone 0.1 mg/kg (5 mg/mL) or normal saline 1 hour before induction of anaesthesia.

On the day before surgery, all patients were taught how to use the visual analogue scale (VAS) and the patient-controlled analgesia (PCA) device. They were instructed to deliver analgesia on their own on feeling pain. We chose cognitively healthy patients who could comprehend the self-report pain assessment tools and the PCA technique in the acute pain setting.

Before the surgery, all patients were premedicated with intramuscular midazolam (2–3 mg). The patients were evaluated with pulse oximetry, automated blood pressure cuff, electrocardiogram, and end-tidal CO₂ monitors. Tympanic temperature was measured immediately before the induction of anaesthesia and again immediately before extubation.

For induction of anaesthesia, a slow (30–60 s) intravenous (IV) bolus of propofol (2 mg/kg) was administered. Tracheal intubation was facilitated with rocuronium (0.9 mg/kg) in all groups. Anaesthesia was maintained with desflurane and a mixture of air and 50% oxygen. When additional desflurane was required, administration was started at an end-tidal concentration of 1 minimum alveolar concentration, and the concentration was adjusted by a 1% stepwise titration according to acceptable hemodynamic limits

(mean arterial blood pressure between –30% and +15% and heart rate between –40% and +15%), and according to a target bispectral index (BIS) between 40 and 60.

Upon completion of the surgery, the neuromuscular blockade was reversed with pyridostigmine (0.2 mg/kg) and glycopyrrolate (0.008 mg/kg) when the train-of-four ratio had returned to 25%. The patients were extubated when BIS values reached 80 and spontaneous breathing was resumed.

The PCA mixture contained morphine (60 mg), ketorolac (150 mg), and ramosetron (0.6 mg) in 100 mL of saline. The device was set to deliver a basal infusion rate of 2 mL/h with bolus doses of 0.5 mL and a 15-min lockout period. Postoperative pain intensity was documented using a 100-mm linear VAS that consisted of a straight line, with the left end of the line representing no pain (0) and the right end of the line representing the worst pain (100). During post anaesthesia recovery, patients with VAS ≥ 40 received IV ketorolac (30 mg) and an additional dose (15 mg) if needed. Postoperative VAS on exertion was measured at 1, 6, 12, and 24 hours from the time of initial arrival at the post anaesthesia care unit (PACU).

The primary outcome was the effect of dexamethasone on cumulative, morphine-containing PCA consumption in both groups. The secondary measures of both groups were the effects of dexamethasone on VAS scores for pain at 1, 2, 6, 12, and 24 hours after surgery, mean morphine consumption adjusted for body weight, time to first rescue analgesia, ketorolac consumption in the PACU, postoperative nausea or vomiting (PONV), and pruritus in both groups. PONV was treated with IV ondansetron (4 mg).

Statistical analysis

Considering a power of 80% and an α -coefficient of 0.05 for effect of dexamethasone on cumulative, morphine-containing PCA consumption in both groups, sample size was calculated as 185 patients for each group. Assuming a 10% dropout rate, the final sample size was determined to be 194 patients per group (97 patients receiving dexamethasone and 97 receiving saline). The statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The results are presented as mean \pm standard deviation (SD) or the number of patients (%). Means between groups were determined using independent t-test and categorical data were evaluated using Chi-square tests. Significance was defined as $p < 0.05$.

RESULTS

Eight of the 388 patients who were included in the study were excluded from the final analysis because of conversion to open surgery or re-exploration for

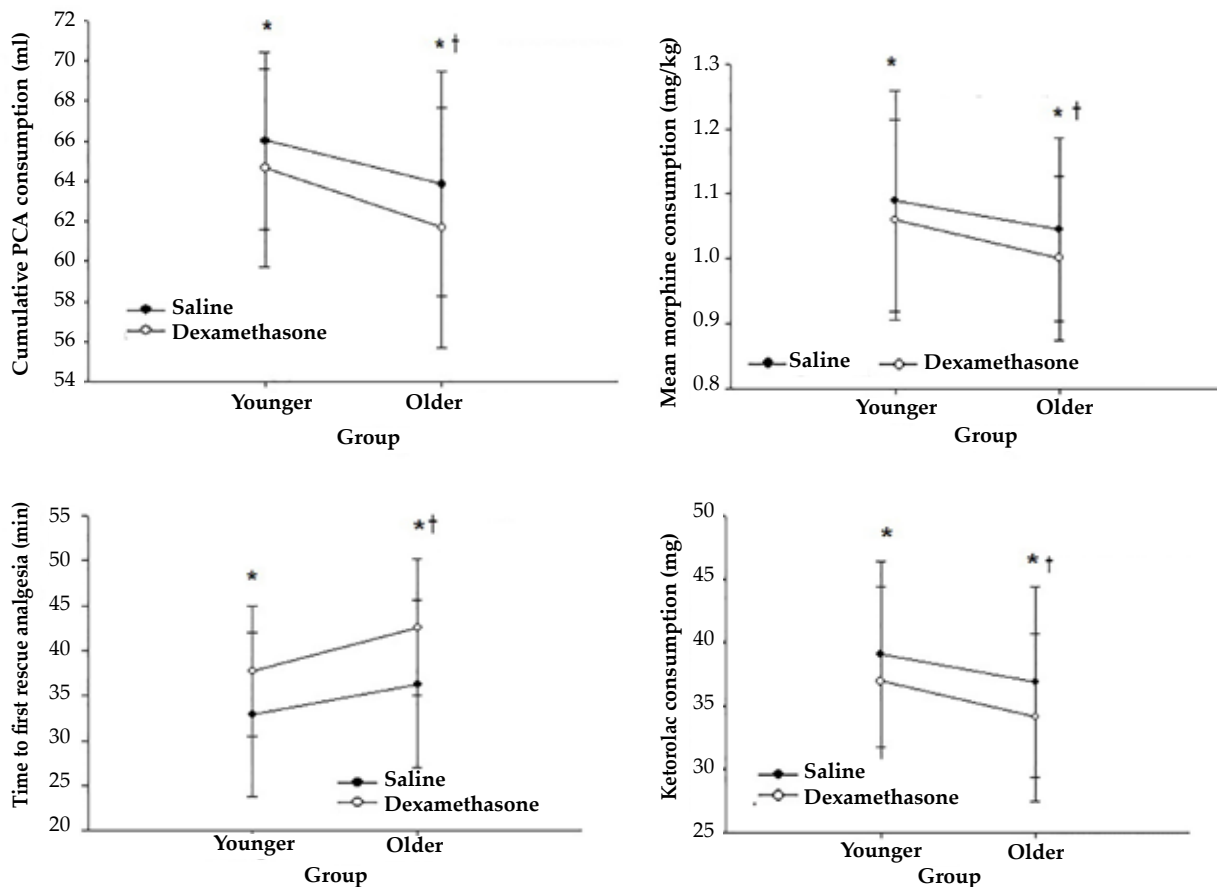
Table 1: Patients' characteristics

Variables	Younger group (n = 193)	Older group (n = 187)	p-value
Age (years)	41.1 ± 2.4	69.2 ± 2*	< 0.001
Sex (male/female)	98/95	93/94	NS
Body weight (kg)	62.6 ± 8.4	61.9 ± 6.2	NS
Duration of surgery (min)	58.2 ± 8.6	57.8 ± 8.8	NS
Time to first rescue analgesia (min)	35.3 ± 8.6	39.4 ± 9*	< 0.001
Ketorolac consumption (mg)	38 ± 7.5	35.5 ± 7.2*	0.001
Cumulative PCA consumption (ml)	65.3 ± 4.7	62.8 ± 5.9*	< 0.001
Mean morphine consumption (mg/kg)	1.06 ± 0.16	1.02 ± 0.14*	0.014
Pain intensity on exertion			
VAS 1 hour	43.9 ± 8.1	40.9 ± 10.2*	0.001
VAS 6 hours	34.5 ± 6.9	33 ± 7*	0.035
VAS 12 hours	26.8 ± 5.5	25.6 ± 6.1 *	0.039
VAS 24 hours	19.9 ± 5	19.6 ± 4.5	NS
Postoperative nausea or vomiting	32 (16.6)	16 (8.6)*	0.019
Pruritus	0	0	NS

Values are expressed as mean ± SD or number (%) of patients. VAS: visual analogue scale, PCA: patient-controlled analgesia; *p < 0.05 vs younger group; NS: not significant

postoperative bleeding. Of the 380 remaining patients, 193 were in younger age group and 187 were in older age group. There were no significant differences between the two groups with respect to sex, weight, and duration of surgery (Table 1).

Compared to the younger group, the older group had a significantly longer time to first rescue analgesia as well as a lower rescue analgesia (ketorolac) requirement, cumulative PCA consumption, and mean morphine consumption adjusted for body weight.



*P < 0.05 vs saline in both groups, †P < 0.05 vs younger group

Fig 1: Clinically relevant pain

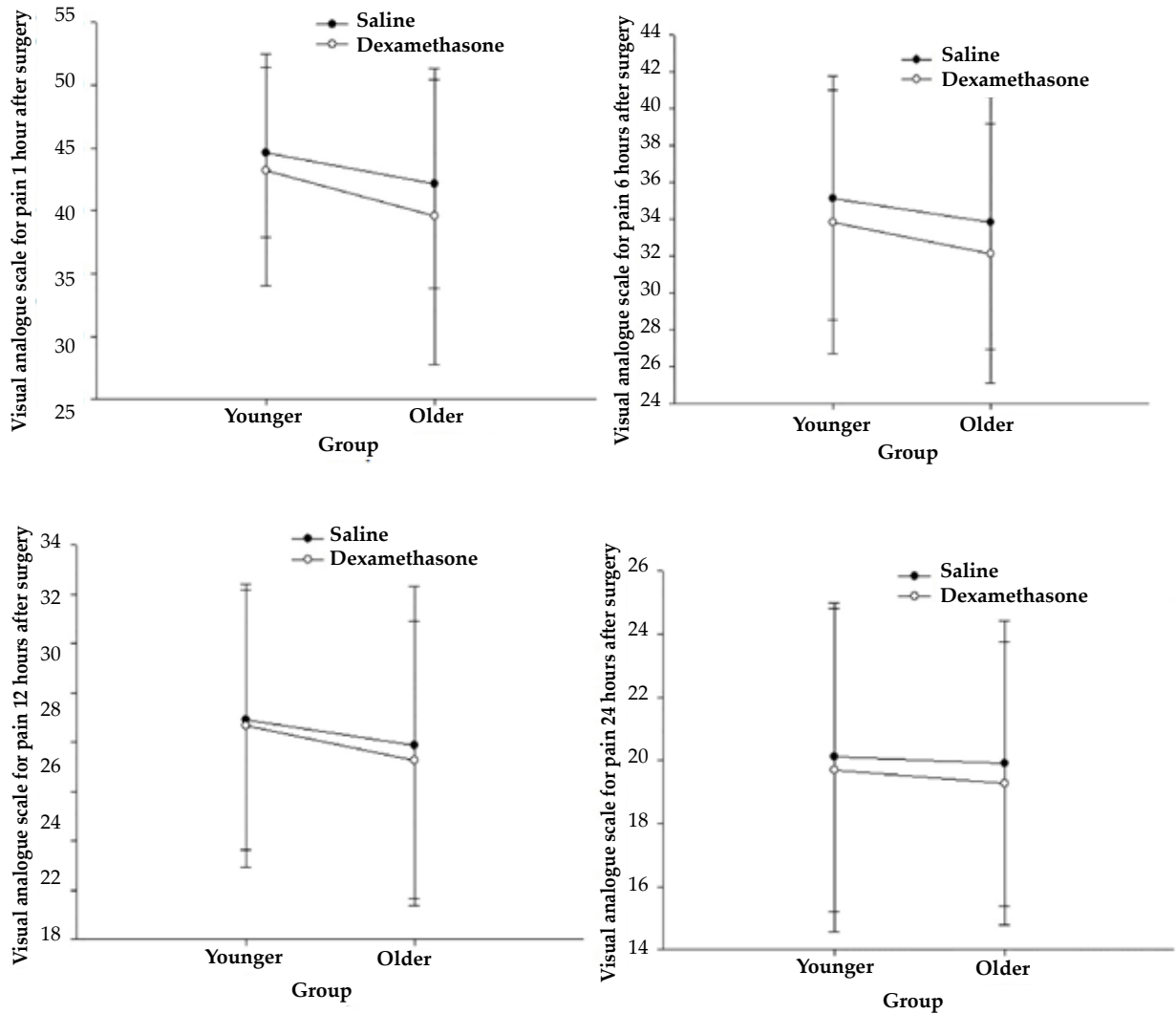


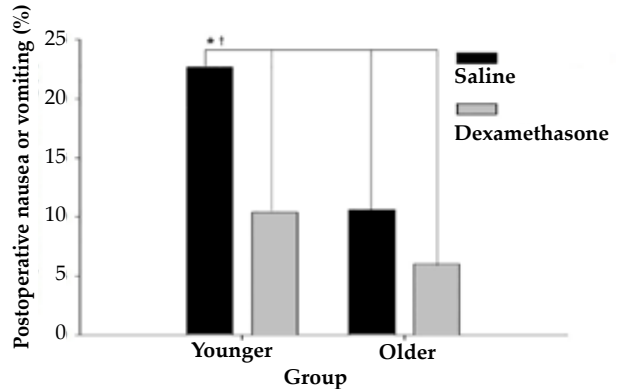
Fig 2: Pain intensity with visual analogue scale 24 hours after surgery

The older group also had lower VAS pain scores on exertion at 1, 6, and 12 hours postoperatively and a lower incidence of PONV (Table 1).

The use of dexamethasone in both age groups had significantly increased the time to first rescue analgesia and lowered the rescue analgesia (ketorolac) requirement, cumulative PCA consumption, and mean morphine consumption adjusted for body weight. These effects of dexamethasone on clinically relevant pain in the older group also appeared to be significantly greater than in the younger group (Fig 1).

The effect of dexamethasone in both groups on VAS for pain 24 hours after surgery was not significant, although these effects appeared to be greater in the older group than in the younger group (Fig 2).

Dexamethasone use in the younger group, rather than in the older group, showed a significant decrease in PONV. However, this effect in older group had a lesser degree of significance (Fig 3).



*P < 0.05 vs Dexamethasone in younger group, †P < 0.05 vs older group

Fig 3: Postoperative nausea or vomiting

DISCUSSION

The present study showed that the older group experienced a lower intensity of pain, with a lesser amount of opioid consumption and a lower PONV than the younger group. The threshold for pain may

be increased in older patients when exposure to stimuli is brief, of lesser spatial extent, and at peripheral, cutaneous or visceral sites. Opioid requirements decrease with increasing patient age^[3].

Age-related changes in the pharmacokinetics of many drugs used for pain management are common. This is primarily due to two factors: the progressive physiological decline that occurs with increasing age; and the increasing likelihood of concurrent disease. The changes that are of most significance to the pharmacokinetics of drugs used in acute pain management relate to renal function in particular, although other changes may also have some effect. Therefore, patients with hepatic or renal insufficiency were excluded in the present study. Age-related changes in pharmacodynamics also occur, although the underlying mechanisms are not fully understood. It appears that brain sensitivity to opioids increases by approximately 50% in older adults. However, it is not clear whether this difference is due to alterations in the number and/or function of opioid receptors in the central nervous system or other factors^[4,5].

Age may influence the risk of PONV as emesis occurs less frequently in older patients. One of the factors responsible for decreased PONV in older adults could be the decrease in the dose of anesthetic agents administered^[8-10].

A number of recent studies have investigated the potential analgesic benefit of dexamethasone and have yielded inconsistent findings, which are thought to be a result of the variability in the type of surgery, dexamethasone dose and timing, anaesthetic regimen, and type of postoperative rescue analgesic^[6,7].

The results of the present study, with respect to the analgesic effects of dexamethasone, are consistent with those of previous clinical trials that have demonstrated the analgesic efficacy of dexamethasone. However, the previous studies have not taken into account potential age-related differences in dexamethasone efficacy.

The results of the present study revealed that the effects of dexamethasone on clinically relevant pain had a greater impact in the older group than the younger group (Fig 1), and the effect of dexamethasone on pain intensity for 24 hours in both groups was not statistically significant (Fig 2). These results may be due to the pharmacokinetic and pharmacodynamic changes of dexamethasone in the older group. A study reported that dexamethasone treatment led to an increase of glucocorticoid response element (GRE) binding activity in aged rats, whereas in young animals, GRE binding activity was decreased^[11]. These changes in the brain induced by dexamethasone treatment is insufficient to explain our results. Dexamethasone has no short-term effects on pain sensitivity in terms of

pain threshold, pain rating, and pain discrimination ability in healthy individuals^[12].

In the present study, the younger group included women with menstrual cycles. Gonadal hormones are known to modulate pain intensity. A cyclical decrease in the pain threshold and an increase in morphine consumption have been observed in menstruating women, notably during the luteal phase. Studies involving healthy women volunteers have shown that women have greater pain sensitivity when they have low estrogen levels^[13,14]. It is known that dexamethasone acts directly on the pituitary gland to suppress the action of estradiol and lowers circulating estrogens^[15,16]. Taken together, in the present study, the effect of dexamethasone on clinically relevant pain in older group may mainly result from pharmacokinetics and pharmacodynamics rather than hormonal effect.

The present study showed that postoperative antiemetic effects of dexamethasone were greater in the younger group than in the older group. The effect of dexamethasone on PONV in the older group was minimal. The antiemetic mechanism of dexamethasone is unclear; it may be due to the release of endorphins that elevate mood and stimulate appetite. Additionally, it could be related to anti-inflammatory action within the gut that leads to reduction in the level of serotonin^[17,18]. The opioid-sparing effect of the analgesic properties of dexamethasone may contribute to lower rates of PONV^[19]. The apparent age-related difference in the efficacy of dexamethasone against PONV may be related to gonadal hormones. Estradiol may sensitize the chemoreceptor trigger zone and/or the vomiting center of the brain^[14]. As mentioned above, pharmacokinetic and pharmacodynamic changes of dexamethasone in the older group may also affect its efficacy in PONV.

This study had some limitations. The individuals were grouped on the basis of only one parameter, *i.e.* age; however, biological "fitness" may be of more significance than chronological age. The physiological changes are progressive, but the rate of decline can be highly variable as physiological aging may or may not be concurrent with chronological aging. The results in the present study do not determine whether the observed changes are caused by the aging process or by other age-associated effects, including an increased presence of comorbid disease, bio-cultural cohort effects, or altered psychosocial influences.

The younger group in the present study included pre-menopausal women. We did not consider the hormonal state of the women or the stages of their menstrual cycles. Thus, this could be another possible, uncontrolled, confounding factor for the difference in the results.

CONCLUSION

The physiologic basis for age-related differences in pain response and analgesic efficacy is not completely understood. An improved understanding of the mechanisms underlying sex-related differences in pain perception and response to analgesic drugs should aid in formulating improved pain management strategies for postoperative patients. Although the observed age-related differences of dexamethasone in opioid effect may be clinically relevant, the lack of knowledge about other factors involved in the large variability of patient sensitivity to opioid analgesics necessitates that practitioners customize their dose regimens on the basis of individual requirements.

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Conflicts of interest: None

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Original Article

The Prognostic Importance of Histological Variants of Well Differentiated Oncocytic Tumors of Thyroid

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ABSTRACT

Objectives: To show whether the prognosis of oncocytic variant of papillary carcinoma (PCOV) differs from the oncocytic variant of follicular carcinoma (FCOV), and to evaluate the importance of histological features influencing tumor recurrence and prognosis

Design: Retrospective study

Setting: Department of Pathology, Faculty of Medicine, Ege University, Izmir, Turkey

Subjects: Thirty cases diagnosed as oncocytic carcinomas of thyroid during the period of January 2000 to December 2011 were included in the study.

Intervention: Demographical data, follow-up time, development of recurrence and/or distant metastasis, and macroscopical features of the tumors were evaluated. Hematoxylin-eosin stained slides of the cases were reviewed retrospectively.

Main outcome measures: To show the prognostic difference of PCOV from FCOV and to evaluate the importance of

histological features influencing tumor recurrence and prognosis

Results: Twenty cases were PCOV and 10 were FCOV. Two of the FCOV and one PCOV case recurred locally. None of the cases of PCOV developed distant metastasis and all of these cases are alive. Only one FCOV case with extrathyroidal extension developed distant metastasis and two cases with extrathyroidal extension recurred locally. Four FCOV cases developed metastasis and three of these died from the disease. Vascular invasion was observed in most of the FCOV, but only in one of the PCOV cases. Significant association was found between the histological type of the tumor and survival, and also the vascular invasion.

Conclusion: The diagnosis of oncocytic carcinomas, whether variants of papillary or follicular carcinomas, is essential, as the presence of vascular invasion and disease-free survival differs between the two variants.

KEY WORDS: oncocyte, oncocytic thyroid carcinoma, prognosis, variants

INTRODUCTION

The Hurthle cell (oncocyte) is a follicular-derived cell which has an abundant eosinophilic granular cytoplasm and centrally placed small to large round nuclei with prominent nucleoli. The presence of numerous mitochondria in the cytoplasm causes this eosinophilic appearance^[1-3]. When the proportion of oncocytes is higher than 75% in a thyroid tumor, it is called an oncocytic cell tumor^[4,5].

Oncocytic cell thyroid neoplasms include a variety of tumor variants according to the 2004 World Health Organization Classification of Endocrine Tumors^[6]. These carcinomas are diagnosed using the

same morphological criteria used for non-oncocytic counterparts^[6-8]. The criteria for the diagnosis of follicular carcinoma, oncocytic variant (FCOV) includes invasion of the capsule and/or vessels of the capsule^[9]. The diagnosis of papillary carcinoma, oncocytic variant (PCOV) is made when the characteristic nuclear features of papillary carcinoma are present^[5,6,10,11].

Oncocytic carcinomas are thought to behave more aggressively as compared with the well-differentiated, non-oncocytic thyroid carcinomas^[12-14]. However, some authors do not agree as they think that the prognosis depends on the stage of the patients^[15,16]. There is also a debate among the pathologists about the prognosis of

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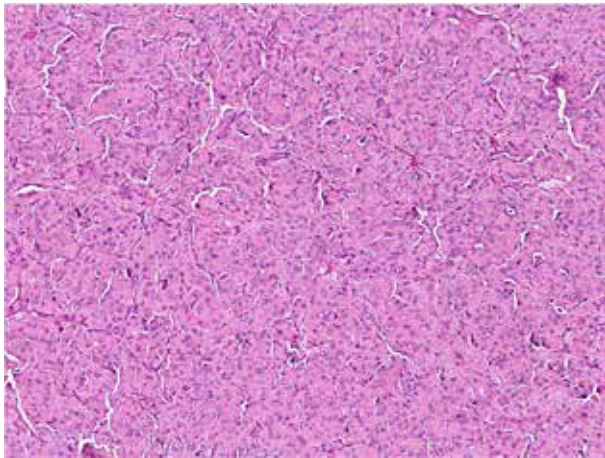


Fig. 1: Histology of oncocytic variant of papillary carcinoma (H&Ex20)

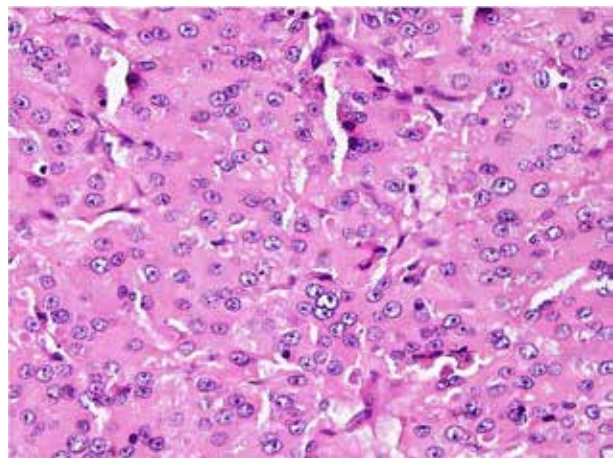


Fig. 2: The nuclei of the tumor cells are enlarged, irregular in shape, with prominent macronucleoli and grooves in oncocytic variant of papillary carcinoma (H&Ex40)

PCOV and FCOV. Compared to PCOV, FCOV more likely presents with distant metastases, but nodal metastases are uncommon^[17].

The aim of this retrospective study is to determine whether the prognosis of FCOV differs from PCOV and to evaluate the importance of various histological features influencing tumor recurrence and prognosis of these tumors.

SUBJECTS AND METHODS

In the present study, 52 cases diagnosed as oncocytic carcinomas of thyroid from 2000 to 2011 in the Department of Pathology were retrospectively reviewed and 30 cases with follow-up were included in the study. Total thyroidectomy was performed in all cases. Dissection of cervical lymph nodes was added if lymph node involvement was documented at imaging staging before operation or at surgical examination.

Medical data of the cases, follow-up time, administration of radioactive iodine, and development of recurrence and/or distant metastasis were obtained from the Department of Nuclear Medicine. Development of recurrence and/or distant metastasis was considered as progression of the disease. The macroscopical features of the tumors were obtained from the archival records of the Department of Pathology.

Hematoxylin-eosin stained slides of the cases were reviewed retrospectively by two pathologists (YE, GE). The histological features of the tumors were evaluated according to the 2004 Classification of Endocrine Tumors of World Health Organization. Each of the cases were evaluated in terms of tumor size, histological subtype, presence of multiple foci, formation of capsule, infiltration to the thyroid parenchyma, capsule and/or vascular invasion, distance of tumor to the surgical margins, presence of

extrathyroidal extension, and lymph node metastasis in cases with cervical lymph node dissection.

Histologically, oncocytic tumors with characteristic papillary carcinoma-like nuclear features such as large, clear, hypochromatic nuclei, with grooves and nuclear membrane irregularities, as well as big eosinophilic nucleoli were defined as PCOV (Fig 1, 2), and the tumors without characteristic papillary carcinoma-like nuclear features, showing capsule (Fig 3) and/or vascular invasion as FCOV (Fig 4).

The cases were grouped according to age as ≤ 45 and > 45 years old, and the tumor diameter as ≤ 2 cm and > 2 cm. Penetration of the tumor through the capsule was evaluated as capsule invasion, tumor plug in the subendothelial location covered by endothelial cells, as well as tumor cell cluster with thrombus within a vein, in or immediately beyond the capsule, as vascular invasion.

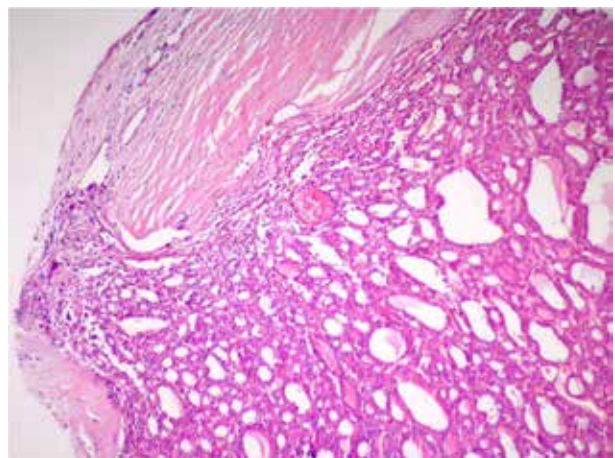


Fig. 3: Infiltration of the tumor through the capsule in oncocytic variant of follicular carcinoma (H&Ex20)

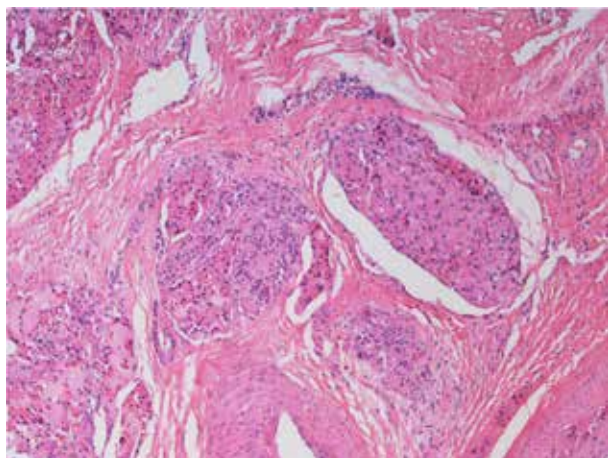


Fig. 4: Vascular invasion in oncocytic variant of follicular carcinoma (H&E x20)

Statistical analyses were carried out by computer based programme IBM SPSS version 18.0. Univariate analysis and frequency analysis were used. Correlations were searched by Pearson Chi-Square test and Fisher's exact test. P-values less than 0.05 was accepted to display the significance of differences.

RESULTS

Of the 30 cases included in the present study, 20 cases were PCOV and 10 were FCOV. PCOV cases consisted of 16 females and 4 males, 16 cases were aged > 45 years and the rest < 45 years old. Seven cases of FCOV were females, three were males, and all of these FCOV cases were > 45 years old. The follow up period of the cases ranged between 49 to 186 months. The clinicopathological characteristics of the cases were summarized in Table 1.

The PCOV case which developed recurrence was a male ($p = 0.200$), > 45 years-old ($p = 1.000$), with a unifocal tumor ($p = 1.000$), < 2 cm diameter ($p = 1.000$). Eight cases of PCOV had a tumor surrounded by a capsule. Five of the 12 cases without capsule formation presented infiltration of the thyroid parenchyma. However, the case that developed recurrence had no capsule ($p = 1.000$), but the tumor was well-circumscribed ($p = 1.000$). Vascular invasion beyond the tumor was only seen in one of the PCOV cases without capsule formation, and this case had no recurrence during the follow-up of 45 months ($p = 1.000$). Tumor was seen at the surgical margins only in two cases of PCOV; however these cases did not develop recurrence. There was no tumor at the surgical margins of the case that had recurrence ($p = 1.000$). None of the PCOV cases showed extrathyroidal extension. Of the 10 cases with cervical lymph node dissection, only two demonstrated lymph node metastasis.

Table 1: Clinicopathological characteristics of oncocytic variants of papillary carcinoma and follicular carcinomas

Parameter	Oncocytic Variant of Papillary Carcinoma n (%)	Oncocytic Variant of Follicular Carcinoma n (%)
Gender		
Female	16 (80)	7 (70)
Male	4 (20)	3 (30)
Age (years)		
< 45	4 (20)	---
> 45	16 (80)	10 (100)
Tumor size		
< 2cm	11 (55)	1 (10)
> 2cm	9 (45)	9 (90)
Recurrence		
Yes	1 (5)	2 (20)
No	19 (95)	8 (80)
Distant metastasis		
M1	---	4 (40)
M0	20 (100)	6 (60)
DOD		
Yes	---	3 (30)
No	20 (100)	7 (70)

DOD: Died of disease

Four cases of FCOV were classified as minimally invasive and six as widely invasive. Of the two cases that recurred locally, one was minimally invasive and the other widely invasive ($p = 1.000$). Distant metastasis was seen in three of the widely invasive follicular carcinomas and in one of the minimally invasive follicular carcinomas ($p = 0.571$). Three of the widely invasive follicular carcinoma cases died because of the disease, but all of the minimally invasive follicular carcinoma cases were alive ($p = 0.200$). Two cases of FCOV that developed recurrence were females ($p = 1.000$), three of the four cases with distant metastasis were females and one was male ($p = 1.000$). The diameter of the tumor was > 2 cm in nine of the FCOV cases. Both cases that developed recurrence and all cases with distant metastasis had tumor size > 2 cm ($p = 1.000$). The tumor diameter was > 2 cm in all three cases that died of the disease ($p = 1.000$).

Vascular invasion beyond the tumor was seen in seven of the FCOV cases including both cases with local recurrence ($p = 1.000$). Three of the seven cases with vascular invasion and one of the three cases without vascular invasion developed distant metastasis, however no statistically significant difference was found between vascular invasion and distant metastasis ($p = 1.000$). Two cases with vascular invasion died in 28 and 72 months, respectively; and only one case without vascular invasion died of disease (died in 96 months). No statistically significant difference was found between vascular invasion and survival ($p = 1.000$).

Table 2: Comparison of prognosis with the clinicopathological features of oncocytic variants of papillary carcinoma and follicular carcinoma cases

Parameter	Oncocytic variant of papillary carcinoma	Oncocytic variant of follicular carcinoma		
	Recurrence n (%)	Recurrence n (%)	Distant metastasis n (%)	DOD n (%)
Gender				
Female	---	2 (20)	3 (30)	2 (20)
Male	1 (5)	---	1 (10)	1 (10)
Age (years)				
< 45	---	---	---	---
> 45	1 (5)	2 (20)	4 (40)	3 (30)
Tumor size				
< 2 cm	---	---	---	---
> 2 cm	1 (5)	2 (20)	4 (40)	3 (30)
Vascular invasion				
Yes	---	2 (20)	3 (30)	2 (20)
No	1 (5)	0 (0)	1 (10)	1 (10)
Tumor at Surgical Margins				
Yes	---	1 (10)	2 (20)	1 (10)
No	1 (5)	1 (10)	2 (20)	2 (20)
Extrathyroidal invasion				
Yes	---	---	1 (10)	1 (10)
No	---	---	---	---

*None of the PCOV cases developed distant metastasis or died of disease

Two cases of FCOV had tumor at the surgical margins. One of the two cases with local recurrence and two of the four cases who developed distant metastasis, had tumor at the surgical margins. Of the three cases that died of disease, one had tumor at the surgical margins. No statistically significant difference was found between surgical margin invasion and recurrence, distant metastasis, and survival ($p = 1.000$, $p = 1.000$, and $p = 1.000$, respectively). Only one of the FCOV cases had extrathyroidal invasion, had distant metastasis, and died of disease. Extrathyroidal invasion was not seen in the two cases that recurred locally. No statistically significant difference was found between extrathyroidal invasion and recurrence, distant metastasis, and survival ($p = 0.900$, $p = 0.133$, and $p = 0.100$, respectively).

One of the PCOV cases and two of the FCOV cases developed recurrence ($p = 0.251$). None of the PCOV cases had distant metastasis and all of them were alive. Four of the FCOV cases had distant metastasis and three of them died of disease. A statistically significant association was found between histological variant of tumor and disease-free survival ($p = 0.031$). Comparison of prognosis with the clinicopathological features of the cases were summarized in Table 2.

Vascular invasion was seen in one of the PCOV cases and seven of the FCOV cases. A statistically significant association was found between histological variant of tumor and vascular invasion ($p = 0.000$).

DISCUSSION

Oncocytic carcinomas of thyroid are one of the controversial issues in endocrine pathology. The main histopathological difficulties of these tumors focus on the histological classification and the differential diagnosis of carcinomas and adenomas^[18,19]. The diagnosis of malignancy of oncocytic thyroid tumors depends on the same criteria with non-oncocytic tumors. The presence of capsular and/or vascular invasion in oncocytic variant of follicular carcinomas, and the presence of characteristic nuclear features of papillary carcinoma in the oncocytic variant of papillary carcinoma are necessary for diagnosis^[3,5,20,21]. In the present retrospective study, we evaluated the demographical and histological characteristics and prognostic features of PCOVs and FCOVs.

Most of the thyroid carcinomas usually occur in the female population, with a female to male ratio of 3-4:1^[22,23]. In the present study, both PCOV and FCOV cases were observed with a higher frequency in the female patients, similar to the literature.

Most of the well-differentiated carcinomas of thyroid can present in any age group. However, PCOV is seen approximately in 40 year-olds and FCOV in 50 year-olds^[6,24]. In the present study, consistent with the literature, the median age of PCOV cases were 46 years and 57 years for FCOV cases.

Some of the subtypes of well-differentiated thyroid carcinomas such as oncocytic variants have been identified as being more aggressive tumors^[25,26].

Unlike these studies, Simoes *et al*^[27] suggested that oncocytic carcinomas are not usually very aggressive tumors because of their low proliferative activity. They emphasized that accumulation of mitochondria in the cytoplasm, from 200 or 300 to 3000 or 4000 mitochondria per cell, needs time; so they suggested that these tumors have decreased propensity for I-131 therapy, thus a higher incidence of metastasis.

In recent years, it is suggested that oncocytic cell carcinomas can behave in a benign as well as in a malignant fashion with good follow-up criteria. PCOVs have been identified with the refinement of malignancy criteria, such as presence of classical papillary carcinoma nuclear features and the development of molecular techniques^[4,28-33].

Ghossein *et al*^[34] have suggested that the most important risk factor for recurrence is the presence of vascular invasion, especially four or more foci of vascular invasion, in encapsulated oncocytic cell carcinomas. Carcangiu *et al*^[4,33] have emphasized that local recurrence of oncocytic cell carcinoma is associated with the extent of surgery, with recurrence rates for lobectomy and total thyroidectomy of 40% and 15%, respectively.

It is well known that follicular carcinoma of thyroid disseminates hematogenously; as a result, distant metastasis is relatively common, found in approximately 10% of patients at presentation, and nodal metastasis is rare^[35]. In the present study, similar to the literature, four of the 10 FCOV cases showed distant metastasis and none of the PCOV cases had distant metastasis, which may be due to the strict criteria of capsule and/or vascular invasion in the diagnosis of FCOV.

Some authors reported that older age, thyroid capsular invasion, and higher TNM stage were significantly predictive of tumor recurrence and it was suggested that tumors > 4 cm were more aggressive and recurred locally^[15,36-42]. Samulski *et al*^[43] showed the malignant potential of the oncocytic tumors based on size, especially in tumors < 2 cm. In the present study, we have also grouped the oncocytic tumors for analysis as > 2 cm or ≤ 2 cm. The only recurred PCOV case was < 2 cm; but unlike PCOV, of the FCOV cases, two that recurred and four with distant metastasis had tumors > 2 cm.

The prognosis of patients with PCOV or FCOV is reported as similar to that of patients with non-oncocytic counterparts, within comparable stages^[44-46]. However, some authors emphasize that the oncocytic carcinomas of the thyroid have less ability to trap iodine, so they are less responsive to radioactive iodine therapy^[16,47,48].

In the literature, oncocytic cell carcinomas were reported as aggressive tumors with low survival rate. A literature review showed an overall recurrence rate of 31.4% and mortality rate of 25% for the oncocytic cell carcinomas^[40]. Pryma *et al*^[49] reported the mortality rate for patients with distant metastasis at presentation as 80% for five years. Kushchayeva *et al*^[40] reported that local invasion and extrathyroidal extension adversely influenced the disease free interval, and 62.5% of their patients with local invasion had metastasis at presentation or developed metastasis during follow-up and died of disease. Also in the literature, a survival rate of 100% for patients with FCOV without vascular invasion is reported, whereas the rate was 33% for patients with FCOV with local invasion^[37].

In the present study, only one of ten cases of FCOV with extrathyroidal extension developed distant metastasis and died in two years, and two cases with extrathyroidal extension recurred locally. However, we could not find any association between extrathyroidal extension and local recurrence, distant metastasis, and overall survival. In the present study, two of the FCOV and one PCOV case recurred locally. None of the cases of PCOV developed distant metastasis and all of these cases are alive. Four of the FCOV cases developed metastasis and three of these died of the disease. We found a statistically significant association between the histological type of the tumor and disease-free survival, and also between the vascular invasion and histological type of the tumor. Vascular invasion was observed in most of the FCOV, but only in one of the PCOV cases.

CONCLUSION

The pathological diagnosis of oncocytic carcinomas, whether variants of papillary or follicular carcinomas, is essential, as the presence of vascular invasion and disease-free survival differs between the two variants. Before diagnosing an oncocytic tumor with capsule and/or vascular invasion as a variant of follicular carcinoma, a pathologist should carefully examine the nuclear features of the tumor cells. We have concluded that, because of the low number of cases in the present study, future studies performed on larger series are required for defining the prognostic features identifying the two histological variants of well differentiated oncocytic tumors of thyroid.

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Original Article

The Effect of Cold Application Performed in Early Post-operative Period for Pain and Bleeding in Patients who had Septoplasty Surgery due to Septum Deviation

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ABSTRACT

Objective: The study was conducted to determine the effect of cold application in the early postoperative period for pain and bleeding in patients who had septoplasty to correct septum deviation.

Design: Randomized, controlled, experimental study

Setting: This study was conducted at Ear, Nose and Throat Clinic, Research and Application Hospital of Düzce University, Turkey.

Subjects: The study was conducted on 60 patients. One half of the patients were included in the experiment group (n = 30) and the other half in the control group (n = 30).

Interventions: Data collection was achieved using a form for patients' identifying information and the Post-

Operative Pain Intensity Assessment Scale and Post-Operative Grading Scale for assessments of bleeding.

Main outcome measures: Post-Operative Pain Intensity Assessment Scale and Post-Operative Grading Scale for assessments of bleeding

Result: Cold application was shown to be effective in reducing pain that developed in the early postoperative period ($p < 0.05$). The degree of bleeding was found to be lower in the experiment group in comparison with the control group ($p > 0.05$).

Conclusion: Applying cold in the early postoperative period to patients who had septoplasty to correct septum deviation is recommended to reduce operation-related pain and bleeding in the postoperative period.

KEY WORDS: bleeding, cold application, pain, septoplasty

INTRODUCTION

Septum deviation is a condition where the septum is displaced towards the right or left, causing blockage of nasal air passages. Deformities of the cartilage and bones forming the septal framework arise from deflection, angulation, and luxation. It is often observed in the population and is one of the most common causes of admission to Ear, Nose, and Throat (ENT) polyclinics^[1,2]. Septoplasty is the treatment for septum deviation and is one of the commonly performed ear, nose, and throat surgeries. Bleeding, adherence, haematoma, abscess, or perforations are complications commonly seen after septoplasty. Pain is one of the major disturbances the patients experience after septoplasty^[3-5].

