ISSN 1302-0072

The Medical Bulletin of Haseki

2021

Volume 59

Issue
March 2

www.hasekidergisi.com

The Medical Bulletin of Haseki

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Publisher Certificate Number: 14521

Online Publishing Date: March 2021

ISSN: 1302-0072 **E-ISSN:** 2147-2688

Üç ayda bir yayımlanan süreli yayındır.
International scientific journal published quarterly.

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The Medical Bulletin of Haseki is the official scientific journal of the University of Health Sciences Haseki Training and Research Hospital. It covers subjects on general medicine, published both in Turkish and English, and is independent, peer-reviewed, international periodical and is published quarterly (March, June, September and December).

The aim of The Medical Bulletin of Haseki is to publish original research papers of highest scientific and clinic value on general medicine. Additionally, educational material reviews on basic developments, editorial short notes and case reports are published.

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Phone: +90 212 529 44 00/1874
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The Medical Bulletin of Haseki

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The manuscript should not exceed 5000 words in total. All pages of the manuscript should be numbered at the top right-hand corner, except for the title page. Papers should include the necessary number of tables and figures in order to provide better understanding.

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The names, affiliated institutions and full addresses of the authors should be given. The author to whom correspondence is to be addressed should be indicated separately. As e-mail addresses will be used preferentially for communication, the e-mail address of the corresponding author should be stated. In addition, telephone and fax numbers must be notified.

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Editor of The Medical Bulletin of Haseki
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Adnan Adıvar Caddesi, 34906 Haseki-Aksaray-İstanbul-Turkey
Phone: +90 212 529 44 00/1874
Fax: +90 212 530 84 23
Web Page: www.hasekidergisi.com
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The Medical Bulletin of Haseki

Contents

Original Article

Original Article

DOI: 10.4274/haseki.galenos.2021.6925
Med Bull Haseki 2021;59:91-95

YouTube as a Health Information Source: COVID-19 and Andrology

Murat Demir, Kerem Taken, Recep Eryilmaz, Rahmi Aslan, Kasim Ertas

Van Yuzuncu Yıl University Faculty of Medicine, Department of Urology, Van, Turkey

Abstract

Aim: The purpose of this study is to evaluate the quality and reliability of YouTube videos about infertility, erectile dysfunction and sex relationship with coronavirus disease-2019 (COVID-19).

Methods: In this prospective study, videos were selected on 20.12.2020 and variable parameters were studied on the same day. Non-variable parameters such as quality and reliability were studied until 25.12.2020. "Corona, infertility", "corona, erectile dysfunction", "corona, sex", "COVID, infertility", "COVID, erectile dysfunction", COVID, sex", "pandemic, infertility" "pandemic, erectile dysfunction" and "pandemic, sex" search words scanned in a private search mode on the YouTube website. Unrelated, not English, do not contain any information videos excluded. The remaining videos were evaluated according to the presenter source and the presented audience with modified discern and Global Quality Scala (GQS) forms.

Results: Fourteen (14%) of 100 videos were about erectile dysfunction, 56 (56%) were about infertility and 30 (30%) were about sex. Fifteen (15%) of the videos were presented by individual sources, 4 (4%) by non-physician healthcare professionals, 48 (48%) by individual physicians, 17 (17%) by physician groups, 13 (13%) by news agencies, and 3 (3%) by private companies. While 87 (87%) of the target group was the general public, 13 (13%) of them were healthcare professionals. According to the presenter source, the modified discern and GQS scores of the physician group were higher than the other groups. However, the number of views and likes in these two groups was low.

Conclusion: Videos offered by physician groups and targeted by healthcare professionals on YouTube are of higher quality and more reliable. However, the popularity of videos is not a suitable indicator of quality.

Keywords: Social media, infertility, erectile dysfunction

Introduction

The new coronavirus disease-2019 (COVID-19) epidemic that started in Wuhan, China in December 2019 caused a serious health crisis worldwide in a short time (1). This infection, which was declared a pandemic by the World Health Organization on March 11 2020, has now caught more than 80 million people and nearly two million people have died (1). Despite social distancing and isolation measures, the number of cases is still increasing.

Pneumonia is the most common complication of COVID-19 (2). However, many studies have shown that other organs are also affected (3).

Andrologically, studies have indicated that the virus can cause erectile dysfunction and infertility (4,5). However, most of these studies are not yet strongly proven. However, such information has led to speculation on websites, news programs, and especially on social media, and has made people nervous (6). It has been stated that incomplete or incorrect information on social media is one of the most damaging issues to fight COVID-19 (7). It is possible that failure to inform the society completely and correctly can cause social chaos and panic (8). Therefore, it is important to filter information sources in this global crisis.

YouTube, which we used in our study, is the largest video site in the world and the second largest search page. This site has more than one billion users and hundreds of millions of videos (9,10). However, since videos do not pass any filter on this site, false and harmful information is shared as well as true information. In a study on breast cancer, most of the YouTube videos have misrepresented self-examination and by explaining that breast cancer is

Address for Correspondence: Murat Demir, Van Yuzuncu Yıl University Faculty of Medicine, Department of Urology, Van, Turkey
Phone: +90 542 621 43 13 E-mail: urologmurat72@gmail.com ORCID: orcid.org/0000-0001-5029-8800
Received: 13.01.2021 **Accepted:** 01.02.2021

seen only in women, it has been observed that there are false and harmful directions (11). YouTube videos on Zika and Ebola infections from previous public health crises have been viewed millions of times. However, studies have shown that most of the videos are misleading (12,13). For these reasons, it is important to evaluate videos in terms of quality and reliability.

In this study, the videos shared on the YouTube website about infertility, erectile dysfunction and sexuality relationship with COVID-19 were evaluated in terms of quality and reliability.

Methods

In this prospective study, after the approval of the local ethics committee (dated 01.12.2020 and numbered 2020/09-22), the videos were selected on 20.12.2020. At the same time, the number of likes, dislikes, views and comments, which are the variable data of the videos, was studied. The unvariable parameters (quality and reliability) were studied until 25.12.2020. On the YouTube website "corona, infertility", "corona, erectile dysfunction", "corona, sex", "COVID, infertility", "COVID, erectile dysfunction", COVID, sex" the keywords "pandemic, infertility" "pandemic, erectile dysfunction" and "pandemic, sex" were searched. The searches were made in incognito mode in the cache-cleared web browser where all updates were available. The upload date from the filters was adjusted according to "this year" and the ranking criterion relevance. Videos with keywords in the video title were included in the study.

After searching, 152 videos were evaluated. Videos that were repeated, non-English, irrelevant, or did not contain any audio or visual information were excluded.

The remaining 100 videos after these exclusion criteria were evaluated separately by two expert urologists (MD, RE). Reliability among experts was calculated by kappa statistics. When no consensus was reached, a third expert (RA) was consulted.

The duration of the videos included in the study, the number of views, upload time, number of comments, likes and dislikes were recorded. The videos were evaluated according to host sources and target audiences. Server sources were categorized into 6 groups as individual, non-physician healthcare provider, individual physician, physician group, journalist and private company.

The target audiences were categorized as healthcare professionals and the general audience.

Video topics were divided into 3 as erectile dysfunction, infertility, sex (transmission during sex, protection, sexual interference, etc.).

The Global Quality Score (GQS) form was used to evaluate the overall quality of the videos. This form consists of five degrees that question the quality, flow, information content and usefulness of the videos. GQS: 1 indicates poor quality, while GQS: 5 shows excellent quality (14).

Discern short modified form was used to evaluate the reliability of the videos. It is a modified version of the form developed by Modified Discern Charnock and Shepperd (15). In this form with a 5-rating, videos with 3 points are considered medium quality, while those who score more than 3 are considered quality, areas less than 3 are considered low quality.

Statistical Analysis

Descriptive statistics for continuous variables; it is expressed as average, standard deviation, minimum and maximum values, and expressed as numbers and percentages for categorical variables. One-way analysis of variance was used to compare group averages in terms of continuous variables. Following the variance analysis, Duncan multiple comparison test was used to identify different groups. Pearson correlation coefficients were calculated to determine the relationship between these variables. Chi-square test was used to determine the relationship between the groups and categorical variables. The statistical significance level was taken as 5% in the calculations and the SPSS statistical package program was used for calculations.

Results

After 152 videos were evaluated according to exclusion criteria, the remaining 100 videos were included in the study. The average upload time of the videos is 224.43±197 days, the length is 859.05±1.313 sec, the number of likes is 293.49±1110.55, the dislike is 112.14±477.60, the number of views is 26586.8±74207.1, and the number of comments is 10.8±397.94. The kappa coefficient among experts (MD, RE) was 0.91.

While there were 14 (14%) videos about erectile dysfunction, 56 (56%) were about infertility, and 30 (30%) were about sex. According to the topics of videos, the groups were homogeneous regarding length, number of likes and dislikes, views, comments, Discern and GQS results. Fifteen (15%) of the videos were individual sources, 4 (4%) non-physician healthcare professionals, 48 (48%) individual physicians, 17 (17%) physicians, 13 (13%) news agencies, 3 (3%) of them were offered by private firms. The properties of the videos by the server source are listed in Table 1.

While 87 (87%) of the target audience in the videos was the public, 13 (13%) were healthcare professionals. Considering the target audience of the videos, the duration of the videos made for healthcare professionals was significantly longer (p=0.001). However, there was no significant difference in terms of upload time, likes,

dislikes, views and comments of the videos. Videos with GQS 5 were significantly longer than other videos (p=0.001). While there was no significant difference in the number of likes according to the GQS values, the GQS 5 was significantly lower in the dislike numbers (p=0.02).

The number of views was highest in GQS 2 with an average of 71421.20 (p=0.02). There was no statistically significant difference in the number of comments compared to the GQS values. GQS scores according to the video source and target audience are in Table 2,3. According to the server, the Discern score was significantly higher in the physician group and compared to the target group in the healthcare group (Table 4).