Postoperative pain is an acute form of pain that starts with surgical trauma and resolves upon tissue healing. Management of postoperative pain becomes increasingly important because of the adverse and recovery-delaying effects caused by pain. If postoperative pain is not treated, increases in catabolic hormones such as cortisol, adrenocorticotrophic hormone, glucagon, aldosterone, and catecholamines, and decreases in anabolic hormones such as insulin and testosterone affect the respiratory, circulating, gastrointestinal, renal, and autonomous nervous systems. All these endocrinal alterations negatively affect hemostasis^[6].

Pain is the main symptom that leads a patient to request assistance of healthcare personnel. However,

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the literature shows that the measures taken for management of pain are extremely inefficient in general, and that pain is not eliminated in the majority of patients. Inefficacies in pain management may include lack of healthcare personnel having adequate knowledge about pain; failure to administer the newly-developed and widely-used pain management methods and applications; lack of attention to pain on part of the nurses; or their not having knowledge about pain elimination methods. There are also concerns about addiction that may develop if a drug is administered; many patients do not complain about the pain or try to hide it; the physician not recommending analgesics for the patients; and a failure to adopt a multidisciplinary approach to pain management^[7,8].

Pharmacological and non-pharmacological methods can be used together as well as individually for pain elimination. Non-pharmacological methods have advantages in terms of cost and pain elimination without introducing a chemical substance to the body; also, these methods can easily be used by nurses. At present, many non-pharmacological methods are used such as massage, hot and cold applications, menthol application to the skin, relaxation by deep inspiration, meditation, drawing attention in another direction, and using the imagination^[9]. Cold applications have major importance in non-pharmacological pain management as simple and inexpensive treatment methods^[10]. Cold application creates capillary contraction, reduces the temperature in the damaged area, slows metabolism and controls edema by reducing capillary permeability and bleeding, reduces the risk of haematoma formation and bacterial activity in infections, prevents the pain signal from reaching higher centers, and eliminates painful spasms^[11-13]. Applying cold after trauma affects the adhesion of leukocytes to the vascular endothelium in tissue; as a result, it reduces microvascular permeability, prevents edema formation by reducing extravasation of macromolecules, and reduces bleeding and formation of haematoma. Also, it decreases the severity of local tissue damage by reducing metabolic activity in the tissue, provides analgesia, and decreases the need for analgesia by slowing down the pain signal conduction at efferent nerves after trauma^[11,13,14].

Since no study has been previously conducted in Turkey to determine the effect of cold application performed in the early postoperative period for pain and bleeding in patients who had septoplasty surgery due to septum deviation, the goal of the present study is to contribute to the existing literature.

The questions the study proposes to answer are;

1. Does cold application performed in the early postoperative period in patients who had septoplasty surgery due to septum deviation

reduce the pain which might occur?

2. Does cold application performed in early postoperative period in patients who had septoplasty due to septum deviation decrease the possibility of consequent bleeding?

SUBJECTS AND METHODS

This study is a randomized, controlled, experimental design research. The study was conducted between January and May 2015 in the ENT clinic at Research and Application Hospital of Duzce University.

The study population included hospitalized patients in the ENT surgical clinic at the Research and Application Hospital of Duzce University. The study was conducted in a single center to ensure randomization and minimize the factors that could affect the result of the study (standardized interventions, physician practice, anesthetic techniques applied to patients, and standardization of environmental conditions of patients).

The Number Cruncher Statistical System and Power Analysis and Sample Size 2007 were used for calculation of sample size. For each group, it was assumed that the power analysis of the study would be 99% when 30 patients with 0.05 alpha level and 95% reliability levels were included in the study. Accordingly, the population was divided into 2 groups: 30 patients for the experiment group and 30 patients for the control group.

The characteristics of patients included in the study:

- Similarity in the number of males and females in both groups to avoid any gender factor related to pain sensation,
- The patients were 18 years old and older,
- The patients had this surgery for the first time to avoid the possibility of comparison with previous experiences,
- Patients were adults who had never been exposed to nasal trauma and had no secondary nasal complaints,
- Patients had no analgesic medication before the procedure that might affect the pain sensation,
- Patients without any mental impairment or perception issues and communication difficulties,
- Patients who were not allergic to cold and had normal vital signs.

Data Collection Tools

A patient identification form was constructed through a review of the literature. The Post-Operative Pain Intensity Assessment Scale (a verbal and numerical scale) and the Post-Operative Grading Scale

for Bleeding, an ice bag, and waterproof bags were used for data collection.

A *Patient Identification Form* was constructed by the researchers based on the literature and included identifying characteristics of the participants.

Post-Operative Pain Intensity Assessment Scale (Numerical Assessment Scale): This method for determining pain intensity has the goal that the patients express their pain sensation with numbers. The numerical scale starts with non-existence of pain (0) and rises to the level of intolerable pain (10 – 100). Numerical scales are more often adopted because they simplify pain definition, providing facility in scoring and recording and evaluation of minimum and maximum effects^[15,16].

Pain scales were used in the 24 hours postoperative in the following way: applied 8 times (hourly) for the first 8 hours, the next 2 times (10th and 12th hours) at 2-hour intervals, and the final 3 times (16th, 20th and 24th hours) at 4-hour intervals.

Post-Operative Pain Intensity Assessment Scale (Verbal Category Scale): The Verbal Category Scale is a simple, descriptive scale based on choosing the most appropriate word to describe the patient's pain status. Pain severity is described by a range from mild to intolerable. The patient is asked to choose an appropriate category for his/her situation^[17].

Post-Operative Bleeding Assessment Scale: No evaluation tool was found in the literature for assessment of nasal bleeding. For this reason, this scale was organized by the study researchers in line with specialists' suggestions. The scale was organized to measure the amount of blood that was leaking through the incisional area during the postoperative 24 hours. The scale was used hourly for the first eight postoperative hours, once every two hours for the next four hours, and once every four hours for the next 12 hours. One piece of sterile gauze dressing (described as a "tampon" in Table 3) with equal and standard size was attached to the incisional areas of each patient by antiallergic plaster to absorb the leaking blood. The gauze dressing was not removed until the upper surface was completely covered by blood; it was changed when there was no observable white area on the upper surface of the dressing. Each change was marked by the corresponding hour on the patient form. Each change was performed under supervision of a nurse, and the bloody gauze bandages were collected in transparent bags and were recounted to avoid any possible errors.

Data Collection

Data were collected by a face-to-face interview by a researcher. The researcher arrived at the

clinic and interviewed with physicians at 08:30 am every morning on weekdays and designated the patients who were to undergo the surgery. The researcher interviewed the patients and determined whether the patients fulfilled the requirements for the study sample. All patients included in the test and control groups were informed about the research both verbally and in written form by the researcher. The researcher informed patients about the visual comparison scale in the data collection form and taught them how to use it. The researcher interviewed the patients and recorded the informed consent of those who agreed to participate in the study. Two patients in the experiment group and one patient in the control group did not agree to participate.

Process Steps for Experiment Group

The researcher applied the data collection method to the patients who were decided to be included in the experiment group and agreed to participate, in the rooms of the ENT clinics and the patient identification form was also recorded. The researcher then took an ice bag from the clinic refrigerator, put it into a waterproof bag, and sealed the bag firmly by allowing room for it to settle on the right and left sides of the nose. Cold applications were performed for 15 minutes^[11]. Two pain assessment forms and one nasal bleeding monitoring form were supplied by the researcher to the patient at 1st and 2nd postoperative hours by explaining face-to-face and showing the scale on the form. Application of all data collection forms took approximately 12 minutes. All cold applications were applied by the researcher (researcher who is clinical nurse of the otorhinolaryngology) in the same order. The researcher then recorded the scores and ended the application. No side effects related to the application of ice were seen in the patients.

Process Steps for Control Group

The researcher supplied the data collection method to the patients who had decided to be included in the control group and had agreed to participate in the rooms of the ENT clinics. The patient identification form was recorded by the researcher. The same clinical routine without cold application was applied to the patients in the control group.

Data Evaluation

The data were analyzed by computer. Data were evaluated using percentages, mean values, chi-square test, and an independent samples t-test. In

analyzing the differences between the groups, the significance level was set as 0.05.

Ethical Principles of the Study

Approval of the ethics committee was received before starting the study. Later, written authority was received from the chief physician after presenting the information form of the study, including aim and contents, to the chief physician. The patients were informed verbally about the aim of the study because using human cases in the study requires the protection of individual rights. The patients were informed that individual information patients shared with the researcher would be preserved.

Strengths of the Study

A randomized, controlled, experimental design was used in the study. The collected data were evaluated by a specialist statistician. Individual skill of the surgeon, the surgeon's level of experience, and the surgical techniques used in the surgical intervention may affect the development of pain and hemorrhage. For this reason, only patients whose surgery were performed by the same surgeon were included in the study.

RESULTS

When the identifying characteristics of the test and control groups were compared (Table 1), the average age was 28.53 years in the experiment group and 34.23 years in the control group; average height was 172.23 cm in the experiment group and 173.23 cm in the control group; average weight was 71.60 kg in the experiment group and 77.23 kg in the control group; average body mass index (BMI) was 23.59 kg/m² in the experiment group and 25.16 kg/m² in the control group. The number of male patients was higher in both groups. The majority of the patients were primary

Table 1: Comparing the identifying characteristics of patients

Characteristics	Test		Control		Test and p-value
	n	%	n	%	
Age					
18 - 30	20	66.7	13	43.3	$\chi^2 = 3.30$ p = 0.06
> 30 ↑	10	33.3	17	56.7	
Gender					
Female	10	33.3	7	23.3	$\chi^2 = 0.73$ p = 0.06
Male	20	66.7	23	76.7	
Education					
Primary school	13	43.3	16	53.4	$\chi^2 = 1.69$ p = 0.42
High school	8	26.7	4	13.3	
College	9	30	10	33.3	
Occupation					
Unemployed	1	3.3	2	6.7	$\chi^2 = 5.50$ p = 0.13
Self-employed	-	-	4	13.3	
Worker	19	63.4	13	43.3	
Officer	10	33.3	11	36.7	
Number of children					
0	16	53.3	14	46.7	$\chi^2 = 0.35$ p = 0.83
1 - 2	8	26.7	10	33.3	
≥ 3	6	20	6	20	
Smoking Status					
Smoker	11	36.7	18	60	$\chi^2 = 3.27$ p = 0.07
Non-smoker	19	63.3	12	40	
Alcohol Using Status					
Using	4	13.3	2	6.7	$\chi^2 = 0.74$ p = 0.38
Not using	26	86.7	28	93.3	
Living in home alone					
Alone	1	3.3	3	10	$\chi^2 = 1.07$ p = 0.30
Not-alone	29	96.7	27	90	
Living with					
Wife-Husband	16	55.2	17	63	$\chi^2 = 0.43$ p = 0.80
Parents	11	37.9	8	29.6	
Housemate	2	6.9	2	7.4	
	Mean ± SS		Mean ± SS		
Age	28.53 ± 9.32		34.23 ± 13.37		t = 1.91, p = 0.06
Height	172.23 ± 6.39		173.23 ± 8.29		t = 0.52, p = 0.60
Weight	71.60 ± 13.57		77.23 ± 16.85		t = 1.42, p = 0.15
Body mass index	23.59 ± 3.47		25.16 ± 4.30		t = 1.56, p = 0.1

school graduates, were workers, had no children, did not use alcohol, were not living at home alone, and were living at home with their partners.

Table 2: Comparing the health characteristics of patients

Characteristics	Test		Control		Test and p-value
	n	%	n	%	
Experiences of constipation					
Experiencing	-	-	1	3.3	$\chi^2 = 1.01$ p = 0.31
Not experiencing	30	100	29	96.7	
Experiences of having chronic disease					
Have	7	23.3	9	30	$\chi^2 = 0.34$ p = 0.55
Not have	23	76.7	21	70	
Chronic drug use					
Using	5	16.7	8	26.7	$\chi^2 = 0.88$ p = 0.34
Not using	25	83.3	22	73.3	
Difficulty in breathing through nose					
Experiencing difficulty	30	100	30	100	Test was not performed
Difficulty in breathing through nose during sleeping					
Experiencing difficulty	30	100	30	100	Test was not performed

No statistically significant difference was found between the groups when the identifying characteristics of the patients in the test and control groups were compared ($p > 0.05$), showing that the groups are homogenous. The comparison of the patients' health characteristics is shown in Table 2.

It was determined that a majority of the patients had no constipation issue, had no chronic disease, did not use continuous medication, had a problem breathing through the nose on a regular basis during the day and while sleeping.

When the amount of postoperative bleeding was compared (Table 3), it was found that the number of tampons changed in the experiment group were fewer compared with the number in control group, meaning that the amount of bleeding was lower in the experiment group, but not at a statistically significant level.

Table 3: Comparing the degree of bleeding in patients

Characteristics	Test		Control		Test and p-value
	n	%	n	%	
1 st hour					
1 tampon	15	100	15	88.2	$\chi^2 = 1.88$ $p = 0.17$
2 tampons	-	-	2	11.8	
6 th hour					
1 tampon	13	100	21	95.5	$\chi^2 = 0.60$ $p = 0.43$
2 tampons	-	-	1	4.5	
12 th hour					
1 tampon	14	87.5	20	90.9	$\chi^2 = 1.48$ $p = 0.47$
2 tampons	1	6.2	2	9.1	
3 tampons	1	6.2	-	-	
16 th hour					
1 tampon	12	100	18	90	$\chi^2 = 1.28$ $p = 0.52$
2 tampons	-	-	1	5	
3 tampons	-	-	1	5	
20 th hour					
1 tampon	16	100	21	95.5	$\chi^2 = 0.74$ $p = 0.38$
3 tampons	-	-	1	4.5	
24 th hour					
1 tampon	11	100	8	88.9	$\chi^2 = 1.28$ $p = 0.25$
2 tampons	-	-	1	11.1	

In the comparison of postoperative pain status (Table 4), the experiment group patients were found to experience less severe pain in comparison with the control group patients during the 24 hours, except for the 1st hour ($p < 0.05$).

When the average visual analog scale scores of the patients within 24 hours postoperative were compared (Table 5), the average pain scores of the patients in the experiment group were much lower in comparison with the patients in control group, and at a level sufficient to build a high level of significance, meaning that the experiment group patients experienced less severe pain ($p < 0.001$).

Table 4: Comparing the degree of post-operative pain in patients

Characteristics	Test		Control		Test and p-value
	n	%	n	%	
1 st hour					
No pain	1	3.3	1	3.3	$\chi^2 = 5.69$ $p = 0.22$
Mild pain	13	43.3	6	20	
Disturbing pain	5	16.7	3	10	
Moderate pain	5	16.7	9	30	
Severe pain	6	20	11	36.7	
6 th hour					
No pain	4	13.3	1	3.3	$\chi^2 = 11.47$ $p = 0.04$
Mild pain	13	43.3	6	20	
Disturbing pain	5	16.7	3	10	
Moderate pain	6	20	10	33.3	
Severe pain	2	6.7	8	26.7	
Intolerable	-	-	2	6.7	
12 th hour					
No pain	5	16.7	1	3.3	$\chi^2 = 18.62$ $p = 0.00$
Mild pain	11	36.7	3	10	
Disturbing pain	9	30	5	16.7	
Moderate pain	4	13.3	18	60	
Severe pain	1	3.3	2	6.7	
Intolerable	-	-	1	3.3	
16 th hour					
No pain	4	13.3	-	-	$\chi^2 = 14.40$ $p = 0.01$
Mild pain	12	40	6	20	
Disturbing pain	8	26.7	6	20	
Moderate pain	3	10	14	46.7	
Severe pain	3	10	3	10	
Intolerable	-	-	1	3.3	
20 th hour					
No pain	5	16.7	-	-	$\chi^2 = 27.21$ $p = 0.00$
Mild pain	18	60	4	13.3	
Disturbing pain	1	3.3	12	40	
Moderate pain	6	20	12	40	
Severe pain	-	-	2	6.7	
Intolerable	-	-	-	-	
24 th hour					
No pain	5	12.2	-	-	$\chi^2 = 15.99$ $p = 0.00$
Mild pain	16	55.3	7	23.3	
Disturbing pain	4	13.8	14	46.7	
Moderate pain	3	10.3	7	23.3	
Severe pain	1	3.4	2	6.7	

Table 5: Comparison of mean post-operative VAS scores

Characteristics	Test	Control	Test and p-value
	Mean \pm SS	Mean \pm SS	
1 st hour	4.46 \pm 2.66	6.2 \pm 2.65	t = 2.52, p = 0.01
2 nd hour	4.36 \pm 2.76	6.26 \pm 2.62	t = 2.73, p = 0.00
3 rd hour	4.03 \pm 2.79	6 \pm 2.51	t = 2.86, p = 0.00
4 th hour	3.80 \pm 2.41	5.96 \pm 2.68	t = 3.28, p = 0.00
5 th hour	3.30 \pm 2.36	5.86 \pm 2.45	t = 4.11, p = 0.00
6 th hour	3.33 \pm 2.45	5.83 \pm 2.46	t = 3.93, p = 0.00
7 th hour	2.89 \pm 2.31	5.7 \pm 2.21	t = 4.74, p = 0.00
8 th hour	2.90 \pm 2.41	5.46 \pm 2.28	t = 4.23, p = 0.00
10 th hour	2.63 \pm 2.35	5.3 \pm 2.36	t = 4.37, p = 0.00
12 th hour	2.70 \pm 2.21	5.5 \pm 2.34	t = 4.75, p = 0.00
16 th hour	2.93 \pm 2.47	5.13 \pm 2.11	t = 3.70, p = 0.00
20 th hour	2.53 \pm 2.59	4.53 \pm 1.87	t = 3.42, p = 0.00
24 th hour	2.33 \pm 2.35	4.1 \pm 1.93	t = 3.17, p = 0.00

DISCUSSION

The data obtained through this study, which was conducted to analyze the effect of cold application in the early postoperative period for pain and bleeding in patients who had septoplasty, were discussed in line with previous literature.

Cold application is a non-pharmacological method used to derive benefit from the effects of cold on prevention or control of pain, edema, and ecchymosis. Cold is known to have been used as a treatment method since ancient times. For example, there is information about cold treatment in the Edwin Smith Papyrus (BC 3500), Egyptians (BC 2500) used the cold effect in the early treatments of wounds and inflammation, and Hippocrates used the cold effect in treatments of edema, pain, and hemorrhage^[18,19]. Cold applications have an analgesic effect by reducing indirectly the pressure and tension on the nerve endings by reducing inflammation, spasm, and edema.

Application of cold is known to decrease local pain and spasm, and suppress edema formation after trauma or surgical intervention by decreasing bleeding and inflammation. The aims of cold application are to provide local vasoconstriction by lowering the temperature of the subcutaneous tissue under the application area, thus reducing vascular permeability, preventing and reducing haematoma or edema formation, and reducing possible bleeding, by slowing down metabolism^[11,20]. The results of the present study are in line with the literature: the amount of bleeding in experiment group patients with applied cold was determined to be less than the amount of bleeding in the control group patients, but not at a high enough level to build statistical significance. When the literature was reviewed, studies aimed at determining the effect of cold application for control of pain, edema, and ecchymosis were found. However, these studies were conducted in patients with soft tissue injury or in patients who underwent oral or orthopedic surgical treatment^[21-25]. There are no studies to date that focus on controlling the pain and bleeding developments after septoplasty.

Many studies have been conducted that focus on the effect of cold application in controlling edema/ecchymosis^[21-30]. In some of these studies^[23,24,26,27,29,30], cold was applied for 14-72 hours together at intervals of 20-30 minutes or continuously, to prevent facial edema formation, and ice packs, cold gel pads, or hilotherapy face masks (a mask that keeps the temperature between 15-20 °C) were used. In our study, ice packs were used to provide an effective cold application for the patients. McMeekan *et al* applied cold on forearms of 26 adults for 20 minutes using 3 different methods to monitor the effect of cold application on cutaneous

temperature and nervous conduction velocity^[31]. These methods were an ice pack, a cold pack covered by a wet towel, and a cold pack covered by a dry towel, applied to the same individuals at different times. The ice pack provided the fastest decline of cutaneous temperature among all measurements taken using the three methods.

Edema and ecchymosis, which negatively affect the esthetic results and cause disturbance by reducing the patient's visual acuity, also generally develop in the periorbital area and on the face after surgical treatments that affect the face, such as rhinoplasty. For this reason, studies have been conducted to prevent or reduce periorbital edema and ecchymosis developing after rhinoplasty, and in these studies the effect of a steroid were emphasized^[32-34]. The results of the studies showed that a single dose of steroid treatment reduced eyelid edema and ecchymosis of upper eyelid for the first 2 days, but this effect diminished after the 2nd day^[34]; therefore, the number of doses had to be increased to bring the effect to a desired level^[32]. However, steroids are known to affect carbohydrate, fat, and protein metabolisms, immune-mediated and inflammatory responses, and the central nervous system; they also cause complications such as headache, thrombocytopenia, adrenal atrophy, gastric ulceration, and gastrointestinal hemorrhage^[28,32-34]. The cold application used in our study was shown to reduce pain and bleeding together with ecchymosis and edema. Periorbital ecchymosis may develop as a result of leakage of accumulated blood in the deep tissues to the periorbital area; that is due to bleeding during facial surgical interventions, especially rhinoplasty. Periorbital ecchymosis generally becomes evident on the 1st or 2nd day of the postoperative period and improves in 1-2 weeks. Color changes occur in the ecchymosis area due to the effects of erythrocytes and hemoglobin. In the beginning, the color is dark red; over time, due to chemical changes in the hemoglobin, the color changes first to purple-brown, then to green-brown, finally to a green-yellow color, and the ecchymosis is healed. Ecchymosis is a normal situation; it is expected to develop after surgical trauma. However, ecchymosis may cause deformation of body, permanent pigmentation changes, anxiety, fear, and thereby, social isolation. Shortening the healing time of the ecchymosis that develops after surgical intervention is important for the patients to recover their work and social lives in a shorter time^[28,34,35].

As a result of the present study, cold application was found to significantly decrease the pain related to the operation. Fee *et al* and De Jesus *et al* studied the effects of cold on nervous conduction velocity and showed that it was reduced by applying cold^[36,37]. Also,

the pain reducing features of cold application have been shown in many studies^[38,39]. Pain is currently defined as the fifth vital sign. For this reason, reducing the pain of patients who undergo septoplasty surgery by applying cold in the postoperative period and improving their quality of life are considered to be extremely important.

This study had several limitations. The study was conducted in only one center, and the study sample reflects only one area of Turkey. The findings, therefore, cannot be generalized to all patients undergoing septoplasty to correct septum deviation in Turkey. Another limitation of this study is that it calculated pain based on the patients' subjective assessments. Therefore, the findings must be interpreted cautiously.

CONCLUSION

As a result of our study, it can be stated that cold application performed in the early postoperative period in patients who had septoplasty surgery due to septum deviation decreases the pain and bleeding that develop as a result of the procedure. In conclusion, applying cold is recommended to be done in the early postoperative period to patients who are not allergic to cold and have no risk of alteration in vital signs to decrease pain and bleeding that develop due to septoplasty.

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Original Article

Diabetes Knowledge Assessment among Type 2 Diabetic Patients

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ABSTRACT

Objective: Diabetes mellitus (DM) is one of the major health problems worldwide. Health knowledge is a main factor in enhancing general health. The primary goal of this study was to assess the level of DM knowledge among a random sample of type 2 diabetic (T2D) patients and these patients' knowledge level in relation to glycemic control and complications.

Design: Cross sectional study

Setting: Diabetes outpatient clinic, Prince Mansour Military Hospital, Taif, Saudi Arabia

Subjects: We interviewed adult T2D patients who had routine follow-up visits between September 2015 and July 2016. Patients with type 1 or gestational DM were excluded.

Intervention: We used the revised Michigan Diabetes Knowledge Scale to assess the patients' diabetes knowledge.

Main outcome measures: Diabetes knowledge

Results: A total of 191 patients with T2D with a mean age of 57.2 ± 12.9 years were enrolled in the study; 54.5% were male, with a mean duration of diabetes for 12.8 ± 8.7 years. The mean diabetes knowledge score was 12.3 ± 3.3 .

Compared to those who are considered to have poor knowledge, those with good knowledge tend to be younger ($p < 0.031$), are less likely to have microvascular complications ($p < 0.04$), and more likely to have a bachelor's degree ($p < 0.018$). The mean DM duration, body mass index, glycosylated hemoglobin, smoking, and physical inactivity appeared to be insignificant between different groups.

Conclusion: This study shows a high prevalence of poor DM knowledge which was positively associated with microvascular complications; however, glycemic control, weight, and/or lifestyle habits were not statistically different between groups.

KEY WORDS: diabetes mellitus, education, knowledge, Michigan, T2D

INTRODUCTION

Diabetes mellitus (DM) is one of the major health problems worldwide. In 1980, the prevalence was 4.1%, which increased significantly by 2014 to reach a prevalence of 8.5% for a total of 422 million patients^[1]. A study that was conducted in 2004 showed a DM prevalence of 23.7% among the Saudi population with a male predominance^[2]. A recent study estimated that 6.2% of the patients were unaware of their disease^[3]. In a literature review about global DM, Saudi Arabia was ranked third with a prevalence of 16.8%^[4].

It is well known that health knowledge is one of the main factors that contribute to enhancement of overall community health. A study in Saudi Arabia showed that patients with a chronic disease had more

lifestyle changes such as a healthy diet and increase in physical activity, which could be attributed to an increase in educational levels^[5]. Another review stated that collaborative health education is one of the best practice methods in the management of nutrition related chronic diseases such as type 2 diabetes (T2D)^[6].

T2D is a lifelong disease that requires multifactorial management including diet, physical activity, drugs, and regular follow ups. A study published by the American Diabetes Association in 2005 showed that gaining more knowledge about diabetes and its complications has a "significant benefit in regards to patient compliance to treatment and to decreasing complications associated with the disease"^[7]. A study done in Singapore also demonstrated that diabetic

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education has improved the actual practice in diabetic patients to better and more effective self-care^[8]. The American Association of Clinical Endocrinologists states that the development of diabetic complications is mainly due to either a lack of understanding of the long- and short-term regulation of blood glucose level or lack of patient control of their blood glucose levels^[9].

There is limited data about the level of knowledge among our T2D patients. The primary goal of this study was to assess the level of DM knowledge among a random sample of T2D patients and its relation to glycemic control and DM-related complications.

SUBJECTS AND METHODS

This cross-sectional study was conducted from September 2015 to July 2016. All subjects were T2D patients attending the Prince Mansour Military Hospital, Diabetes Center, Taif, Saudi Arabia. Type 1 diabetes and gestational DM patients were excluded. Participation was voluntary, and verbal consent was taken from each participant. The study was founded by Taif University and the Institutional Review Board at the Military Hospital reviewed the proposal and approved the research.

All subjects completed a five-section interview that included personal data, methods of management, DM complications, health-related social habits, and a diabetes knowledge scale. Anthropometric measures were taken in addition to blood pressure and body mass index (BMI). Recent lab work results were collected from files using the subjects' medical record numbers. We considered those who reported monthly income \geq 4000 US dollars as high income, and those reporting monthly income $<$ 1335 US dollars as low income.

We also collected data about diabetes-related complications. We considered those with a history of retinopathy, nephropathy, or neuropathy to have microvascular complications and those who had a history of coronary artery disease or stroke to have macrovascular complications.

We used the revised Michigan Diabetes Knowledge Scale to assess the patients' diabetes knowledge. It contains 20 statements about diabetes, and the participants were asked to indicate whether each statement is true, false, or did not know. The participants who didn't use insulin were asked only 18 out of 20 statements, while those on insulin completed all 20 statements. If a patient answered $>$ 13 of 20 questions (or $>$ 12 of 18) correctly, they were considered to have good awareness. If the patient answered $<$ 12 of 20 questions (or $<$ 11 of 18) correctly, they were considered to have poor awareness, while those answering $>$ 65% of the questions were considered to have good diabetes knowledge.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 20. Frequencies and percentages were used for each variable; the Chi-squared test was used to study the relationship between variables and the T-test was used to compare between means.

RESULTS

A total of 191 T2D patients were enrolled in the study. The mean age was 57.2 ± 12.9 years; 54.5% were male, and patients had a mean diabetes duration of 12.8 ± 8.7 years and mean BMI of 31.5 ± 5.4 kg/m² (Table 1). Most of the participants were married, and 50.8% were considered low income with low levels of education consisting of high school or less. The most common complication was microvascular, and most patients had undergone a recent follow-up clinic

Table 1: Baseline characteristics of the whole cohort

Baseline characteristics (N= 191)	
Mean age (years)	57.2 \pm 12.9
Male (%)	54.5
Mean diabetes duration (years)	12.8 \pm 8.7
Mean BMI (kg/m ²)	31.5 \pm 5.4
Mean waist circumference (cm)	108.4 \pm 17.8
Mean systolic blood pressure (mmHg)	133.2 \pm 22.3
Mean diastolic blood pressure (mmHg)	76.3 \pm 10.5
Mean diabetes knowledge score	12.3 \pm 3.3
Hypoglycemia (%)	36.6
Microvascular complications (%)	77
Macrovascular complications (%)	13.3
Patients who had a clinic visit within the last 6 months (%)	96.9
Socioeconomic	
Single/divorced (%)	6.8
Married (%)	93.2
Bachelor degree or higher (%)	12.6
Low income (%)	50.8
High income (%)	6.3
Medications	
Metformin (%)	82.2
Sulfonylurea (%)	36.1
Thiazolidinediones (TZDs) (%)	2.1
DPP-4 inhibitors (%)	18.8
Insulin (%)	69.1
Statin (%)	72.3
Laboratory data	
Fasting glucose (mmol/L)	10.2 \pm 4.7
HbA1c (%)	8.85 \pm 2.4
Total cholesterol (mmol/L)	4.5 \pm 1.1
LDL (mmol/L)	2.7 \pm 0.9
HDL (mmol/L)	1.04 \pm 0.3
Triglyceride (mmol/L)	1.7 \pm 0.98
ACR	12.5 \pm 39.8
Calculated GFR (ml/min/1.73 m2)	86.3 \pm 23.9
Lifestyle habits	
Sedentary lifestyle (%)	55
Active smoking (%)	12.6
Duration of smoking for the smokers (years)	12.1 \pm 16.2

BMI: body mass index; HbA1c: glycosylated hemoglobin; LDL: low-density lipoprotein; HDL: high-density lipoprotein; ACR: albumin/creatinine ratio; GFR: glomerular filtration rate

visit. Metformin was the most commonly prescribed medication in addition to insulin and statin.

The mean diabetes knowledge score was 12.3 ± 3.3 . The mean fasting glucose was 10.2 ± 4.7 mmol/L and the mean HbA1c was $8.85 \pm 2.4\%$. Fifty-five percent of the patients had a sedentary life style, and 12.6% were actively smoking with a mean duration of smoking for 12.1 ± 16.2 years. Fifty-four percent of the patients were considered to have good diabetes knowledge (Table 2). Compared to those who are considered to have poor knowledge, those with good knowledge tend to be younger ($p = 0.031$), were less likely to have microvascular complications ($p = 0.04$), and more likely to have a bachelor's degree or higher

($p = 0.018$). The mean diabetes duration, BMI, waist circumference, fasting glucose level, glycosylated hemoglobin (HbA1c), active smoking, and physical inactivity appeared to be insignificantly different between the groups. Lipid profile and systolic blood pressure were better in the good knowledge group, but not statistically significant.

Compared to the poor knowledge group, those who were considered to have good knowledge were significantly more likely to know that HbA1c did not reflect the average blood glucose level over the past week, exercise had an effect on blood glucose, and diet soft drinks shouldn't be used to treat hypoglycemia (Fig 1).

Table 2: Baseline characteristics based on revised Michigan Knowledge Questionnaire score

Characteristics	Good Knowledge	Poor Knowledge	P value
Baseline characteristic			
Number of patients	100	91	n/a
Mean age (years)	55.3 ± 12.5	59.4 ± 13.1	0.031
Male (%)	56	52.8	0.652
Mean diabetes duration (years)	13.1 ± 9	12.5 ± 8.4	0.605
Mean BMI (kg/m ²)	32 ± 5.2	31 ± 5.7	0.183
Mean waist circumference (cm)	107.6 ± 13.6	109.2 ± 21.5	0.545
Mean systolic blood pressure (mmHg)	132.2 ± 18.2	134.5 ± 22.4	0.437
Mean diastolic blood pressure (mmHg)	77.4 ± 11.5	75 ± 9.1	0.128
Mean diabetes knowledge score	14.8 ± 1.6	9.6 ± 2.6	0.000
Hypoglycemia (%)	39	34.1	0.474
Microvascular complications (%)	71	83.5	0.04
Macrovascular complications (%)	12	14.6	0.616
Patients who had a clinic visit within the last 6m (%)	98	95.6	0.343
Socioeconomic			
Single/divorced (%)	6	7.7	0.535
Married (%)	94	92.3	
Bachelor degree or higher (%)	18	6.6	0.018
Low income (%)	43	59.3	0.57
High income (%)	6	6.6	
Medications			
Metformin (%)	82	82.4	0.631
Sulfonylurea (%)	33	39.6	0.346
Thiazolidinediones (TZDs) (%)	1	3.3	0.308
DPP-4 inhibitors (%)	18	19.8	0.753
Insulin (%)	76	61.5	0.18
Statin (%)	67	78	0.089
Laboratory data			
Fasting glucose (mmol/L)	10.1 ± 4.7	10.4 ± 4.7	0.62
HbA1c (%)	8.9 ± 2.5	8.8 ± 2.3	0.797
Total cholesterol (mmol/L)	4.4 ± 1.1	4.6 ± 1.1	0.2
LDL (mmol/L)	2.6 ± 0.9	2.7 ± 0.9	0.333
HDL (mmol/L)	1 ± 0.3	1.1 ± 0.2	0.786
Triglyceride (mmol/L)	1.7 ± 1	1.8 ± 1	0.569
ACR	14.2 ± 39	10.7 ± 40.9	0.563
Calculated GFR (ml/min/1.73 m ²)	84.8 ± 26.1	88.1 ± 21	0.346
Lifestyle habits			
Sedentary lifestyle (%)	52	58.2	0.799
Active smoking (%)	12	13.2	0.554
Duration of smoking for the smokers (years)	11.1 ± 14.7	13.1 ± 17.6	0.654

BMI: body mass index; HbA1c: glycosylated hemoglobin; LDL: low-density lipoprotein; HDL: high-density lipoprotein; ACR: albumin/creatinine ratio; GFR: glomerular filtration rate

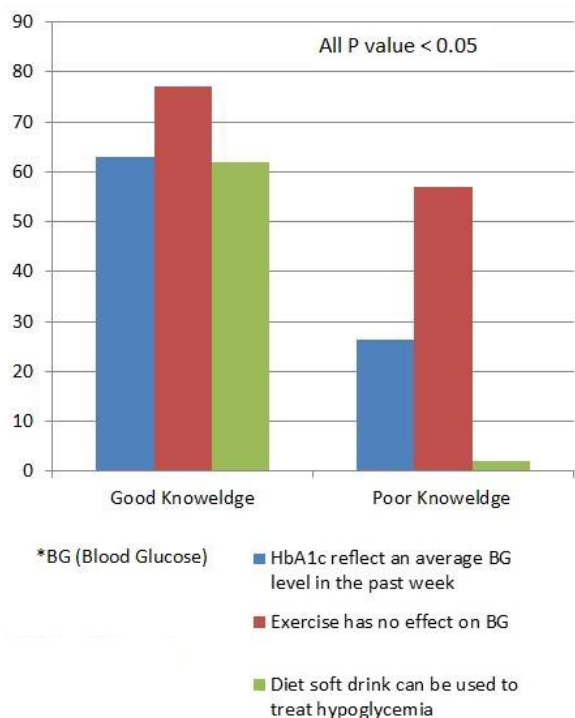


Fig 1: Percentage of correct answers (those who chose False as an answer for the above listed questions)

Partial correlation adjustment for age, income, gender, BMI, educational level, T2D duration, DM management, smoking, exercise, and marital status showed non-significant negative correlations between revised Michigan Knowledge Questionnaire score and either HbA1c and waist circumference, but there was a non-significant positive correlation with BMI (Table 3).

Table 3: Partial correlation done adjusting for age, income, educational level, T2D duration, managements, smoking, exercise and marital status

Characteristics	Diabetes Knowledge score
HbA1c	r = -0.052 p = 0.491
Waist Circumference	r = -0.033 p = 0.565
BMI	r = 0.095 p = 0.200

BMI: body mass index; HbA1c: glycosylated hemoglobin

DISCUSSION

Fifty-two percent of our T2D patients have good knowledge about diabetes. Other studies from different parts of the world have found a higher prevalence of poor knowledge among DM patients despite using different knowledge scores^[10-12]. Another study conducted in Riyadh, Saudi Arabia showed that the majority of DM patients (72%) had a

moderate level of knowledge^[13]. Our assessment tool did not have a moderate knowledge category, but if it did, we would have found that the majority of our patients have moderate knowledge, since the mean score was 12.3, which is border line between good and poor knowledge.

Our findings did not show any relationship between gender and knowledge level. Recent study results showed better knowledge among females, but other studies showed better knowledge among males, and another study showed insignificant differences, which were similar to our result^[10,11,13,14]. It seems likely that DM knowledge was related to education level and age rather than gender.

With regard to age, our study showed that participants with good knowledge significantly tended to be younger. Other studies' data agreed with our results^[14,15]. Also, Alaboudi *et al* showed that younger patients tend to have better knowledge; however, it was not statistically significant^[10]. This is likely because younger patients are more inclined to have access to the modern health resources and be more familiar with new technology, unlike older participants.

Our data showed that poor knowledge was associated with higher prevalence of microvascular complications. A recent study showed that 75% of the screened diabetics were aware that DM can cause eye disorders^[16]. Another one showed that highly educated patients tend to see an ophthalmologist regularly^[17]. This seems to prove that knowledge improves compliance and disease-specific awareness improves overall self-care.

Our data showed no significant association between knowledge and HbA1c levels. Several previous studies showed either weak correlation or no significant association^[10,16,18-21]. A Singaporean prospective cohort showed a statistically significant improvement in the HbA1c in an intervention group after education, compared to the control group^[22]. This is likely because of the variable sample size in each study.

Our findings showed that a high level of education is positively associated with the knowledge score, and this finding agrees with several published studies^[10,11,15,16,22,23].

Our strengths included using a standardized validated questionnaire, comprehensive medical history, and inquiries about many related variables. Our weaknesses included single center and small sample size.

CONCLUSION

This study shows a high prevalence of poor knowledge which was positively associated with microvascular complications; however glycemic

control, weight, or lifestyle habits weren't statistically different between groups.

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Original Article

Incidence of HIV Seroconversion in Pregnancy in a Tertiary Hospital, Nigeria

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ABSTRACT

Objective: To evaluate the incidence of human immunodeficiency virus (HIV) seroconversion in pregnancy for effective prevention of its mother to child transmission

Design: Longitudinal study

Setting: Niger Delta University Teaching Hospital, Bayelsa, Nigeria

Subjects: One hundred and sixty pregnant mothers who booked for prenatal care within the first 20 weeks of gestation and were negative to HIV testing at the booking visit were recruited, followed up and retested for HIV seropositivity on delivery at term. Data was collected from 1st September 2015 to 31st May 2016.

Intervention: Prenatal counselling on prevention of mother to child transmission of HIV

Main outcome measure: The incidence of HIV seroconversion on delivery at term

Results: There was no HIV seropositivity at term, there was zero seroconversion in this data. The mean age of the respondents was 30.2 ± 4.5 years and ranged from 19 - 43 years. Over 92% of the participants attained secondary level of education or above, about the same proportion (95%) was married and 29% was unemployed. There was a low level of HIV-related risk behaviours among the participants.

Conclusion: The zero prenatal HIV seroconversion in this study indicates significant progress in intervention programs against HIV transmission in Nigeria. The findings set the stage for sustained efforts in every part of the country. Periodic nationwide studies are recommended.

KEY WORDS: HIV, mother-to-child, seropositivity, transmission, window period

INTRODUCTION

Human immunodeficiency virus (HIV) is the leading infectious killer with over 70 million persons affected globally; an estimated 36 million people dead and some 35.3 million people currently living with it since onset^[1].

It has a frightening mortality and morbidity rate, with the burden maximal in Sub-Saharan Africa. Women and children are the most affected. Mother to child transmission (MTCT) is second to heterosexuality as the leading route of its acquisition. Some 3.34 million children are currently living with the virus globally, with more than 700 newly infected children daily, mostly due to vertical transmission from their HIV-positive mothers during pregnancy, labour or breastfeeding^[1]. Data from Nigeria showed

increasing incidence since its onset, with 2.98 million people currently living with HIV or acquired immunodeficiency syndrome (AIDS) and a national prevalence of 4.6%^[2].

For effective control of the HIV/AIDS scourge, among other measures, the prevention of mother to child transmission (PMTCT) of HIV is crucial. Without antiretroviral therapy (ART), MTCT is as high as 15 - 30% in Europe and America and 25 - 35% in Africa^[3,4]. These transmission rates have improved since the introduction of ART for PMTCT, yet only a minority of women receive PMTCT.