Discussion

Today, the Internet has become a platform where information about health can be easily obtained. More than 80% of Americans use the Internet to obtain health information (16). The Internet is an easily accessible tool to obtain information on issues that have become taboo in society, especially sexual and reproductive health (17,18).

YouTube is the most popular video website with over 1 billion users and millions of videos. In a study conducted on male infertility, it was observed that Twitter, one of the social media platforms, refers to YouTube videos with the hashtag #maleinfertility and online traffic is directed to YouTube (19). In the study by Fode et al. (20), they showed that every month millions of people watch erectile dysfunction videos on YouTube.

In addition, according to YouTube data, 95% of Internet users use YouTube (21). For these reasons, the results we obtained are generalizable.

It was seen that most of the videos about the relationship between COVID-19 and ED, infertility and sexual health was shared by individual physicians, targeting the public. The highest scores in terms of the

Table 1. Video properties by server source

	Individual sources	Non-physician healthcare professionals	Individual physicians	Physician groups	News agencies	Private companies	p
Number of views	49402.27	3834.75	13863.94	341.35	94627.08	294.67	0.004*
Like	376.80	98.00	135.35	3.18	1286.62	9.33	0.02*
Dislike	35.73	52.75	44.85	0.12	639.15	1.0	0.002*
Comments	73.47	10.25	77.14	0.82	432.23	0.67	0.053
Upload time	136.27	159.50	181.94	147.94	117.00	164.00	0.92
Daily viewing	362.5	24.04	76.19	2.30	808.17	1.79	0.001*
Video duration	598.60	1193.75	464.00	2795.24	168.62	56.00	0.001*

(Number of views: News agency significantly high, Like: Physician groups significantly low, Dislike: Physician groups significantly low, Daily viewing: News agency significantly high and Video Duration: Physician groups significantly high) (one-way analysis of variance)

Table 2. GQS score according to target audience, physician's GQS were significantly high (p=<0.001) (chi-square-χ^2)

Target group	GQS 1	GQS 2	GQS 3	GQS 4	GQS 5	total
General	11	20	29	19	8	87
Physician	0	0	0	7	6	13
Total	11	20	29	26	14	100

GQS: Global Quality Scala

Table 3. GQS score by server resource, physician groups' GQS were significantly high (chi-square-χ2)

Video Source	GQS					Total	
	GQS 1	GQS 2	GQS 3	GQS 4	GQS 5		
Individual sources	4	9	2	0	0	15	
Non-physician healthcare professionals	0	0	1	2	1	4	
Individual physicians	0	4	24	16	4	48	p<0.001*
Physician groups	0	0	0	8	9	17	
News agencies	5	6	2	0	0	13	
Private companies	2	1	0	0	0	3	
Total	11	20	29	26	14	100	

GQS: Global Quality Scala

Table 4. Discern score according to the target audience		
	Discern score	**p (χ2)**
	Server resource	
Individual sources	1.3±0.48	-
Non-physician healthcare professionals	1.75±0.5	-
Individual physicians	2.6±0.49	p<0.05*
Physician groups	3.35±0.7	-
News agencies Private companies	1.3±0.47 1.3±0.50	- -
	Target Audience	
General population	2.14±0.84	p<0.05*
Healthcare professionals	3.30±0.63	-
(According to the server resource; the physician group, and according to the target audience; the healthcare professionals are significantly higher) (chi-square-χ2)		

quality and usefulness of the videos were the videos of the physician group. It is natural that there is more than one physician as a scientific resource in the physician group, and scientific quality increases due to the exchange of ideas and the transformation of speech into a scientific environment. Despite this, Discern and GQS scores of both physician groups and individual physicians were not at a satisfactory level in our study. The reason for this may be that the relationship between COVID-19 and andrological diseases is dark, the literature is inadequate, and there is no consensus among international health organizations. In the study in which Culha et al. (22) evaluated YouTube videos about pelvic floor muscle exercises, it was seen that the quality and reliable information was shared by healthcare professionals (doctors, nurses, physiotherapists) regardless of the branch. In addition, the Discern scores of the videos presented by healthcare professionals were higher than our study. This may be due to the general lack of knowledge between COVID-19 and andrological diseases. In the same study, healthcare providers obtained the highest GQS scores in line with our study (22). In addition, when the target audience in our study was healthcare professionals, it is thought that the increase in both the quality and reliability of the videos is because the information is given with more detailed and literature information.