The highest viral burden in blood and genital secretions occurs during the ramp-up phase of viraemia in acute HIV infection (AHI)^[5]. This poses a high risk of MTCT of HIV during pregnancy in AHI. There are

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few studies to investigate HIV seroconversion during the gestational period in a high HIV-prevalent area like Nigeria, as the detection of AHI requires extra testing best to detect HIV RNA or p24 antigen in antibody seronegative subjects. This requires costly equipment and special training; however, the World Health Organization has recommended the use of only rapid HIV testing for HIV diagnosis in resource poor countries. This has been shown to have satisfactory sensitivity and specificity, especially when used in combination as in dual rapid testing algorithm^[6].

Window period phenomenon and new infections will negate the gains of voluntary confidential counselling and testing (VCCT) and treatment at booking in early pregnancy. This underscores the compelling need for retesting pregnant women during the gestational period for effective PMTCT. HIV seronegative window period phenomenon is the period taken for the immune system of an individual exposed and infected by the virus to recognize and generate detectable specific antibodies in the blood system^[7]. The infected individual, though false negative to HIV antibodies in window period, is infectious and can transmit the virus to others before seroconversion. This indicates return of those who tested negative to HIV antibodies test for retesting in 2 - 3 months. Clearly this window period is a major obstacle in the path of early and complete detection of HIV infection, and therefore a major challenge in prevention and control of HIV infection, especially in the PMTCT program. HIV seroconversion is the period of time during which HIV antibodies become detectable in a victim's blood following a window period of 2 - 3 months of initial infection. The significance is that the person can transmit the virus to others, in this study mother to child transmission. It may be accompanied by a transient period of flu-like symptoms such as fever, malaise, muscle pains, rash and lymphadenopathy.

Detecting infection via specific antibodies in the blood is routinely used in any clinical laboratory and seropositivity to HIV is considered the gold standard. Pregnant women in the window period are a missed opportunity to treat and save the babies. On the other hand, there is usually one chance to save the fetus from infection, reducing the risk of MTCT from 28 - 30% to 1 - 2% by giving the mother a short course of ARV treatment during pregnancy and child birth^[8-9]. This chance is during the initial and sometimes only visit to the doctor or antenatal clinic. However, the provision of ART is contingent on the expecting mother testing antibody positive, hence inadvertently excluding from treatment those who are in the window period at the time of testing^[10]. Therefore, the efficacy of the PMTCT programs that include HIV testing to

all pregnant women and ART to all those who are HIV seropositive depends among other factors on overcoming the seronegative window period to get early and complete detection of the infected mothers^[11]. Babies born to seronegative mothers, even from a high risk population, are not suspected to be infected. Meanwhile, children born to seronegative yet infected mothers in the window period could get infected.

Risk and incidence of new infection in the course of gestation is equally possible apart from the window period phenomenon at the booking visit, further underscoring the need for retesting late in pregnancy for effective PMTCT.

A study on Malawian pregnant women reported the incidence of acute HIV infection in pregnancy as 0.21%. This was retrospectively detected during the last trimester using HIV RNA detection^[12]. The infected seronegative women around conception period were not isolated by this study. There was a zero seroconversion report in a multicentre Cape Town South Africa study of 524 antenatal attendees who were tested at booking between 16th and 18th weeks and retested at 36.7 - 38.1 weeks^[13]. An incidence of 14.7% HIV seroconversion during pregnancy at Pelonomi Free State South Africa was reported among 416 attendees who were HIV seronegative at or before 24 weeks. They had retesting after 24 weeks until 34 weeks, with first retesting six weeks after, using HIV enzyme linked immunosorbent assay (ELISA)^[14]. High risk sexual behaviours are still very common among pregnant women in some parts of Africa, which predisposes them to an increased risk of new infection and MTCT^[15]. In South East Nigeria, a seroconversion incidence of 3.91% was reported. The first testing was done within the first half of pregnancy, while the exact gestational age of the third trimester retesting was not stated^[16]. This was in a tertiary hospital setting. Seroconversion of 3 - 14.9% has been reported in some other parts of Africa^[14,17].

Nigeria is one of the countries with the highest HIV burden in Sub-Saharan Africa, with a national seroprevalence of 4.6% in a population of about 160 million. It is clear therefore, that a single screening at first contact when booking an antenatal visit in such a high risk population as this setting may not be enough and may miss the opportunity to detect most of the maternal infection in window period and new infections of up to 2 - 3 months before parturition. Therefore, an in-depth knowledge of its new seropositivity rate within the gestational period is crucial to its effective prevention and control through PMTCT. As the magnitude of seroconversion later in pregnancy in South-South Nigeria is currently unknown, it is imperative to conduct a study to measure it. Data from

the study can then inform improved PMTCT strategy development and implementation in the region. It is hoped that data from this study will add to the growing pool of evidence in furthering the concerted efforts at combating the HIV/AIDS scourge.

This study investigated the incidence of HIV seroconversion at term among antenatal clinic attendees who were seronegative in the first half of pregnancy for more effective PMTCT of HIV.

SUBJECTS AND METHODS

Niger Delta University Teaching Hospital (NDUTH) is a tertiary hospital domicile at Okolobiri in Bayelsa State in the South-South geopolitical region of Nigeria. It serves as a referral centre to other health facilities within the state and surrounding states. The centre offered, among other services, the PMTCT of HIV. This is a riverine or Niger Delta area. Bayelsa state is rich in crude oil and natural gas deposits. She is one of the major oil producing states in the country. It is home to many ethnic groups, predominant among whom are the Ijaw. The state is also resident to people from other states across the country and other parts of the world. Her main native occupations are fishing and farming. The estimated population of the state was 2 million according to the 2011 census. The neighbouring states are Delta to the north, Rivers to the west and the Atlantic Ocean to the east and south.

This was a longitudinal analytical study on antenatal clinic attendees who were seronegative to HIV testing at booking within the first half of pregnancy. The HIV serostatus of the subjects was determined at prenatal registration in their first half of gestation and repeated as they presented in labour at or after term for possible HIV-seroconversion. This allowed enough time for infection in the HIV window period of 2 - 3 months in peri-conception period and for new infections within the gestational period to be detectable by term using HIV antibody kits. The participants were recruited from 1st September to 6th October, 2015 and subsequently followed up till 31st May, 2016. The study population consisted of antenatal attendees at NDUTH, Okolobiri, Bayelsa state. An average of 200 attendees was seen weekly, with an annual delivery rate of about a thousand at the centre. Those who received blood transfusions or surgical intervention before child birth and those who were seronegative early in the pregnancy but failed to present for delivery at term were excluded. All the unbooked parturient and those who registered for prenatal care later than two months to delivery were not eligible for the study. Those who experienced spontaneous abortion or preterm delivery after initial recruitment at booking were dropped from the final

analysis. The eligible patients who declined consent to participation in the study were also excluded. Sample size was calculated using the formula by Cochran WG^[18] and prevalence rate of 3.9%^[16] as below:

$$n = \frac{z^2pq}{d^2}$$

Where

p = Maximum known proportion of the relevant variable, here expressed as the proportion of HIV seronegative antenatal care patients found to be seroconverted on delivery at term. In this study p = 3.9% (or 0.039)^[16]

q = 1-p (proportion of HIV seronegative antenatal care women at booking who remained so at delivery). This is 1-0.039 or 0.961

d = Allowable error margin of estimate (precision) = 0.03, the p is less than 10% (0.1)^[19]

z = this is Z statistic for 95% confidence level (CI) (value for selected alpha level $\alpha = 0.05$ which is 1.96.)

n = 160 attendees

All the eligible attendees who registered for prenatal care and gave consent for the study were selected on each of the four antenatal clinic days using purposive sampling technique. An average of 8 and a range of 3 - 11 such participants were recruited daily on each antenatal day for a period of five weeks.

Data was collected with a structured, pre-tested, quantitative questionnaire (Appendix) with sections on independent variables and sociodemographic characteristics. The dependent (outcome) variables were HIV risk practices and seropositivity (seroconversion) at delivery or after term. The questionnaire was pre-tested and changes effected as necessary. The instrument was used by the researchers and two trained assistants to collect data during the antenatal clinic periods on a one-on-one basis. At booking, data based on sociodemographic characteristics such as age, marital status, education, occupation, ethnic group, religion, and parity of each attendee was raised. For the purpose of this study, the women were occupationally grouped into those employed by the government (civil servants), those employed by private or non-governmental companies (private organization), those in their own private business (self-employed), those in schooling (students), housewives and unmarried participants who do not belong to any of the other groups (unemployed). The sexual practices such as multiple sex partners, sex with partners of unknown HIV serostatus or seropositive by the participants during pregnancy were recorded both at booking and delivery.

Appendix

Questionnaire (Instrument)

Study Title: The incidence of HIV sero-positivity in parturient at term who were seronegative in first half of pregnancy in a tertiary hospital, South South Nigeria

Section A (Sociodemographic characteristics)

1. Hospital number.....
2. Age (years).....
3. Educational level: a. Nil formal education [] b. primary [] c. secondary [] d. tertiary []
4. Occupation: a. Employed (government) [] b. Employed (private organization) [] c. Self-employed [] d. Unemployed []
e. Student []
5. Occupation of spouse: a. Employed (government) [] b. Employed (private organization) [] c. Self-employed [] d. Unemployed []
e. Student []
6. Marital status: a. Single [] b. Married [] c. Remarried [] d. Divorced/separated [] e. Widowed []
7. How many wives has your spouse?
8. Religion.....
9. Tribe.....
10. Parity.....
11. Gravidity.....

Section B (Previous sexual & HIV prevention practices)

12. Number of previous spontaneous abortions.....
13. Number of previous induced abortions.....
14. Is this pregnancy planned Yes [] No []
15. Have you had HIV testing before? [] Yes [] No If yes, what was the result? [] Seronegative [] Seropositive
16. If yes, when was the last time you had HIV testing? [] Less than 3 months [] 3-6 months [] 6-12 months [] > 12 months
17. What is the serostatus of your spouse? [] Seropositive [] Seronegative [] Don't know

Questions 18-21: To be filled at booking and labor at term

18. How many sexual partners have you in the
 - a. last 12 months?
 - b. last 6 months?
 - c. last 3 months?
 - d. gestational period?
19. How often did you use condom during sex in the last 12 months?
[] Always [] Sometimes [] Never

Section C

20. Gestational age (weeks) at the first/ last HIV-testing in this pregnancy (Booking/Term)
21. The first/last (booking/Term) HIV -testing results: tick as appropriate

Booking	Term/labor
seropositive []	seronegative []
seropositive []	seronegative []

At booking visit, each woman was offered routine HIV testing and counselling with an opt-out option. Group counselling of the prenatal attendees was carried out, while the designated PMTCT laboratory scientists performed the test according to the national rapid HIV testing algorithm. The testing was done using two-step rapid HIV antibody test kit algorithm. Determine[®] HIV test kit was used for screening all blood specimens and Stat-Pak HIV test kit used to confirm all the seropositive results of the former kit. Any specimen that showed positive with both kits was reported as positive while discordant reaction was reconfirmed with ELISA test. The PMTCT unit staff carried out pre-test and post-test counselling and testing of the participants. This procedure was repeated at individual level when the participants presented in labour anytime from term.

The data was collated in a spreadsheet created using EPI INFO computer software. Data was presented in tables as appropriate. Statistical analyses were done with EPI INFO Version 3.5.1 developed by Centre for disease control and prevention (CDC) in Atlanta, Georgia, USA, released August 2008 and INSTAT software. The outcomes measured from the primary data included the proportion of the participants who seroconverted at delivery, and the proportion that involved in HIV risk behaviour in the pregnancy. Statistical testing was done with Fisher's exact test using 2 x 2 contingency tables. The statistical significance was set at 95% CI excluding nullity and $p < 0.05$.

Ethical approval was sought and obtained for the study from the Research and Ethical Committee (REC) of NDUTH, Okolobiri. Informed consent

for the research was sought and obtained from each participant in addition to the general clinical informed consent. Confidentiality was ensured. Those participants who tested positive received ART among other measures throughout prenatal, childbirth, postpartum and subsequently along with the neonate in line with PMTCT program.

RESULTS

A total of 431 women booked for prenatal care at the centre during the study period with 8 of them being HIV seropositive, showing an HIV seroprevalence of 1.9% among prenatal clinic attendees at booking visit at the centre. The majority of the attendees (423, 98.1%) were seronegative to HIV testing. About half of these seronegative attendees (236, 55.8%) registered for prenatal care within the first 20 weeks of gestation and these qualified for inclusion as study participants. One hundred and sixty of these gave consent to participate in the study and were so recruited.

One hundred and forty one (88.1%) of the 160 participants presented and delivered at the centre.

Table 1: Sociodemographic characteristics of participants (N = 141)

Characteristic	n	Percentage
Age (years)		
<20	1	0.7
20 – 24	12	8.5
25 – 29	45	31.9
30 – 34	60	42.6
≥35	23	16.3
Marital Status		
Married	134	95
Unmarried	7	5
Parity		
0	25	17.7
≥1	116	82.3
Educational Level		
Nil	1	0.7
Primary	10	7.1
Secondary	54	38.3
Tertiary	76	53.9
Occupation		
Civil servant	30	21.3
Private organisation	9	6.4
Self employed	61	43.2
Unemployed*	34	24.1
Student	7	5
Religion		
Christianity	140	99.3
Islam	1	0.7
Ethnic Groups		
Ijaw	78	55.3
Igbo	29	20.6
Isoko	11	7.8
Urhobo	6	4.3
Nembe	2	1.4
Others	15	10.6

* Housewives and unemployed single participants

The other 19 (12%) either had spontaneous abortion (2), preterm birth (1), received blood transfusion after recruitment (2) or was considered lost to follow up (8.8%) (after 3 weeks beyond the last expected date of delivery among the participants). These were excluded from subsequent analyses. The mean age of the participants was 30.2 ± 4.5 years with a range of 19 - 43 years and modal age group 30 - 34 years (42.6%) (Table 1). A majority of 9 out of every 10 parturient attained at least secondary level of education. A similar proportion was married (Table 1). About 7% of the subjects were in a polygamous marriage. The mean gestational age at booking and first prenatal HIV testing was 16.3 ± 4.1 weeks with a range of 5 – 20 weeks. The corresponding values at delivery and last testing from term were 39.1 ± 1.4 weeks and 37 - 42 weeks, respectively. Table 1 also shows that about 7 (70.9%) and 3 (29.1%) out of every 10 parturient were gainfully employed and unemployed, respectively. A majority (82.3%) of the women have had at least one previous childbirth, with a range of 0 - 7 deliveries. Almost all the parturient were Christians, with over half of them (78/141, 55.3%) of Ijaw ethnicity. One hundred and forty one (100%) of the subjects tested negative and none (0%) tested positive to HIV retesting at the time of delivery at or after term; after an average of 5 months follow up and observation of each participant for seroconversion. There was zero HIV sero-incidence in this study.

Table 2: HIV-related risk behaviours among participants (N = 141)

Risk behaviour	Number of participants	Percentage
Polygamous marriage	9	6.7
Unaware of partner's HIV serostatus	43	30.5
Sex with seropositive partner	1	0.6
Multiple sexual partners (>1) in the last 12 months	1	0.6
Condom use in the last 12 months	17	12.1

Table 2 shows the HIV-related risk behaviours of the participants. Forty three (30.5%) of the participants were unaware of their male partner's HIV serostatus, one respondent reported that she had sex with a seropositive partner, and another had more than one sexual partner in the preceding 12 months. Seventeen of the participants used male condom during the gestational period or in the previous twelve months from the time of interview, 16 (11.4%) of them used it sometimes and only 1 (0.7%) used it frequently.

DISCUSSION

The HIV seroprevalence among the prenatal clinic attendees at the booking visit was 1.9%. This figure was lower than the 2010 Nigerian national prenatal survey

report of 4.1% and the Bayelsa state seroprevalence rate of 9.1%^[2,20]. There was a zero sero-incidence of HIV (seroconversion) in this study. The finding was similar to the findings by another comparable study^[13], but contrasted with a report showing a sero-incidence of 3.91% from another region in Nigeria^[16] and reports of 0.21 - 14.7% from other parts of the world^[12,14,21-22]. The zero sero-incidence was attributed to the low risk behaviour rate among the subjects, as evidenced in the data. An earlier report in the literature noted high risk sexual behaviours among pregnant women in some parts of Africa, predisposing them to increased HIV transmission in pregnancy^[15]. There was a report of increased likelihood of women from the south-south region of Nigeria (the study area) indulging in multiple sexual partners^[23]. This could not be corroborated by this study. This data equally failed to confirm other high risk sex behaviours reported among women in this region^[23]. The population of this study differed from the general female population, as the sexual behaviour of married women was expected to differ in some restraints from the unmarried. Again, the zero seroconversion could be due to the increasing general awareness about HIV/AIDS transmission and its prevention. The fairly quality prenatal care with well-organized and intense HIV prevention campaign at the centre also possibly contributed to the reduced and absence of HIV seroconversion in this population. During the prenatal sessions, interactive discussions were held with the attendees on HIV/AIDS among other health conditions. They have the opportunity to ask questions and receive advice on measures to stay HIV transmission free, protect their pregnancy and babies including PMTCT. It was evident that good attention to HIV prevention measures reduces new infection^[22]. A majority of the parturient were in a monogamous marriage and adequately empowered by their education and gainful employment. HIV infection has been found to be low in women with these attributes^[23-27]. Even the lack of education in the partners of pregnant women has been noted to increase the risk of HIV transmission^[21]. Polygamous marriage exposes the partners to inadvertent multiple sexual partners, yet there was no seroconversion in the subgroup. If a group of seronegative, uninfected sexual partners remain in a sexual relationship with only one another, there is a reduced risk of HIV infection in them, as demonstrated in the subset of participants in polygamous relationship in this data. The proportion of women that did not know the serostatus of their spouses in this study was significant, similar to another report in the literature citing less than 60% of the mothers in their study knew the HIV serostatus of the infants' fathers during

pregnancy, indicating very low rates of HIV disclosure among sexually active couples^[13]. Sexual intercourse with partners of unknown HIV serostatus is one of the confirmed HIV transmission risk behaviours. Knowing the serostatus of spouse has been shown to have the potential of reducing MTCT by engendering intense and earlier preventive measures^[22]. Condom use in this population was low. This was expected in this population, with the majority in a monogamous marriage with little or no perception of the risk of HIV infection. Consistent use of condom and limiting sexual intercourse to one uninfected partner evidently reduces the risk of HIV transmission^[21,23]. The few that occasionally used condoms in this study were probably for contraception prior to index pregnancy, though this data did not explore the reasons for their use of condom. Those who used condoms during pregnancy most probably were for the prevention of sexually transmitted infections (STI) /HIV. Those who indulge in sexual intercourse with multiple sex partners or sex with persons of unknown serostatus are advised to consistently use condoms to prevent HIV infection^[23,28]. Condoms offer the dual protection from HIV/other STIs and unplanned pregnancy, making it an effective option for prevention of HIV for both concordant and discordant partners. The cited serostatus of the majority of spouses of the participants was seronegative, only a couple were cited discordant serostatus (the male partner seropositive and the female seronegative) in this data. These couples were candidates for correct and consistent use of condom^[20,29], planned pregnancy^[20] and semen preparations and assisted reproductive techniques to avert infection in the woman and MTCT^[30].

The data for this study came from only one centre. Findings from multicenter data are known to be more generalizable. In addition, the sample size appeared small; a larger sample size would have increased the power of the study. The study derived its strength from its prospective design and the absence of a similar previous study in its locale.

CONCLUSION

There was a zero prenatal HIV seroconversion in this study. This was an indication for more intense and coordinated HIV transmission prevention campaign if an HIV-free generation is the target.

Recommendations

Periodic nationwide studies are recommended to have a nationwide profile and for monitoring. Further studies to evaluate what interventions work in different settings are also required.

A multicentre study and a much larger sample size

will have greater power and increase the detection rate of HIV sero conversion cases, therefore more generalizable evidence.

Sustained testing of all prenatal care attendees early at the first visit and retesting at 32-36 weeks gestation, in labour or before commencement of breastfeeding and/or interpregnancy or preconception period is also recommended to increase the chance of detection of HIV seroconversion for PMTCT.

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Original Article

The Clinical Importance of Percentage Free Prostate-specific Antigen (PSA) in the PSA level of 4-20 ng/ml

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ABSTRACT

Objective: The current study aimed to evaluate the diagnostic efficacy of percentage free/total prostate-specific antigen ratio (%fPSA = free/total PSA*100) for prostate cancer diagnosis in different PSA levels (4.1 - 10 ng/ml and 10.01 - 20 ng/ml).

Design: Retrospective study

Setting: Department of Urology, Çorum Training and Research Hospital, Hitit University

Subjects: Patients who underwent prostate biopsy with a PSA level of 4.1 - 20 ng/ml

Intervention: Prostate biopsy was performed for patients who had PSA level > 4 ng/ml.

Main outcome measures: The patients who underwent transrectal ultrasound guided prostate biopsy between January 2010 and January 2015 were evaluated retrospectively. The patients were divided into two groups according to the PSA levels. The PSA levels of patients in

Group 1 was 4.1 - 10 ng/ml and 10.01 - 20 ng/ml in Group 2. The receiver operating characteristic (ROC) curves were analyzed for the diagnostic efficacy of %fPSA in different PSA levels.

Results: There were 1213 patients in the present study. Of these patients, 876 and 337 patients were in groups 1 and 2, respectively. The mean age and PSA level of the patients was 66.21 ± 7.45 years, 6.48 ± 1.58 ng/ml and 69.36 ± 8.56 years, 13.63 ± 270 ng/ml in groups 1 and 2, respectively. The ROC curve analyzes demonstrated the diagnostic efficacy of percentage fPSA and there was a significant difference between percentage fPSA and PSA in two groups.

Conclusion: The %fPSA is effective for the diagnosis of prostate cancer in Turkish patients having both PSA level of 4.1 - 10 and 10.01 - 20 ng/ml. Clinicians should consider that %fPSA can predict biopsy outcomes.

KEY WORDS: biopsy, percentage free PSA, prostate cancer

INTRODUCTION

Prostate cancer (PCa) is one of the most common cancer and one of the leading causes of death worldwide^[1]. The widespread use of serum prostate-specific antigen (PSA) contributes to the early detection of prostate cancer^[2]. There are different isoforms of PSA in serum; approximately 70 - 90% of PSA is complexed with α 1 antichymotripsin (ACT), <5% is complexed with inter- α -trypsin inhibitor and protein C inhibitor, some undetectable PSA is complexed with α 2 macroglobulin^[3]. The rest of PSA (10 - 30%) is not complexed with serum proteins and is called free PSA (fPSA). Since the 1990s, when PSA was first used in PCa screening, many authors investigated the usefulness of PSA to detect PCa and avoid unnecessary biopsies^[4].

Although PSA is a specific marker for the prostate tissue, this biomarker is not cancer-specific as it can be elevated in some benign conditions such as enlargement of prostate volume and inflammation of prostate tissue^[5]. Approximately 70% of men with an increased serum PSA (>4 ng/ml) do not have prostate cancer, and thus undergo unnecessary biopsies^[6]. In the intermediate level of PSA (4 - 10 ng/ml) that is called the grey zone, prostate cancer is detected in 25% of patients^[7]. The detection rate of PCa when PSA level is >10 ng/ml is more than 30%^[2]. Additional parameters have been developed to increase the efficiency of PSA because of low specificity. One of these parameters is percentage of free PSA (%fPSA) that can be calculated using the formula:

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$$\%fPSA = \frac{fPSA \times 100}{tPSA}$$

where tPSA = total PSA

The purpose of the present study is to evaluate the diagnostic efficacy of %fPSA for prostate cancer in different PSA levels (4.1 - 10 ng/ml and 10.01 - 20 ng/ml).

MATERIALS AND METHODS

The data from 1850 transrectal ultrasound-guided prostate biopsies performed between January 2010 and January 2015 were evaluated retrospectively. The patients' age, levels of free PSA and total PSA, and pathological results were recorded. Patients with a history of acute or chronic prostatitis, total PSA >20 ng/ml, older than 90 years, dutasteride therapy, radiotherapy, urethral instrumentation in the last 1 month, and previous prostate surgery were excluded from the study. All patients had at least eight core prostate biopsy with transrectal ultrasound guided under local anesthesia. The prostate biopsy was taken with 18 gauge tru cut biopsy needle. The patients were divided into two groups according to the PSA level. The PSA levels of the patients in Group 1 was 4.1 - 10 ng/ml and those with PSA levels ranging from 10.01 - 20 ng/ml were placed in Group 2.

Serum tPSA was measured by immunometric assay (Immulite 2000, DPC, Los Angeles, USA). Free PSA levels were analyzed using a solid phase, two-site, sequential chemiluminescent assay (Immulite 2000, DPC, Los Angeles, USA). The %fPSA was calculated as the ratio of fPSA to tPSA x 100.

The receiver operating characteristic (ROC) curves were analyzed to assess the diagnostic efficacy of free/total PSA in different PSA levels (4.1 - 10 and 10.01 - 20 ng/ml). Data were expressed as mean ± standard

Table 1: Characteristics of the patients in groups

Groups	Group 1	Group 2	p-value
No. of patients (n(%))	876 (100)	337 (100)	
Age (mean ± SD)	66.21 ± 7.45	69.36 ± 8.56	<0.0001
PSA (mean ± SD)	6.48 ± 1.58	13.63 ± 2.7	<0.0001
Percentage of fPSA (mean ± SD)	19.4 ± 8.4	18.16 ± 10.81	0.0339
Prostate cancer (n(%))	192 (21.91)	121 (35.9)	<0.0001*

*chi squared test; p < 0.05: statistically significant

PSA: prostate-specific antigen; fPSA: free prostate-specific antigen

error and p < 0.05 was considered with statistical significance and independent sample t test and chi-squared tests were used for comparison of the results.

RESULTS

There were 1213 patients in the present study. Groups 1 and 2 had 876 and 337 patients respectively. The mean age of the patients was 66.21 ± 7.45 and 69.36 ± 8.56 years in groups 1 and 2, respectively. The mean PSA and free/total PSA of the patients was 6.48 ± 1.58 ng/ml, 0.19 ± 0.08 and 13.63 ± 2.7 ng/ml and 0.18 ± 0.1 in groups 1 and 2, respectively (Table 1).

Prostate cancer was diagnosed in 313 patients (25.8%). In the two groups, prostate cancer detection rate was 21.91% and 35.9% respectively (p < 0.0001). The patients with prostate cancer were older than those without cancer in each group. There was no significant difference between PSA levels of the patients with and without prostate cancer in the two groups. The %fPSA was higher in patients with benign prostate hyperplasia (Table 2). The ROC curve analysis demonstrated the diagnostic efficacy of %fPSA in both groups (Figure 1). Area under curve (AUC) of %fPSA was bigger in patients with PSA levels ranging from 4.1 - 10 ng/ml than in the patients in group 2 (0.653 - 0.615).

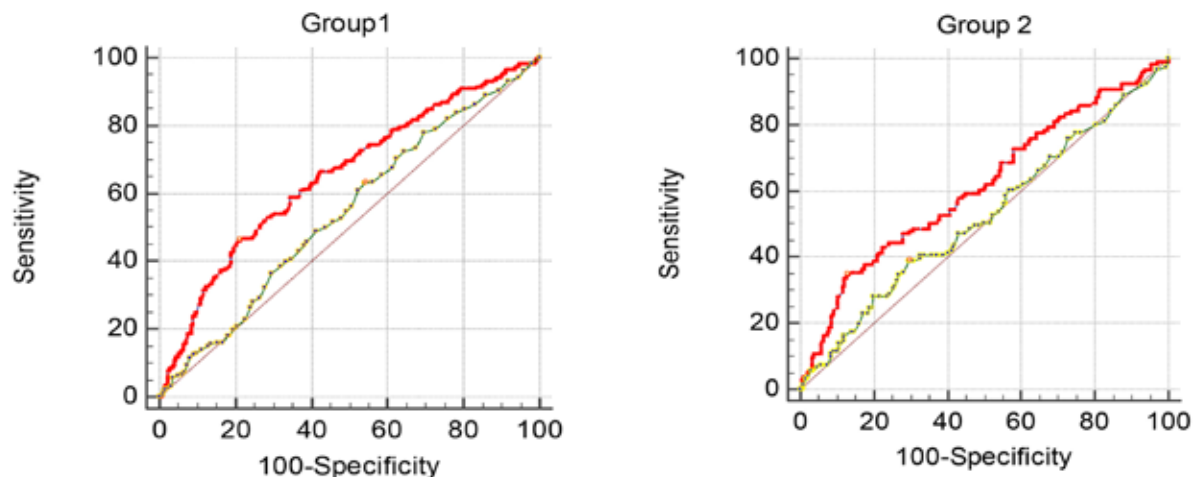


Fig. 1: Area under curve of the percentage fPSA and PSA in groups (red line: percentage of fPSA, yellow line: PSA) (AUC : 0.653&0.542 p: 0.0003 in group 1 and 0.615&0.521 p: 0.0345 in group2)

Table 2: Comparison of the patients with and without prostate cancer in groups

Diagnosis	Pca	BPH	p-value
Group 1			
No. of patients (n)	192	684	
Age (years)	67.61 ± 7.55	65.82 ± 7.38	0.0032*
PSA (ng/ml)	6.65 ± 1.57	6.43 ± 1.58	0.0943
Percentage of fPSA	16.33 ± 7.71	20.26 ± 8.38	<0.0001*
Group 2			
No. of patients (n)	121	216	
Age (years)	71.11 ± 9.08	68.38 ± 8.12	0.0049*
PSA (ng/ml)	13.79 ± 2.82	13.53 ± 2.63	0.4067
Percentage of fPSA	16.08 ± 10.58	19.32 ± 10.79	0.0081*
Total	313	900	

Data was expressed as mean ± standard deviation; *: statistically significant

Pca: prostate cancer; BPH: benign prostate hyperplasia; PSA: prostate-specific antigen

The specificity and sensitivity was 92.69 - 17.71, 74.42 - 48.96, 45.03 - 73.96 and 23.25 - 88 in the cutoff for fPSA% ≤10, ≤15, ≤20 and ≤25 in group 1 (Table 3). The specificity and sensitivity was 88.43 - 29.75, 63.43 - 50.41, 35.65 - 76.58 and 18.98 - 89.26 in the level of fPSA% ≤10, ≤15, ≤20 and ≤25 in group 2.

Table 3: Sensitivity and specificity of percentage free PSA

Percentage free PSA	Group 1	Group 2
	Sensitivity-Specificity (%)	Sensitivity-Specificity (%)
≤ 10	17.71 - 92.69	29.75 - 88.43
≤ 15	48.96 - 74.42	50.41 - 63.43
≤ 20	73.96 - 45.03	76.58 - 35.65
≤ 25	88 - 23.25	89.26 - 18.98

DISCUSSION

Prostate specific antigen is a 33 kDa glycoprotein that is produced by prostatic epithelium^[8]. Most of the serum PSA is complexed with serine protease inhibitors; α 1-antichymotripsin or α 2-macroglobulin. A small proportion of PSA is not complexed with any protein and called free PSA^[9]. Although the measurement of PSA in serum is the most widely used and efficient method for the early detection of prostate cancer, only 25% of patients with PSA level of 4.1 - 10 ng/ml are diagnosed with prostate cancer^[2]. Due to low specificity, other parameters such as PSA density and velocity, age specific reference ranges, %fPSA, and molecular forms of PSA have been investigated^[8]. One of these tests is %fPSA, which has been applied in low and intermediate PSA levels to improve cancer detection^[9]. Using a threshold of 25, 90% of cancers would have been detected and 18% of prostate biopsies avoided. Percentage of fPSA is significantly lower in patients with prostate cancer than in patients with benign prostate hyperplasia or prostatitis.

When PSA level is between 4 - 10 ng/ml, %fPSA is contributive to prostate cancer diagnosis. In addition, it is helpful in detecting the need for prostate biopsy, so that unnecessary biopsies are avoided^[10]. Catalonia *et al*^[11] reported the use of percentage of fPSA increases the specificity of total PSA reduces the number of unnecessary biopsies in men with PSA 4 - 10 ng/ml. The authors reported that diagnostic efficacy of %fPSA is better than PSA in men with PSA levels of 4.1 - 10 ng/ml (0.718 vs 0.547, $p < 0.0001$)^[2]. The authors from China found that %fPSA did not improve the effectiveness of prostate cancer as compared to PSA alone in men with PSA levels of 2.5 - 10 ng/ml^[12]. Similarly, in the study of Chen *et al*^[13], ROC curve analysis indicated that %fPSA does not outperform total PSA in predicting any PCa in PSA range of 4 - 10 ng/ml (0.554 vs 0.534, $p = 0.205$). The specificity and sensitivity of cut off 25 for %fPSA were reported as 71.7% - 95.3%^[2] and 13.7% - 88.4%^[13] in the studies. The current study showed %fPSA improved AUC significantly in men with PSA level of 4.1 - 10 ng/ml (0.653 vs 0.542, $p = 0.0003$). The specificity and sensitivity of cut off 25 for %fPSA was 23.25% and 88% respectively.

In the literature, there are many studies about the clinical advantage of %fPSA for prostate cancer with a PSA level of 4 - 10 ng/ml, and less number of studies with PSA level 10 - 20 ng/ml. There are various cancer detection rates of patients with PSA level of 10.1 - 20 ng/ml. Morote *et al*^[2] reported that prostate cancer diagnosis rate was 37.7% in Spanish patients and Huang *et al*^[12] from China demonstrated the detection rate of prostate cancer was 30.5%. Chen *et al*^[14] found that prostate cancer detection rate was 36.53% when PSA was 10.1 - 20 ng/ml. Although the European Association of Urology guidelines does not recommend the clinical use of free/total PSA in patients with PSA > 10 ng/ml^[15], Morote *et al*^[2] showed the diagnostic efficacy of %fPSA and using the cut off 25 for %fPSA provides a sensitivity of 95% and specificity of 58.8% in patients with PSA levels of 10.1 - 20 ng/ml. The authors reported that %fPSA had no better diagnostic efficacy in the PSA of 10 - 20 ng/ml^[12-16]. Huang *et al*^[12] hypothesized that the gray zone of PSA in Asian men may be higher than in Western men. As a result, the use of %fPSA may improve prostate cancer detection rates in Western populations and may not be directly applicable to Asian men. The authors from China reported that %fPSA was a good prostate cancer predictor and had higher AUC than PSA alone, but statistical difference was detected in age groups of 60 - 69 years and 70 - 79 years in the PSA levels of 10 - 20 ng/ml (0.650 vs 0.542, $p < 0.001$ for 60 - 69 years, 0.632 vs 0.531, $p = 0.003$ for 70 - 79 years)^[14]. The cut off of 25 for %fPSA yielded a detection

rate of 90.2 - 93.4% in patients aged 60 – 69, 70 – 79 and ≥ 80 years. On the contrary, Chen *et al*^[13] investigated the performance of %fPSA comparing PSA with ROC curve analysis to predict PCa and found that %fPSA improved the cancer diagnosis in the range of 10.1 – 20 ng/ml (0.614 vs 0.586, $p < 0.0001$). The sensitivity and specificity of the cut off 25 for the %fPSA was 92.4% and 12.2% respectively. In the present study, the prostate cancer detection rate was 34.19% and the cut off of 25 for %fPSA had a sensitivity of 89.26% and specificity of 18.98%, AUC was bigger for %fPSA with statistical significance in men with PSA level of 10.01 - 20 ng/ml (0.615 vs 0.521, $p = 0.0345$). The difference of the cut off %fPSA results for sensitivity and specificity may be a result of patient selection and ethnicity. The study of Morote included 228 Spanish patients and Chen's study included 2754 Chinese men and cancer detection rate was 37.7% and 36.5% respectively, which are higher than our study.

The present study is limited in that it is of retrospective design, included data from a single center, and lacked prostate weights and rectal examination findings. This study is important for the diagnostic value of %fPSA for the diagnosis of prostate cancer in Turkish patients with PSA levels of 4.1 - 20 ng/ml.

CONCLUSION

The percentage of fPSA is statistically effective for the diagnosis of prostate cancer in Turkish patients with both PSA levels of 4.1 - 10 and 10.01 - 20 ng/ml. Using the percentage of fPSA may be helpful for clinicians to predict biopsy outcomes when the PSA level ranges from 4.1 - 20 ng/ml. These findings should be confirmed in future multicenter studies.

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Original Article

The Effects of Preoperative Dextrose Loading on Hyperalgesia Induced by High-Doses Remifentanyl in Patients undergoing Laparoscopy-assisted Distal Gastrectomy

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ABSTRACT

Objective: This study aimed to investigate the effect of preoperative administration of 5% dextrose on hyperalgesia induced by high-doses remifentanyl.

Design: Randomized, prospective

Setting: Operating room of a Wonkwang university hospital, South Korea

Subjects: One hundred and twenty-six patients undergoing laparoscopy-assisted distal gastrectomy

Intervention: Three groups received either 250 ml Hartmann's solution (HS) or 5% dextrose in HS for 1 hour before anesthesia and intraoperative remifentanyl infusion. Group LHS received HS and 0.05 µg/kg/min remifentanyl; group HHS received HS and 0.3 µg/kg/min remifentanyl, and group HHD received 5% dextrose in HS and 0.3 µg/kg/min remifentanyl.

Main outcome measures: Mechanical hyperalgesia threshold at 1 hour after surgery, time to first postoperative analgesic

requirement, cumulative patient-controlled analgesia (PCA) volume containing morphine for 24 hours after surgery, and pain intensity using visual analog scale (VAS) for 24 hours after surgery were measured.

Results: Mechanical hyperalgesia threshold of group HHS and HHD were significantly lower than that of LHS group. Cumulative PCA volume containing morphine for 24 hours after surgery and pain intensity for 12 hours after surgery of group LHS were significantly reduced than that of both HHS and HHD groups, both of which were not significant. Time to first postoperative analgesic requirement was longer in group LHS than in groups HHS and HHD, both of which were not significant.

Conclusion: Preoperative intravenous administration of dextrose in patients undergoing laparoscopy-assisted distal gastrectomy didn't show any effects on hyperalgesia induced by high-doses remifentanyl

KEY WORDS: analgesia, glucose, opioid

INTRODUCTION

Previously, both animal and clinical investigations into the impact of hyperglycemia on pain perception and analgesic effect of opioids have reported variable results^[1-6]. Pain threshold induced by hyperglycemia shows a significant decrease^[1,4], or increase^[2,5], or no change^[3,6]. The analgesic effect of opioids modulated by hyperglycemia is diminished^[3], or enhanced^[2], or not altered^[6,7]. Due to these varying results, the association between hyperglycemia, pain perception, and possible glucose modulation of opioid has not been established.

Remifentanyl, an ultra-short-acting µ-opioid

receptor agonist is commonly used as an effective anesthetic adjuvant in general anesthesia. It has unique pharmacokinetic characteristics with a predictable and rapid recovery that is independent of the dose and duration of infusion. However, considerable evidence suggests that high doses or prolonged exposure of remifentanyl paradoxically heightens pain sensitivity and enhances analgesic requirements^[8,9]. Supplemental opioids are thus often given prophylactically to patients who are likely to experience postoperative pain. Despite this precaution, postoperative analgesic requirement in patients given intraoperative

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remifentanyl is often surprisingly great^[10]. Therefore, we designed this study to investigate the effect of preoperative administration of 5% dextrose on opioid induced hyperalgesia (OIH) caused by high-dose remifentanyl.

SUBJECTS AND METHODS

Ethical approval for this study (Registration No. 3749) was provided by the Institutional Review Board of Wonkwang University Hospital, Iksan, Republic of Korea (Chairperson Prof ML Park) on December 2014. Written informed consent was obtained from all participants. The study was performed at Wonkwang University Hospital from January 2015 to September 2016.

One hundred and twenty-six ($n = 42$ per group) American Society of Anesthesiologists I-II patients (aged 20 - 70 years) who were scheduled for laparoscopy-assisted distal gastrectomy were enrolled in this study. Patients were excluded if they had severe hypertension, coagulopathy, significant hepatic or renal disease, diabetes mellitus, abnormal blood glucose on the morning of surgery, withdrawal of consent, a history of alcohol or drug abuse, or were taking opioid-containing pain or sedative medications. Patients were excluded from analysis for severe intraoperative hypotension requiring large volume intravascular fluid treatment or protocol violation including nitrous oxide administration. Patients were taught how to use the visual analog scale (VAS) and the patient-controlled analgesia (PCA) device on the day before surgery. They were instructed to self-deliver analgesia whenever they began to feel pain.

All patients were pre-medicated with midazolam (2 - 3 mg) intramuscularly before arrival in the operating room. The patients were randomly assigned using a computer-generated random number table into one of the following three treatment groups, each of which received either 250 ml Hartmann's solution (HS) or 5% dextrose in HS and intraoperative remifentanyl infusion. The study fluid with pharmacy-controlled allocation concealment was administered over about 1 hour before anesthesia. Group LHS received HS and 0.05 $\mu\text{g}/\text{kg}/\text{min}$ remifentanyl; group HHS received HS and 0.3 $\mu\text{g}/\text{kg}/\text{min}$ remifentanyl, and group HHD received 5% dextrose in HS and 0.3 $\mu\text{g}/\text{kg}/\text{min}$ remifentanyl.

The patients were placed on a pulse oximeter, automated blood pressure cuff, electrocardiogram, and end-tidal CO_2 devices. In addition, arterial and urinary catheters were placed as part of routine management. Induction of anesthesia was commenced with a slow (30 - 60 s) IV bolus dose of remifentanyl (1 $\mu\text{g}/\text{kg}$), followed by propofol (1 - 2 mg/kg), and

tracheal intubation was facilitated with rocuronium (0.9 mg/kg) in all groups. Infusion of remifentanyl in all groups was fixed, and anesthesia was maintained with desflurane at an initial end-tidal concentration of 1 minimum alveolar concentration (MAC) and oxygen-air mixture (fraction of oxygen, 50%). Anesthesia levels were monitored during surgery by stepwise titration of the desflurane concentration by 1% volume, based on hemodynamic changes and targeting a bispectral index (BIS) of 40 - 60. Perioperative blood glucose level was measured using a point-of-care device (Accu-Chek®, Roche Pharmaceuticals, Basel, Switzerland) at pre-surgical preparation area baseline, 10 minutes after study fluid infusion, 30 minutes after start of operation and 1 hour after arrival at post-anesthesia care unit (PACU) by nurses.

Upon completion of the surgery, neuromuscular blockade was reversed with pyridostigmine (0.2 mg/kg) and glycopyrrolate (0.008 mg/kg) when the train-of-four (TOF) ratio had returned to 25%. A morphine intravenous bolus of 0.25 mg/kg was administered 30 minutes before the end of surgery. When BIS values reached 80 and spontaneous breathing was achieved, extubation was performed. The remifentanyl infusion was discontinued once the final surgical stitch had been placed. Each patient was treated via PCA pump (Accufuser® WooYoung Medical, Seoul, Korea) with analgesics containing morphine (40 mg), ketorolac (180 mg), and ramosetron (0.6 mg) in normal saline and in a total volume of 100 ml. This device was set to deliver a basal infusion of 2 ml/h, and bolus doses of 0.5 ml with a 15 minute lockout time. Postoperative pain scores on movement in the first hour after surgery were documented using the 100 mm linear VAS. The VAS is a straight line with the left end of the line representing no pain and the right end of the line representing the worst imaginable pain. During PACU recovery, patients with $\text{VAS} \geq 40$ received IV ketorolac (30 mg), with an additional dose of 15 mg if needed.

The methods used to test mechanically evoked pain in this study were the same as those described in a previous report^[11]. The mechanical hyperalgesia threshold was measured preoperatively using Von Frey filaments (Bioseb™, Chaville, France) on areas 5 cm from umbilicus (preoperatively) or from port incision site of umbilicus at 1 hour after surgery.

The primary outcome was mechanical hyperalgesia threshold at 1 hour after surgery. Secondary measures were time to first postoperative analgesic requirement, cumulative PCA volume containing morphine for 24 hours after surgery, pain intensity using visual analog scale immediately after PACU, and at 1, 6, 12 and 24 hours after surgery, ketorolac consumption during the first hour after surgery, postoperative nausea

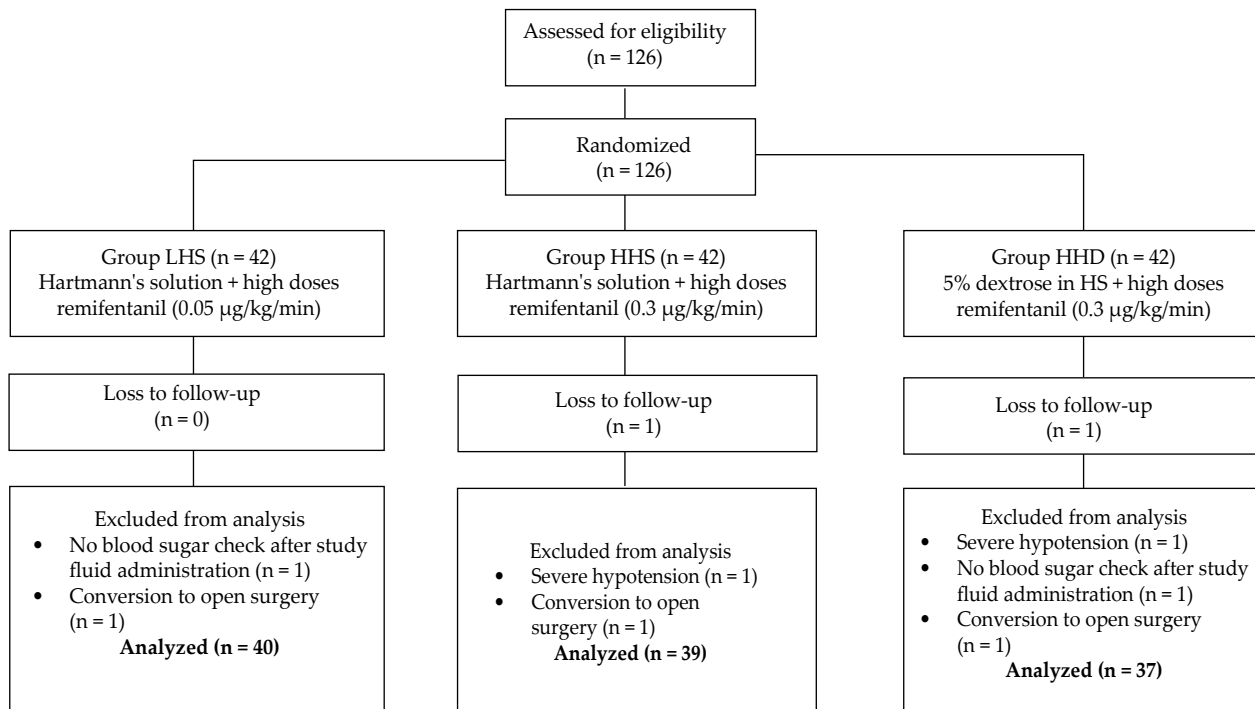


Fig 1: CONSORT diagram

and antiemetic required. An independent observer-investigator who was blinded to group assignment collected data in the PACU to establish inter-rater reliability.

A preliminary investigation showed that the hypothesized means of the three treatment groups (group LHS, group HHS, and group HHD) for mechanical hyperalgesia threshold at 1 hour after surgery were 146.8, 124.3 and 120.2 g/mm², respectively, with effect size of 0.298 and a standard deviation of subjects of 39.2 g/mm². Thus, a sample size of 38 patients per group was needed to demonstrate a significant difference with a power of 80% and an α -coefficient of 0.05. Assuming a 10% dropout rate, the final sample size was determined to be 42 patients per group. Mechanical hyperalgesia threshold, time to first postoperative analgesic requirement, cumulative PCA volume containing morphine for 24 hours after surgery, pain intensity and ketorolac consumption during the first hour after surgery were conducted using one-way ANOVA. Post hoc comparisons were performed with Bonferroni correction of the significance level. Postoperative nausea or antiemetic required were analyzed by Chi-square tests

RESULTS

As shown in Fig 1, a total of 126 patients were assessed for eligibility and received study medication after randomization. Eight of the 126 patients were excluded from analysis because of severe intraoperative

hypotension requiring large volume intravascular fluid treatment, not checking blood sugar after study fluid administration, or conversion to open surgery.

The three groups were comparable regarding the distribution of age, weight, type of surgery, duration of surgery, duration of anesthesia, intraoperative administration of fluid, postoperative nausea or antiemetic required. The mean volume % of desflurane of group LHS was significantly greater than that of both group HHS and group HHD, both of which were not significant. Mechanical hyperalgesia threshold at 1 hour after surgery of group HHS and group HHD, both of which received high doses remifentanyl, were significantly reduced than that of group LHS. The difference in mechanical hyperalgesia at 1 hour after surgery between group HHS and group HHD, which received dextrose, was not significant (Table 1).

Blood glucose level at 10 minutes after study fluid infusion and 30 minutes after start of operation in group HHD was significantly increased than in the other two groups (Table 2).

Cumulative PCA volume containing morphine for 24 hours after surgery, analgesic consumption, and pain intensity for 12 hours after surgery were significantly greater in group HHS and group HHD than in group LHS. Time to first postoperative analgesic requirement was shorter in group HHS and group HHD than in group LHS. Cumulative PCA volume containing morphine for 24 hours after surgery, analgesic consumption, pain intensity for

Table 1: Patient characteristics

Variables	Group LHS (n = 40)	Group HHS (n = 39)	Group HHD (n = 37)
Age (years)	58.3 ± 6.5	55.4 ± 7.1	57 ± 7.3
Weight (kg)	59.6 ± 4.7	61.3 ± 5.9	60.6 ± 5
Sex (M/F)	16/24	19/20	16/27
Type of surgery			
Gastrectomy and Billroth-I	19	17	22
Gastrectomy and Roux-en Y	21	22	15
Mean vol (%) of desflurane	6.1 ± 0.7	5 ± 0.8*	5.1 ± 0.7*
Duration of anesthesia (min)	310.2 ± 14.2	308.2 ± 17.1	308.6 ± 18.4
Preoperative mechanical hyperalgesia threshold (g/mm ²)	195 ± 40.5	195.6 ± 41.1	194.9 ± 41.3
Mechanical hyperalgesia threshold at 1 hour after surgery (g/mm ²)	156.8 ± 45.3	132.6 ± 50.4*	129.9 ± 34.5*
Intraoperative administration of fluid (ml)	1487 ± 99.1	1490.9 ± 108.7	1518 ± 77.6
Postoperative nausea	18 (45)	15 (38.5)	14 (37.8)
Antiemetic required	11 (27.5)	7 (17.9)	12 (32.4)

Values are expressed as mean ± SD or numbers (%); Group LHS: Hartmann's solution + low dose of remifentanyl (0.05 µg/kg/min); Group HHS: Hartmann's solution + high-doses remifentanyl (0.3 µg/kg/min); Group HHD: 5% dextrose in Hartmann's solution + high-doses remifentanyl (0.3 µg/kg/min); *p < 0.05 versus group LHS

Table 2: Perioperative blood glucose level

Blood glucose (mg/dl)	Group LHS (n = 40)	Group HHS (n = 39)	Group HHD (n = 37)
Baseline	94.9 ± 7.2	93.8 ± 8.5	94.2 ± 8.2
10 min after study fluid infusion	93.8 ± 5.4	92.9 ± 7.3	139 ± 8.9*
30 min after operation starting	112.2 ± 6.3	109.5 ± 7.1	136.7 ± 7.9*
1 hour after PACU arrival	106.3 ± 6.4	102.1 ± 7.5	118.1 ± 7.8

Values are expressed as mean ± SD or numbers (%); PACU: post-anesthesia care unit; Group LHS: Hartmann's solution + low dose of remifentanyl (0.05 µg/kg/min); Group HHS: Hartmann's solution + high-doses remifentanyl (0.3 µg/kg/min); Group HHD: 5% dextrose in Hartmann's solution + high-doses remifentanyl (0.3 µg/kg/min); *p < 0.05 versus other groups

12 hours after surgery, time to first postoperative analgesic requirement between group HHS and group HHD, which received dextrose, did not show significant differences (Table 3).

DISCUSSION

High-doses remifentanyl resulted in mechanical hyperalgesia and clinically relevant pain including shortening of time to first postoperative analgesic requirement, and increased postoperative pain intensity and opioid consumption. Hyperglycemia induced by IV dextrose administered preoperatively in our study was to prevent OIH induced by high-doses remifentanyl as preemptive analgesia, which is controversial about major benefits in terms of immediate postoperative pain relief or reduced need for supplemental analgesics. Hyperglycemia in our study couldn't affect mechanical hyperalgesia threshold and clinically relevant pain.

Previous investigations into the impact of IV dextrose administration on pain perception and antinociceptive potency of opioids have reported variable results^[1-7]. Some investigators have reported that hyperglycemia increased pain perception due to the antagonistic effect of glucose on opiate

Table 3: Postoperative clinically relevant pain

Variables	Group LHS (n = 40)	Group HHS (n = 39)	Group HHD (n = 37)
Time to first postoperative analgesic requirement (min)	29.6 ± 8.8	23.6 ± 6.6*	22.8 ± 7.4*
Cumulative PCA volume containing morphine for 24 hours after operation (ml)	59.9 ± 1.3	61.2 ± 1.5*	62.1 ± 1.3*
Pain intensity after operation			
VAS immediately after PACU	55.2 ± 12.4	64.8 ± 10.8*	66.8 ± 11.7*
VAS at 1 hr	46.5 ± 10.7	54.4 ± 10.4*	57.3 ± 11.2*
VAS at 6 hr	37.4 ± 9.6	46.8 ± 8.5*	49.1 ± 10.2*
VAS at 12 hr	28.3 ± 8.9	36.4 ± 9.5*	38.2 ± 10.1*
VAS at 24 hr	18.3 ± 8.3	23.6 ± 10.4	24.6 ± 10.1
Analgesic consumption (ketorolac) during the first hour after operation (mg)	39.8 ± 10.7	48.6 ± 10.9*	49.1 ± 11.5*

Values are expressed as mean ± SD or numbers (%); PCA: patient controlled analgesia; VAS: visual analog scale; PACU: post-anesthesia care unit; Group LHS: Hartmann's solution + low dose of remifentanyl (0.05 µg/kg/min); Group HHS: Hartmann's solution + high-doses remifentanyl (0.3 µg/kg/min); Group HHD: 5% dextrose in Hartmann's solution + high-doses remifentanyl (0.3 µg/kg/min); *p < 0.05 versus group LHS

receptors and a decrease in hypothalamic β -endorphin synthesis and concentration^[1,3,4], enhanced sensitivity to autonomic components of visceral nociception^[12] and elevated plasma cholecystokinin, which is involved in development of tolerance to analgesic potency of opioids^[13]. Other studies have shown that hyperglycemia increased pain threshold by modulating endogenous opioid system, altered hormonal stress response especially increasing insulin secretion^[2,5].

There were no significant differences in mechanical hyperalgesia at 1 hour after surgery, cumulative PCA volume containing morphine for 24 hours after surgery, analgesic consumption, pain intensity for 12 hours after surgery, and time to first postoperative analgesic requirement between group HHS and group HHD in our study. These results in this study might be the consequence of a compensatory increase in the synthesis and secretion of β -endorphin from the anterior pituitary and by the regulation of other pain-modulating peptides such as serotonin, dopamine, glucocorticoids, substance P, and somatostatin^[3]. There may be several reasons for the inconsistent findings in the effect of glucose on pain perception and analgesic effect of opioids. Several different methods have been used to assess pain threshold. Some studies have used various strains of diabetic rats and others diabetic mice or different patient populations, different type and duration of surgical procedures, anesthetic techniques or all formulations of dextrose containing fluids.

There are some limitations in our study. First, the mild form of hyperglycemia induced by IV glucose in this study can't be compared directly with marked hyperglycemia, when it comes to the influence of acute hyperglycemia on pain sensation and analgesic effect of opioids. Therefore, we cannot jump to a conclusion that hyperglycemia itself has no effect on pain threshold and analgesic effect of opioids. Second, we should have measured serum insulin concentrations to further address the controversial issue about the relationship between hyperglycemia and OIH. Other than hyperglycemia, consequences of insulinemia or insulinemia itself may play an important role in mechanical nociception in this study.

CONCLUSION

This study showed a lack of correlation between blood glucose level and the magnitude of pain threshold changes, analgesic effect of opioids or postoperative nausea. Administration of solutions which cause hyperglycemia may be insufficient to justify. However, further studies are needed to investigate the relationship of pain perception and analgesic effect of opioids to the optimal dose and timing of dextrose administration.

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Original Article

Does Laparoscopic Tubal Sterilization cause Premature Menopause?

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ABSTRACT

Objective: Laparoscopic tubal sterilization is a commonly preferred contraceptive method in women. This surgical intervention can be associated with certain complications in the short term and it also has the risk of failure in the long term. On the other hand, relationship between laparoscopic tubal sterilization and premature menopause in the long term has not been elucidated. The present study addresses this subject.

Design: Retrospective cohort study

Setting: The local hospital of Ankara, Turkey

Subjects: The study group included 76 patients with the laparoscopic coagulation (Group 1) and 76 healthy women (Group 2).

Intervention: The study aimed to determine age at menopause between patients who underwent tubal sterilization using the laparoscopic coagulation method and the control group.

Main outcome measure: Age at menopause

Results: There was no statistically significant difference between the groups with regard to age of menopause (47.86 ± 1.72 vs. 48.19 ± 1.61 ; $p = 0.271$).

Conclusions: Tubal sterilization using the laparoscopic coagulation method does not result in premature menopause. However, further studies should focus on the effects of salpingectomy, which has proved to be protective against ovarian cancer.

KEY WORDS: contraception, menopause, sterilization

INTRODUCTION

Sterilization is a frequently used contraceptive method. This method is more commonly employed in females and can be performed employing various surgical approaches. These include laparoscopic, abdominal, and hysteroscopic approaches. Laparoscopic surgical approach is the most frequently employed method^[1]. In laparoscopic tubal sterilization, techniques such as coagulation, occlusion, or tubal excision are used^[1]. A combination of these techniques can also be used. However, coagulation is a more frequently preferred technique because of advantages such as experience of clinicians as well as shorter operation time.

Similar to all surgical interventions, comprehensive counseling must be provided to the women when employing this method. The outline of this counseling must include all perioperative complications and

problems (*i.e.*, anesthesia complications, bleeding, organ injury, and death)^[2]. In addition, a long-term counseling including outcomes would better reveal the safety and outcomes of the surgical approach. The long-term failure rate regarding the risk of pregnancy has been reported to be 0% in the first 3 years and 1.85% in 10 years^[2,3].

In our clinical practice, failure rate has been the first concern raised by women presenting with the desire to undergo tubal sterilization procedure; the risk of premature menopause has been the second-most frequently raised concern. The reason for this is that women feel more anxious about menopause with advancing age. Surgeons usually respond according to the theoretical knowledge that laparoscopic tubal sterilization does not cause premature menopause. The present study was conducted because of the lack of a study conducted on this subject in the literature.

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Table 1: Comparison of the groups with or without laparoscopic tubal sterilization

Parameter	LS tubal sterilization group (n = 76)		Control group (n = 76)		p-value
	Mean	SD	Mean	SD	
Parity	2.74	0.62	2.58	0.69	0.051
BMI (kg/m ²)	26.8	1.9	27.48	2.14	0.041
FSH (IU/l)	68.19	14.47	64.93	10.96	0.233
Age at menopause (years)	47.86	1.72	48.19	1.61	0.271

LS: laparoscopy; BMI: body mass index; FSH: follicle stimulating hormone; SD: standard deviation

MATERIALS AND METHODS

The research was designed as a retrospective cohort study. Patient records at a local hospital for the period between 2002 and 2016 were utilized. An approval was obtained from the local ethics committee (Ethics Committee Decision dated April 5, 2016, Issue number: 197). Medical data of women who presented with the desire to undergo tubal sterilization for contraception between 2002 and 2010 were reviewed. The study group consisted of patients who underwent laparoscopic tubal sterilization with the coagulation method as the most frequently preferred method. Medical records of these women for the period between 2010 and 2016 were reviewed. The patients who presented with climacteric complaints and then diagnosed with menopause between 2010 and 2016 were included in the study. The criteria for menopause were lack of menstrual cycle for the last 6 months and follicle-stimulating hormone (FSH) levels of >40 IU/l^[4].

The inclusion criteria of the study were as follows: not diagnosed with or received therapy for infertility, no history of ovarian surgery, non-smoking status, lack of a systemic disorder (*e.g.*, diabetes mellitus and hypertension), and absence of family history for premature menopause. Seventy-six women meeting these criteria were included in the study. The control group consisted of 76 healthy women meeting the same inclusion criteria.

Statistical Analysis

For statistical analyses, SPSS for windows version 15.0 (SPSS, Inc., Chicago, IL) was used. The one-sample Kolmogorov–Smirnov test was used to analyze normality for continuous variables. For comparison of continuous variables, the Mann–Whitney U-test was used. Data were presented as mean ± standard deviation. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Parity, FSH levels, and age at menopause did not significantly differ between patients who underwent

tubal sterilization using the laparoscopic coagulation method and the control group. Body mass index (BMI) was higher in the control group.

The mean age was 47.86 ± 1.72 years in the laparoscopic tubal sterilization group and 48.19 ± 1.61 years in the control group. The mean parity was 2.74 ± 0.62 and 2.58 ± 0.69, the mean BMI was 26.8 ± 1.9 and 27.48 ± 2.14 (p = 0.041), and the mean FSH levels were 68.19 ± 14.47 IU/l and 64.93 ± 10.96 IU/l, respectively, in the laparoscopic tubal sterilization and control groups (Table 1).

The mean age at operation was 38.1 ± 1.86 years in the laparoscopic tubal sterilization group.

DISCUSSION

Tubal sterilization is a commonly preferred contraceptive method in women. Lower failure rate compared to other methods, the lack of need to take drugs every day similar to other oral contraceptives, and the absence of complications commonly observed with intrauterine devices are important factors for preferring tubal sterilization. However, due to the need for surgical intervention, surgeons must be proactive against many complications, and women must be informed accordingly.

Along with anesthesia-related complications during surgery, many other surgical complications such as intraoperative bleeding and injury to the adjacent organs may also occur. Respiratory problems and infectious complications may also occur after surgery.

Failure rate is extremely low in the long term^[5]. Whether laparoscopic tubal sterilization causes premature menopause in the long term is one of the most frequently asked questions among women. Until recently, we have managed these questions by informing patients that no clear studies on this subject exist in the literature, but such outcomes are not expected. The present study was conducted to provide women clearer answers about this subject; our findings indicate that laparoscopic tubal sterilization does not cause premature menopause.

Nelson *et al* compared 134 patients who

underwent bilateral tubal ligation in premenopausal period with 172 control subjects^[6]. After a 4-year follow-up period, no significant difference was found between the patients with regard to perimenopausal symptoms. The symptoms evaluated were hot flashes, decreased libido, and anxiety with increasing intensity with advancing age. The previous study did not intend to assess age at menopause. In addition, the study was conducted in perimenopausal women and set targets that were different from the present study by following the patients for 4 years. Another study using a similar design reported more common occurrence of perimenopausal symptoms in women that underwent tubal sterilization^[7]. In their study, Harlow *et al* examined the effects of tubal sterilization on menorrhagia and dysmenorrhea^[8]. Hormonal changes were also evaluated, although this was not the focus of the study. The results suggest that there is no significant difference between women with and without tubal sterilization with regard to hormonal changes. Another study conducted by Ercan *et al* examined the effects of tubal sterilization on ovarian reserves^[9]. FSH, luteinizing hormone, estradiol, anti-mullerian hormone, antral follicle count, and ovarian volume criteria were evaluated at baseline before sterilization and 3 months after surgery. No significant difference was found between the measurements. The present study focused on the ovarian reserve. In a similar study, Dede *et al*^[10] reported that bilateral tubal sterilization (electrocoagulation) had no effect on ovarian reserve and its function. On the other hand, the study conducted by Goynumer *et al* suggested that tubal sterilization using the same method decreased the ovarian reserve. As we glance at these studies, all examined ovarian reserve and function in women undergoing tubal sterilization with electrocoagulation method and focused mainly on perimenopausal symptomatology. The focus of the present study was age at menopause in women who underwent laparoscopic tubal sterilization with electrocoagulation method and the objectives of the study were set accordingly. This method was found to not change the menopausal age.

Our study evaluated the outcomes of coagulation method in laparoscopic sterilization. This is the most frequently used method since 1990s, when this method was introduced into our clinic for the first time^[1]. Therefore, we are unable to report data on other methods, which are rarely performed at our clinic. It is also obvious that many unknown factors could also affect menopause. We therefore suggest that our data and study sample are insufficient in this regard. In addition, BMI of the control population was higher than that of the study population. Mid-life obesity is

associated with a different menopausal experience, including associations with age at menopause^[11]. On the other hand, in both groups, age at menopause has not changed statistically significantly.

Bilateral salpingectomy has been preferred during tubal sterilization in recent years to avoid peritoneal and ovarian tumors^[12]. In the last 5 years, we prefer bilateral salpingectomy in patients presenting with the desire to undergo sterilization procedure. It can be considered that periovarian vascular structures could become injured during salpingectomy and, theoretically, such injuries could cause premature menopause by affecting the ovarian reserve. However, before drawing such conclusions, prospective, randomized studies should be conducted; alternatively, retrospective studies that are designed similar to the present study could be conducted in future.

CONCLUSION

Tubal sterilization using the laparoscopic coagulation method does not affect age at menopause. However, further studies should focus on the effects of salpingectomy use recently, which has proved to be protective against ovarian cancer.

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Original Article

Red Cell Distribution Width (RDW) is a Prognostic Factor for Mortality in the Patients with Sepsis and Septic Shock

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ABSTRACT

Objective: Red cell distribution width (RDW) is a measure of the range of variation of red blood cell (RBC) volume. It can be calculated automatically as part of a standard complete blood count. Our aim in this study is to evaluate the relationship between RDW and mortality in patients with sepsis and septic shock.

Design: Retrospective study

Setting: Internal Medicine Intensive Care Unit (ICU), Evliya Celebi Training and Research Hospital, Kutahya, Turkey

Subjects: One hundred and forty-four patients followed up in the ICU with diagnosis of sepsis and septic shock between Sep 2014 and Nov 2016 were included.

Interventions: Demographic, clinical, and laboratory data were obtained from the patients' medical records.

Main outcome measures: Evaluate RDW as a prognostic factor for mortality in sepsis

Results: A total of 144 patients were included in the study. Mortality rate of the patients in the ICU is 54.9% and hospital mortality rate of the patients is 64.6%. RDW values were statistically significant in the patients developing mortality in the ICU, compared to the patients not developing mortality in the ICU ($p < 0.05$). A statistically significant relationship was determined between the presence of mortality in the ICU and 17.2 cut-off point of RDW value ($p < 0.05$). The risk for observation of ICU mortality in patients with RDW value ≥ 17.2 is 2.148-fold higher. The risk for observation of hospital mortality in the patients with RDW value ≥ 17.2 is 1.945-fold higher.

Conclusion: RDW is a prognostic factor than can be used routinely for early prediction of mortality in patients with sepsis and septic shock.

KEY WORDS: intensive care unit, mortality, red cell distribution width

INTRODUCTION

Sepsis, described as systemic inflammatory response of the host against infections, is a clinical syndrome with high morbidity and mortality. The prediction of outcome for patients with sepsis may facilitate more aggressive interventions associated with sepsis. Many prognostic factors such as age, gender, comorbid diseases, biomarkers and severity of the disease are associated with the outcome. Inflammatory response occurring in sepsis causes release of biomarkers, which may play a role in prediction of the prognosis. However, some biomarkers have not been a part of routine practice due to reasons such as contradictory results of some

studies performed, no adaptation of them to routine test methods or limited contribution^[1,2].

Red cell distribution width (RDW) is a measure of the range of variation of red blood cell (RBC) volume, and if required, it can be calculated automatically as part of a standard complete blood count. RDW is used in the differential diagnosis of anemia and it is elevated in any condition where reticulocytes are released into the circulation. Recent studies report that RDW is associated with prognosis in congestive heart failure, acute myocardial infarction, pulmonary embolism, critical diseases and cardiac arrest, in addition to evaluation of anemia^[2-9].

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Recent studies showed that RDW was a prognostic factor in sepsis and septic shock and associated with mortality in patients with these diseases^[2,10,11]. Inflammation may increase erythropoiesis with many mechanisms as it is in sepsis. Inflammatory cytokines may cause release of immature erythrocytes into the circulation and consequently elevation in RDW levels by inhibiting erythrocyte maturation^[12,13]. Our aim in this study is to evaluate the relationship between RDW and intensive care unit (ICU) mortality and hospital mortality in patients followed up in the ICU with diagnosis of sepsis and septic shock.

SUBJECTS AND METHODS

The patients followed up in the Internal Medicine ICU with diagnosis of sepsis and septic shock between September 1st, 2014 and November 1st, 2016 were evaluated retrospectively. The patients over 18 years of age admitted to the ICU with diagnosis of sepsis and septic shock as defined according to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) were included in the study^[14]. Patients who were less than 18 years of age, pregnant, on immunosuppressive treatment, patients receiving steroid or radiation treatment, leukemia patients, patients with myelodysplastic syndrome, hematological disease like myeloproliferative disease, patients with metastatic bone marrow involvement, patients receiving RBC transfusion before admission to the ICU (<2 weeks) and the patients with acute bleeding were not included in the study.

Demographic, clinical, and laboratory data were obtained from the patients' medical records. Age, gender, comorbid diseases (Charlson comorbidity index score)^[15], Simplified Acute Physiology Score II (SAPS II)^[16], Glasgow coma score (GCS) values measured during admission to the ICU were obtained from the patients' medical records. The values measured during admission to the ICU were taken into consideration for RDW. RDW analysis was performed using Beckman Coulter LH 780 Hematology Analyzer. The normal reference range for RDW in the laboratory of our hospital is 11.5 - 14.5%.

Our primary aim in this study is to evaluate the relationship between RDW and mortality in the ICU, and the secondary aim is to evaluate the relationship between RDW and hospital mortality. The Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for statistical analysis. During the evaluation of the study data, regarding the comparisons of descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum and maximum) as well as quantitative data, Student t test was used for the intergroup comparisons

of parameters with normal distribution, and Mann-Whitney U test was used for the intergroup comparisons of parameters without normal distribution. Pearson's Chi-Square test, Fisher-Freeman-Halton test, Fisher's exact test and Yates's Continuity Correction test (Yates-corrected Chi-squared test) were used for comparison of qualitative data. Diagnostic screening

Table 1: Characteristic features of the patients

Characteristics	n (%)
Age (years)	75.08 ± 12.79
Men	76 (52.8)
Sepsis	95 (66)
Septic shock	49 (34)
Source	
Respiratory	64 (44.4)
Urinary	66 (45.8)
Soft tissue	9 (6.3)
Abdomen	5 (3.5)
Vasopressor therapy	116 (80.6)
Hemodialysis	36 (25)
Mechanical ventilation	57 (39.6)
Total parenteral nutrition	133 (92.4)
Comorbid diseases	
Diabetes mellitus	63 (43.8)
Hypertension	66 (45.8)
Congestive heart failure	18 (12.5)
Coronary artery disease	17 (11.8)
Chronic renal failure	37 (25.7)
Cerebrovascular accident	35 (24.3)
Chronic obstructive pulmonary disease	18 (12.5)
Alzheimer's disease	55 (38.2)
Malignancy	18 (12.5)
Glasgow coma score	7.37 ± 2.76
Charlson comorbidity index	3.25 ± 1.36
SAPS II	67.08 ± 18.14
Vital signs	
Mean arterial pressure (MAP)	68.35 ± 7.99
Heart rate	97.74 ± 8.25
Body temperature	37.53 ± 0.81
Laboratory findings	
White blood cell (103 /μL)	2.6 - 56 (14.2)
Thrombocyte (103 /μL)	24 - 976 (217)
Erythrocyte (103 /μL)	2.2 - 6.6 (4.1)
Hemoglobin	5.7 - 20.4 (11.5)
Hct	18.1 - 63.5 (35.2)
RDW	10.6 - 27.2 (16.9)
MCV	63.7 - 120.3 (87.2)
MPV	5.9 - 13.6 (8.5)
C-reactive protein	5 - 518 (157)
T bilirubin	1.14 ± 0.91
Albumin	2.73 ± 0.57
Creatinine	3.01 ± 2.25
INR	1.61 ± 1.34
ICU mortality	79 (54.9)
Hospital mortality	93 (64.6)
Hospitalization duration (days)	19.62 ± 16.53
Length of ICU stay (days)	15.22 ± 13.9

SAPS II: Simplified Acute Physiology Score II; Hct: hematocrit; RDW: red cell distribution width; MCV: mean corpuscular volume; MPV: mean platelet volume; INR: international normalized ratio; ICU: intensive care unit

Table 2: Evaluation of demographic, clinical and laboratory features according to ICU mortality

Characteristics	ICU Mortality		p-value
	Absent (n = 65)	Present (n = 79)	
Age (years)	72.29 ± 13.2	77.37 ± 12.05	0.017
Men	30 (39.5)	46 (60.5)	0.149
Sepsis	45 (47.4)	50 (52.6)	0.567
Septic shock	20 (40.8)	29 (59.2)	
Sources			0.002
Respiratory	18 (28.1)	46 (71.9)	
Urinary	38 (57.6)	28 (42.4)	
Soft tissue	6 (66.7)	3 (33.3)	
Abdomen	3 (60)	2 (40)	
Vasopressor therapy	39 (33.6)	77 (66.4)	0.001
Hemodialysis	11 (30.6)	25 (69.4)	0.042
Mechanical ventilation	9 (15.8)	48 (84.2)	0.001
Total parenteral nutrition	57 (42.9)	76 (57.1)	0.066
Comorbid diseases			
Diabetes mellitus	28 (44.4)	35 (55.6)	0.883
Hypertension	32 (48.5)	34 (51.5)	0.458
Congestive heart failure	6 (33.3)	12 (66.7)	0.411
Coronary artery disease	7 (41.2)	10 (58.8)	0.928
Chronic renal failure	16 (43.2)	21 (56.8)	0.938
Cerebrovascular accident	16 (45.7)	19 (54.3)	1.000
Chronic obstructive pulmonary disease	7 (38.9)	11 (61.1)	0.752
Alzheimer's disease	18 (32.7)	37 (67.3)	0.029
Malignancy	5 (27.8)	13 (72.2)	0.184
Glasgow coma score	8.48 ± 2.63	6.46 ± 2.54	0.001
Charlson comorbidity index	2.97 ± 1.24	3.48 ± 1.42	0.015
SAPS II	60.45 ± 18.09	72.54 ± 16.37	0.001
Vital signs			
Mean arterial pressure (MAP)	71 ± 9.27	66.16 ± 5.98	0.005
Heart rate	98.08 ± 8.64	97.46 ± 7.95	0.711
Body temperature	37.57 ± 0.8	37.49 ± 0.82	0.628
Laboratory findings			
White blood cell (103 / μ L)	15.84 ± 8.71	15.9 ± 9.58	0.933
Thrombocyte (103 / μ L)	255.12 ± 150.82	223.94 ± 112.11	0.300
Erythrocyte (103 / μ L)	4.18 ± 0.86	4.14 ± 0.95	0.762
Hemoglobin	11.54 ± 2.49	11.43 ± 2.37	0.793
Hct	35.73 ± 7.84	35.66 ± 7.45	0.959
RDW	16.6 ± 2.31	17.56 ± 2.77	0.023
MCV	85.56 ± 8.4	87.42 ± 7.6	0.377
MPV	8.79 ± 1.57	8.74 ± 1.61	0.791
C-reactive protein	153.71 ± 105.39	187.2 ± 116.72	0.085
T bilirubin	1.06 ± 0.88	1.2 ± 0.93	0.283
Albumin	2.77 ± 0.47	2.69 ± 0.64	0.277
Creatinine	2.83 ± 2.74	3.15 ± 2.39	0.363
INR	1.45 ± 0.99	1.74 ± 1.57	0.009
Hospitalization duration (days)	16.72 ± 12.21	13.97 ± 15.11	0.014

SAPS II: Simplified Acute Physiology Score II; Hct: hematocrit; RDW: red cell distribution width; MCV: mean corpuscular volume; MPV: mean platelet volume; INR: international normalized ratio; ICU: intensive care unit

tests and receiving operating characteristic (ROC) curve analysis were used for determination of the cut-off point for RDW. The effects of risk factors on the ICU mortality and hospital mortality were evaluated by using Cox regression analysis as multivariate analysis. Significance was evaluated at the levels of $p < 0.01$ and $p < 0.05$. A statistically significant relationship was determined between the presence of hospital mortality and 17.2 cut-off point of RDW value ($p = 0.006$; $p < 0.05$). The risk for observation of hospital mortality in the patients with RDW value ≥ 17.2 is 1.945-fold higher.

The odds ratio for RDW is 1.945 (95% confidence interval (CI): 1.209 - 3.128).

RESULTS

A total of 144 patients were included in the study. Seventy-six (52.8%) of the patients were males and their mean age was 75.08 ± 12.79 years (min: 18, max: 102). The main characteristic features of the patients are shown in Table 1. Mortality rate of the patients in the ICU is 54.9% and hospital mortality rate of the patients is 64.6%. When the patients were evaluated as the ones

Table 3: Univariate and multivariate analysis of risk factors effective on ICU mortality

Characteristics	Univariate analysis				Multivariate analysis			
	p-value	Odds ratio	95% CI		p-value	Odds ratio	95% CI	
			Lower	Upper			Lower	Upper
Age	0.017	1.033	1.005	1.062	0.368	1.013	0.985	1.043
Sources of the sepsis	0.001	3.64	1.801	7.356	0.078	1.633	0.947	2.818
Glasgow come score	0.001	0.737	0.637	0.853	0.003	0.817	0.716	0.932
Charlson comorbidity index	0.015	1.343	1.034	1.745	0.073	1.198	0.983	1.461
SAPS II	0.001	1.041	1.02	1.064	0.794	0.997	0.978	1.018
Alzheimer's disease	0.029	2.3	1.142	4.634	0.023	2.006	1.1	3.659
Mean arterial pressure	0.001	0.918	0.874	0.965	0.001	0.916	0.869	0.964
Vasopressor therapy	0.001	25.667	5.791	113.762	0.022	5.724	1.283	25.54
Hemodialysis	0.042	2.273	1.018	5.074	0.378	0.761	0.414	1.398
Mechanical ventilation	0.001	9.634	4.175	22.234	0.707	1.123	0.614	2.051
RDW (≥ 17.2)	0.025	2.148	1.097	4.203	0.009	2.010	1.190	3.393

SAPS II: Simplified Acute Physiology Score II; RDW: red cell distribution width

with and without mortality in the ICU, the average age, presence of pneumonia-related sepsis, a high Charlson comorbidity index and a high SAPS score, presence of Alzheimer's disease, receiving vasopressor agents and mechanical ventilation were statistically significantly higher in the patients developing mortality and mean arterial pressure (MAP), GCS and prolonged stay in the ICU were determined to be less in the patients developing mortality ($p < 0.05$). When the laboratory values were investigated, it was determined that RDW values were statistically significant in the patients developing mortality in the ICU compared to the patients not developing mortality in the ICU ($p < 0.05$). International normalized ratio (INR) was stastically higher in the patients with mortality ($p < 0.05$). While c-reactive protein (CRP) was higher in the patients developing mortality, the difference was not statistically significant. No significant difference was determined regarding the other laboratory values ($p > 0.05$) (Table 2).

The cut-off point for RDW was determined to be ≥ 17.2 with respect to presence of mortality in the ICU. The sensitivity, specificity, positive predictive value and negative predictive value for 17.2 cut-off value of RDW were 55.7%, 63.08%, 64.71% and 53.95% respectively. The area under curve (AUC) value was determined to be 0.61 in the ROC curve obtained (Fig. 1). A statistically significant relationship was determined between the presence of mortality in the ICU and 17.2 cut-off point of RDW value ($p = 0.025$; $p < 0.05$). The risk for observation of ICU mortality in patients with RDW value of ≥ 17.2 is 2.148-fold higher. The odds ratio for RDW is 2.148 (95 CI%: 1.097 - 4.203). In multivariate analysis of the values effective on ICU mortality, MAP, GCS, presence of Alzheimer's disease, receiving vasopressor agents and RDW were determined to be independent variables ($p < 0.05$) (Table 3).