In a study evaluating erectile dysfunction videos on YouTube, it was observed that the videos provided by groups of healthcare professionals were of higher quality than individual professionals and nonprofessional groups, in accordance with our study (13). Similar results were also obtained in a study on laryngeal cancer (23). Ku et al. (24) stated that YouTube videos can be useful for informing about infertility, but high-quality videos are needed. In the field of urology, Fode et al. (20) found the videos suspicious in their study, where they evaluated videos on erectile dysfunction on YouTube (20). In a study by Gul and Diri (25), they stated that there were many misleading videos about prematüre ejeculation on YouTube and they suggested that they should be removed. In our study, although the Discern and GQS scores were higher in the videos presented by the physician groups, it was still not at the desired level. In addition, these scores decrease even more in groups other than the physician group. These data also show that YouTube videos are not reliable and of sufficient quality.

In our study, it was observed that high-quality and reliable videos had a small number of views and likes. In another study on YouTube videos about COVID-19 and pregnancy relationship, it was observed that news agencies were the most watched videos, but their discern scores were low (26). Therefore, popularity does not seem to be a suitable criterion for predicting video quality. However, according to the results of our study, the number of dislikes can be a criterion in terms of reliability and quality.

Study Limitations

Our working together with all of these has some limitations. Since YouTube has a dynamic structure, new videos can be added and removed constantly, and the number of views, likes and dislikes can change. However, as only English language videos were used in our study, it had a relatively small sample. It should be kept in mind that although the video searches are made in incognito mode with the cache cleared, our geographic location and computer language may affect the search results.

Conclusion

As a result, although YouTube website has an important source of information in terms of COVID-19 and andrological problems, it is important to be careful in terms of the reliability and quality of the videos. It should also be known that non-physician server resources are unreliable enough.

Authorship Contributions

Concept: M.D., K.T., K.E., Design: M.D., K.T., R.E., R.A., K.E., Data Collection or Processing: M.D., K.T., R.E., R.A., K.E., Analysis or Interpretation: M.D., K.T., R.E., R.A., K.E., Literature Search: M.D., K.T., R.E., R.A., K.E., Writing: M.D., R.A., R.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2021.6601
Med Bull Haseki 2021;59:96-102

How did the COVID-19 Pandemic Affect Inappropriate Adult Emergency Department Attendances?: A Prospective Cross-Sectional Study

Perihan Simsek, Engin Ilhan*, Ozlem Bulbul*, Esra Ucuncu*, Murat Topbas**, Abdulkadir Gunduz*

Trabzon University, Faculty of Applied Science, Department of Emergency Aid and Disaster Management, Trabzon, Turkey

**Karadeniz Technical University Faculty of Medicine, Department of Emergency Medicine, Trabzon, Turkey*

***Karadeniz Technical University Faculty of Medicine, Department of Public Health, Trabzon, Turkey*

Abstract

Aim: During the coronavirus disease-2019 (COVID-19) pandemic, the strict limitations imposed on access to many healthcare institutions may effect emergency department (ED) attendances with regards to appropriateness. Thus, this study aimed to investigate the urgency level of ED attendances and the frequency of inappropriate use (IU) during the COVID-19 pandemic.

Methods: A prospective cross-sectional study was conducted in the university hospital ED during one week (May 11-17, 2020) of the post-peak period of the first wave of the COVID-19 pandemic. All adult (≥18 years) ED attendances were evaluated by emergency residents in terms of clinical and demographic characteristics and appropriateness. The data were recorded on data collection forms.

Results: IU rate detected was 45.1%. In the study, 3.9% and 9.5% of attendances were in Emergency Severity Index categories 1 and 2, respectively. A significant negative correlation was found between age and IU (odds ratio=0.978; 95% confidence interval: 0.96-0.99). According to the binary logistic regression analysis, it is most likely that IUs are young people who are employed and have no chronic disease.

Conclusion: This study showed that the frequency of IU decreased while the urgency level of the ED attendances increased in the post-peak period of the pandemic compared to a previous study conducted outside of the pandemic, in the same center. There was an inverse relationship between IU frequency and age. The results will help with planning ED services in future pandemic periods.

Keywords: Emergency department, COVID-19, inappropriate use, pandemic

Introduction

Affecting the whole world, coronavirus disease-2019 (COVID-19) infection was defined by the World Health Organization as a pandemic on March 11, 2020 (1). As the COVID-19 pandemic coincides with the seasonal influenza period and being the first center of attendance for infected people, there has been an increase in attendances at alarm levels in some emergency department (EDs) worldwide (2,3). Following the restrictive measures were taken to control the pandemic, ED attendance fell by approximately half (4). This may be owing to reasons such as people's fear of infection or reluctance to place a further strain on the healthcare system (5). However, delaying medical help, despite symptom progression may lead to the progression of the disease and a subsequent increase in very urgent ED attendances (6,7). On the other hand, limited access to health institutions during the pandemic and interruptions in the normal provision of healthcare services may also lead to the use of EDs for health problems that do not require urgent care (8).

The use of EDs for health problems that do not require urgent care is generally called "inappropriate use" (IU). No clear distinction has been made in terms of which attendances are "appropriate" and which are "inappropriate". However, the general approach in the

Address for Correspondence: Perihan Simsek, Trabzon University, Faculty of Applied Science, Department of Emergency Aid and Disaster Management, Trabzon, Turkey
Phone: +90 531 263 34 21 E-mail: p_simsek19@hotmail.com ORCID: orcid.org/0000-0002-0216-3968
Received 10.10.2020 **Accepted:** 10.02.2021

scientific world is that the appropriateness of the attendance is in line with the urgency level, and attendances that do not require urgent care are inappropriate (9). IU poses an important problem for EDs (10).

The IU of EDs prevents those who are in real need of ED services from benefiting from the limited resources of these departments in the best way possible, and it can lead to increased workloads for healthcare providers and disruption to ED service functions (9,10). It can also increase the costs of health services (11). Moreover, IU can contribute to ED crowding. ED crowding aggravates the workload and prolongs patient waiting times, diagnosis, and treatment processes (12). Furthermore, patients' use of EDs for monitoring chronic diseases deprives them of the preventative, specialized, and ongoing treatment services required to manage these diseases (13).

Examining the urgency level of ED attendances during pandemic periods and determining the IU rate are important for planning service resources, expanding capacity, and increasing efficiency during future pandemics (14). However, few studies have been conducted on how the urgency level of ED attendances is distributed and affected during pandemic periods (6,7).

In a two-seasonal-stage project (no: 216S972) (March and July 2018), the overall IU frequency in three EDs of different levels, including this study center, was found to be extremely high at 75.6%. In this study center only, the IU frequency was 74.1% in March (15). This study aimed to investigate if the urgency level of ED attendances and IU rate changed during the COVID-19 pandemic period.

Methods

Study Design and Setting

Ethical approval (no: 24237859-308) was obtained from the regional scientific research ethics committee. The necessary legal permission for the study was obtained from the Ministry of Health (no: 2020-05-06T041633). The participating patients were informed by the researcher physicians and verbal consent was obtained.

In Turkey, the highest number of daily new COVID-19 cases were reported on April 11th, 2020, the peak of the pandemic, and the pandemic curve began bending as of April 20th, 2020 (16,17). This cross-sectional study was conducted in the ED of a university hospital in Turkey's Eastern Black Sea Region for a week in the post-peak period of the COVID-19 pandemic (May 11th-17th, 2020). The ED has 38 beds. Daily attendances numbered around 250 before the pandemic, falling to approximately 100 during the COVID-19 pandemic. The ED serves as an emergency care center where patients who need advanced treatment are transferred from across the city and other provinces in the region. All patients admitted to the ED are assessed by the triage officers and the urgency level is determined according to the color-coding triage system, which was proposed by the Ministry of Health in 2009. According to this system, outpatients whose general condition is stable are green; patients who are at risk of death or limb loss are yellow; urgent patients who need immediate care are coded in red (18).

Selection of Participants

All ED attendances by adults (≥18) during the study week constituted the study sample. Patients meeting the following inclusion criteria were included in the study ≥18 years of age, volunteered participants (consent was obtained from relatives of patients who were unconscious because of mental disorders, substance influence, etc.). Attendances to establish vascular access for diagnostic tests (computerized tomography, magnetic resonance imaging, etc.) were excluded.

Data Collection

In the study period, all ED attendances were evaluated in terms of clinical and demographic characteristics, and appropriateness. The evaluation was prospectively made by ED residents and the data were recorded on the data collection form developed by the researchers based on their experiences and the literature (9,10). In determining the appropriateness of the attendances, the IU criteria used in the project (no: 216S973) conducted by the researchers in 2018 were used (15). The IU criteria are as follows: being in the fifth or fourth category of the Emergency Severity Index (ESI), being able to wait at least 24 hours for medical care without any life-threatening risk or organ dysfunction according to physician assessment, not being referred from another institution, being able to access medical care and treatment required by current health problems from primary care centers, not requiring any surgical procedures.

Emergency Severity Index

The Emergency Nurses Association and the American College of Emergency Physicians reported five-level systems to be more suitable for determining the urgency level (19). Therefore, the ESI, a five-level triage system, was used to evaluate the urgency and appropriateness of attendance in this study. According to the system, patients are divided into main categories based on symptoms and need for resource use (20).

One week before the data were collected, training on the IU criteria and the ESI was organized for the resident physicians, who evaluated the attendances during the study period. This training included general information and decision points for the ESI 1 [40 minutes (min)], ESI

2 (30 min), ESI 3-5, and expected resource requirement (30 min), the role of vital findings in ESI (30 min).

Outcomes

The primary outcomes of the study were the appropriateness and urgency level of the ED attendances. These outcomes were measured according to the criteria mentioned above. The secondary outcomes of the study were the variables that can be related to IU, including demographic characteristics (age, gender, marital status, education, chronic disease, smoking, alcohol use), general characteristics of the attendances (attendance time, arrival type, triage category according to the ESI and color system, number of attendances in the last 6 months), and the clinical features (diagnosis, complaints, time of complaints onset). The diagnoses were presented according to the International Statistical Classification of Diseases and Related Health Problems-10 diagnostic codes.