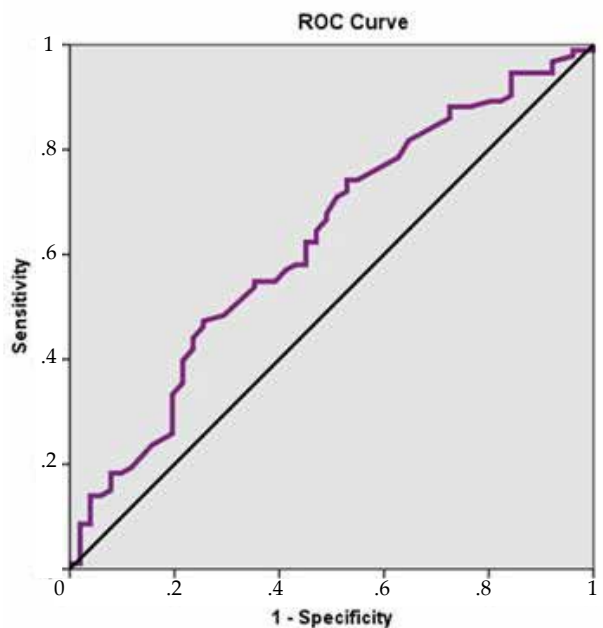


Fig. 1: Receiver operating curve for RDW for prediction of ICU mortality

When the patients were evaluated as the ones with and without hospital mortality; the advanced age, male gender, presence of pneumonia-related sepsis, a high Charlson comorbidity index and a high SAPS II score, presence of Alzheimer's disease, receiving vasopressor agents, mechanical ventilation and total parenteral nutrition were statistically significantly higher in the patients developing hospital mortality and MAP, GCS and prolonged stay in the hospital were determined to be less in the patients developing hospital mortality ($p < 0.05$). When the laboratory values were investigated, it was determined that RDW values were statistically significantly higher in the patients developing hospital

Table 4: Evaluation of demographic, clinical and laboratory features according to hospital mortality

Hospital Mortality				Hospital Mortality			
Characteristics	Absent (n = 51)	Present (n = 93)	p-value	Characteristics	Absent (n = 51)	Present (n = 93)	p-value
Age (years)	70.86 ± 13.75	77.39 ± 11.68	0.003	Malignancy	12 (21.8)	43 (78.2)	0.012
Men	21 (27.6)	55 (72.4)	0.039	Glasgow coma score	15.02 ± 10.71	15.32 ± 15.42	0.268
Sepsis	37 (38.9)	58 (61.1)	0.294	Charlson comorbidity index	2.88 ± 1.19	3.45 ± 1.41	0.015
Septic shock	14 (28.6)	35 (71.4)	0.004	SAPS II	58.15 ± 18.77	71.98 ± 15.86	0.001
Source				Vital signs			
Respiratory	14 (21.9)	50 (78.1)		Mean arterial pressure	71.73 ± 9.84	66.5 ± 6.06	0.005
Urinary	30 (45.5)	36 (54.5)		Heart rate	97.55 ± 8.82	97.84 ± 7.96	0.773
Soft tissue	6 (66.7)	3 (33.3)		Body temperature	37.52 ± 0.77	37.53 ± 0.84	0.84
Abdomen	1 (20)	4 (80)		Laboratory findings			
Vasopressor therapy	30 (21.8)	86 (74.1)	0.001	White blood cell (103 /μ)	16.51 ± 9.16	15.52 ± 9.2	0.484
Hemodialysis	8 (22.2)	28 (77.8)	0.087	Thrombocyte (103 /μ)	251.78 ± 154.74	230.46 ± 116.96	0.634
Mechanical ventilation	5 (8.8)	52 (91.2)	0.001	Erythrocyte (103 /μ)	4.21 ± 0.86	4.13 ± 0.93	0.600
Total parenteral nutrition	43 (32.3)	90 (67.7)	0.017	Hemoglobin	11.6 ± 2.61	11.41 ± 2.32	0.660
Comorbid diseases				Hct	35.97 ± 8.04	35.54 ± 7.39	0.746
Diabetes mellitus	22 (34.9)	41 (65.1)	1.000	RDW	16.48 ± 2.25	17.52 ± 2.72	0.013
Hypertension	25 (37.9)	41 (62.1)	0.57	MCV	85.5 ± 8.95	87.17 ± 7.42	0.541
Congestive heart failure	4 (22.2)	14 (77.8)	0.323	MPV	8.88 ± 1.69	8.7 ± 1.53	0.514
Coronary artery disease	7 (41.2)	10 (58.8)	0.928	C-reactive protein	150.1 ± 108.71	184.14 ± 113.46	0.060
Chronic renal failure	12 (32.4)	25 (67.6)	0.81	T bilirubin	1.07 ± 0.87	1.18 ± 0.93	0.494
Cerebrovascular accident	16 (45.7)	19 (54.3)	0.716	Albumin	2.81 ± 0.47	2.69 ± 0.61	0.174
Chronic obstructive pulmonary disease	7 (38.9)	11 (61.1)	0.947	Creatinine	2.62 ± 2.3	3.22 ± 2.67	0.195
Alzheimer's disease	12 (21.8)	43 (78.2)	0.012	INR	1.45 ± 1.04	1.7 ± 1.48	0.038
				Number of days of hospitalization	25.12 ± 13.82	16.61 ± 17.17	0.001

SAPS II: Simplified Acute Physiology Score II; Hct: hematocrit; RDW: red cell distribution width; MCV: mean corpuscular volume; MPV: mean platelet volume; INR: international normalized ratio

mortality compared to the patients not developing hospital mortality ($p < 0.05$). INR was stastically higher in the patients with hospital mortality ($p < 0.05$). While CRP was determined to be higher in the patients developing hospital mortality, the difference was not statistically significant. No significant difference was determined regarding the other laboratory values ($p > 0.05$) (Table 4).

The cut-off point for RDW was determined to be ≥ 17.2 with respect to presence of hospital mortality. The sensitivity, specificity, positive predictive value and negative predictive value for 17.2 cut-off value of RDW were 53.76%, 64.71%, 73.53% and 43.42% respectively. AUC value was determined to be 0.625 in the ROC curve obtained (Fig. 2). A statistically significant relationship was determined between the presence of hospital mortality and 17.2 cut-off point of RDW value ($p = 0.006$; $p < 0.05$). The risk for observation of hospital mortality in the patients with RDW value ≥ 17.2 is 1.945-fold higher. The odds ratio for RDW is 1.945 (95 CI%: 1.209 - 3.128). In multivariate analysis of the values effective on hospital mortality; MAP, GCS, presence of Alzheimer's disease, Charlson comorbidity index and RDW were determined to be independent variables ($p < 0.05$) (Table 5).

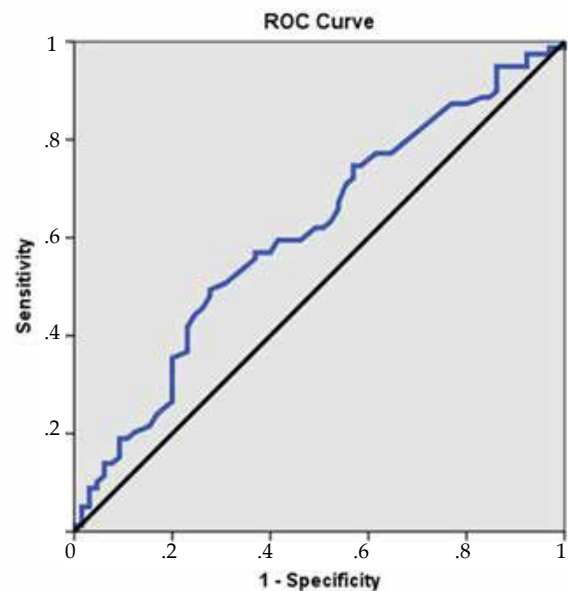


Fig. 2: Receiver operating curve for RDW for prediction of hospital mortality

Table 5: Univariate and multivariate analysis of risk factors effective on hospital mortality

Characteristics	Univariate analysis				Multivariate analysis			
	p-value	Odds ratio	95% CI		p-value	Odds ratio	95% CI	
			Lower	Upper			Lower	Upper
Age (years)	0.003	1.042	1.012	1.072	0.360	1.012	0.986	1.040
Men	0.039	2.068	1.033	4.140	0.359	0.803	0.502	1.284
Sources of the sepsis	0.002	3.073	1.469	6.427	0.134	1.450	0.892	2.356
Glasgow coma score	0.003	0.824	0.721	0.942	0.034	0.887	0.793	0.991
Charlson comorbidity index	0.009	1.415	1.060	1.888	0.007	1.273	1.067	1.520
SAPS II	0.001	1.046	1.024	1.070	0.296	1.010	0.991	1.029
Alzheimer's disease	0.012	2.795	1.301	6.005	0.178	1.808	0.763	4.284
Mean arterial pressure	0.000	0.918	0.875	0.963	0.001	0.920	0.875	0.967
Vasopressor therapy	0.001	8.600	3.323	22.260	0.307	0.755	0.440	1.295
Mechanical ventilation	0.001	11.668	4.251	32.025	0.490	1.211	0.703	2.086
Total parenteral nutrition	0.017	5.581	1.410	22.091	0.887	1.092	0.321	3.712
RDW (≥ 17.2)	0.034	2.132	1.054	4.311	0.006	1.002	1.000	1.004

SAPS II: Simplified Acute Physiology Score II; RDW: red cell distribution width

DISCUSSION

In this study, a strong relationship was determined between RDW and ICU mortality and hospital mortality in the patients followed-up with diagnosis of sepsis and septic shock. RDW is an independent variable for mortality occurring both in the ICU and hospital in the patients followed up with diagnosis of sepsis and septic shock. Similarly, in the study performed by Sadaka *et al*, RDW was determined to be an independent variable for mortality occurring both in the ICU and hospital in the patients followed up with diagnosis of sepsis and septic shock^[10]. In another study performed by Jo YH *et al*, the authors determined that RDW was an independent prognostic factor for 28-day mortality in the patients followed up with diagnosis of sepsis and septic shock^[2]. In our study, a moderate discrimination power was determined for RDW in prediction of mortality in the ROC curve performed to determine the point of discrimination for mortality occurring in the ICU and hospital (AUROC was 0.610 and 0.625, respectively). This value is also consistent with the other studies^[2,10].

Increase in RDW levels is associated with increased mortality in the patients followed up with diagnosis of sepsis and septic shock^[2,10,11]. In the study performed by Mahmood *et al*, the authors demonstrated that RDW value ≥ 16 was an independent prognostic factor for mortality in the patients with sepsis^[11]. In a study performed, when the patients were grouped according to RDW value, it was determined that both ICU mortality and hospital mortality increased statistically significantly in the groups with RDW value of ≥ 17.6 , compared to the groups with RDW value of ≤ 13.5 ^[10]. In another study, it was determined that 28-day mortality increased 1.66-fold and 2.57-fold in the groups with RDW value of 14.1 – 15.7 and ≥ 15.8

respectively, compared to the groups with RDW value of ≤ 14 ^[2]. Similarly in our study, it was determined ICU mortality increased 2.14-fold and hospital mortality increased 1.94-fold in the group with RDW value of ≥ 17.2 compared to the group with RDW value of ≤ 17.2 and this increase was statistically significant.

In a study performed in the patients with sepsis and septic shock; age, urinary infection, chronic liver disease, Ph, blood urea nitrogen, creatinine, albumin, APACHE 2 score and RDW were determined to be independent risk factors for 28-day mortality^[2]. Again in another study performed, APACHE 2 score, sequential organ failure assessment (SOFA) score, the number of organ failure and RDW were determined to be independent risk factors for hospital mortality in the patients with septic shock^[10]. In our study, while GCS, presence of Alzheimer's disease, MAP, receiving vasopressor agent and RDW value were found to be independent risk factors for ICU mortality and presence of Alzheimer's disease; MAP, GCS, Charlson comorbidity index and RDW value were found to be independent risk factors for hospital mortality. All of these results suggest that RDW value is a good prognostic factor in sepsis and septic shock.

In our study, when the patients alive and dead were compared regarding CRP value among inflammatory markers, no statistically significant difference was determined between the 2 groups. When the independent variables were evaluated for both ICU mortality and hospital mortality, CRP was not among independent variables in the multivariate analyses. In the study performed by Kim *et al*, it was determined that CRP was not a good predictor for prediction of 30-day mortality in the patients followed-up with diagnosis of sepsis and septic shock, the results of ROC analysis were more remarkable in prediction of

prognosis of RDW^[17]. Similarly, in the study performed by Ozdogan *et al*, when the patients alive and dead among the patients followed-up with diagnosis of intra-abdominal sepsis were evaluated, while RDW was determined to be an independent variable in prediction of mortality, CRP value was shown not to be an independent variable^[18].

The relationship between RDW and mortality has been well documented, with many studies performed for commonly seen cardiovascular diseases and critically ill patients^[2-9]. However, the mechanism of relationship between RDW and outcome of the patient could not be understood exactly. It was determined that different etiologies causing chronic inflammation, malnutrition and anemia could be a potential etiology^[17]. The role of RDW in prediction of the prognosis of the disease is important, because RDW can be easily measured from complete blood count and additional charging is not necessary.

The mechanism of relationship between RDW and mortality in sepsis and septic shock is unclear. Tumor necrosis factor-alpha, interleukin-6 and interleukin-1 β released in sepsis may suppress the maturation of RBC and decrease half-lives of RBCs^[12,13,19]. Systemic inflammatory response affects bone marrow function and iron metabolism, and proinflammatory cytokines decrease erythrocyte maturation and proliferation by inhibiting erythropoietin. Also, erythropoietin receptor expression decreases in consequence of cytokine release^[12,19,20]. As a result of oxidative stress and neurohormonal response together with inflammation, half-lives of RBCs may decrease. In consequence of reduction of RBCs, an increase may occur in RDW together with increased RBC production^[21,22].

There are some limitations in our study. First, our study design was a retrospective design. Secondly, the levels of iron, folate and vitamin B12, which could affect RDW, were not evaluated.

CONCLUSION

In conclusion, RDW value measured during admittance to the ICU in patients followed up with diagnosis of sepsis and septic shock in our study was found to be significant in prediction of mortality occurring both in the ICU and in the hospital. Although the mechanism of relationship between RDW and mortality in sepsis is not known exactly, a strong relationship was determined between RDW value measured during admittance to the ICU and ICU mortality and hospital mortality in our study. Since RDW can be easily measured from complete blood count and additional charging is not necessary, we think that it is a prognostic factor than can be used routinely for early prediction of mortality in patients

with sepsis and septic shock who are followed up in the ICU.

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Original Article

Nutritional Screening of Outpatient Type 2 Diabetes Mellitus Patients

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ABSTRACT

Objective: To examine the parameters affecting the existence and prevalence of malnutrition in type 2 diabetic patients at initial presentation

Design: Cross-sectional study

Setting: Department of Internal Medicine, Sakarya University Research and Education Hospital, Turkey

Subjects: Nutritional screening of 580 outpatients with the diagnosis of type 2 diabetes who presented to an outpatient clinic

Intervention: Medical treatment of diabetic patients

Main outcome measure: The parameters affecting the existence and prevalence of malnutrition in type 2 diabetic patients

Results: Mean \pm standard deviation age of the patients was 54.6 ± 10.7 years. Of the 580 patients, 327 were women (56.4%). Malnutrition prevalence was 11.4% with Subjective Global Assessment and 9% with Mini Nutritional Assessment and Malnutrition Universal Screening Tool. Body mass index (BMI), albumin, fat%, mid-arm circumference and

calf circumference were significantly lower and glycated hemoglobin (HbA1c) was significantly higher in patients with malnutrition, compared to patients without malnutrition. Malnutrition was significantly associated with weight loss, change in dietary intake and diminished physical activity ($p = 0.005$). Logistic regression model, including BMI ≤ 30.35 kg/m², HbA1c ≥ 8.69 mmol/mol, fat% $\leq 35.85\%$ cut-off values, presence/absence of change in dietary intake and diminished physical activity as independent predictors of malnutrition revealed that patients with HbA1c ≥ 8.69 mmol/mol, fat% $\leq 35.85\%$, who had change in dietary intake or had diminished physical activity were 3.7, 2.9, 29.2 and 4.4 times more likely to have malnutrition.

Conclusion: Type 2 diabetic patients are often obese and thus higher cut-off for BMI and fat% may be necessary to detect malnutrition. Poor glucose control, decreased fat%, change in dietary intake and especially diminished physical activity are independent predictors of malnutrition in this population.

KEY WORDS: anthropometric measurements, laboratory parameters, malnutrition, type 2 diabetes mellitus

INTRODUCTION

Malnutrition comprises various clinical states resulting from low intake of macronutrients. It is associated with prolonged hospital stay, increase in frequency of readmissions, severity of infections, poor wound healing, disturbance in walking, falls and fractures. Malnutrition is more frequent in patients with chronic diseases^[1].

Type 2 diabetes mellitus (DM) is a chronic metabolic disorder that is characterized

by high blood glucose, insulin resistance and relative lack of insulin. Long term complications from high blood glucose include heart disease, stroke, and diabetic retinopathy that can result in blindness, kidney failure and poor blood flow in the limbs, which may lead to amputations^[2]. Diabetes is associated with an increased risk of suffering malnutrition. Inflammation, oxidative stress and some genetic components can cause malnutrition in DM^[3].

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Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment (MNA), Nutrition Risk Screening-2002 (NRS-2002), and Subjective Global Assessment (SGA) are malnutrition scales that have been used in various patient populations. Also, anthropometric measurements and several laboratory parameters are used for malnutrition screening^[4,5].

There are few studies about malnutrition in DM. Diabetic complications, inability to adapt to the diabetic diet, diabetic gastropathy, loss of appetite, decrease of energy intake and problems associated with high blood glucose, nausea, and vomiting can cause malnutrition in diabetic patients.

In this study, we aimed to examine the parameters affecting the existence and prevalence of malnutrition in type 2 diabetic patients on initial presentation to an outpatient diabetes clinic.

SUBJECTS AND METHODS

A total of 580 outpatients with the diagnosis of type 2 DM who presented to the diabetes outpatient clinic at Sakarya University Hospital from 2012 to 2015 have been included in this study. We used American Diabetes Association Criteria 2012 to diagnose type 2 DM.

Patients who were pregnant or younger than 18 years, had a diagnosis of malignancy, type 1 diabetes mellitus, cerebrovascular diseases, thyroid dysfunction, cirrhosis, chronic renal failure (Cockcroft-Gault formula GFR < 60 ml/min) or in whom anthropometric measurements or nutrition tests could not be performed were excluded from the study.

Patients' age, gender, diabetes duration, medications, additional diseases and history of smoking were recorded. Height, weight and anthropometric measurements (mid-arm circumference and calf circumference) of all patients were measured. Mid-arm circumference was defined as the circumference taken at the mid-point between the shoulder and elbow of the bare left arm using a tape measure. Calf circumference was measured from the largest part of right calf using a tape measure while the patient was sitting in the chair (leg from the knee bent at 90 °C). Basal metabolic rate (BMR), fat mass, fat free mass, total body water (TBW), body mass index (BMI) and fat% were measured by Tanita Composition Analyzer TBF-300. Demographic, anthropometric and laboratory data were compared between groups with and without malnutrition.

SGA as well as MUST and MNA screening tests were performed for nutritional evaluation. MUST was used for patients below 65 years and MNA for those over 65 years, whereas SGA was performed for the whole group. After recording the parameters, patients

were evaluated in three categories: (A) "nutritional status good/sufficient," (B) "high risk of malnutrition" and (C) "severe malnutrition". The last two categories were merged in all screening tests and patients were divided into two groups: normal nutritional status or malnutrition. After determination of malnutrition rates for each test, SGA was applied to all patients and was accepted as the gold standard for nutritional status.

In our study, change in dietary intake was defined as decreasing food intake during the last one month, whereas diminished physical activity was defined as working suboptimally and decreasing physical activity in the last one month.

Parameters that were used in SGA evaluation were assessed for their effect on nutritional status. Receiver operating characteristic (ROC) analysis was performed to determine cut-off values of the continuous parameters affecting nutritional status. Then, a logistic regression model was constructed using cut-off values and categorical variables to determine independent predictors of malnutrition.

Statistical Analysis

Data was analyzed using statistical software SPSS, version 15.0 [SPSS Inc, Chicago, IL] and MedCalc 16.4.3 [1993-2016 MedCalc Software bvba] trial version. Distribution characteristics of continuous data were determined using histogram examination and one-sample Kolmogorov-Smirnov test. Normally distributed data were presented as mean (standard deviation) and compared with 1-way analysis of variance. Non-normally distributed data were analyzed using Mann-Whitney U test. ROC analysis was used to determine cut-off values for significant continuous data. Categorical associations were evaluated using χ^2 test and logistic regression analysis. Statistical significance was defined by $p \leq 0.05$.

Ethical Statement

Ethical approval was obtained through the medical school ethic committee (Ethical recommendations of the Declaration of Helsinki and the Ethical Committee of Sakarya University, Faculty of Medicine). Informed consent were obtained from all patients.

RESULTS

We included 580 patients in this study. Mean (SD) age was 54.7 (10.4) years. There were 327 women (56.4%). Malnutrition prevalence was the same (9%) with MNA and MUST. Malnutrition prevalence was 11.4% according to SGA. Other characteristics and demographic data are summarized in Table 1. BMI, albumin, fat%, mid-arm circumference and calf circumference were significantly lower, and glycated

Table 1: Demographic, laboratory and anthropometric data in patients with and without malnutrition

Parameters	Normal n = 514	Malnutrition n = 66	p-value
Age (mean \pm SD)	54.7 \pm 10.4	54.1 \pm 12.5	0.678
Gender (W/M)	297/217	30/36	0.57
Smoking (n(%))	65 (13)	8 (12)	0.904
Drug usage (OAD/Insulin)	344/170	48/18	0.343
Additional disease (n(%))			0.962
Hypertension	192 (37)	24 (36)	
Coronary disease	36 (7)	6 (9)	
Other	5 (1)	0	
DM duration (month, median)*	48 (119)	36 (119)	0.204
BMI (kg/m ² , median)*	34.2 (7.98)	28 (7.6)	0.002
Fat free mass (kg, median)*	52.3 (14.5)	51.7 (14)	0.689
Basal metabolic rate (kcal, median)*	1587 \pm 253	1499 (336.5)	0.351
Fat mass (kg, median)*	29.3 \pm 17	25.6 (16.6)	0.016
TBW (kg, median)*	38.4 (11.4)	36 (9.2)	0.743
Fat mass (%)	29.2 (17.1)	25.4 (16.4)	0.005
Mid-arm circ (cm, median)*	33 (6)	30 (5)	0.018
Calf circ (cm, median)*	39 (6)	36 (5.5)	0.09
LDL (mg/dL median(SD))	132 (41.7)	126.7 (28.6)	0.365
FBS (mg/dL median)*	173 (106.5)	174 (154)	0.101
HbA1c (% , median)*	8.1 (3.1)	9 (4.4)	0.01
Albumin (g/dL, median)*	4.4 (0.5)	4.3 (1.7)	0.031
Creatinine (mg/dL, median)*	0.8 (0.2)	0.9 (0.3)	0.126

*: interquartile range

OAD: oral antidiabetic drugs; DM: diabetes mellitus; BMI: body mass index, LDL: low density lipoprotein; FBS: fasting blood glucose; HbA1c: glycated hemoglobin; TBW: total body water

hemoglobin (HbA1c) was significantly higher in patients with malnutrition, compared to patients without malnutrition (Table 1 and Fig 1).

Malnutrition was significantly associated with weight loss, change in dietary intake and diminished physical activity (Table 2) (Pearson $\chi^2 = 7.758, 222.2, 238.4, 190.5, 4.958$ and $p = 0.005, <0.001, <0.001$ and $=0.026$, respectively). It was not

associated with gender, smoking, oral antidiabetic drugs/insulin or presence of additional disease (hypertension, coronary artery disease or others).

The effects of BMI, HbA1c and fat% on malnutrition were analyzed by ROC curve and areas under curve (AUCs) were found to be statistically significant (Figure 2 and Table 3). Sensitivity, specificity, positive predictive value, negative predictive value (NPV),

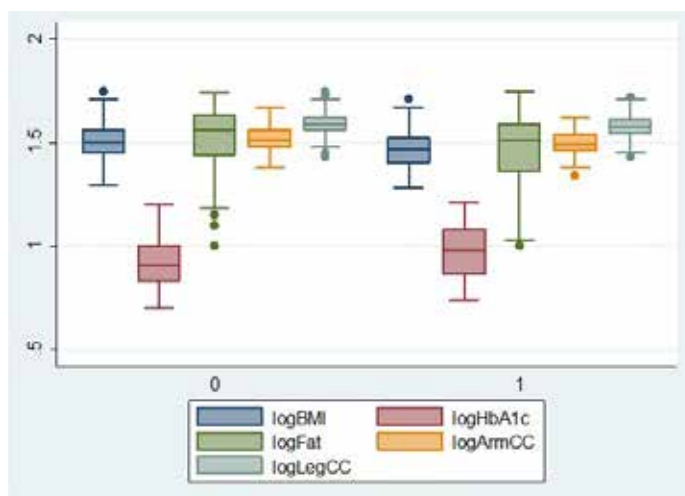


Fig 1: Mean logarithms of BMI, HbA1c, fat%, mid-arm circumference and calf circumference in the groups with(1) and without(0) malnutrition. CC= circumference

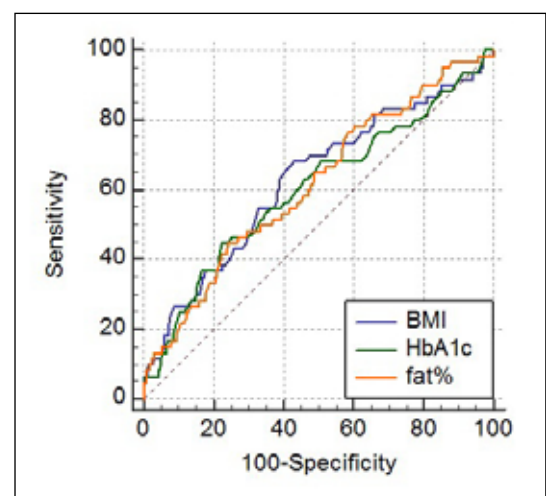


Fig 2: ROC curve of BMI, HbA1c and fat% where state variable is the malnutrition

Table 2: Items of SGA in patients with and without malnutrition

Items of SGA	Normal n(%) n = 514	Malnutrition n(%) n = 66	p-value
Weight loss	26 (5)	43 (65)	<0.001
Change in dietary intake	23 (5)	44 (67)	<0.001
Diminished physical activity	29 (6)	43 (65)	<0.001

SGA: Subjective Global Assessment

Table 3: Area under curve for BMI, HbA1c and fat % where the state variable is malnutrition.

Parameters	Area	Standard Error	p-value	95% Confidence Interval
BMI \leq 30.35	0.618	0.039	0.002	0.54 to 0.69
HbA1c \geq 8.69	0.602	0.042	0.01	0.52 to 0.68
Fat% \leq 35.85	0.606	0.038	0.05	0.53 to 0.60

BMI: body mass index; HbA1c: glycated hemoglobin

positive likelihood ratio, negative likelihood ratio values and the disease prevalence for these parameters are shown in Table 4. A logistic regression model was developed using BMI \leq 30.35 kg/m², HbA1c \geq 8.69 mmol/mol, fat% \leq 35.85% cut-off values as well as presence or absence of change in dietary intake and diminished physical activity as independent predictors for malnutrition. It revealed that patients with HbA1c \geq 8.69 mmol/mol, fat% \leq 35.85%, who had change in dietary intake or had diminished physical activity were 3.7, 2.9, 29.2 and 4.4 times as likely to have malnutrition compared to patients with HbA1c

Table 4: Sensitivity, specificity, PPV, NPV, LR+ and LR- values for BMI \leq 30.35, HbA1c \geq 8.69, fat % \leq 35.85 in assessment of malnutrition

Parameters	Sensitivity	Specificity	PPV	NPV	LR+	LR-
BMI \leq 30.35	0.62	0.60	16.9	92.5	1.57	0.63
HbA1c \geq 8.69	0.60	0.56	14.3	92	1.37	0.71
Fat% \leq 35.85	0.55	0.60	15.4	91	1.38	0.75

BMI: body mass index; HbA1c: glycated hemoglobin; Malnutrition prevalence: 11.4%; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio

Table 5: Logistic regression analysis model evaluating BMI \leq 30.35, HbA1c \geq 8.69 mmol/mol, fat % \leq 35.85, presence or absence of change in dietary intake and decreased physical activity as independent predictors of malnutrition risk

Parameters	B	Standard Error	Wald	Df	p-value	Odds Ratio
Constant	-4.88	0.55	79.81	1	<0.001	0.008
BMI	0.53	0.5	1.13	1	0.287	1.7
HbA1c	1.3	0.45	8.32	1	0.004	3.65
Fat%	1.07	0.54	3.86	1	0.048	2.91
Change in dietary intake	3.37	0.65	26.93	1	<0.001	29.22
Diminished physical activity	1.49	0.6	6.25	1	0.012	4.44

BMI: body mass index; HbA1c: glycated hemoglobin

<8.69 mmol/mol, fat% $>$ 35.85%, without change in dietary intake or with normal physical activity (Table 5). Assumptions of logistic regression were met and Nagelkerke R² was 54.1%.

DISCUSSION

Performing nutritional evaluation has an important impact on patients' outcome and healthcare costs^[5,6]. In a study on diabetic patients over the age of 65, malnutrition risk was reported to be higher in patients with DM compared to non-diabetic patients^[7]. We analyzed the nutritional status in a large sample of type 2 diabetic patients on their initial presentation and obtained a snapshot of the nutritional status of this specific population.

Malnutrition is well known to be common among patients with chronic diseases. The prevalence of malnutrition was 44% in pre-dialysis patients with end stage renal failure^[8], and 16% and 25 – 40% in patients with chronic heart failure^[9] and advanced chronic obstructive pulmonary disease^[10], respectively. In a Spanish study including 1090 elderly hospitalized diabetic patients, malnutrition was detected in 39.1%^[11]. Nutritional risk on admission to various clinics was found to be 15% in a large multi-center study conducted in our country^[12], but the prevalence of malnutrition in diabetic patients was not determined. Malnutrition prevalence was reported to be 76% among 2329 elderly hospital inpatients^[13]. However, in this study, the malnutrition prevalence was statistically similar in patients with and without diabetes. On the other hand, presence of diabetic complications on admission was associated with a higher probability of being malnourished in a Spanish multicentre study^[11]. Prevalence of malnutrition was 11.4% in our study. Younger age and outpatient-based characteristics might explain detection of lower prevalence of malnutrition in our study.

MUST, MNA, NRS-2002 and SGA are malnutrition scales that have been used in daily clinical practice and studies^[14]. In a study of 134 participants, there was fair agreement between the SGA and MNA,

with MNA identifying more "at-risk" patients and the SGA better identifying existing malnutrition^[15]. In another study, the sensitivity and specificity of MUST were 61% and 76%, respectively, when SGA was used as the gold standard^[16]. We found lower prevalence of malnutrition with MNA and MUST compared to SGA.

In our study, we also assessed the differences between the items of SGA on their effects on malnutrition. Weight loss, change in dietary intake and diminished physical activity were the parameters in SGA^[4]. We found that malnutrition was significantly associated with weight loss, change in dietary intake and diminished physical activity; and our logistic regression model revealed that change in dietary intake and diminished physical activity increased malnutrition risk by 29.2 and 4.4 times, respectively.

It appears prudent to adopt a higher normal reference value for BMI in diabetic patients than what is currently used for the general population. A BMI between 24 and 29 kg/m² has been suggested as an ideal cut off value to be used in elderly patients admitted to hospital in order to avoid underestimating malnutrition; however, adjustments have not been made for the presence of diabetes^[17]. We found that BMI ≤ 30.35 kg/m² was the cut-off for malnutrition, and this figure agreed with a Spanish study on malnutrition in elderly diabetic patients where 15.5% of the malnourished subjects and 31.9% of those at risk had a BMI ≥ 30 kg/m²^[11]. Lower fat%, mid-arm circumference and calf circumference are related with malnutrition^[14]. In agreement, we found that BMI, fat%, mid-arm circumference and calf circumference were significantly lower in patients with malnutrition. An increased number of subjects in our study sample had a BMI within the overweight or obese ranges, as would be expected in a type 2 diabetic population. We developed a logistic regression model using BMI ≤ 30.35 kg/m² as an independent predictor for malnutrition, and found that malnutrition increased 1.7 times in diabetic patients who had a BMI ≤ 30.35 kg/m². Ideal fat% is 23.6 according to Jackson & Pollock in our patient groups^[18,19]. We found a cut-off value as fat $\leq 35.85\%$ in diabetic patients for malnutrition screening. Malnutrition increased 2.9 times in diabetic patients who had a fat% $\leq 35.85\%$.

There is no study about relation between malnutrition and HbA1c level in diabetic patients. We found that malnutrition increased 3.7 times in diabetic patients who had a HbA1c ≥ 8.69 mmol/mol. It needs to be clarified whether uncontrolled DM causes malnutrition or vice versa.

Albumin is one of the most frequently used parameters in the evaluation of nutritional status.

There is a close association between serum albumin levels and malnutrition^[1]. In agreement, albumin was significantly lower in patients with malnutrition in our study.

Association of malnutrition with gender is controversial^[11,13]. Malnutrition was not associated with gender, smoking and oral antidiabetic drugs/insulin in our study, and this finding agreed with a study from Belgium^[13], although it did not agree with another one^[11].

Association between disease duration and malnutrition varies according to the studied group of patients in the literature. In one study, malnutrition prevalence was higher in patients having diabetes for more than 10 years compared to those having diabetes for less than 10 years, and this condition has been associated with complications of diabetes^[11]. An increased prevalence of malnutrition has been described in patients with nephropathy and diabetic foot ulcers^[20,21]. In our study, there was no association between diabetes duration and malnutrition. This may have been due to the shorter duration of diabetes in our patient.

We found in this study that a higher cut-off for BMI and fat% may be necessary to rule out malnutrition in type 2 diabetic patients. A HbA1c < 8.69 mmol/mol had a NPV of 92% for malnutrition. We also found that change in dietary intake and especially diminished physical activity were independent predictors of malnutrition in this population, with an odds ratio of 29.2 and 4.4 respectively.

CONCLUSION

Type 2 diabetic patients are often obese and thus, a higher cut-off for BMI and fat% may be necessary to detect malnutrition. Poor glucose control, decreased fat%, change in dietary intake and especially diminished physical activity are independent predictors of malnutrition in this population.

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Ali Tamer monitored the patients, participated in study design, statistics and coordination and helped to interpret the data and to draft the manuscript. Mustafa Volkan Demir participated in data analysis and interpretation and wrote the manuscript. Hakan Cinemre, Tezcan Kaya and Ahmet Nalbant participated in the study design and statistics, oriented the data collection and revised the manuscript critically. All authors read and approved the final manuscript.

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Original Article

New Protocols for Treatment of Class IV Lupus Nephritis with Emphasis on Rituximab as the Sole Maintenance Therapy

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ABSTRACT

Objective: A safe and effective treatment for lupus nephritis (LN)

Design: An 8-year prospective study

Setting: Hospital-based

Subjects: Three groups of patients with class IV LN; comparison of 2 new treatment-protocols for class IV LN with a retrospective group of patients who had received the standard treatment for LN

Intervention: The 2 treatment groups had received an induction phase of monthly intravenous Cyclophosphamide, Mycophenolate (MP) and Prednisone (P). The maintenance phase in the first group was only MP and P, while patients in the second group had received only yearly Rituximab infusions.

Main outcome measures: Morbidity and mortality

Results: Patients in the first group did not have significant

relapses, yet had 10 episodes of infections during the maintenance phase. In the second group, there were five treatment failures, yet none had renal deterioration, infections or death. In the third group, seven relapses occurred during the induction period and three in the maintenance one. Moreover, complications included 1 death of disseminated sepsis, 12 cases of chronic renal failure, three kidney losses, 16 episodes of major infections, two cases of aseptic necrosis, two cases of gonadal failure, two cases of hemorrhagic cystitis and 2 cases of retinal deposits.

Conclusions: Rituximab infusions, used once yearly, are effective and a safe maintenance therapy for most patients with LN after a short course of three anti-proliferative agents. In those who failed to respond, MP and P are more effective and safer than the standard protocol.

KEY WORDS: nephritis, rituximab, systemic lupus erythematosus, treatment

INTRODUCTION

Lupus nephritis (LN) is a common disease in our area, as it represents 12% of those biopsied for glomerulopathy with a calculated incidence of 6.5 per 100,000 in adult female Kuwaiti nationals^[1]. It is one of the most serious complications of systemic lupus erythematosus (SLE) since it is a major predictor of poor prognosis^[2]. Previous and standard treatment protocols included 3 - 6 months of high dose corticosteroids and either cyclophosphamide (Cyclo) or mycophenolate mofetil (MP), followed by maintenance therapy with MP, small dose prednisone

(P) and hydroxychloroquine^[3-8]. Those protocols were associated with malignant potentials and significant infectious complications viz. bacterial, fungal and cytomegalovirus^[9-11]. Gonadal failure was a particular risk with Cyclo use, and osteoporosis as well as aseptic necrosis with P^[9-11]. Since LN is a chronic disease, induction and maintenance therapy should be safe, efficient and tolerable to improve the patient's compliance and survival. Those were the basis of testing two new protocols of using all the three anti-proliferative agents (P, Cyclo and MP) for a relatively short induction phase of 3 months to limit their

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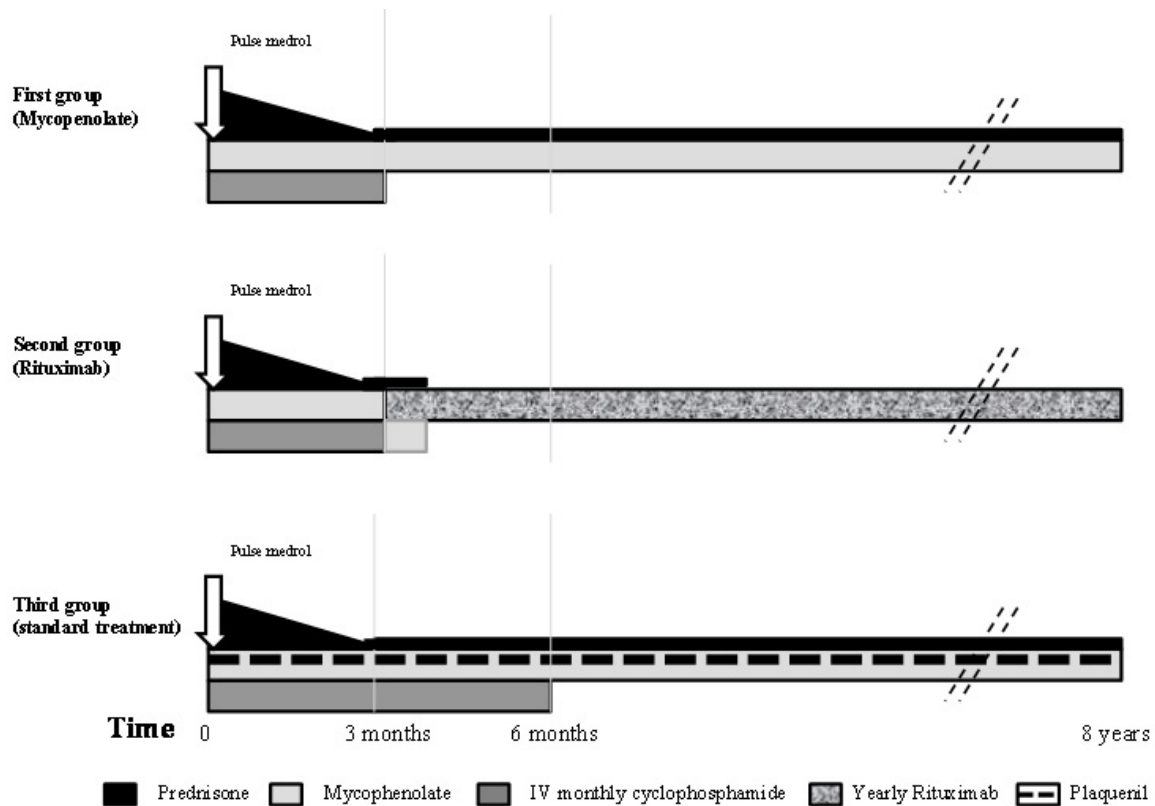


Fig 1: Study design of the 3 treatment groups

cumulative long-term side effects, followed by either MP with a small dose of P or yearly Rituximab (R) infusions as the sole maintenance in the second.

SUBJECTS AND METHODS

The study started from 1st January, 2008 until 31st December, 2015. It included all patients who had their first attack of class IV LN. The latter was defined as: (a) kidney biopsy showing diffuse segmental or global endo- or extracapillary glomerulonephritis involving >50% of all glomeruli; (b) all patients showed diffuse wire loop deposits with or without fibrinoid necrosis and/or cellular crescents; (c) immunofluorescent stains were positive for immunoglobulin G (IgG), IgM, IgA and complement C3; (d) patients with already high chronicity index at the time of biopsy viz. sclerotic glomeruli, fibrous crescents, tubular atrophy, and interstitial fibrosis were excluded from the study^[12].

Study design

All patients received induction therapy with 1 g of intravenous solumedrol for 3 days, followed by P at 1 mg/kg/day for 1 month to be tapered down to 5 mg daily by the 3rd month. Moreover, they received Cyclo infusions at 1 g/m² every month for 3 consecutive months and oral MP. The latter was started at a dose

of 250 mg every 12 hours and was adjusted higher gradually, upto a maximum of 1 g twice daily, if total peripheral leucocytic count remained above 4x10⁹/L. Subsequently, patients were assigned, at random, to either of two maintenance groups. In the first (MP) group, the maintenance regimen consisted of P 5 mg daily in addition to 1 g of MP twice daily. In the second (R) group, two infusions of 1 g of R were given two weeks apart. One month later and once CD20 levels were confirmed to be <0.5% of total lymphocytes by flow cytometry^[13], MP and P dose was reduced to 1/2 and both drugs were discontinued one month later. Patients in the R group received the same R dose every year as the sole maintenance immunosuppressive therapy. Moreover, these two groups were compared with a third retrospective group of 63 of our previous patients, with the same inclusion criteria, who had received a standard treatment for LN and were followed for eight years prior to the current study. Their standard treatment consisted of six months of 1 g/m² of IV Cyclo and 1 g solumedrol for 3 days, followed by 1 mg/kg/day of P for 1 month to be tapered down to 5 mg daily by the 3rd month. This induction phase was followed by a similar maintenance dose of MP, P and hydroxychloroquine. The latter was administered as 200 mg twice daily. The study design is summarized in

Fig 1. The study was approved by the Health Science Center Ethical Committee of Kuwait University and Ministry Of Health (Re: VDR/EC/2508).

Technique of R administration

Patients were pre-medicated with two 500 mg Paracetamol and one Piriton tablets, followed by an infusion of 125 mg of Solumedrol in 50 ml of D5W over 30 minutes before infusions. The 100 ml of 1 g of R was diluted in 400 ml of normal saline leading to a concentration of 2 mg/ml. The first infusion rate was 20 ml/h for the first 30 minutes, followed by 20 ml increments/30 minute until reaching 100 ml/h, until the total dose is given.

Periodic assessment

Patients were reassessed every two months for disease activity both clinically and by routine laboratory investigations, which included complete blood count and serum estimates of glucose, renal, liver and lipid function tests as well as urine routine. Twenty-four hour urine collections for assessment of creatinine clearance (Cr Cl) and daily urinary protein output (UPO) were done after the end of the induction phase, and every six months during the maintenance phase. Testing for serum complements (C3 & C4) and anti-double stranded DNA (dsDNA) was conducted at months 1, 4, 8 and 12 for the first year only. In a similar fashion, CD20 level was tested for patients in R group. In the subsequent years, serum complements and anti-dsDNA tests were done twice per year, or if clinical or laboratory assessment indicated new activity. Statistical analysis of repeated measurements of Cr Cl and UPO was used to assess kidney function, and C3 as well as anti-dsDNA are measures of immunological activity of LN^[2].