Statistical Analysis

The data were analyzed using the IBM Statistical Package for Social Sciences (IBM; Armonk, NY, USA) program. Normal distribution was evaluated with the Kolmogorov-Smirnov test. The relationship between categorical variables was analyzed using the chi-square test. Factors associated with IU were evaluated using binary logistic regression analysis and the analysis results are presented as odds ratios (ORs) and 95% confidence intervals (CI). The statistical significance level was set to $p<0.05$. In multiple group comparisons, the significance level was determined according to the Bonferroni correction.

Results

During the study period, there were 578 adult attendances to the ED where the research was conducted. Of these, 11 patients refused to participate and the study was completed with 567 patients. The IU rate was determined as 45.1%.

The median age of the patients was 49 years (range=18-101 years), 55.2% were male, 82.2% were married, and 46.2% had completed primary education. The frequency of IU was found to be lower in patients over 65 years of age compared to other age groups (18-40 years, p=0.000; 41-64 years, p=0.000). It was found that IU was significantly lower in illiterate patients than other patients (p=0.000), while the IU rate of those with a bachelor's degree or higher education were significantly higher than those with just primary (p=0.006). The IU rate was higher in single people (p=0.012), smokers (p=0.001), and patients without the chronic disease (p=0.000). The IU rate for unemployed people was lower than for others (unemployed and official: p=0.001; unemployed and employed: p=0.000; unemployed and other: p=0.005) (Table 1).

Of the total attendances, 3.9% were in ESI 1; 9.5% were in ESI 2; 40.9% in the ESI 3; 31.0% were in ESI 4 and 14.6% were in ESI 5 category. According to the color triage system, 25.2% of the attendances were red, 26.5% yellow and 48.3% green. The highest frequency of inappropriate attendances (IA) was seen at night between 24:00 and 07:59, and there was a significant difference between this time interval and daytime (08:00-

Table 1. Characteristics of patients admitted to the ED (n=567)

Characteristics	Inappropriate n (%)	Appropriate n (%)	p
Age			
18-40	119[a] (58.6)	84 (41.4)	p=0.000
41-64	99[a] (48.5)	105 (51.5)	
≥65	38[b] (23.8)	122 (76.3)	
Gender			
Male	150 (47.9)	163 (52.1)	0.141
Female	106 (41.7)	148 (58.3)	
Marital status			
Married	199 (42.7)	267 (57.3)	0.012
Single	57 (56.4)	44 (43.6)	
Education			
Illiterate	17[a] (20.7)	65 (79.3)	p=0.000
Primary education	114[b] (43.1)	149 (56.9)	
High school	82[b,c] (53.9)	70 (46.1)	
Bachelor or higher	43[c] (61.4)	27 (38.6)	
Profession			
Officer	32[a] (60.4)	21 (39.6)	p=0.000
Employed	53[a] (44.2)	67 (55.8)	
Other	50[a] (48.5)	53 (51.5)	
Unemployed	187[b] (64.3)	104 (35.7)	
Chronic disease			
Yes	76 (29.7)	186 (59.8)	p=0.000
No	180 (59.0)	125 (41.0)	
Smoking			
Yes	98 (55.7)	78 (44.3)	0.001
No	158 (40.4)	233 (59.6)	
Alcohol			
Yes	13 (40.6)	19 (59.4)	0.729
No	243 (45.4)	292 (54.6)	
ED visits in the last 6 months			
First	92 (50.5)	90 (49.5)	0.076
≥2	164 (42.6)	221 (57.4)	

*There was no significant difference between the variables marked with the same letter (significance level according to Bonferroni correction is p<0.016 for age; p<0.008 for occupation and education) ED: Emergency department

15:59) in terms of IU rate (p=0.004). IA during the week (48.9%) were significantly higher than at the weekend (38.1%) (p=0.013) (Table 2).

The most frequent presenting complaint (18.8%) and diagnosis (14.8%) in IUs was headache. Appropriate attendances (AAs) were mostly diagnosed with chest pain, falls, nausea, and vomiting (7.1%), and the most common complaint was abdominal pain (22.2%) for AAs. The most common attendance time for IA after the onset of symptoms was more than 48 hours (24.6%), whereas AAs were often made within the first 3 hours of the complaint (42.8%) (Table 3).

Logistic regression analysis showed that the appropriateness of the attendances increased with age. The analysis revealed that employed people (OR: 1.75; 95% CI: 1.12-2.73) and people without chronic disease (OR: 2.22; 95% CI: 1.41-3.50) were more likely to make IAs. It was also ascertained that attendances on weekdays (OR: 2.00; 95% CI: 1.33-3.02), at least 12 hours after the onset of symptoms (OR: 3.36; 95% CI: 2.27-4.98), and between 24:00 and 07:59 (OR: 1.97; 95% CI: 1.14-3.43) were more likely to be inappropriate. It was determined that alcohol users (OR: 0.36; 95% CI: 0.15-0.88), and those who made more than one attendance within the last 6 months (OR: 0.62; 95% CI: 0.41-0.94) were less likely to make IAs (Table 4).

Table 2. General characteristics of ED attendances (n=567)

	Inappropriate	Appropriate	p
	n (%)	n (%)	
Time			
08:00-15:59	88[a] (40.6)	129 (59.4)	0.013
16:00-23:59	109[a,b] (44.0)	139 (56.0)	
24:00-07:59	59[b] (57.8)	43 (42.2)	
Day			
Weekdays	181 (48.9)	189 (51.1)	0.013
Weekends	75 (38.1)	122 (61.9)	
Type of arrival			
Ambulance	11[a] (7.5)	135 (92.5)	p=0.000
Car	206[b] (55.1)	168 (44.9)	
On foot	39[c] (83.0)	8 (17.0)	
Color triage			
Green	249 (90.9)	25 (9.1)	p=0.000
Yellow/red	7 (2.4)	286 (97.6)	
ESI			
ESI 1	-	22 (100.0)	-
ESI 2	-	54 (100.0)	
ESI 3	-	232 (100.0)	
ESI 4	174 (98.9)	2 (1.1)	
ESI 5	82 (98.8)	1 (1.2)	

*There was no statistically significant difference between the variables marked with the same letter (the significance level was set to p<0.016 according to the Bonferroni correction) ED: Emergency department, ESI: Emergency Severity Index

Discussion

The results showed that during the COVID-19 pandemic period, approximately half of the ED attendances were inappropriate. It was also found that IAs increased during the weekdays and at night. The frequency of IA was high in young people and low in illiterate patients. In addition, employed patients and patients without chronic diseases were found to be more likely to make IAs.

In this study conducted during the COVID-19 pandemic period, the frequency of IA was determined to be 45.1%. In the previous study conducted in the same center using the same descriptive criteria in March 2018, the frequency of IU was found to be 74.1% (15). The use of different IU criteria and seasonal differences may limit the comparison of IU rates between studies (10). However, on comparing the results of the current study to a study by Gündüz et al. (15), it is observed that the frequency of IAs decreased during the pandemic period. Similarly, according to Brick et al. (6), the "non-urgent" attendance rate, which was 31.9% in March 2019, dropped to 7.5% in March 2020 as a result of the COVID-19 pandemic. Moreover, Czeisler et al. (21)

Table 3. Clinical characteristics of ED attendances (n=567)

Inappropriate		Appropriate	
Diagnosis	**n (%)**		**n (%)**
R51 headache	38 (14.8)	R07.4 chest pain	22 (7.1)
J06.9 URTI	29 (11.3)	R11 nausea and vomiting	22 (7.1)
M79.18 myalgia	22 (8.6)	W19 fall	22 (7.1)
Z51.9 medical care	17 (6.6)	R10.4 abdominal pain	19 (6.1)
R52.9 pain	15 (5.9)	I67.8 cerebrovascular disease	17 (5.5)
Attendance complaints			
Headache	48 (18.8)	Abdominal pain	69 (22.2)
Nausea vomiting	35 (13.7)	Nausea vomiting	53 (17.0)
Joint limb pain	25 (9.8)	Joint limb pain	47 (15.1)
Backache	23 (9.0)	Weakness	34 (10.9)
Throat ache	22 (8.6)	Chest pain	33 (10.6)
Complaint starting time before attending the hospital			
≤3 hours	55 (21.5)	≤3 hours	133 (42.8)
>3 hours, <24 hours	34 (13.3)	>3 hours, <24 hours	59 (19.0)
24 hours	53 (20.7)	24 hours	50 (16.1)
48 hours	51 (19.9)	48 hours	40 (12.9)
>48 hours	63 (24.6)	>48 hours	29 (9.3)

ED: Emergency department, URTI: Upper respiratory tract infection

found that, during the pandemic, there was a decrease in the number of ED attendances for health problems such as otitis media, superficial injuries, and sprains and strains for which treatment and care could be provided in primary care. Czeisler et al. (21) also reported that pandemic-related concerns caused potential ED attendees to avoid presenting to the ED. In the current study, the decrease in IAs was presumed closely related to concern about the pandemic. Furthermore, during the pandemic period, social restrictions and curfews can be considered among other main factors that may reduce the IA rate.