Renal deterioration was defined as any 20% decrease in Cr Cl or 50% increase in serum creatinine and/or doubling of daily urinary protein excretion.

Statistical analysis

The SPSS statistical package version 21 was used for data entry and processing. The p-value <0.05 was used as the cut-off level for significance. Mean and standard deviation were used to describe the normally distributed variables viz. age and duration of lupus disease before LN. Since duration of treatment was not normally distributed, it was expressed as a median (interquartile range) and the Kruskal-Wallis test was used to assess the difference between the 3 groups. Analysis of variance (ANOVA) with repeated measures was used to examine the difference between the groups and within the groups on follow up, using means, of the normally distributed C3, anti-dsDNA and Cr Cl, while the non-parametric Kruskal-Wallis

and Wilcoxon Signed Ranks test were used for the difference between the groups of UPO since it was not normally distributed.

RESULTS

The demographical data on patients in the 3 groups are summarized in Table 1. They were all adult Asians. There was no statistical difference between the three groups with regards to gender, age, duration of disease before development of LN, and their length of treatment.

Table 1: Baseline characteristics of patients with class IV LN in the three treatment groups

Characteristic of groups *	Group MP n = 56	Group R n = 58	Retrospective n = 63
Gender (Female/Male)	52/4	54/4	59/4
Age (years)	25.6 ± 5	25.8 ± 5	25.6 ± 4
Duration of SLE prior to LN	12.7 ± 4	12.4 ± 4	11.7 ± 5
Duration of treatment	49 (23-75)	48 (20-76)	45 (13-77)

* No statistical difference between the three groups

SLE: systemic lupus erythematosus; LN: lupus nephritis; R: rituximab; MP: mycophenolate

Periodic assessment

The details of the means of Cr Cl, C3 and anti-dsDNA titers, as well as medians of UPO of the 3 groups at baseline, 3 months, 2 years and 5 years is displayed in Table 2. Statistical analysis of the differences between the groups and response to treatment at those time-intervals is shown in the lower row of the table. Moreover, Fig 2 shows the changes in the activity markers (C3 and anti-dsDNA) as well as the kidney function (Cr Cl and UPO) over the study period. As seen in both, there was no statistical difference between the 3 groups with regards to their initial Cr Cl, UPO, C3 and anti-dsDNA titers. However, subsequent follow up data showed the following results:

1. The initially high activity parameters of LN viz. C3 and anti-dsDNA declined at 3 months in all patients, yet the decline was more in those in groups 1 and 2 compared to group 3 (p <0.001). As expected, the difference between patients in groups 1 and 2 who had received similar induction therapy was not significant.
2. The initially low Cr Cl and high UPO improved by the 3rd month, yet such improvement was more in groups 1 and 2 compared to group 3 (p <0.001). The difference between patients in groups 1 and 2 was not significant.
3. Improvement in Cr Cl and lowering of anti-dsDNA levels were maximal in all groups by the 3rd month. Further improvement in C3 and UPO were evident upto 1 year in patients in groups 1 and 2. Patients

Table 2: Results of laboratory and serological assessment during follow up of the three groups of LN

Variable*	Baseline				3 months				2 years				5 years			
	Cr Cl	UPO	C3	DNA	Cr Cl	UPO	C3	DNA	Cr Cl	UPO	C3	DNA	Cr Cl	UPO	C3	DNA
Group I	47 ± 1	2500 (700 - 3900)	55 ± 1	139 ± 2	91 ± 1	1250 (200 - 1800)	95 ± 2	13 ± 7	96 ± 1	300 (100 - 400)	121 ± 1	11 ± 3	101 ± 8	150 (100 - 160)	125 ± 1	11 ± 2
Group II	48 ± 1	2200 (800 - 3800)	56 ± 9	138 ± 2	92 ± 1	1250 (250 - 1900)	93 ± 1	12 ± 6	96 ± 9	155 (100 - 200)	119 ± 1	10 ± 2	102 ± 7	130 (100 - 150)	122 ± 2	11 ± 3
Group III	46 ± 1	2500 (1200 - 3950)	54 ± 9	138 ± 2	68 ± 2	1700 (800 - 2000)	84 ± 2	28 ± 1	70 ± 7	900 (400 - 1100)	85 ± 5	22 ± 6	63 ± 1	1000 (800 - 1600)	84 ± 6	21 ± 6

** Significance (p) NS ←----- GI vs II: NS, GI & II vs GIII: < 0.001 -----→

Cr Cl: creatinine clearance (ml/min.), UPO: urinary protein output (mg/day), C3: serum complement 3 (mg/dl), DNA: anti-dsDNA (IU/ml), NS: not significant

Normal levels of C3: > 79 mg/dl, anti-dsDNA: < 20 IU, Cr Cl: > 80 ml/minute and UPO: < 150 mg/day.

* All variables are expressed in mean ± SD except for UPO in median (range)

** Significance: if p-value is < 0.05

in group 3 had similar improvement in UPO by year 1, but not in C3 levels.

- Further improvement in Cr Cl, UPO, C3 and anti-dsDNA levels persisted until the end of the study in groups 1 and 2. However, in group 3, Cr Cl and UPO deteriorated with time. Their C3 levels and anti-dsDNA remained stable, yet remained above normal (Fig 2).

Cr Cl decreased by >20% in 12 patients in group 3 compared to none in the two prospective groups.

Complications in the MP group

As seen in Table 3, only one minor relapse occurred in a patient during the induction phase that was easily treated with a second 3-day treatment with 1 g IV solumedrol, followed by an increase in the dose of P to 1 mg/kg/day for 1 month to be tapered gradually over three months again. Subsequently, all patients enjoyed a stable treatment without relapse, significant

Table 3: Complications in the three treatment groups of class IV LN

Complications	Group MP n = 56	Group R n = 58	Retrospective n = 63
Induction relapse	1	1	3*
Maintenance relapse	0	5*	7*
Treatment failure	0	3*	3*
Side effects:			
Autoimmune	0	2*	0
Infections	10*	0	16*
Renal failure	0	0	12*
ESRD	0	0	3*
Death	0	0	1*
Aseptic necrosis	0	0	2*
Gonadal failure	0	0	2*
Hemorrhagic cystitis	0	0	2*
Retinal deposits	0	0	2*

*: major incidents

R: rituximab, MP: mycophenolate, ESRD: end stage renal disease

renal damage or death during the maintenance phase. However, 10 episodes of infections were encountered. They were herpes zoster (n = 3), Epstein Barr virus (n = 2), cytomegalovirus (n = 4), and fungal chest infection (n = 1).

Complications in R-group

Again, only 1 minor relapse occurred in a patient during the induction phase that was easily treated as in the first group. Unfortunately, three patients could not tolerate the initial R infusions for allergic reactions. They were treated as patients in the first group, yet were excluded from the study. Out of the 58 patients who tolerated R initially, 5 had minor complications. One had an allergic reaction to the R infusion given one year later, and hence was shifted to maintenance therapy with MP and P and was excluded from the study. Two patients developed active SLE 3 and 4 months after R infusions in the first year, and hence were considered R-failure and excluded from the study. They were retreated with the same initial induction therapy yet without Cyclo and were kept on the same maintenance protocol of the first group. The 4th patient relapsed within 1 month following conception that developed two months into her second year of R therapy after an unplanned pregnancy. She was retreated with 1 g solumedrol for three days, followed by 1 mg/kg/day of P for 1 month to be tapered down to 5 mg daily by the 3rd month, followed by a tapering dose of P in addition to Imuran 100 mg daily. Subsequently, she was retreated with R after delivery without any relapse for 48 months. The 5th patient had a minor relapse after her self-medication with an oral contraceptive. She also had received induction therapy without Cyclo for three months followed by R-maintenance, without any subsequent relapse

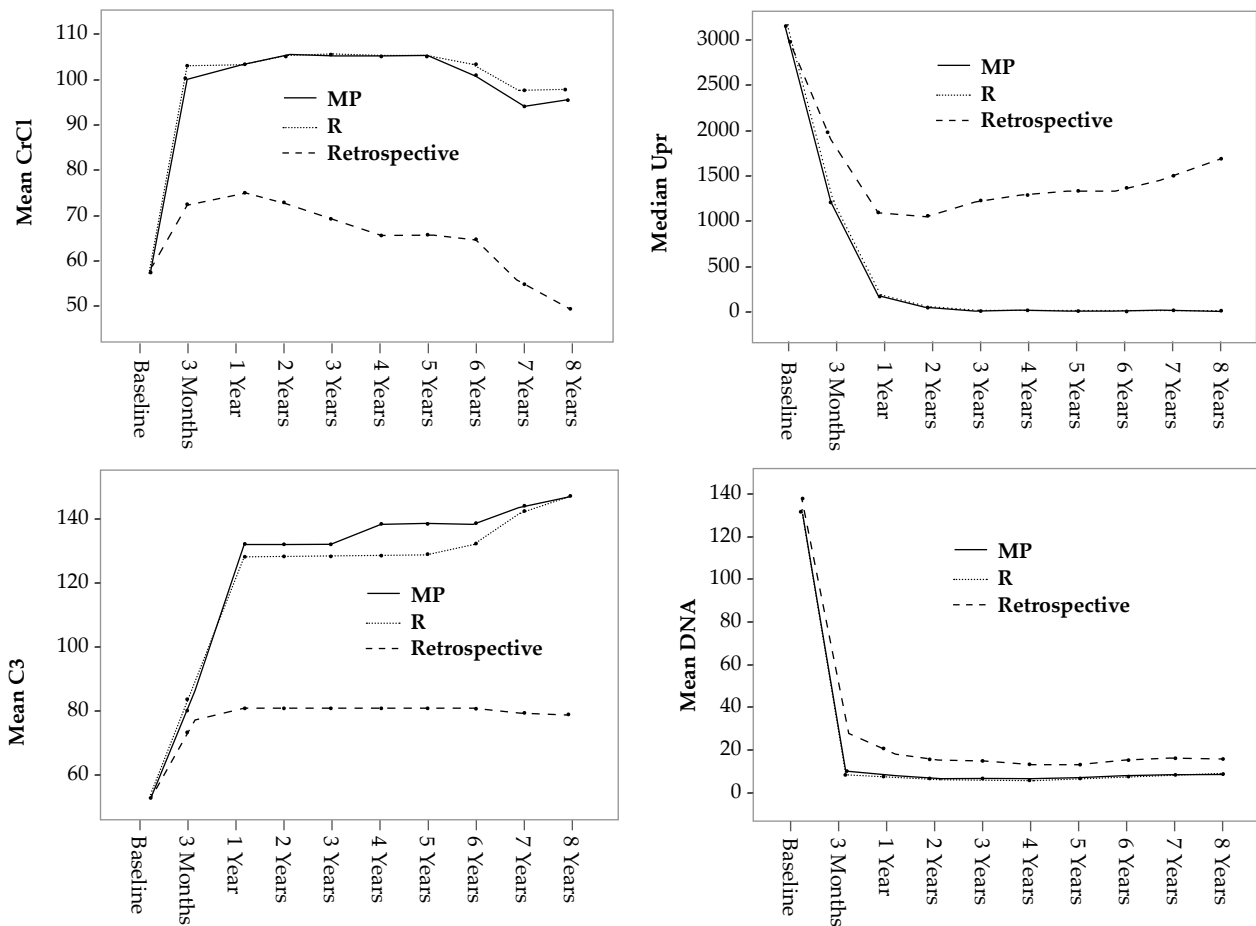


Fig 2: Changes from baseline to the end of the study (year 8) in C3, anti-dsDNA, Cr Cl and UPO in the 3 treatment groups of LN. Normal levels of C3: > 79 mg/dl, anti-dsDNA: < 20 IU, Cr Cl: > 80 ml/minute and UPO: < 150 mg/day.

for nearly 36 weeks. The cumulative number of patients at the end of each year was as follows: 7+15+22+28+32+40+46+55. Hence, 46 patients had completed 2 years and 28 had completed five years on such prophylaxis without signs of SLE activity, renal deterioration, infections or serious side effects of treatment, as described in Table 2. However, two patients had autoimmune side effects within four weeks of R infusions viz. arthritis and hemorrhagic colitis. They responded to four weeks treatment with P without any recurrence. In the R group, five patients also had antiphospholipid syndrome. They were controlled with R and warfarin without any difference from others.

Lymphocyte subpopulation in R group

As expected, none of the patients had a significant reduction in their total circulating lymphocyte counts, yet all had achieved decline of their initially normal CD20 to <0.5% one month after the first infusion. CD20 cells were not adequately suppressed in those who had developed active LN after R treatment, while the rest

had achieved adequate suppression at 8 months (n = 32) and at 12 months (n = 14).

Pregnancy while on R prophylaxis

Despite our clear instructions to avoid pregnancy as well as oral contraceptives and to use intrauterine contraceptive devices in married females, four pregnancies occurred during the study. Two patients had conceived in the second year after rituximab treatment and one in the fourth. Of the first two women, one had relapsed one month later and her management was described previously. The other one did not have complications, and she conceived again 2 years later. The first two conceptions occurred two months after the last R infusions, while the other two were four and six months later. In those patients, azathioprine at a dose of 1-2 mg/kg/day was added to avoid relapse of LN. Except for the one patient who had developed a relapse, the other three pregnancies progressed normally without flare of LN and all were delivered, as planned, at 36 weeks. Their siblings were healthy and remained so until the end of the study.

After delivery, the R infusions were resumed as scheduled initially.

Complications in the retrospective group

In this group, three relapses occurred in the induction phase and seven in the maintenance phase. They required an additional IV solumedrol, major increment of P and even repeating Cyclo pulses for an extra 3 months. Despite those efforts, 12 patients had renal failure, three patients lost their kidneys and one had died of fulminant sepsis. Infections were common and included herpes zoster (n = 5), severe bacterial sepsis (4), pneumocystis carinii (3), fungal infection (n = 3) and unlocalized fulminant sepsis in one patient. Moreover, gonadal failure was confirmed by persistent high luteinizing hormone and follicle stimulating hormone in two patients who had a total dose of nine months of Cyclo infusions. Those two patients also had recurrent hemorrhagic cystitis. In this group, osteoporosis was common despite early treatment with calcium and vitamin D. Moreover, one patient had a bilateral hip replacement and another one had bilateral knee replacement for aseptic necrosis. Two patients had significant retinal deposits which were attributed to hydroxychloroquine.

Ancillary medications

The diuretics (lasix ± aldactone) were rarely used beyond the induction period (first three months) in the two prospective groups contrary to the retrospective one. In the prospective groups, antihypertensive drugs used in the initial induction period were discontinued on follow up except in 2 patients. However, angiotensin converting-enzyme inhibitors or angiotensin II receptor antagonists were used in 28 patients during the induction period and were kept subsequently for kidney protection.

DISCUSSION

Knowledge of the specific immunopathogenesis of LN is essential in planning its induction and maintenance therapy. In susceptible individuals suffering from SLE, *in situ* formation and deposition of immune complexes (ICs) from apoptotic bodies occur in the kidneys due to an amplified epitope immunological response. IC glomerular deposits generate the release of pro-inflammatory cytokines and cell adhesion molecules, causing inflammation. This leads to monocytes and polymorphonuclear cells chemotaxis. Their subsequent release of proteases generates endothelial injury and mesangial proliferation. The presence of ICs promotes adaptive immune response and causes dendritic cells to release type I interferon. The latter induces maturation and

activation of infiltrating T cells, and amplification of Th2, Th1 and Th17 lymphocytes. Each of them amplify B cells and activates macrophages to release more pro-inflammatory molecules, generating effector cells that promote kidney epithelial proliferation and fibrosis^[14]. Hence, in our two prospective groups, three potent anti-proliferative (cytotoxic) agents viz. high dose corticosteroids, Cyclo and MP were used simultaneously to treat active LN in the induction phase, since multiple effector cells are involved. MP was added to the standard protocol since it was shown to be as effective as Cyclo as an antiproliferative agent in induction phase of non-renal lupus^[15]. The combination of the three agents proved to be a potent tool in limiting disease activity (decline in C3 to <0.97 mg/dl and high anti-dsDNA levels >20 IU/ml) and preservation of kidney function (Cr Cl >80 ml/minutes and low UPO). This combination therapy resulted in less early and late relapses in the two prospective groups as compared to the retrospective one. Limiting such relapses was clearly associated with better kidney survival and less need for repeating corticosteroid and even Cyclo pulses. The latter may explain the lack of infections in the R group and limited non-infectious complications in the MP group.

Since B lymphocytes are the most essential in maintenance of SLE, glomerular damage and fibrosis, R was tested solely for such phase in one group, since it is a potent cytotoxic agent only to mature B-lymphocytes^[16]. R is a chimeric human/mouse monoclonal antibody that binds avidly to CD20 antigen expressed on normal differentiated B-lymphocytes, but not stem cells or plasma cells. It destroys the B-cell by multiple mechanisms, including complement-dependent cellular cytotoxicity, induction of apoptosis and sensitization to other chemotherapeutic agents^[16]. Such a potent therapeutic effect is associated with limited mild to moderate infusion-related reactions; hence, it has to be administered slowly over hours^[17]. Moreover, the clinical remission induced by R may persist beyond the effect of peripheral B-cell ablation, since alteration of memory cells has been reported up to six years^[18]. The latter character, its long-lasting efficacy (months) and safety were the bases of our protocol for selecting such an agent as a sole maintenance therapy in one group of our study. However, R-use was limited in three patients by its infusion reactions. Interestingly, one more patient developed allergic reactions one year later, indicating the possibility of encountering the rare antibody formation^[19]. Overall, two patients failed to achieve sustained remission with R and had to be shifted to maintenance treatment with

MP and small dose P. The latter indicates the limited efficacy of R in certain patient's population and confirms the heterogeneity of SLE disease in different patient population^[20]. Despite our explicit instruction regarding contraception, few accidental pregnancies were encountered after the second month of treatment with R. Fortunately, there were no significant side effects on the mother or fetus^[21]. However, one patient developed relapse after conception and another one after an accidental use of oral contraceptives, indicating the risk of disease activation in those situations.

Hydroxychloroquine was recommended for treatment of LN^[22], yet it was avoided in our two prospective groups, since we believed that our protocol could offer adequate maintenance immunosuppression without the added risk of its retinal disease^[23].

Two previous randomized and controlled trials in extra-renal SLE (The EXPLORER study) and LN (LUNAR study) have questioned the role of R in treatment of SLE and claimed its failure to improve the clinical outcomes after 1 year of therapy^[24,25]. Contrary to our study, the drug was used in the induction phase, which may explain its limited efficacy. Interestingly, despite its limited role in their induction therapy, the authors have described fewer flares in those treated with R in the first study, and more responders as well as greater reductions in anti-dsDNA and C3/C4 levels in the second. In our protocol, we limited R-use to the maintenance phase, based on the essential role of B-lymphocytes in disease progression and not in the active phase of LN^[26-29].

CONCLUSION

Our study describes an efficient and safe three-month induction therapy with three anti-proliferative agents in treatment of active LN. Moreover, it has shown that R is an effective maintenance therapy for this chronic autoimmune disease. With its ease of administration, as once yearly, the drug will improve patient's compliance and will limit the long-term infectious and non-infectious side-effects of Cyclo, MP, azathioprine, P and hydroxychloroquine. However, nephrologists should be aware and patients should be informed about its limitations in some patient population. If so, the MP-protocol as in the first treatment group is the best alternative.

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Case Report

A Rare Case of Eosinophilic Cholecystitis

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ABSTRACT

Eosinophilic cholecystitis is a rare form of cholecystitis. It is characterised by eosinophilic infiltration of the gallbladder. The etiology is not completely understood, but many hypotheses have been made. Presentation is similar to typical cholecystitis and histopathology

remains the mainstay for diagnosis. Surgery is the treatment of choice. We report a case of eosinophilic cholecystitis presented as recurrent acute attacks of cholecystitis and laparoscopic cholecystectomy was performed.

KEY WORDS: acalculous cholecystitis, eosinophilic cholecystitis

INTRODUCTION

Eosinophilic cholecystitis (EC) is a rare inflammatory condition of the gallbladder. It is diagnosed when the cellular infiltrate of the gallbladder wall is composed of more than 90% eosinophils^[1]. It is an uncommon condition that was first described in 1949^[2]. The etiology of EC is not completely understood, but might be associated with hypersensitivity to antibiotics, other drugs, herbal medicines, hepatic echinococcosis, or as a variant of eosinophilic gastroenteritis^[3,4]. We report a case of EC in which a specific cause could not be identified.

CASE REPORT

A 55-year-old woman, with a known case of bronchial asthma, presented to the emergency department complaining of abdominal pain. The pain was epigastric, radiating to the right upper quadrant and right shoulder. It was associated with nausea and vomiting for two days. This was her third attack over one year, during which she was investigated by abdominal ultrasound that showed thickened wall of the gallbladder with no stones. The patient also underwent upper gastrointestinal endoscopy that showed gastritis, and a biopsy was taken which revealed moderate chronic gastritis that was negative for *H. pylori* and intestinal metaplasia. She also

underwent lower gastrointestinal endoscopy with normal findings. The general examination of the patient revealed a good general condition with no jaundice. Abdominal examination showed positive Murphy's sign. Laboratory analysis showed eosinophil of 1.4 (RR: 0.02 – 0.5 10⁹/L) and alkaline phosphatase of 124 (RR: 22– 88 IU/L), which were elevated in her previous tests also. An abdominal ultrasound was performed and showed a picture of acalculous cholecystitis with positive sonographic Murphy's sign (Fig. 1). The patient was admitted for further evaluation. A CT scan of the abdomen with intravenous contrast was performed, which also showed a picture of acalculous cholecystitis (Fig. 2). The case was discussed with the patient and cholecystectomy was offered, for which she agreed. A laparoscopic cholecystectomy was done and showed mildly thickened gallbladder wall with no stones. The histopathological examination showed eosinophilic cholecystitis (Fig. 3 A and B). The patient did well post-operatively; and on follow-up, she was free of any abdominal pain.

DISCUSSION

Eosinophilic cholecystitis is an uncommon form of cholecystitis, with an incidence ranging from 0.25 – 6.4% in cholecystectomy specimen^[5]. It has a clinical presentation similar to typical cholecystitis, with right

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Fig 1: An ultrasonography of the abdomen showing mildly thickened gallbladder wall



Fig 2: A CT scan of the abdomen showing the same ultrasonography findings

upper quadrant pain and an elicited Murphy's sign. In clinical practice, EC is clinically indistinguishable from the most common form of acute cholecystitis^[5].

Although the etiology of EC is obscure, a literature review showed that most patients with EC had an idiopathic etiology^[3,6]. Eosinophils are one of the immune system white blood cell components responsible for combating multicellular parasites and infections in vertebrates. Along with mast cells, eosinophils also control the mechanisms associated with allergy and asthma. An increase in eosinophils typically occurs in people with parasite infection of the intestine, collagen vascular disease (rheumatoid arthritis), malignant disease (Hodgkin's disease), extensive skin disease (exfoliative dermatitis), Addison's disease, and the use of certain drugs (penicillin)^[7]. In patients with eosinophilic infiltrate affecting other organs and tissues or as a part of a syndrome (Eosinophilic granulomatosis with polyangitis, also known as Churg-Strauss Syndrome), it has been reported that the disease can be divided into three stages: first, a prodromal stage characterized by asthma and allergic manifestations; second, eosinophilic infiltration into tissue, predominantly the lungs and myocardium; and finally, a systemic stage, associated with the development of necrotizing vasculitis^[8]. Regarding imaging tests, ultrasound results may be normal or show signs suggestive of cholecystitis (gallbladder distension, wall thickening, perivesicular liquid or sonographic Murphy's sign). A CT scan may reveal similar features, with perivesicular oedema or decreased attenuation in adjacent liver, indicative of perihepatitis^[9]. Histopathology remains the mainstay for diagnosis of EC as there is no specific clinical presentation^[10]. The treatment of choice is cholecystectomy^[10]. However, steroids can be used as a treatment and good symptomatic response has been reported, especially if it is associated with gastroenteritis. Sphincterotomy can also be done if the case is associated with ampullary stenosis^[11].

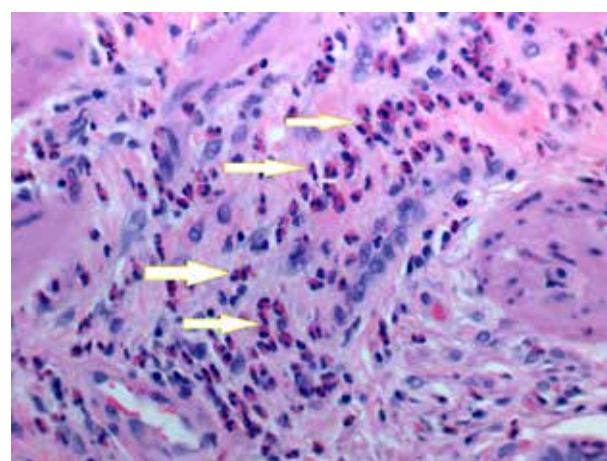
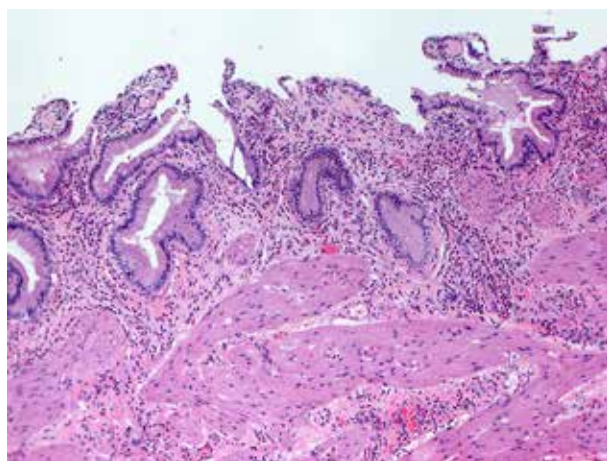


Fig 3 A and B: The histopathological examination (stain=hematoxylin and eosin stain) showing (A) dense eosinophilic infiltration of the gallbladder wall, (B) A magnified slide (40x)

CONCLUSION

Eosinophilic cholecystitis is a rare form of cholecystitis in which the etiology is not completely understood. The diagnosis is made by histopathology and cholecystectomy remains the treatment of choice.

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Case Report

Unstable Angina as the First Manifestation of a Relapse in Polyarteritis Nodosa

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ABSTRACT

Coronary involvement with polyarteritis nodosa (PAN) has been identified in post-mortem studies, yet rarely in clinical practice. We report a 38-year-old woman who presented with unstable angina for two days. She had a history of PAN and had received immunosuppressive therapy for two years, six years ago. Her initial ECG showed ST depression in most leads. Troponins were not elevated. Coronary arteriography revealed multiple aneurysms and stenotic

lesions without obstruction. She also had anemia and progressive renal failure, indicating acute flare of PAN. She was treated with infusions of heparin, nitroglycerin, and oral Clopidogrel. Moreover, she received three daily infusions of 1 g solumedrol, followed by tapering dose of prednisone and three monthly 1 g Cyclophosphamide infusions, followed by Mycophenolate 1 g twice daily. She improved and remained stable for the next two years.

KEY WORDS: arteriography, coronary arteritis, polyarteritis nodosa, vasculitis

INTRODUCTION

Polyarteritis nodosa (PAN) is an autoimmune, systemic, inflammatory vasculitis that results in transmural fibrinoid necrosis with surrounding inflammation in small and medium-size vessels^[1]. It is a rare disease with an annual incidence of 2.4 per million^[2]. It typically presents with generalized fatigue, myalgia, testicular pain and arthralgia, mononeuritis multiplex as well as renal and mesenteric ischemia. At autopsy, vascular involvement with arteritis, thrombosis, dissections, aneurysms, and stenosis was evident in 79% of kidneys and 62% of coronary arteries^[3,4]. However, ischemic heart disease is rarely reported as the initial manifestation of the disease or its relapse^[5-7]. In this case report, we describe a young woman who presented with unstable angina that preceded her relapse with PAN.

CASE REPORT

A 38-year-old woman was admitted with recurrent retrosternal chest pain for two days. The pain had progressed rapidly from few minutes to 30 minutes

and lately even at rest. The ECG on admission showed ST depression in most leads (Fig 1), yet repeated serum troponin were not elevated. Her pain regressed after intravenous (IV) nitroglycerin and unfractionated heparin as well as oral aspirin and Clopidogrel. Review of her past medical history revealed that she had PAN six years ago. At that time, she had recurrent abdominal pain, weight loss and progressive renal failure with serum creatinine of 570 $\mu\text{mol/L}$ at presentation. Diagnosis of PAN was established by a kidney biopsy that showed leukocytoclastic vasculitis. At that time, she was treated with pulse Methylprednisone (1 g IV daily for three days) followed by Prednisone 1 mg/kg daily. Subsequently, the dose was tapered down gradually after the first month to 5 mg/day by the sixth month. The latter was maintained for a total of two years. In addition, she had received 1 g of Cyclophosphamide infusions on a monthly basis for three consecutive months. Subsequently, she received Azathioprine 1 mg/kg daily for 21 months. She improved clinically, and serum creatinine fell to 180 $\mu\text{mol/L}$ and albumin returned to normal by the end of the third month. The

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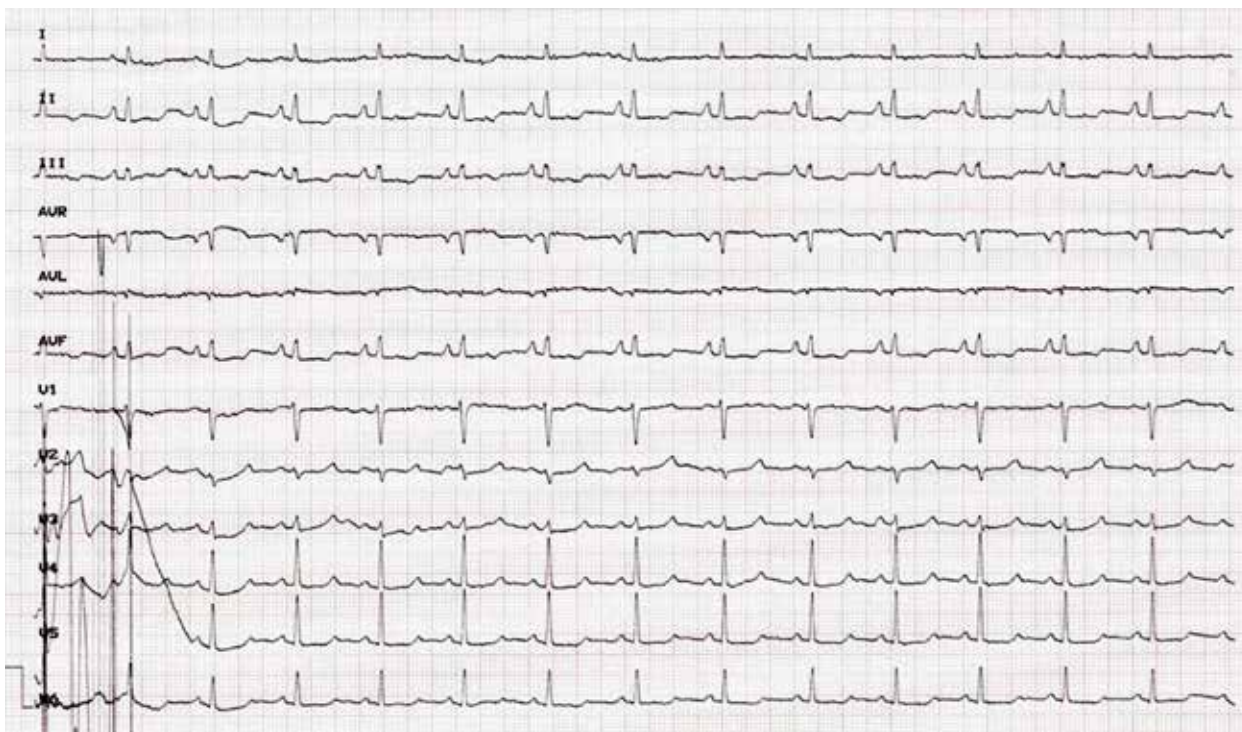


Fig 1: ECG showing ST-segment depression and T-wave inversion in leads I, II, III, AVF, and V3-6

patient did not have a history of hypertension, diabetes mellitus, dyslipidemia, or smoking.

At the present admission, her physical examination did not show any abnormality. However, she had normocytic normochromic anemia with hemoglobin at 105 g/L. Her biochemical profile showed increase of

serum creatinine to 360 $\mu\text{mol/L}$ and decrease of albumin to 25 g/L. Urine showed 2 (+) proteinuria and excess red cells per high power field, yet without pyuria. A transthoracic echocardiography did not show significant valvular or wall-motion abnormalities. Due to her age, unstable angina and history of PAN, she was subjected to coronary angiography. The latter showed multiple aneurysms and stenotic lesions in all coronary arteries (Fig. 2 & 3). MRI scanning excluded involvement of the aorta and its major branches. She received the

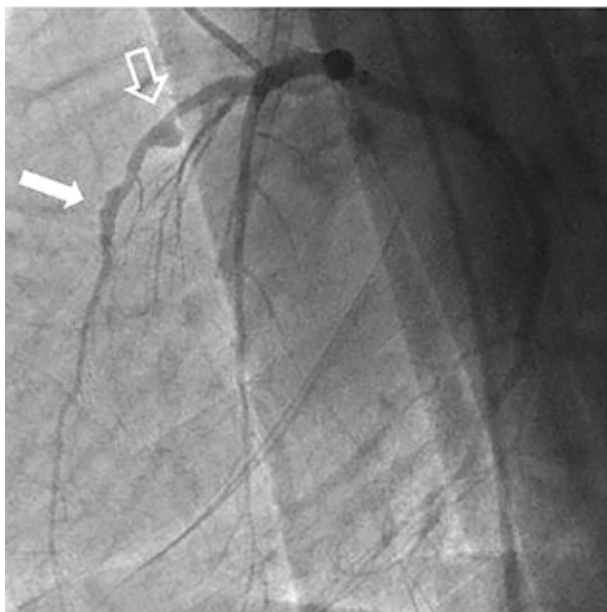


Fig 2: Left lateral projection of the left coronary system showing eccentric aneurysmal dilatation of the anterior descending artery (open arrow) after first septal branch and diagonal branch, followed by irregularities in the mid segment. The vessel tapers distally towards its apical part

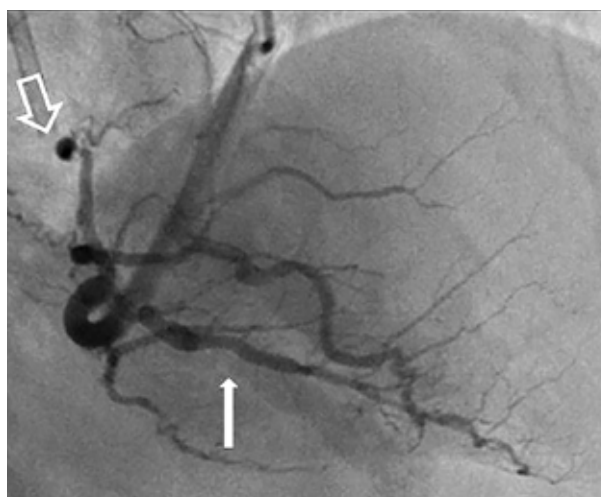


Fig 3: Left lateral projection of the right coronary system showing normal main trunk and irregularities of the posterior descending branch (solid arrow) as well as a localized aneurysmal dilatation (open arrow)

same corticosteroid therapy and Cyclophosphamide. However, in view of the recurrence of her vasculitis and the potentially fatal coronary lesions, a more powerful immune-suppressive regimen was chosen as a maintenance therapy. The latter consisted of oral Mycophenolate mofetil 1 g twice daily for 21 months instead of Azathioprine. She improved clinically, and her serum creatinine fell to 120 $\mu\text{mol/L}$. She remained stable for the last two years.

DISCUSSION

PAN, unlike other vasculitides, is an insidious disease that usually manifests as gastrointestinal bleed/perforation or rapidly progressive renal failure. Florid systemic manifestations or positive antineutrophil cytoplasmic antibodies (ANCA) tests are rare. Diagnosis of PAN rests on radiological investigations and/or the finding of active leukocytoclastic vasculitis with loss of the internal elastic membrane in medium-sized vessels, or at autopsy in unfortunate cases^[1,8,9]. Classic PAN is progressive vascular attacks with focal and acute inflammatory infiltration, followed by fibroblasts proliferation leading to either wall weakness with aneurysmal dilatation and subsequent rupture or dense fibrosis with luminal stenosis and ischemia^[3]. Those angiographic findings of microaneurysm, ectasia, and/or occlusive disease are not pathognomonic of PAN and can be seen in other vasculitides, including rheumatoid vasculitis, Churg-Strauss syndrome, necrotizing angitis associated with drug abuse, and systemic lupus erythematosus^[10]. As in our patient, the correlation of the angiographic features with the clinical findings was essential for establishing the diagnosis of PAN. Cardiac involvement with PAN was studied extensively by Holsinger *et al*^[3]. Hypertension was the most common cardiovascular manifestation of PAN and accounted for 37% of the cases studied, while congestive heart failure was present in 27%. Interestingly, coronary arteritis was described in 62% of the cases studied and 89% of them had histological evidence of myocardial infarction, yet most were clinically silent. As has been described earlier and as the name implies, vascular involvement with PAN is a perivascular disease, contrary to the diffuse disease associated with systemic vasculitides, *viz.* Wegner's or Churg-Strauss^[4]. In the latter ones, the early endocardial involvement and subsequent thickening triggers thrombosis and overt ischemic heart disease during disease activity, contrary to the silent PAN.

In general, survival of untreated or misdiagnosed PAN is grim, with an average survival of only 6 - 12 months after diagnosis^[3,4]. Hence, cardiac involvement justifies immediate and aggressive immunosuppressive treatment in addition to conventional antiplatelet agents as well as bypass surgery for the persistently stenotic lesions^[11].

CONCLUSION

Coronary artery disease is not rare in polyarteritis nodosa.

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Case Report

Neuroleptic Malignant Syndrome Induced by Concomitant Use of Multiple Antipsychotic Drugs: A Case Report

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is a rare but life threatening condition induced by neuroleptic medications. In severe cases, NMS can rapidly lead to death. NMS is reported less frequently since the advent of new antipsychotic drugs.

We discuss a 44-year-old male diagnosed with schizoaffective disorder who presented with NMS induced by multiple antipsychotic drugs.

KEY WORDS: creatine phosphokinase, hyperthermia, hyponatremia

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is an infrequent, but potentially life-threatening neurologic emergency associated with the use of neuroleptic or antipsychotic drugs. Its main symptoms include the rapid onset of fever, severe extrapyramidal symptoms, autonomic nervous system dysfunction, and impaired consciousness^[1]. Incidence rates for NMS ranges from 0.02% to 3% and mortality from 10% to 20% among patients taking neuroleptic drugs. It is most often associated with typical high-potency neuroleptics. The motor and behavioral symptoms include muscular rigidity, dystonia, akinesia/bradykinesia, chorea, dysarthria, agitation and tremor. The autonomic symptoms include high fever, sweating, tachycardia and increased blood pressure. Laboratory findings include leucocytosis and increased levels of creatine phosphokinase (CPK), liver enzymes, plasma myoglobin and myoglobinuria, occasionally associated with renal failure^[2-4]. A need for awareness of the syndrome in view of the widespread use of neuroleptics and its potential lethality which can be averted by early detection and specific treatment have prompted the present report.

CASE REPORT

A 44-year-old male, formerly diagnosed with schizoaffective disorder, was admitted to the emergency clinic with the complaints of fever, perspiration, generalized stiffness and restlessness for one day. He was taking biperidene 2 mg tablet twice a day, haloperidol 10 mg tablet twice a day, olanzapine 20 mg tablet once daily, alprazolam 0.5 mg tablet once daily and aripiprazole 20 mg tablet once daily. It was learned that he was living in a nursing home and receiving these drugs for 3 years irregularly.

On physical examination, the patient was agitated, confused and disoriented to time and place. The pupils were normal size and reactive to light. Deep tendon reflexes were flexor in both side. His body temperature was 38.1 °C, blood pressure 170/80 mm-Hg, heart rate 102/min and respiratory rate 20/min. In laboratory test results, white blood cell (WBC) count: 19,200/mm³ (normal range: 4500 – 10,000/mm³), hemoglobin: 13.4 g/dl (normal range: 12–16 g/dl), serum CPK: 20.871 IU/L (normal range: 30–200 IU/L), sodium: 99 mmol/L (normal range: 135–145 mmol/L), chlorine: 73 mmol/L (normal range: 98–109 mmol/L) and C-reactive protein (CRP): 0.47 mg/dl (normal range: 0-0.5).

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His chest X-ray, EEG, ECG, liver and renal function tests, and blood gases were within normal limits. Cranial computerized tomography was normal. He was admitted to internal medicine intensive care unit with the suspicion of NMS. Meningitis, encephalitis, substance overdose or withdrawal, seizure were excluded due to normal CRP level and neuro-imaging and lack of neck stiffness. Serotonin syndrome was ruled out because of presence of severe rigidity, absence of hyperreflexia, clonus and diarrhea. There was no history of serotonergic reuptake inhibitors usage. Lethal catatonia was ruled out because patient did not have initial psychotic symptoms. Since the patient was fulfilling all the major and minor criteria of Levenson, which are widely accepted in diagnosis of NMS, he was diagnosed with NMS. Olanzapine, alprazolam and aripiprazole were discontinued. Saline was given for hydration and hyponatremia, besides paracetamol for hyperthermia. Bromocriptine 15 mg in three divided doses and diazepam 10 mg twice a day was started. Resolution of fever and muscular rigidity occurred within 72 hours with discontinuation of neuroleptics, supportive care and diazepam. The recovery was complete at the end of two weeks without any recurrence of psychotic symptoms. The serum CPK levels and WBC count fell concomitant with clinical recovery and the patient was discharged.

DISCUSSION

Diagnosis of NMS was made on the basis of risk factor, persisting hyperthermia, muscular rigidity, and ruling out other medical diseases. Due to variability in the clinical presentation of NMS and difficulty in differential diagnosis, specific criteria have been proposed for the diagnosis of NMS^[5,6]. Levenson's criteria have been commonly accepted. Hyperthermia, rigidity and elevated levels of CPK are accepted major criteria whereas tachycardia, high blood pressure, tachypnea, altered consciousness, over-sweating and leucocytosis are accepted minor criteria. The presence of all the three major, or two major and four minor criteria, is essential for the diagnosis of NMS^[3]. In our case, there was no doubt in diagnosis because the patient fulfilled all the criteria.

Most consistent risk factors for developing NMS are prominent psychomotor agitation, higher doses of neuroleptics, rapid neuroleptic dose increments over a short period of time, simultaneous use of two or more neuroleptic drugs and concomitant use of predisposing drugs (such as lithium, anti-cholinergics), dehydration, young age and male gender, and past history of NMS^[7]. In our case, the patient was receiving biperidene, haloperidol, olanzapine, alprazolam and aripiprazole. Among these, haloperidol is considered to

be the principal contributing factor in the development of NMS, by causing a sudden and massive down-regulation of dopaminergic transmission^[8]. A systematic review study reports this statistical analysis (n = 155): 42 cases of NMS were induced by olanzapine, 44 by risperidone, 19 by quetiapine, 36 by clozapine, and 14 by aripiprazole^[9]. Irregular and multiple antipsychotic drug use of the patient could contribute to developing NMS.

The rigidity and hyperthermia in NMS contribute to myonecrosis, which is reflected in elevated blood levels of CPK. Nevertheless, none of the laboratory findings are specific or pathognomic, elevated serum creatinine phosphokinase has been reported in 95% of NMS cases and myoglobinuria in 67% of cases^[9]. In our case, CPK level increased up to 20,871 IU/L (normal range: 30–200 IU/L). Early diagnosis and aggressive fluid replacement prevented renal failure. Aggressive fluid resuscitation and alkalization of urine can help prevent acute renal failure and enhance excretion of muscle breakdown products. Antipyretics, evaporative cooling, ice packs, and cooled IV fluids can be used to reduce hyperthermia^[10]. However, it must be kept in mind that the most important intervention is to discontinue all antipsychotics, especially haloperidol. Apart from early discontinuation of haloperidol, specific agents were used to reverse the symptoms of NMS. Bromocriptine, a dopamine agonist enhances the dopaminergic transmission, while lorazepam reduces rigidity and muscle necrosis.

Caroff and Mann reported 16% of patients developed NMS within 24 hour of initiating neuroleptics, 66% by 1 week, 96% within 30 days and is found to be less likely after 30 days^[12]. In our case, he was using neuroleptic drugs for three years, but irregularly.

CONCLUSION

It is hard to diagnose NMS due to a broad range of disorders presenting with fever, rigidity, mental status changes, and autonomic dysfunction. Therefore, exclusion of other disease and Levenson's criteria are cornerstones in a patient treated by neuroleptics to diagnose NMS. Haloperidol and concomitant use of neuroleptics may contribute to development of NMS, so drug use questioning should be done carefully. Given the relatively rare incidence of the disease and insufficient literature, this life threatening condition is still represented by high values of mortality. A better understanding of this syndrome would be helpful in reducing its fatalities. Discontinuation of neuroleptics especially haloperidol, enhancing dopaminergic transmission by dopamin-agonist such as bromocriptine and

reducing myonecrosis are the key points of NMS treatment. This case draws attention to the risk of NMS associated with haloperidol and concomitant use of multiple antipsychotic drugs.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2018; 50 (3) : 360 - 362

Gall stone ileus: Unfamiliar cause of bowel obstruction. Case report and literature review

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INTRODUCTION: Gallstone ileus is a rare sequela of cholelithiasis. The pathology occurs as a result of bilioenteric fistula due to erosion by the offending gallbladder stone. It is most commonly encountered in elderly females and CT imaging is diagnostic in the majority of cases. Surgical intervention aims to promptly relieve the obstruction by removing the gallstone and dealing with the fistula. Morbidity and mortality are usually high since it usually occurs in elderly patients.

PRESENTATION OF CASE: An 88-year-old lady with multiple chronic medical problems and no history of biliary manifestation presented with acute small bowel obstruction. Abdominal CT imaging revealed a bilioenteric fistula and an impacted gallstone in the jejunum causing occlusion. Laparotomy was performed and the stone was removed via enterolithotomy. Manipulation of the cholecystoduodenal fistula was not attempted due to severe inflammatory adhesions. The patient had uneventful postoperative course and remained symptom free on one year follow-up.

DISCUSSION AND CONCLUSION: Management of gallstone ileus is mainly surgical. Delay in detection and treatment of gallstone ileus may result in significant morbidity and mortality. The choice of surgical option is influenced by the preoperative medical status of the patient. A literature review generally supports the employment of enterolithotomy in high-risk patients and reserving cholecystectomy and resection of the fistula for less comorbid patients with feasible anatomy.

The impact of hypermobility spectrum disorders on musculoskeletal tissue stiffness: an exploration using strain elastography

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Hypermobility spectrum disorders (HSDs) are conditions associated with chronic joint pain and laxity. HSD's diagnostic approach is highly subjective, its validity is not well studied, and it does not consider many of the most commonly affected joints. Strain elastography (SEL) reflects musculoskeletal elasticity with sonographic images. The study explored the impact of HSD on musculoskeletal elasticity using SEL.

A cross-sectional design compared 21 participants with HSD against 22 controls. SEL was used to assess the elasticity of the deltoid, biceps brachii, brachioradialis, rectus femoris, and gastrocnemius muscles, and the patellar and Achilles tendon. SEL images were analyzed using strain index, strain ratio, and color pixels. Mean strain index (standard deviation) was significantly reduced in the HSD group compared to the control group in the brachioradialis muscle 0.43 (0.10) vs. 0.59 (0.24), patellar 0.30 (0.10) vs. 0.44 (0.11), and Achilles tendons 0.24 (0.06) vs. 0.49 (0.13). Brachioradialis muscle and patellar tendon's strain ratios were significantly lower in the HSD group compared to the control group, 6.02 (2.11) vs. 8.68 (2.67) and 5.18 (1.67) vs. 7.62 (1.88), respectively. The percentages (%) of red color (soft tissues) in the SEL images were significantly increased in the HSD group compared to the control group in the biceps brachii muscle, 34.72 (7.82) vs. 26.69 (3.89), and Achilles tendon, 18.14 (13.21) vs. 5.59 (8.23) ($p \leq 0.01$). The elasticity of the musculoskeletal system seems to be lower in people with HSD. SEL could be a supplementary tool for diagnosing and monitoring HSD.

Invasive *Candida auris* infections in Kuwait hospitals: epidemiology, antifungal treatment and outcome

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PURPOSE: *Candida auris* is a recently recognized yeast pathogen, which has attracted worldwide attention due to its multidrug-resistant nature and associated high mortality rates. Its persistence in hospital environment and propensity of nosocomial transmission underscores the need of continuous monitoring to prevent outbreaks. Since the first case of *C. auris* candidemia in May, 2014, we have identified 17 additional invasive cases, which are described here.

METHODS: Identity of 17 isolates originating from proven or possible cases of invasive *C. auris* infection and identified as *Candida haemulonii* by Vitek 2 yeast identification system was confirmed by PCR-sequencing of rDNA. Information about risk factors, treatment and outcomes were retrospectively retrieved from case files. Antifungal susceptibility testing was performed by Etest.

RESULTS: Thirteen cases of candidemia and 4 cases of other invasive infections were detected in 6 hospitals across Kuwait. Major risk factors included adult patients with cancer, diabetes, gastrointestinal/liver diseases and extended (> 25 days) hospital stay. All isolates were resistant to fluconazole. Additionally, 5 and 4 isolates were also resistant to voriconazole and amphotericin B, respectively. Despite antifungal treatment, 9 of 15 patients died. Most patients ($n = 12$) were hospitalized in 2 hospitals that are in close proximity, whereas 5 other patients were from 3 hospitals that are situated > 10 km apart.

CONCLUSIONS: Occurrence of successive cases of invasive *C. auris* infections with resulting mortality in nine patients suggests persistence of this multidrug-resistant yeast in major hospitals in Kuwait. Early detection by continuous surveillance and enforcement of infection control measures are recommended.

Association of protein tyrosine phosphatase non-receptor type 22 gene functional variant C1858T, HLA-DQ/DR genotypes and autoantibodies with susceptibility to type-1 diabetes mellitus in Kuwaiti Arabs

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The incidence of type-1 Diabetes Mellitus (T1DM) has increased steadily in Kuwait during recent years and it is now considered amongst the high-incidence countries. An interaction between susceptibility genes, immune system mediators and environmental factors predispose susceptible individuals to T1DM. We have determined the prevalence of protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene functional variant (C1858T; R620W, rs2476601), HLA-DQ and DR alleles and three autoantibodies in Kuwaiti children with T1DM to evaluate their impact on genetic predisposition of the disease. This study included 253 Kuwaiti children with T1DM and 214 ethnically matched controls. The genotypes of PTPN22 gene functional variant C1858T (R620W; rs2476601) were detected by PCR-RFLP method and confirmed by DNA sequencing. HLA-DQ and DR alleles were determined by sequence-specific PCR. Three autoantibodies were detected in the T1DM patients using radio-immunoassays. A significant association was detected between the variant genotype of the PTPN22 gene (C1858T, rs2476601) and T1DM in Kuwaiti Arabs. HLA-DQ2 and DQ8 alleles showed a strong association with T1DM. In T1DM patients which carried the variant TT-genotype of the PTPN22 gene, 93% had at least one DQ2 allele and 60% carried either a DQ2 or a DQ8 allele. Amongst the DR alleles, the DR3-DRB5, DR3-3, DR3-4 and DR4-4 showed a strong association with T1DM. Majority of T1DM patients who carried homozygous variant (TT) genotype of the PTPN22 gene had either DR3-DRB5 or DRB3-DRB4 genotypes. In T1DM patients who co-inherited the high risk HLA DQ, DR alleles with the variant genotype of PTPN22 gene, the majority were positive for three autoantibodies. Our data demonstrate that the variant T-allele of the PTPN22 gene along with HLA-DQ2 and DQ8 alleles constitute significant determinants of genetic predisposition of T1DM in Kuwaiti children.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2018; 50 (3): 363 - 372

13th International **Hepato - Pancreato - Biliary**

Association World Congress

Sep 3 - 7, 2018

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Email: ihpba2018@mci - group.com

2018 **Foodmicro** Conference

Sep 3 - 6, 2018

Germany / Berlin

Contact: Astrid Wilch, MCI Deutschland GmbH

Phone: 011 - 49 - 30 - 204 - 590

Fax: 011 - 49 - 30 - 204 - 5950

Email: foodmicro@mci - group.com

64th South African **Orthopaedic** Congress

Sep 3 - 6, 2018

South Africa / Pretoria

Contact: South African Orthopaedic Association

2018 **Tissue Engineering** International & **Regenerative Medicine** Society (TERMIS) World Congress

Sep 4 - 7, 2018

Japan / Kyoto

Contact: Congress Management Office, C/O Japan Convention Service, Inc.

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Email: termis - wc2018@convention.co.jp

Topics in **Anesthesia** - Las Vegas

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Supervisor, Gulfcoast Ultrasound Institute, Inc

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Email: learn@gcus.com

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Supervisor, Gulfcoast Ultrasound Institute, Inc

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Email: learn@gcus.com

17th World Congress on **Pain**

Sep 12 - 16, 2018

United States / Massachusetts / Boston

Contact: International Association for the Study of Pain

Phone: 202 - 856 - 7400; Fax: 202 - 856 - 7401

19th Annual Fall Conference on **Integrative Medicine** in Women's Health

Sep 12 - 15, 2018

United States / Arizona / Sedona

Contact: Symposia Medicus

Phone: 800 - 327 - 3161 or 925 - 969 - 1789

20th Annual Meeting of the European **Pressure Ulcer**
Advisory Panel
Sep 12 - 14, 2018
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Phone: +420 - 251 - 019 - 379
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37th Annual European Society of **Regional**
Anaesthesia & Pain Therapy Congress: ESRA 2018
Sep 12 - 15, 2018
Ireland / Dublin
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United States / Nevada / Las Vegas
Contact: University Learning Systems
Phone: 800 - 940 - 5860; Fax: 716 - 529 - 0550
Email: info@universitylearning.com

1st Conference on **Liver Disease** in Africa
Sep 13 - 15, 2018
Kenya / Nairobi
Contact: Virology Education
Phone: +31 - 30 - 230 - 7142
Email: info@virology - education.com

Advanced **Emergency Medicine** & Critical Care
Ultrasound
Sep 13 - 14, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development
Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727 - 363 - 4500; Fax: 727 - 363 - 0811
Email: learn@gcus.com

Medicine24
Sep 13 - 14, 2018
United Kingdom / Glasgow
Contact: Wilma Paterson, Coordinator, Royal College
of Physicians and Surgeons of Glasgow
Phone: +44 - 14 - 1227 - 3212
Email: wilma.paterson@rcpsg.ac.uk

17th Biennial Meeting of the International
Gynecologic Cancer Society
Sep 14 - 16, 2018
Japan / Kyoto
Contact: Josh Margo, Kenes Group
Phone: +972 - 3 - 972 - 7450
Email: jmargo@kenes.com

6th Annual UCLA Review of **Clinical Neurology**
Sep 14 - 16, 2018
United States / California / Los Angeles
Contact: Continuing Medical Education, University of
California, Los Angeles
Phone: 310 - 794 - 2620
Fax: 310 - 794 - 2624

Societies for **Pediatric Urology** 2018 Pediatric Urology
Fall Congress
Sep 14 - 16, 2018
United States / Georgia / Atlanta
Contact: Societies for Pediatric Urology
Phone: 978 - 927 - 8330
Fax: 978 - 524 - 0498

Blended **Pediatric Emergency** & Critical Care
Ultrasound
Sep 15, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development
Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727 - 363 - 4500; Fax: 727 - 363 - 0811
Email: learn@gcus.com

16th World Congress of the International Society for
Diseases of the Esophagus (ISDE)
Sep 16 - 19, 2018
Austria / Vienna
Contact: International Conference Services Ltd.
Phone: 604 - 681 - 2153
Fax: 604 - 681 - 1049
Email: isde2018@icsevents.com

Current **Anesthesia** Practice
Sep 17 - 20, 2018
United States / Arizona / Sedona
Contact: Northwest Seminars
Phone: 800 - 222 - 6927
Fax: 509 - 547 - 1265
Email: info@northwestseminars.com

Challenges in **Obstetrics & Gynecology**
Sep 18 - 27, 2018
Spain / Barcelona
Contact: Symposia Medicus
Phone: 800 - 327 - 3161 or 925 - 969 - 1789

Dermatology & Emergency Medicine CME Cruise
Sep 19 - 29, 2018
Tahiti / Papeete
Contact: Sea Courses, Sea Courses
Phone: 800 - 268 - 3273
Email: cruises@seacourses.com

Eurospine 2018

Sep 19 - 21, 2018

*Spain / Barcelona*Contact: Liesa Wessely, Organizing Secretariat,
Mondial Congress & Events

Phone: +43 - 1 - 58 - 8040

Email: eurospine2018@mondial - congress.com

32nd Annual Fall Conference on High Risk Obstetrics

Sep 20 - 22, 2018

United States / California / San Francisco

Contact: Symposia Medicus

Phone: 800 - 327 - 3161 or 925 - 969 - 1789

Musculoskeletal Ultrasound Registry Review Course

Sep 20 - 21, 2018

*United States / Florida / St. Petersburg*Contact: Casey Green, Business Development
Supervisor, Gulfcoast Ultrasound Institute, Inc

Phone: 727 - 363 - 4500; Fax: 727 - 363 - 0811

Email: learn@gcus.com

Relevant Topics in Anesthesia

Sep 20 - 23, 2018

United States / South Carolina / Hilton Head Island

Contact: Northwest Seminars

Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

Advanced Radiology Life Support (ARLS)

Sep 22, 2018

*United States / Minnesota / Rochester (MN)*Contact: Department Of Radiology CME Office,
Mayo Clinic

Phone: 507 - 284 - 3317

Email: radiologycme@mayo.edu

Hospitalist and Emergency Procedures Course - Seattle

Sep 22, 2018

*United States / Washington / Seattle*Contact: Joseph Esherick, President, Hospital
Procedures Consultants

Phone: 805 - 339 - 0225; Fax: 805 - 339 - 0375

Email: jesherrick@hospitalprocedures.org

36th Annual Occupational & Environmental Medical Association of Canada (OEMAC) Scientific Conference

Sep 23 - 25, 2018

*Canada / Alberta / Calgary*Contact: Chantal Champagne, Event Manager,
OEMAC

Phone: 888 - 223 - 3808

Email: cchampagne@oemac.org

Anesthesia Update

Sep 24 - 28, 2018

United States / Wyoming / Jackson Hole

Contact: Northwest Seminars

Phone: 800 - 222 - 6927

Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

Pediatric and Adult Emergency Medicine Personal and Career Development

Sep 24 - 27, 2018

United States / Arizona / Sedona

Contact: Northwest Seminars

Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

Society of Obstetricians & Gynaecologists of Canada 2018 Quebec CME Program

Sep 24 - 25, 2018

*Canada / Quebec / Montreal*Contact: Society of Obstetricians and Gynaecologists
of Canada

Phone: 800 - 561 - 2416 or 613 - 730 - 4192

Fax: 613 - 730 - 4314

Email: meetings@sogc.com

2018 Rural Health Clinic Conference

Sep 25 - 26, 2018

United States / Missouri / Kansas City

Contact: National Rural Health Association

Phone: 816 - 756 - 3140; Fax: 816 - 756 - 3144

2018 Critical Access Hospital Conference

Sep 26 - 28, 2018

United States / Missouri / Kansas City

Contact: National Rural Health Association

Phone: 816 - 756 - 3140

Fax: 816 - 756 - 3144

6th Annual Fall Conference on Current Concepts in Neonatal Care

Sep 26 - 29, 2018

United States / California / Newport Beach

Contact: Symposia Medicus

Phone: 800 - 327 - 3161 or 925 - 969 - 1789

Topics in Infection 2018

Sep 26, 2018

*United Kingdom / London*Contact: Royal Society of Tropical Medicine and
Hygiene

Phone: +44 - 20 - 7405 - 2628

Fax: +44 - 20 - 7242 - 4487

Email: Info@Rstmh.Org

23rd Asean Federation of **Cardiology** Congress
Sep 28 – Oct 1, 2018
Thailand / Bangkok
Contact: Warapa Saipow, Mr., Kenes Group
Phone: +66 - 2 - 748 - 7881
Email: wsaipow@kenes.com

19th Meeting of the European Association for
Haematopathology
Sep 29 - Oct 4, 2018
United Kingdom / Edinburgh
Contact: Mandy Pekar, MCI Deutschland GmbH
Phone: 011 - 49 - 30 - 204 - 590
Fax: 011 - 49 - 30 - 204 - 5950
Email: eahp@mci - group.com

18th International Society for Pediatric & Adolescent
Diabetes Science School for Physicians
Sep 30 - Oct 3, 2018
Japan / Tokyo
Contact: K.I.T. Group GmbH
Phone: 011 - 49 - 30 - 2460 - 3210
Fax: 011 - 49 - 30 - 2460 - 3200
Email: secretariat@ispad.org

2018 World **Cancer** Congress Malaysia
Oct 1 - 4, 2018
Malaysia / Kuala Lumpur
Contact: Congress Team, Union for International
Cancer Control
Phone: 011 - 41 - 22 - 809 - 1834
Email: congress@uicc.org

2nd **Adolescence** Workshop on HIV
Oct 1 - 2, 2018
South Africa / Cape Town
Contact: Virology Education
Phone: +31 - 30 - 230 - 7142
Email: info@virology - education.com

9th International Workshop on **HIV & Aging**
Oct 1 - 2, 2018
United States / New York / New York
Contact: Virology Education
Phone: +31 - 30 - 230 - 7142
Email: info@virology - education.com

22nd International Congress on **Palliative Care**
Oct 2 - 5, 2018
Canada / Quebec / Montreal
Contact: Congress Secretariat, O'donoughue &
Associates Event Management
Phone: 450 - 292 - 3456 Ext. 227
Fax: 450 - 292 - 3453

32nd International **Papillomavirus** Conference (IPVC
2018)
Oct 2 - 6, 2018
Australia / Sydney
Contact: Ipvs Secretariat, Kenes Group
Phone: +41 - 22 - 908 - 0488
Email: lprodanova@kenes.com

12th International Symposium on **Catheter Ablation**
Techniques
Oct 3 - 5, 2018
France / Paris
Contact: Congress Organizer, Overcome
Phone: 011 - 33 - 1 - 4192 - 0127
Fax: 011 - 33 - 1 - 4088 - 9790
Email: iscat@overcome.fr

2018 North American **Menopause** Society (NAMS)
Annual Meeting
Oct 3 - 6, 2018
United States / California / San Diego
Contact: NAMS
Phone: 440 - 442 - 7550; Fax: 440 - 442 - 2660
Email: info@menopause.org

2018 Society of Radiologists in **Ultrasound** Annual
Meeting
Oct 5 - 7, 2018
United States / California / San Diego
Contact: Emma Schons, Program Coordinator, Society
of Radiologists in Ultrasound
Phone: 703 - 858 - 9210; Fax: 703 - 264 - 2093
Email: eschons@acr.org

Anesthesia Spectrum
Oct 5 - 8, 2018
United States / Tennessee / Gatlinburg
Contact: Northwest Seminars
Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265
Email: info@northwestseminars.com

Glasgow **Gastro** Conference 2018
Oct 5, 2018
United Kingdom / Glasgow
Contact: Wilma Paterson, Coordinator, Royal College
of Physicians and Surgeons of Glasgow
Phone: +44 - 14 - 1227 - 3212
Email: wilma.paterson@rcpsg.ac.uk

21st World Congress of the International Society of
Hypertension in Pregnancy
Oct 7 - 9, 2018
Netherlands / Amsterdam
Contact: Groningen Congress Bureau
Phone: 011 - 31 - 50 - 316 - 8877
Email: info@gcb.nl

Medical CBT: 10 - Minute Techniques For Real Doctors (**Cognitive Behavior Therapy**)
Oct 7, 2018
Japan / Tokyo
Contact: Greg Dubord, MD, CME Director, CBT Canada
Phone: 877 - 466 - 8228
Email: registrar@cbt.ca

53rd Annual **Scoliosis** Research Society Meeting & Course
Oct 10 - 13, 2018
Italy / Bologna
Contact: Scoliosis Research Society
Phone: 414 - 289 - 9107; Fax: 414 - 276 - 3349
Email: info@srs.org

2018 Joint Congress of the Asia Pacific Association of **Allergy, Asthma & Clinical Immunology** / Asia Pacific Association of Pediatric Allergy, Respiriology & Immunology
Oct 11 - 14, 2018
Thailand / Bangkok
Contact: Warapa Saipow, Kenes Group
Phone: +66 - 2 - 748 - 7881
Email: wsaipow@kenes.com

4th Central and Eastern European Meeting on **Viral Hepatitis** and Co - Infection
Oct 11 - 12, 2018
Czech Republic / Prague
Contact: Virology Education
Phone: +31 - 30 - 230 - 7142
Email: info@virology - education.com

4th International Workshop on Microbiome in **HIV** Pathogenesis, Prevention & Treatment
Oct 11 - 12, 2018
United States / Maryland / Bethesda
Contact: Virology Education
Phone: +31 - 30 - 230 - 7142
Email: info@virology - education.com

50th Annual Western **Neuroradiological** Society Meeting
Oct 11 - 14, 2018
United States / California / Dana Point
Contact: K Cammarata, Western Neuroradiological Society
Phone: 630 - 574 - 0220 Ext. 226

Society for Education in **Anesthesia** 2018 Fall Meeting
Oct 12, 2018
United States / California / San Francisco
Contact: Society for Education in Anesthesia
Phone: 414 - 389 - 8614; Fax: 414 - 276 - 7704
Email: info@seahq.org

40th Annual North American Meeting of the Society for **Medical Decision Making**
Oct 14 - 17, 2018
Canada / Quebec / Montreal
Contact: Society for Medical Decision Making
Phone: 908 - 359 - 1184
Fax: 908 - 450 - 1119
Email: info@smdm.org

11th World **Stroke** Congress
Oct 17 - 20, 2018
Canada / Quebec / Montreal
Contact: Wsc 2018 Secretariat, Kenes International
Phone: 011 - 972 - 3 - 972 - 7971
Email: ygrysmen@kenes.com

18th European **Neuroendocrine** Association Congress
Oct 17 - 20, 2018
Poland / Wroclaw
Contact: Standing Office, Endoscience Service GmbH
Phone: 011 - 49 - 91 - 8797 - 42411
Fax: 011 - 49 - 91 - 8797 - 42471
Email: then@endoscience.de

34th World Congress of **Internal Medicine**
Oct 18 - 22, 2018
South Africa / Cape Town
Contact: Sarah Krein, Paragong Group
Phone: 011 - 41 - 22 - 533 - 0948
Email: skrein@paragong.com

13th **HIV** Transmission Workshop
Oct 19 - 20, 2018
Spain / Madrid
Contact: Virology Education
Phone: +31 - 30 - 230 - 7142
Email: info@virology - education.com

26th United European **Gastroenterology** Week
Oct 20 - 24, 2018
Austria / Vienna
Contact: United European Gastroenterology
Phone: +43 - 1 - 997 - 1639
Fax: +43 - 1 - 997 - 1639 Ext. 10
Email: office@ueg.eu

17th Annual National **Family Medicine** Board Review
Oct 21 - 24, 2018
United States / Nevada / Las Vegas
Contact: Donna Ackroyd, Center for Medical Education
Phone: 800 - 458 - 4779
Email: donna@ccme.org

Introduction to Carotid Duplex/Color Flow Imaging

Oct 22 - 23, 2018

United States / Florida / St. Petersburg

Contact: Casey Green, Business Development
Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727 - 363 - 4500; Fax: 727 - 363 - 0811
Email: learn@gcus.com

DKOU 2018: German Congress of Orthopaedics and Traumatology

Oct 23 - 26, 2018

Germany / Berlin

Contact: Nicole Lange, Ms, Intercongress GmbH
Phone: +49 - 611 - 977 - 160
Email: nicole.lange@intercongress.de

18th Biennial Meeting of the European Society for Immunodeficiencies

Oct 24 - 27, 2018

Portugal / Lisbon

Contact: ESID Secretariat, Mr., Kenes Group
Phone: +972 - 3 - 972 - 7971
Email: esid@kenes.com

34th Annual Fall Conference on Pediatric Emergencies

Oct 24 - 27, 2018

United States / Hawaii / Oahu

Contact: Symposia Medicus
Phone: 800 - 327 - 3161 or 925 - 969 - 1789

49th Union World Conference on Lung Health

Oct 24 - 27, 2018

Netherlands / Den Hague

Contact: International Union against Tuberculosis and
Lung Disease
Phone: +33 - 1 - 4432 - 0360
Email: thehague2018@theunion.org

Musculoskeletal Ultrasound in Hemophilia

Oct 24 - 26, 2018

United States / California / San Diego

Contact: Marlene Zepeda, Continuing Medical
Education, UC San Diego
Phone: 858 - 534 - 3940
Email: ocme@ucsd.edu

9th Annual Breakthroughs in Neurologic Therapies:

Restoring Function to the Nervous System

Oct 26 - 27, 2018

United States / California / San Francisco

Contact: Dianna Ziehm, CME Conference
Coordinator, Stanford Health Care
Phone: 650 - 724 - 7166
Email: dziehm@stanford.edu

Ultrasound - Guided Joint Injection Training Course

Oct 27, 2018

United States / California / San Diego

Contact: Marlene Zepeda, Continuing Medical
Education, UC San Diego
Phone: 858 - 534 - 3940
Email: ocme@ucsd.edu

Anesthesia Topics

Oct 28 - Nov 2, 2018

United States / Hawaii / Maui

Contact: Northwest Seminars
Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265
Email: info@northwestseminars.com

Current Issues in Women's Health

Oct 29 - Nov 5, 2018

Switzerland / Basel

Contact: Symposia Medicus
Phone: 800 - 327 - 3161 or 925 - 969 - 1789

Hot Topics in Pediatric Emergencies

Oct 29 - Nov 5, 2018

Switzerland / Basel

Contact: Symposia Medicus
Phone: 800 - 327 - 3161 or 925 - 969 - 1789

7th Congress of the European Academy of Paediatric Societies (EAPS 2018)

Oct 30 - Nov 3, 2018

France / Paris

Contact: Josh Margo, Mr., Kenes Group
Phone: +9723 - 972 - 7450
Email: jmargo@kenes.com

26th Annual Fall Conference on Issues in Women's Health

Oct 31 - Nov 3, 2018

United States / Hawaii / Maui

Contact: Symposia Medicus
Phone: 800 - 327 - 3161 or 925 - 969 - 1789

29th Annual Fall Conference on Hot Topics in Primary Care

Oct 31 - Nov 3, 2018

Cayman Islands / Grand Cayman

Contact: Symposia Medicus
Phone: 800 - 327 - 3161 or 925 - 969 - 1789

Keys in Anesthesia

Nov 1 - 4, 2018

United States / Florida / Key West

Contact: Northwest Seminars
Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265
Email: info@northwestseminars.com

Clinical Pearls in Family Medicine

Nov 3 - 10, 2018

Barbados / Bridgetown

Contact: Sea Courses, Sea Courses

Phone: 800 - 268 - 3273

Email: cruises@seacourses.com

Hospitalist and Emergency Procedures Course - San Antonio

Nov 3, 2018

United States / Texas / San Antonio

Contact: Joseph Esherick, President, Hospital Procedures Consultants

Phone: 805 - 339 - 0225; Fax: 805 - 339 - 0375

Email: jesherrick@hospitalprocedures.org

Ophthalmic Regional Block Hands - On Workshop

Nov 3 - 4, 2018

United States / Florida / Orlando

Contact: Northwest Seminars

Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

2018 Imaging Advances

Nov 4 - 7, 2018

Puerto Rico / San Juan

Contact: Department Of Radiology, Penn Medicine

Phone: 800 - 789 - 7366

Current Topics in Anesthesia

Nov 4 - 9, 2018

Turks / Caicos / Providenciales

Contact: Northwest Seminars

Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

Hospitalist and Emergency Procedures Course - San Antonio

Nov 4, 2018

United States / Texas / San Antonio

Contact: Joseph Esherick, President, Hospital Procedures Consultants

Phone: 805 - 339 - 0225

Fax: 805 - 339 - 0375

Email: jesherrick@hospitalprocedures.org

Introduction to Abdominal and Primary Care Ultrasound

Nov 5 - 7, 2018

United States / Florida / St. Petersburg

Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc

Phone: 727 - 363 - 4500; Fax: 727 - 363 - 0811

Email: learn@gcus.com

VIVA 18 (Vascular Interventional Advances)

Nov 5 - 8, 2018

United States / Nevada / Las Vegas

Contact: Tony Jakovcevic, Viva Physicians

Phone: 888 - 513 - 8482; Fax: 408 - 225 - 3240

Email: tony@vivaphysicians.org

5th International HBV Cure Workshop

Nov 7, 2018

Canada / Ontario / Toronto

Contact: Virology Education

Phone: +31 - 30 - 230 - 7142

Email: info@virology - education.com

19th Annual Fall Scientific Meeting of Sexual Medicine Society of North America (SMSNA)

Nov 8 - 11, 2018

United States / Florida / Miami Beach

Contact: Executive Office C/O Status Plus, SMSNA

Phone: 952 - 683 - 1917; Fax: 612 - 808 - 0491

Email: info@smsna.org

Introduction to Ob/Gyn Ultrasound

Nov 8 - 9, 2018

United States / Florida / St. Petersburg

Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc

Phone: 727 - 363 - 4500; Fax: 727 - 363 - 0811

Email: learn@gcus.com

Addressing Complications Commonly Seen In Mentally Ill Patients

Nov 11 - 18, 2018

United States / New Jersey / Cape Liberty

Contact: University Learning Systems

Phone: 800 - 940 - 5860; Fax: 716 - 529 - 0550

Email: info@universitylearning.com

Reviews for Anesthesia Professionals

Nov 11 - 16, 2018

Jamaica / Port Maria

Contact: Northwest Seminars

Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

International Pediatric Transplant Association 2018 Fellows Meeting On Pediatric Transplantation

Nov 12 - 13, 2018

Costa Rica / San Jose

Contact: Eugenia Siu, International Headquarters, International Pediatric Transplant Association

Phone: 514 - 874 - 1717

Fax: 514 - 874 - 1716

Email: eugenia.siu@tts.org

Topics in Pediatric Emergency Medicine

Nov 12 - 16, 2018

United States / Hawaii / Maui

Contact: Northwest Seminars

Phone: 800 - 222 - 6927

Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

19th Annual Fall Conference on Emergency Medicine

Nov 14 - 17, 2018

United States / Hawaii / Big Island

Contact: Symposia Medicus

Phone: 800 - 327 - 3161 or 925 - 969 - 1789

24th Annual Conference on Women's Health: Care of Women Over 50

Nov 14 - 17, 2018

Cayman Islands / Grand Cayman

Contact: Symposia Medicus

Phone: 800 - 327 - 3161 or 925 - 969 - 1789

25th Annual Fall Conference on Challenges in Taking Care of the High Risk Pregnancy

Nov 14 - 17, 2018

United States / Florida / Naples

Contact: Symposia Medicus

Phone: 800 - 327 - 3161 or 925 - 969 - 1789

Blended Introduction to Critical Care Ultrasound

Nov 15 - 16, 2018

United States / Florida / St. Petersburg

Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc

Phone: 727 - 363 - 4500; Fax: 727 - 363 - 0811

Email: learn@gcus.com

Blended Introduction to Emergency Medicine Ultrasound

Nov 15 - 16, 2018

United States / Florida / St. Petersburg

Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc

Phone: 727 - 363 - 4500

Fax: 727 - 363 - 0811

Email: learn@gcus.com

Blended Trauma and Acute Care Sonography

Nov 15, 2018

United States / Florida / St. Petersburg

Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc

Phone: 727 - 363 - 4500

Fax: 727 - 363 - 0811

Email: learn@gcus.com

Topics in Emergency Medicine

Nov 15 - 18, 2018

United States / Florida / Key West

Contact: Northwest Seminars

Phone: 800 - 222 - 6927

Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

Blended Ultrasound - Guided Nerve Blocks for the Emergency Physician

Nov 16, 2018

United States / Florida / St. Petersburg

Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc

Phone: 727 - 363 - 4500

Fax: 727 - 363 - 0811

Email: learn@gcus.com

Blended Ultrasound - Guided Vascular Access

Nov 16, 2018

United States / Florida / St. Petersburg

Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc

Phone: 727 - 363 - 4500

Fax: 727 - 363 - 0811

Email: learn@gcus.com

Immunology Short Course for Clinicians & Scientists: From Basic Immunology to the Latest Advances in Clinical Research

Nov 20 - 22, 2018

United Kingdom / London

Contact: Liz Lightstone, Continuing Professional Development, Imperial College London

Phone: +44 - 20 - 7589 - 5111

Email: l.lightstone@imperial.ac.uk

2018 World Conference on Regenerative Medicine

Nov 21 - 23, 2018

Germany / Leipzig Genetics

Contact: Conference Office, Event Lab. GmbH

Phone: 011 - 49 - 341 - 240 - 596 Ext. 50

Fax: 011 - 49 - 341 - 240 - 596 Ext. 51

Email: info@wcrm - leipzig.com

44th International Dexeus Forum: Update in Obstetrics, Gynaecology & Reproductive Medicine

Nov 21 - 23, 2018

Spain / Barcelona

Contact: Comtec Med

Phone: +972 - 3 - 566 - 6166

Email: dexeus@comtecmed.com

26th World Congress on Controversies in **Obstetrics, Gynecology & Infertility**

Nov 23 - 25, 2018

United Kingdom / London

Contact: Secretariat, Congressmed

Phone: +972 - 72 - 279 - 0306

Email: cogi@congressmed.com

Relevant Topics in **Anesthesia**

Nov 27 - Dec 2, 2018

United States / California / Napa Valley

Contact: Northwest Seminars

Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

2018 **Tropical Medicine** Excursion to Ghana

Nov 28 - Dec 8, 2018

Ghana / Accra

Contact: Kay Schaefer, MD, Tropical Medicine

Excursions

Phone: +49 - 152 - 5569 - 8101

Society of **Obstetricians & Gynaecologists** of Canada

2018 Ontario CME Program

Nov 29 - Dec 1, 2018

Canada / Ontario / Toronto

Contact: Society of Obstetricians and Gynaecologists of Canada

Phone: 800 - 561 - 2416 or 613 - 730 - 4192

Fax: 613 - 730 - 4314

Email: meetings@sogc.com

18th International Congress of **Endocrinology** / 53rd

Annual Society for Endocrinology, Metabolism &

Diabetes of South Africa Congress

Dec 1 - 4, 2018

South Africa / Cape Town

Contact: Event Management, Scatterlings Conference & Events

Phone: 011 - 27 - 21 - 422 - 2402

Fax: 011 - 27 - 11 - 463 - 3265

21st International Symposium on **Endoscopic**

Ultrasonography (EUS 2018)

Dec 1 - 2, 2018

Thailand / Bangkok

Contact: Warapa Saipow, Kenes Group Thailand

Phone: +66 - 2 - 748 - 7881

Email: wsaipow@kenes.com

2018 National **Osteoporosis** Society (NOS)

Conference

Dec 2 - 4, 2018

United Kingdom / Birmingham

Contact: NOS

Phone: 011 - 44 - 80 - 8800 - 0035

Topics in **Emergency Medicine**

Dec 2 - 7, 2018

Aruba / Palm Beach (Aruba)

Contact: Northwest Seminars

Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

Introduction to Adult **Echocardiography**

Dec 3 - 7, 2018

United States / Florida / St. Petersburg

Contact: Casey Green, Business Development

Supervisor, Gulfcoast Ultrasound Institute, Inc

Phone: 727 - 363 - 4500; Fax: 727 - 363 - 0811

Email: learn@gcus.com

Current Topics in **Anesthesia**

Dec 4 - 7, 2018

Georgia / Savannah

Contact: Northwest Seminars

Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

Cardiothoracic and Vascular Anesthesia Update

Dec 11 - 14, 2018

United States / Nevada / Las Vegas

Contact: Northwest Seminars

Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

Current Topics in **Emergency Medicine**

Dec 13 - 16, 2018

United States / Florida / Miami

Contact: Northwest Seminars

Phone: 800 - 222 - 6927; Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

10th Annual Conference on Emergencies & Challenges in **Pediatrics**

Dec 14 - 15, 2018

United States / New York / New York

Contact: Symposia Medicus

Phone: 800 - 327 - 3161 or 925 - 969 - 1789

22nd Annual Conference on Emergencies & Challenges in **Primary Care**

Dec 14 - 15, 2018

United States / New York / New York

Contact: Symposia Medicus

Phone: 800 - 327 - 3161 or 925 - 969 - 1789

24th Annual Conference on Challenges in **Gynecology**

Dec 14 - 15, 2018

United States / New York / New York

Contact: Symposia Medicus

Phone: 800 - 327 - 3161 or 925 - 969 - 1789

Current Topics in Anesthesia

Dec 17 – 20, 2018

United States / Florida / Miami

Contact: Northwest Seminars

Phone: 800 - 222 – 6927

Fax: 509 - 547 - 1265

Email: info@northwestseminars.com

Endocrinology & Family Medicine CME Cruise

Dec 30 - Jan 6, 2018

United States / Florida / Fort Lauderdale

Contact: Sea Courses, Sea Courses

Phone: 800 - 268 - 3273

Email: cruises@seacourses.com

Update on Cardiology, Palliative Care and Primary Care CME Cruise

Jan 6 - 20, 2018

Chile / Valparaiso

Contact: Sea Courses, Sea Courses

Phone: 800 - 268 - 3273

Email: cruises@seacourses.com

Society of Nuclear Medicine & Molecular Imaging

2019 Mid - Winter Meeting

Jan 17 - 20, 2018

United States / California / Palm Springs

Contact: Society of Nuclear Medicine & Molecular Imaging

Phone: 703 - 708 – 9000; Fax: 703 - 708 - 9015

2019 Tropical Medicine Excursion to Uganda

Jan 27 - Feb 8, 2018

Uganda / Entebbe

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2019 Semi - Annual NRG Oncology Meeting

Feb 7 - 9, 2018

United States / Arizona / Phoenix

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St.Gallen International Breast Cancer Conference:

Primary Therapy of Early Breast Cancer - Evidence, Controversies, Consensus

Mar 20 - 23, 2018

Austria / Vienna

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Medical CBT: 10 - Minute Techniques for Real Doctors (Cognitive Behavior Therapy)

Apr 13 - 27, 2018

Tahiti / Papeete

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WHO-Facts Sheet

1. Household air pollution and health
2. Japanese encephalitis
3. Meningococcal meningitis
4. Tuberculosis
5. Yellow fever

Compiled and edited by
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1. HOUSEHOLD AIR POLLUTION AND HEALTH

among women and young children, who spend the most time near the domestic hearth.

KEY FACTS

- Around 3 billion people cook using polluting open fires or simple stoves fuelled by kerosene, biomass (wood, animal dung and crop waste) and coal.
- Each year, close to 4 million people die prematurely from illness attributable to household air pollution from inefficient cooking practices using polluting stoves paired with solid fuels and kerosene.
- Household air pollution causes noncommunicable diseases including stroke, ischaemic heart disease, chronic obstructive pulmonary disease (COPD) and lung cancer.
- Close to half of deaths due to pneumonia among children under 5 years of age are caused by particulate matter (soot) inhaled from household air pollution.

Indoor air pollution and household energy: the forgotten 3 billion

Around 3 billion people still cook using solid fuels (such as wood, crop wastes, charcoal, coal and dung) and kerosene in open fires and inefficient stoves. Most of these people are poor, and live in low- and middle-income countries.

These cooking practices are inefficient, and use fuels and technologies that produce high levels of household air pollution with a range of health-damaging pollutants, including small soot particles that penetrate deep into the lungs. In poorly ventilated dwellings, indoor smoke can be 100 times higher than acceptable levels for fine particles. Exposure is particularly high

Impacts on health

3.8 million people a year die prematurely from illness attributable to the household air pollution caused by the inefficient use of solid fuels and kerosene for cooking. Among these 3.8 million deaths:

- 27% are due to pneumonia
- 18% from stroke
- 27% from ischaemic heart disease
- 20% from chronic obstructive pulmonary disease (COPD)
- 8% from lung cancer.

Pneumonia

Exposure to household air pollution almost doubles the risk for childhood pneumonia and is responsible for 45% of all pneumonia deaths in children less than 5 years old. Household air pollution is also risk for acute lower respiratory infections (pneumonia) in adults, and contributes to 28% of all adult deaths to pneumonia.

Chronic obstructive pulmonary disease

One in four or 25% of premature deaths from chronic obstructive pulmonary disease (COPD) in adults in low- and middle-income countries are due to exposure to household air pollution. Women exposed to high levels of indoor smoke are more than two times as likely to suffer from COPD than women who use cleaner fuels and technologies. Among men (who already have a heightened risk of COPD due to their higher rates of smoking), exposure to household air pollution nearly doubles that risk.

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Stroke

12% of all premature deaths due to stroke can be attributed to the daily exposure to household air pollution arising from cooking with solid fuels and kerosene.

Ischaemic heart disease

Approximately 11% of all deaths due to ischaemic heart disease, accounting for over a million premature deaths annually, can be attributed to exposure to household air pollution.

Lung cancer

Approximately 17% of premature lung cancer deaths in adults are attributable to exposure to carcinogens from household air pollution caused by cooking with kerosene or solid fuels like wood, charcoal or coal. The risk for women is higher, due to their role in food preparation.

Other health impacts and risks

More generally, small particulate matter and other pollutants in indoor smoke inflame the airways and lungs, impairing immune response and reducing the oxygen-carrying capacity of the blood.

There is also evidence of links between household air pollution and low birth weight, tuberculosis, cataract, nasopharyngeal and laryngeal cancers.

Mortality from ischaemic heart disease and stroke are also affected by risk factors such as high blood pressure, unhealthy diet, lack of physical activity and smoking. Some other risks for childhood pneumonia include suboptimal breastfeeding, underweight and second-hand smoke. For lung cancer and chronic obstructive pulmonary disease, active smoking and second-hand tobacco smoke are also main risk factors.

Impacts on health equity, development and climate change

Without a substantial policy change, the total number of people lacking access to clean fuels and technologies will remain largely unchanged by 2030 (International Energy Agency, 2017 (1)) and therefore hinder the achievement of the 2030 Agenda for Sustainable Development.

- Fuel gathering increases the risk of musculoskeletal damage, consumes considerable time for women and children, limits other productive activities (such as income generation) and takes children away from school. In less secure environments, women and children are at risk of injury and violence during fuel gathering.

- Black carbon (sooty particles) and methane emitted by inefficient stove combustion are powerful climate change pollutants.
- Many of the fuels and technologies used by households for cooking, heating and lighting present safety risks. The ingestion of kerosene is the leading cause of childhood poisonings, and a large fraction of the severe burns and injuries occurring in low- and middle-income countries are linked to household energy use for cooking, heating and/or lighting.
- The lack of access to electricity for 1 billion people (many of whom then use kerosene lamps for lighting) exposes households to very high levels of fine particulate matter. The use of polluting lighting fuels introduces other health risks, such as burns, injuries, poisonings, and constrains other opportunities for health and development, like studying or engaging in small crafts and trades, which require adequate lighting.

WHO response

WHO provides technical support to countries in their own evaluations and scale-up of health-promoting household fuels and technologies. WHO is building capacity at the country and regional level to address household air pollution through direct consultations and workshops on household energy and health. This is further complemented by the ongoing development of the Clean Household Energy Solutions Toolkit (CHEST) to support the implementation of *WHO Guidelines for indoor air quality: household fuel combustion*. CHEST is a suite of tools and information resources that help countries identify stakeholders working on household energy and/or public health to design, implement and monitor policies addressing household energy.

Guidelines for indoor air quality: household fuel combustion

To ensure healthy air in and around the home, WHO's Guidelines for indoor air quality: household fuel combustion provide health-based recommendations on the types of fuels and technologies to protect health as well as strategies for the effective dissemination and adoption of such home energy technologies. These build upon existing WHO outdoor air quality guidelines and WHO guidance on levels of specific indoor pollutants.

Household energy database

The WHO Household energy database is used to monitor global progress in the transition to cleaner fuels and stove combinations in households. It also supports

assessments of disease burden from the household air pollution generated from the use of polluting fuel and technologies. Currently the database includes housing data from more than 1100 surveys, representing 157 countries. It has been expanded to include information on household fuels and technologies used for heating and lighting.

As the custodial agency for Sustainable Development Goal Indicator 3.9.1 (mortality rate from the joint effects of household and ambient air pollution) and 7.1.2 (population with primary reliance on clean fuels and technologies), WHO uses the Household energy database to derive estimates for tracking progress towards achieving universal clean energy access and related health impacts.

Research and programme evaluation

WHO is working with countries, researchers and other partners to harmonize methods of evaluation across settings so that health impacts are assessed consistently and rigorously and incorporate economic assessment of health benefits.

Leadership and advocacy in the health, energy and climate community

Health sector

In May 2015, the World Health Assembly unanimously adopted a resolution on air pollution and health, calling for the integration of health concerns into national, regional and local air pollution-related policies. The following year, the World Health Assembly adopted a "Roadmap for Enhanced Action," calling for increased cross-sector cooperation to address the health risks of air pollution.

Building on this mandate, WHO is working to integrate guidance and resources for supporting clean household energy into global health initiatives and decision-support tools, such as the Global Action Plan for Pneumonia and Diarrheal Disease (GAPPD), or Global Strategy for Women and Children's Health, as well as into other aspects of WHO's own health policy guidance. WHO emphasizes the compelling health arguments for cleaner household energy in a range of global forums addressing maternal and child health issues related to pneumonia as well as forums concerned with noncommunicable diseases. This advocacy can help increase awareness of the importance of providing and scaling up of cleaner household energy as a core preventive public health measure.

Health and climate change

WHO is a partner of the Climate and Clean Air Coalition to Reduce Short-Lived Climate Pollutants

(CCAC). As a member of the CCAC's health task force, WHO is providing technical support for harnessing health benefits from actions to reduce short-lived climate pollutants, and working to scale up health sector engagement to address such pollutants and improve air quality.

Health, energy and sustainable development

Reductions in air pollution-related disease burden (both for household and outdoor) will be used to monitor the progress towards attaining the Sustainable Development Goal on Health (SDG 3).

Ensuring universal access to clean fuel and technologies is a target of the Sustainable Development Goal on energy (SDG 7). Achieving this goal could prevent millions of deaths and improve the health and well-being of the billions of people relying on polluting technologies and fuels for cooking, heating and lighting.

To better assess the health risks of household energy use, as well as differentiated gender impacts from household energy practices, WHO is leading an effort with countries and surveying agencies (e.g. USAID's DHS, UNICEF'S MICS, World Bank's LSMS) to enhance, harmonize and pilot questions for national censuses and surveys. The effort will ensure that surveys better capture information on all the fuels and technologies used in the home for cooking, heating and lighting, as well as other impacts like time lost to fuel collection disaggregated by sex.

WHO also supports international initiatives to improve air pollution and related health impacts such as the Global Alliance for Clean Cookstoves and the Climate Clean Air Coalition.

(1) WEO-2017 Special Report: Energy Access Outlook, International Energy Agency, 2017 (<https://webstore.iea.org/weo-2017-special-report-energy-access-outlook>)

2. JAPANESE ENCEPHALITIS

KEY FACTS

- Japanese encephalitis virus (JEV) is a flavivirus related to dengue, yellow fever and West Nile viruses, and is spread by mosquitoes.
- JEV is the main cause of viral encephalitis in many countries of Asia with an estimated 68 000 clinical cases every year.
- Although symptomatic Japanese encephalitis (JE) is rare, the case-fatality rate among those with encephalitis can be as high as 30%. Permanent neurologic or psychiatric sequelae can occur in 30%–50% of those with encephalitis.

- 24 countries in the WHO South-East Asia and Western Pacific regions have endemic JEV transmission, exposing more than 3 billion people to risks of infection.
- There is no cure for the disease. Treatment is focused on relieving severe clinical signs and supporting the patient to overcome the infection.
- Safe and effective vaccines are available to prevent JE. WHO recommends that JE vaccination be integrated into national immunization schedules in all areas where JE disease is recognized as a public health issue.

Japanese encephalitis virus JEV is the most important cause of viral encephalitis in Asia. It is a mosquito-borne flavivirus, and belongs to the same genus as dengue, yellow fever and West Nile viruses.

The first case of Japanese encephalitis viral disease (JE) was documented in 1871 in Japan.

The annual incidence of clinical disease varies both across and within endemic countries, ranging from <1 to >10 per 100 000 population or higher during outbreaks. A literature review estimates nearly 68 000 clinical cases of JE globally each year, with approximately 13 600 to 20 400 deaths. JE primarily affects children. Most adults in endemic countries have natural immunity after childhood infection, but individuals of any age may be affected.

Signs and symptoms

Most JEV infections are mild (fever and headache) or without apparent symptoms, but approximately 1 in 250 infections results in severe clinical illness. Severe disease is characterized by rapid onset of high fever, headache, neck stiffness, disorientation, coma, seizures, spastic paralysis and ultimately death. The case-fatality rate can be as high as 30% among those with disease symptoms. Of those who survive, 20%–30% suffer permanent intellectual, behavioural or neurological problems such as paralysis, recurrent seizures or the inability to speak.

Transmission

24 countries in the WHO South-East Asia and Western Pacific regions have JEV transmission risk, which includes more than 3 billion people.

JEV is transmitted to humans through bites from infected mosquitoes of the *Culex* species (mainly *Culex tritaeniorhynchus*). Humans, once infected, do not develop sufficient viraemia to infect feeding mosquitoes. The virus exists in a transmission cycle between mosquitoes, pigs and/or water birds (enzootic cycle). The disease is predominantly found in rural and periurban settings, where humans live in closer proximity to these vertebrate hosts.

In most temperate areas of Asia, JEV is transmitted mainly during the warm season, when large epidemics can occur. In the tropics and subtropics, transmission can occur year-round but often intensifies during the rainy season and pre-harvest period in rice-cultivating regions.

Diagnosis

Individuals who live in or have travelled to a JE-endemic area and experience encephalitis are considered a suspected JE case. To confirm JEV infection and to rule out other causes of encephalitis requires a laboratory testing of serum or, preferentially, cerebrospinal fluid.

Surveillance of the disease is mostly syndromic for acute encephalitis. Confirmatory laboratory testing is often conducted in dedicated sentinel sites, and efforts are undertaken to expand laboratory-based surveillance. Case-based surveillance is established in countries that effectively control JE through vaccination.

Treatment

There is no antiviral treatment for patients with JE. Treatment is supportive to relieve symptoms and stabilize the patient.

Prevention and control

Safe and effective JE vaccines are available to prevent disease. WHO recommends having strong JE prevention and control activities, including JE immunization in all regions where the disease is a recognized public health priority, along with strengthening surveillance and reporting mechanisms. Even if the number of JE-confirmed cases is low, vaccination should be considered where there is a suitable environment for JE virus transmission. There is little evidence to support a reduction in JE disease burden from interventions other than the vaccination of humans.

There are 4 main types of JE vaccines currently in use: inactivated mouse brain-derived vaccines, inactivated Vero cell-derived vaccines, live attenuated vaccines, and live recombinant vaccines.

Over the past years, the live attenuated SA14-14-2 vaccine manufactured in China has become the most widely used vaccine in endemic countries, and it was prequalified by WHO in October 2013. Cell-culture based inactivated vaccines and the live recombinant vaccine based on the yellow fever vaccine strain have also been licensed and WHO-prequalified. In November 2013, Gavi opened a funding window to support JE vaccination campaigns in eligible countries.

All travellers to Japanese encephalitis-endemic areas should take precautions to avoid mosquito bites to reduce the risk for JE. Personal preventive measures include the use of repellents, long-sleeved clothes, coils and vaporizers. Travellers spending extensive time in JE endemic areas are recommended to get vaccinated.

Disease outbreaks

Major outbreaks of JE occur every 2-15 years. JE transmission intensifies during the rainy season, during which vector populations increase. However, there has not yet been evidence of increased JEV transmission following major floods or tsunamis. The spread of JEV in new areas has been correlated with agricultural development and intensive rice cultivation supported by irrigation programmes.

WHO responds to JE by:

- providing global recommendations for JE control, including the use of vaccines. WHO recommends JE immunization in all regions where the disease is a recognized public health priority and supports implementation.
- providing technical support for JE surveillance, JE vaccine introduction and large-scale JE vaccination campaigns, and evaluation of JE vaccine effectiveness and programmatic impact.

3. MENINGOCOCCAL MENINGITIS

KEY FACTS

- Meningococcal meningitis is a bacterial form of meningitis, a serious infection of the thin lining that surrounds the brain and spinal cord.
- Meningococcal meningitis is associated with high fatality (up to 50% when untreated) and high frequency (more than 10%) of severe sequelae. Early antibiotic treatment is the most important measure to save lives and reduce complications.
- Meningococcal meningitis is observed worldwide but the highest burden of the disease is in the meningitis belt of sub-Saharan Africa, stretching from Senegal in the west to Ethiopia in the east. Around 30 000 cases are still reported each year from that area.
- Serogroup specific vaccines are used for prevention (routine immunization) and in response to outbreaks (prompt reactive vaccination).
- Since 2010 and the roll-out of a meningococcal A conjugate vaccine through mass preventive immunization campaigns in the meningitis belt, the proportion of the A serogroup has declined dramatically.

A variety of organisms including different bacteria, fungi or viruses, can cause meningitis. Meningococcal meningitis, a bacterial form of meningitis, is a serious infection of the meninges that affects the brain membrane. It can cause severe brain damage and is fatal in 50% of cases if untreated.

Meningococcal meningitis, caused by *Neisseria meningitidis* bacteria, is of particular importance due to its potential to cause large epidemics. Twelve types of *N. meningitidis*, called serogroups, have been identified, six of which (A, B, C, W, X and Y) can cause epidemics.

Meningococcal meningitis is observed in a range of situations, from sporadic cases, small clusters, to huge epidemics throughout the world, with seasonal variations. The disease can affect anyone of any age, but mainly affects babies, preschool children and young people.

The geographic distribution and epidemic potential differ according to the serogroup. There are no reliable estimates of global meningococcal disease burden due to inadequate surveillance in several parts of the world. The largest burden of meningococcal disease occurs in an area of sub-Saharan Africa known as the meningitis belt, which stretches from Senegal in the west to Ethiopia in the east (26 countries). During the dry season between December to June, dust winds, cold nights and upper respiratory tract infections combine to damage the nasopharyngeal mucosa, increasing the risk of meningococcal disease. At the same time, transmission of *N. meningitidis* may be facilitated by overcrowded housing. This combination of factors explains the large epidemics which occur during the dry season in the meningitis belt.

Transmission

Neisseria meningitidis only infects humans; there is no animal reservoir. The bacteria are transmitted from person-to-person through droplets of respiratory or throat secretions from carriers. Smoking, close and prolonged contact – such as kissing, sneezing or coughing on someone, or living in close quarters with a carrier – facilitates the spread of the disease. Transmission of *N. meningitidis* is facilitated during mass gatherings (recent examples include the Haj pilgrimage, and jamborees).

The bacteria can be carried in the throat and sometimes overwhelms the body's defences allowing the bacteria to spread through the bloodstream to the brain. It is believed that 1% to 10% of the population carries *N. meningitidis* in their throat at any given time. However, the carriage rate may be higher (10% to 25%) in epidemic situations.

Symptoms

The average incubation period is four days, but can range between two and 10 days. The most common symptoms are a stiff neck, high fever, sensitivity to light, confusion, headaches and vomiting. In addition in infants bulging fontanelle and ragdoll appearance are commonly found. A less common but even more severe (often fatal) form of meningococcal disease is meningococcal septicaemia, which is characterized by a haemorrhagic rash and rapid circulatory collapse. Even when the disease is diagnosed early and adequate treatment is started, 8% to 15% of patients die, often within 24 to 48 hours after the onset of symptoms. If untreated, meningococcal meningitis is fatal in 50% of cases and may result in brain damage, hearing loss or disability in 10% to 20% of survivors.

Diagnosis

Initial diagnosis of meningococcal meningitis can be made by clinical examination followed by a lumbar puncture showing a purulent spinal fluid. The bacteria can sometimes be seen in microscopic examinations of the spinal fluid. The diagnosis is supported or confirmed by growing the bacteria from specimens of spinal fluid or blood, by agglutination tests or by polymerase chain reaction (PCR). The identification of the serogroups and susceptibility testing to antibiotics are important to define control measures.

Surveillance

Surveillance, from case detection to investigation and laboratory confirmation is essential to the control of meningococcal meningitis. Main objectives include:

- Detect and confirm outbreaks.
- Monitor the incidence trends, including the distribution and evolution of meningococcal serogroups.
- Estimate the disease burden.
- Monitor the antibiotic resistance profile.
- Monitor the circulation, distribution and evolution of specific meningococcal strains (clones).
- Estimate the impact of meningitis control strategies, particularly preventive vaccination programs.

Treatment

Meningococcal disease is potentially fatal and should always be viewed as a medical emergency. Admission to a hospital or health centre is necessary. Isolation of the patient is not necessary. Appropriate antibiotic treatment must be started as soon as possible, ideally after the lumbar puncture has been carried out if such a puncture can be performed immediately. If treatment is started prior to the lumbar puncture it may

be difficult to grow the bacteria from the spinal fluid and confirm the diagnosis. However confirmation of the diagnosis should not delay treatment.

A range of antibiotics can treat the infection, including penicillin, ampicillin and ceftriaxone. Under epidemic conditions in Africa in areas with limited health infrastructure and resources, ceftriaxone is the drug of choice.

Prevention

1. Vaccination

Licensed vaccines against meningococcal disease have been available for more than 40 years. Over time, there have been major improvements in strain coverage and vaccine availability, but to date no universal vaccine against meningococcal disease exists. Vaccines are serogroup specific and confer varying degrees of duration of protection.

There are three types of vaccines available:

- Polysaccharide vaccines are used during a response to outbreaks, mainly in Africa:
 - They are either bivalent (serogroups A and C), trivalent (A, C and W), or tetravalent (A, C, Y and W).
 - They are not effective before 2 years of age.
 - They offer a 3-year protection but do not induce herd immunity.
- Conjugate vaccines are used in prevention (into routine immunization schedules and preventive campaigns) and outbreak response:
 - They confer longer-lasting immunity (5 years and more), prevent carriage and induce herd immunity.
 - They can be used as soon as of one year of age.
 - Available vaccines include:
 - Monovalent C
 - Monovalent A
 - Tetravalent (serogroups A, C, Y, W).
- Protein based vaccine, against *N. meningitidis B*. It has been introduced into the routine immunization schedule (one country as of 2017) and used in outbreak response.

2. Chemoprophylaxis

Antibiotic prophylaxis for close contacts, when given promptly, decreases the risk of transmission.

- Outside the African meningitis belt, chemoprophylaxis is recommended for close contacts within the household.
- In the meningitis belt, chemoprophylaxis for close contacts is recommended in non-epidemic situations.

Ciprofloxacin antibiotic is the antibiotic of choice, and ceftriaxone an alternative.

Global public health response – the recent meningococcal A conjugate vaccine introduction success in Africa

WHO promotes a strategy comprising epidemic preparedness, prevention, and outbreak control. Preparedness focuses on surveillance, from case detection to investigation and laboratory confirmation. Prevention consists of vaccinating individuals from age groups at major risk using a conjugate vaccine targeting appropriate serogroups. Epidemic response consists of prompt and appropriate case management and reactive mass vaccination of populations not already protected through vaccination.

Meningitis epidemics in the African meningitis belt constitute an enormous public health burden. In December 2010, a new meningococcal A conjugate vaccine was introduced in Africa through mass campaigns targeting persons 1 to 29 years of age. As of November 2017, more than 280 million persons have been vaccinated in 21 African belt countries.

The vaccine is remarkably safe and cheap (around US\$ 0.60 per dose while other meningococcal vaccine prices range from US\$ 2.50 to US\$ 117.00 per dose (1)). In addition, its thermostability allows its use under Controlled Temperature Chain (CTC) conditions. Its impact on carriage and the reduction in disease and epidemics is significant: a 58% decline in meningitis incidence and 60% decline in the risk of epidemics were described. It is now introduced into routine infant immunization. Maintaining high coverage is expected to eliminate meningococcal A epidemics from this region of Africa. However, other meningococcal serogroups such as W, X and C still cause epidemics and around 30 000 cases are reported each year in the meningitis belt. WHO is committed to eliminating meningococcal disease as a public health problem.

(1) These are indicative prices from the public and private sector, as reported by UNICEF, PAHO and CDC.

4. TUBERCULOSIS

KEY FACTS

- Tuberculosis (TB) is one of the top 10 causes of death worldwide.
- In 2016, 10.4 million people fell ill with TB, and 1.7 million died from the disease (including 0.4 million among people with HIV). Over 95% of TB deaths occur in low- and middle-income countries.
- Seven countries account for 64% of the total, with India leading the count, followed by Indonesia, China, Philippines, Pakistan, Nigeria, and South Africa.
- In 2016, an estimated 1 million children became ill

with TB and 250 000 children died of TB (including children with HIV associated TB).

- TB is a leading killer of HIV-positive people: in 2016, 40% of HIV deaths were due to TB.
- Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. WHO estimates that there were 600 000 new cases with resistance to rifampicin – the most effective first-line drug, of which 490 000 had MDR-TB. Globally, TB incidence is falling at about 2% per year. This needs to accelerate to a 4–5% annual decline to reach the 2020 milestones of the End TB Strategy.
- An estimated 53 million lives were saved through TB diagnosis and treatment between 2000 and 2016.
- Ending the TB epidemic by 2030 is among the health targets of the Sustainable Development Goals.

Tuberculosis (TB) is caused by bacteria (*Mycobacterium tuberculosis*) that most often affect the lungs. Tuberculosis is curable and preventable.

TB is spread from person to person through the air. When people with lung TB cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected.

About one-quarter of the world's population has latent TB, which means people have been infected by TB bacteria but are not (yet) ill with the disease and cannot transmit the disease.

People infected with TB bacteria have a 5–15% lifetime risk of falling ill with TB. However, persons with compromised immune systems, such as people living with HIV, malnutrition or diabetes, or people who use tobacco, have a much higher risk of falling ill.

When a person develops active TB disease, the symptoms (such as cough, fever, night sweats, or weight loss) may be mild for many months. This can lead to delays in seeking care, and results in transmission of the bacteria to others. People with active TB can infect 10–15 other people through close contact over the course of a year. Without proper treatment, 45% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die.

Who is most at risk?

Tuberculosis mostly affects adults in their most productive years. However, all age groups are at risk. Over 95% of cases and deaths are in developing countries. People who are infected with HIV are 20 to 30 times more likely to develop active TB (see TB and HIV section below). The risk of active TB is also greater in persons suffering from other conditions that impair the immune system.

One million children (0–14 years of age) fell ill with TB, and 250 000 children (including children with HIV associated TB) died from the disease in 2016.

Tobacco use greatly increases the risk of TB disease and death. 8% of TB cases worldwide are attributable to smoking.

Global impact of TB

TB occurs in every part of the world. In 2016, the largest number of new TB cases occurred in Asia, with 45% of new cases, followed by Africa, with 25% of new cases.

In 2016, 87% of new TB cases occurred in the 30 high TB burden countries. Seven countries accounted for 64% of the new TB cases: India, Indonesia, China, Philippines, Pakistan, Nigeria, and South Africa. Global progress depends on advances in TB prevention and care in these countries.

Symptoms and diagnosis

Common symptoms of active lung TB are cough with sputum and blood at times, chest pains, weakness, weight loss, fever and night sweats. Many countries still rely on a long-used method called sputum smear microscopy to diagnose TB. Trained laboratory technicians look at sputum samples under a microscope to see if TB bacteria are present. Microscopy detects only half the number of TB cases and cannot detect drug-resistance.

The use of the rapid test Xpert MTB/RIF® has expanded substantially since 2010, when WHO first recommended its use. The test simultaneously detects TB and resistance to rifampicin, the most important TB medicine. Diagnosis can be made within 2 hours and the test is now recommended by WHO as the initial diagnostic test in all persons with signs and symptoms of TB. More than 100 countries are already using the test and 6.9 million cartridges were procured globally in 2016.

Diagnosing multi-drug resistant and extensively drug-resistant TB (see Multidrug-resistant TB section below) as well as HIV-associated TB can be complex and expensive. In 2016, 4 new diagnostic tests were recommended by WHO – a rapid molecular test to detect TB at peripheral health centres where Xpert MTB/RIF cannot be used, and 3 tests to detect resistance to first- and second-line TB medicines.

Tuberculosis is particularly difficult to diagnose in children and as yet only the Xpert MTB/RIF assay is generally available to assist with the diagnosis of paediatric TB.

Treatment

TB is a treatable and curable disease. Active, drug-susceptible TB disease is treated with a standard 6 month course of 4 antimicrobial drugs that are provided with information, supervision and support

to the patient by a health worker or trained volunteer. Without such support, treatment adherence can be difficult and the disease can spread. The vast majority of TB cases can be cured when medicines are provided and taken properly.

Between 2000 and 2016, an estimated 53 million lives were saved through TB diagnosis and treatment.

TB and HIV

People living with HIV are 20 to 30 times more likely to develop active TB disease than people without HIV.

HIV and TB form a lethal combination, each speeding the other's progress. In 2016 about 0.4 million people died of HIV-associated TB. About 40% of deaths among HIV-positive people were due to TB in 2016. In 2016, there were an estimated 1.4 million new cases of TB amongst people who were HIV-positive, 74% of whom were living in Africa.

WHO recommends a 12-component approach of collaborative TB-HIV activities, including actions for prevention and treatment of infection and disease, to reduce deaths.

Multidrug-resistant TB

Anti-TB medicines have been used for decades and strains that are resistant to 1 or more of the medicines have been documented in every country surveyed. Drug resistance emerges when anti-TB medicines are used inappropriately, through incorrect prescription by health care providers, poor quality drugs, and patients stopping treatment prematurely.

Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, the 2 most powerful, first-line anti-TB drugs. MDR-TB is treatable and curable by using second-line drugs. However, second-line treatment options are limited and require extensive chemotherapy (up to 2 years of treatment) with medicines that are expensive and toxic.

In some cases, more severe drug resistance can develop. Extensively drug-resistant TB (XDR-TB) is a more serious form of MDR-TB caused by bacteria that do not respond to the most effective second-line anti-TB drugs, often leaving patients without any further treatment options. In 2016, MDR-TB remains a public health crisis and a health security threat. WHO estimates that there were 600 000 new cases with resistance to rifampicin – the most effective first-line drug – of which 490 000 had MDR-TB. The MDR-TB burden largely falls on 3 countries – India, China and the Russian Federation – which together account for nearly half of the global cases. About 6.2% of MDR-TB cases had XDR-TB in 2016.

Worldwide, only 54% of MDR-TB patients and 30% of XDR-TB are currently successfully treated. In 2016, WHO approved the use of a short, standardised regimen for MDR-TB patients who do not have strains that are resistant to second-line TB medicines. This regimen takes 9–12 months and is much less expensive than the conventional treatment for MDR-TB, which can take up to 2 years. Patients with XDR-TB or resistance to second-line anti-TB drugs cannot use this regimen, however, and need to be put on longer MDR-TB regimens to which 1 of the new drugs (bedaquiline and delamanid) may be added.

WHO also approved in 2016 a rapid diagnostic test to quickly identify these patients. More than 35 countries in Africa and Asia have started using shorter MDR-TB regimens. By June 2017, 89 countries had introduced bedaquiline and 54 countries had introduced delamanid, in an effort to improve the effectiveness of MDR-TB treatment regimens.

WHO response

WHO pursues 6 core functions in addressing TB:

- Providing global leadership on matters critical to TB.
- Developing evidence-based policies, strategies and standards for TB prevention, care and control, and monitoring their implementation.
- Providing technical support to Member States, catalyzing change, and building sustainable capacity.
- Monitoring the global TB situation, and measuring progress in TB care, control, and financing.
- Shaping the TB research agenda and stimulating the production, translation and dissemination of valuable knowledge.
- Facilitating and engaging in partnerships for TB action.

The WHO *End TB Strategy*, adopted by the World Health Assembly in May 2014, is a blueprint for countries to end the TB epidemic by driving down TB deaths, incidence and eliminating catastrophic costs. It outlines global impact targets to reduce TB deaths by 90%, to cut new cases by 80% between 2015 and 2030, and to ensure that no family is burdened with catastrophic costs due to TB.

Ending the TB epidemic by 2030 is among the health targets of the newly adopted Sustainable Development Goals. WHO has gone one step further and set a 2035 target of 95% reduction in deaths and a 90% decline in TB incidence – similar to current levels in low TB incidence countries today.

The Strategy outlines three strategic pillars that need to be put in place to effectively end the epidemic:

- Pillar 1: integrated patient-centred care and prevention
 - Pillar 2: bold policies and supportive systems
 - Pillar 3: intensified research and innovation
- The success of the Strategy will depend on countries respecting the following 4 key principles as they implement the interventions outlined in each pillar:
- government stewardship and accountability, with monitoring and evaluation
 - strong coalition with civil society organizations and communities
 - protection and promotion of human rights, ethics and equity
 - adaptation of the strategy and targets at country level, with global collaboration.

5. YELLOW FEVER

KEY FACTS

- Yellow fever is an acute viral haemorrhagic disease transmitted by infected mosquitoes. The “yellow” in the name refers to the jaundice that affects some patients.
- Symptoms of yellow fever include fever, headache, jaundice, muscle pain, nausea, vomiting and fatigue.
- A small proportion of patients who contract the virus develop severe symptoms and approximately half of those die within 7 to 10 days.
- The virus is endemic in tropical areas of Africa and Central and South America.
- Large epidemics of yellow fever occur when infected people introduce the virus into heavily populated areas with high mosquito density and where most people have little or no immunity, due to lack of vaccination. In these conditions, infected mosquitoes of the *Aedes aegypti* species transmit the virus from person to person.
- Yellow fever is prevented by an extremely effective vaccine, which is safe and affordable. A single dose of yellow fever vaccine is sufficient to confer sustained immunity and life-long protection against yellow fever disease. A booster dose of the vaccine is not needed. The vaccine provides effective immunity within 10 days for 80-100% of people vaccinated, and within 30 days for more than 99% of people vaccinated.
- Good supportive treatment in hospitals improves survival rates. There is currently no specific antiviral drug for yellow fever.
- The Eliminate Yellow fever Epidemics (EYE) Strategy launched in 2017 is an unprecedented initiative. With more than 50 partners involved,

the EYE partnership supports 40 at-risk countries in Africa and the Americas to prevent, detect, and respond to yellow fever suspected cases and outbreaks. The partnership aims at protecting at-risk populations, preventing international spread, and containing outbreaks rapidly. By 2026, it is expected that more than 1 billion people will be protected against the disease.

Signs and symptoms

Once contracted, the yellow fever virus incubates in the body for 3 to 6 days. Many people do not experience symptoms, but when these do occur, the most common are fever, muscle pain with prominent backache, headache, loss of appetite, and nausea or vomiting. In most cases, symptoms disappear after 3 to 4 days.

A small percentage of patients, however, enter a second, more toxic phase within 24 hours of recovering from initial symptoms. High fever returns and several body systems are affected, usually the liver and the kidneys. In this phase people are likely to develop jaundice (yellowing of the skin and eyes, hence the name 'yellow fever'), dark urine and abdominal pain with vomiting. Bleeding can occur from the mouth, nose, eyes or stomach. Half of the patients who enter the toxic phase die within 7 - 10 days.

Diagnosis

Yellow fever is difficult to diagnose, especially during the early stages. A more severe case can be confused with severe malaria, leptospirosis, viral hepatitis (especially fulminant forms), other haemorrhagic fevers, infection with other flaviviruses (such as dengue haemorrhagic fever), and poisoning.

Polymerase chain reaction (PCR) testing in blood and urine can sometimes detect the virus in early stages of the disease. In later stages, testing to identify antibodies is needed (ELISA and PRNT).

Populations at risk

Forty seven countries in Africa (34) and Central and South America (13) are either endemic for, or have regions that are endemic for, yellow fever. A modelling study based on African data sources estimated the burden of yellow fever during 2013 was 84 000–170 000 severe cases and 29 000–60 000 deaths.

Occasionally travellers who visit yellow fever endemic countries may bring the disease to countries free from yellow fever. In order to prevent such importation of the disease, many countries require proof of vaccination against yellow fever before they will issue a visa, particularly if travellers come from, or have visited yellow fever endemic areas.

In past centuries (17th to 19th), yellow fever was transported to North America and Europe, causing large outbreaks that disrupted economies, development and in some cases decimated populations.

Transmission

The yellow fever virus is an arbovirus of the flavivirus genus and is transmitted by mosquitoes, belonging to the *Aedes* and *Haemogogus* species. The different mosquito species live in different habitats - some breed around houses (domestic), others in the jungle (wild), and some in both habitats (semi-domestic). There are 3 types of transmission cycles:

- Sylvatic (or jungle) yellow fever: In tropical rainforests, monkeys, which are the primary reservoir of yellow fever, are bitten by wild mosquitoes of the *Aedes* and *Haemogogus* species, which pass the virus on to other monkeys. Occasionally humans working or travelling in the forest are bitten by infected mosquitoes and develop yellow fever.
- Intermediate yellow fever: In this type of transmission, semi-domestic mosquitoes (those that breed both in the wild and around households) infect both monkeys and people. Increased contact between people and infected mosquitoes leads to increased transmission and many separate villages in an area can develop outbreaks at the same time. This is the most common type of outbreak in Africa.
- Urban yellow fever: Large epidemics occur when infected people introduce the virus into heavily populated areas with high density of *Aedes aegypti* mosquitoes and where most people have little or no immunity, due to lack of vaccination or prior exposure to yellow fever. In these conditions, infected mosquitoes transmit the virus from person to person.

Treatment

Good and early supportive treatment in hospitals improves survival rates. There is currently no specific anti-viral drug for yellow fever but specific care to treat dehydration, liver and kidney failure, and fever improves outcomes. Associated bacterial infections can be treated with antibiotics.

Prevention

1. Vaccination

Vaccination is the most important means of preventing yellow fever.

The yellow fever vaccine is safe, affordable and a single dose provides life-long protection against yellow fever disease. A booster dose of yellow fever vaccine is not needed.

Several vaccination strategies are used to prevent yellow fever disease and transmission: routine infant immunization; mass vaccination campaigns designed to increase coverage in countries at risk; and vaccination of travellers going to yellow fever endemic areas.

In high-risk areas where vaccination coverage is low, prompt recognition and control of outbreaks using mass immunization is critical. It is important to vaccinate most (80% or more) of the population at risk to prevent transmission in a region with a yellow fever outbreak.

There have been rare reports of serious side-effects from the yellow fever vaccine. The rates for these severe 'adverse events following immunization' (AEFI), when the vaccine provokes an attack on the liver, the kidneys or on the nervous system are between 0 and 0.21 cases per 10 000 doses in regions where yellow fever is endemic, and from 0.09 to 0.4 cases per 10 000 doses in populations not exposed to the virus (1).

The risk of AEFI is higher for people over 60 years of age and anyone with severe immunodeficiency due to symptomatic HIV/AIDS or other causes, or who have a thymus disorder. People over 60 years of age should be given the vaccine after a careful risk-benefit assessment.

People who are usually excluded from vaccination include:

- infants aged less than 9 months;
- pregnant women – except during a yellow fever outbreak when the risk of infection is high;
- people with severe allergies to egg protein; and
- people with severe immunodeficiency due to symptomatic HIV/AIDS or other causes, or who have a thymus disorder.

In accordance with the International Health Regulations (IHR), countries have the right to require travellers to provide a certificate of yellow fever vaccination. If there are medical grounds for not getting vaccinated, this must be certified by the appropriate authorities. The IHR are a legally binding framework to stop the spread of infectious diseases and other health threats. Requiring the certificate of vaccination from travellers is at the discretion of each State Party, and it is not currently required by all countries.

2. Vector control

The risk of yellow fever transmission in urban areas can be reduced by eliminating potential mosquito breeding sites, including by applying larvicides to water storage containers and other places where standing water collects.

Both vector surveillance and control are components of the prevention and control of vector-borne diseases,

especially for transmission control in epidemic situations. For yellow fever, vector surveillance targeting *Aedes aegypti* and other *Aedes* species will help inform where there is a risk of an urban outbreak.

Understanding the distribution of these mosquitoes within a country can allow a country to prioritize areas to strengthen their human disease surveillance and testing, and consider vector control activities. There is currently a limited public health arsenal of safe, efficient and cost-effective insecticides that can be used against adult vectors. This is mainly due to the resistance of major vectors to common insecticides and the withdrawal or abandonment of certain pesticides for reasons of safety or the high cost of re-registration.

Historically, mosquito control campaigns successfully eliminated *Aedes aegypti*, the urban yellow fever vector, from most of Central and South America. However, *Aedes aegypti* has re-colonized urban areas in the region, raising a renewed risk of urban yellow fever. Mosquito control programmes targeting wild mosquitoes in forested areas are not practical for preventing jungle (or sylvatic) yellow fever transmission.

Personal preventive measures such as clothing minimizing skin exposure and repellents are recommended to avoid mosquito bites. The use of insecticide-treated bed nets is limited by the fact that *Aedes* mosquitoes bite during the daytime.

3. Epidemic preparedness and response

Prompt detection of yellow fever and rapid response through emergency vaccination campaigns are essential for controlling outbreaks. However, underreporting is a concern – the true number of cases is estimated to be 10 to 250 times what is now being reported.

WHO recommends that every at-risk country have at least one national laboratory where basic yellow fever blood tests can be performed. A confirmed case of yellow fever in an unvaccinated population is considered an outbreak. A confirmed case in any context must be fully investigated. Investigation teams must assess and respond to the outbreak with both emergency measures and longer-term immunization plans.

WHO response

In 2016, two linked urban yellow fever outbreaks – in Luanda (Angola) and Kinshasa (Democratic Republic of the Congo), with wider international exportation from Angola to other countries, including China – have shown that yellow fever poses a serious global threat requiring new strategic thinking. The Eliminate Yellow Fever Epidemics (EYE) Strategy

was developed to respond to the increased threat of yellow fever urban outbreaks with international spread. Steered by WHO, UNICEF, and Gavi, the Vaccine Alliance, EYE supports 40 countries and involves more than 50 partners.

The global EYE Strategy is guided by three strategic objectives:

1. protect at-risk populations
2. prevent international spread of yellow fever
3. contain outbreaks rapidly.

These objectives are underpinned by five competencies of success:

1. affordable vaccines and sustained vaccine market
2. strong political commitment at global, regional and country levels
3. high-level governance with long-term partnerships
4. synergies with other health programmes and sectors
5. research and development for better tools and practices.

The EYE strategy is comprehensive, multi-component and multi-partner. In addition to recommending vaccination activities, it calls for building resilient urban centres, planning for urban

readiness, and strengthening the application of the International Health Regulations (2005).

The EYE partnership supports yellow fever high and moderate risk countries in Africa and the Americas by strengthening their surveillance and laboratory capacity to respond to yellow fever cases and outbreaks. EYE partners also support the implementation and sustainability of routine immunization programmes and vaccination campaigns (preventive, pre-emptive, reactive) whenever and wherever needed.

To guarantee a rapid and effective response to outbreaks, an emergency stockpile of 6 million doses of yellow fever vaccine, funded by Gavi, is continually replenished. This emergency stockpile is managed by the International Coordinating Group for Vaccine Provision, for which WHO serves as secretariat.

It is expected that by the end of 2026, more than 1 billion people will be protected against yellow fever through vaccination.

(1) WHO. Detection and investigation of serious adverse events following yellow fever vaccination, Geneva, World Health Organization (WHO); 2008.