Table 4. Factors associated with inappropriate use (n=567)

	OR*	95% CI	B	Wald	Sig.
Age	0.98	0.96-0.99	-0.02	7.41	0.006
Marital status					
Single	Reference				
Married	1.20	0.66-2.15	0.18	0.35	0.553
Attendance time					
08:00-15:59	Reference				
16:00-23:59	1.01	0.66-1.55	0.01	0.00	0.948
24:00-07:59	1.97	1.14-3.43	0.68	5.82	0.016
Attendance day					
Weekend	Reference				
Weekdays	2.00	1.33-3.02	0.69	10.91	0.001
Education					
Illiterate	Reference				
Primary education	1.10	0.51-2.35	0.09	0.06	0.808
High school	1.08	0.44-2.66	0.07	0.03	0.872
Graduate and higher	1.33	0.48-3.65	0.28	0.30	0.583
Chronic disease					
Yes	Reference				
No	2.22	1.41-3.50	0.80	11.82	0.001
Number of attendances in the last 6 months					
First	Reference				
>1	0.62	0.41-0.94	-0.48	5.08	0.024
Onset of symptoms					
≤12 hours	Reference				
>12 hours	3.36	2.27-4.98	1.21	36.62	0.000
Profession					
Unemployed	Reference				
Employed	1.75	1.12-2.73	0.56	6.00	0.014
Alcohol use					
No	Reference				
Yes	0.36	0.15-0.88	-1.01	5.04	0.025
Smoking status					
No	Reference				
Yes	1.46	0.90-2.36	0.38	2.31	0.128
Constant	1.62		0.48	1.21	0.272

*Odds ratio, CI: Confidence interval

The attendances in the ESI 1 category constituted 3.9% of all attendances and code-red attendances were 25.2% of all attendances. Gündüz et al. (15) reported that the proportion of ESI 1 category attendances was 1.8% and the proportion of red-coded attendances was 8.8%. The results obtained from the studies conducted at the same center before and during the COVID-19 pandemic period showed that the attendances with high-level urgency increased significantly during the COVID-19 pandemic. The clinical picture worsens and the level of urgency increases as a result of delaying attendance because of concern about getting infected during the pandemic period.

During the COVID-19 pandemic, there were more IAs at night than in the daytime. Conversely, it was reported by Gündüz et al. (15) and for other studies conducted around the world that IAs were concentrated in the daytime (08:00-18: 00), while attendances made at night were more urgent (22,23). However, other studies have reported that IAs increase after working hours owing to difficulties accessing primary healthcare services (24,25). During the COVID-19 pandemic period, patients may prefer to attend ED at night for non-urgent health problems because there are likely to be fewer people so the contact risk is lower.

The rate of IAs was higher on weekdays than on weekends. This finding is consistent with the study by Gündüz et al. (15). On the contrary, in Eroğlu et al. (25) study in Turkey and McHale et al. (23) study in the UK, it was reported that the highest numbers of IAs were on Saturday. The current study center is located within the university campus so the high IA rate during the week before the pandemic is thought to be related to university students preferring the center for non-urgent health problems. In addition, the curfew applied on weekends may have caused higher rates of weekday IAs.

The IA rate was higher in the young. Similarly, in the majority of studies worldwide (9,10,26) the frequency of IA was found to be higher in the young. However, there are also studies showing that the frequency of IA is not affected by age (27,28). The presence of chronic diseases in the elderly and their care needs being more complicated than those of young people are among the reasons why attendances are more urgent in this age group (29). Furthermore, during the COVID-19 pandemic in Turkey, the strict curfew for those over 65 years old may have a protective effect against some health problems because they are staying home and not falling, having accidents etc.

The frequency of IA was lower in illiterate individuals compared to others. This result is thought to be related to the fact that the majority of illiterate individuals are over 65 years old. It was also determined that employed people made more IAs. This difference may have arisen from unemployed people avoiding going outside unless it is essential during the pandemic.

The majority of IAs were made due to headaches and the second most common reason for IAs was upper respiratory tract infection (URTI). Gündüz et al. (15) reported that URTI was the most frequent reason for IAs. Comparing two studies, the decrease in URTI-related IAs during the pandemic period may be associated with the social distancing rules and the use of masks to control the spread of respiratory-borne diseases. Examing the pre-pandemic literature, the most common causes of IAs are URTI and pain (26,27,30,31).

Study Limitations

Our work clearly has some limitations. Conducting the research in a single-center is the main limitation of the study. Furthermore, the study period was limited to one week and it was conducted only during the post-peak period of the pandemic, and other periods of the pandemic (the initial and peak periods, and when restrictions were lifted) were not compared with the non-pandemic periods. In addition, the fact that the study was conducted in Ramadan month creates an important limitation for the study because fasting can have a confounding effect on ED attendance.

Conclusion

This study showed that the rate of IU decreased and the urgency level of the attendances increased during the COVID-19 pandemic period. There were more IAs at night than during the daytime. There was an inverse relationship between the frequency of IA and age. The results of this study are important for planning ED resources and increasing service capacity during pandemics. In this regard, multi-center studies on a large sample are needed.

Author Contributions

Concept: P.S., A.G., E.I., O.B., E.U., M.T., Design: P.S., A.G., M.T., Data Collection or Processing: E.I., O.B., E.U., Analysis or Interpretation: P.S., M.T., A.G., Literature Search: P.S., E.I., A.G., M.T., O.B., E.U., Writing: P.S., M.T., A.G., E.I.,

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2021.6764
Med Bull Haseki 2021;59:103-107

SARS-CoV-2 Infection in Intensive Care Unit Healthcare Workers in Turkey: A Tertiary Center Cohort Study

Sinan Uzman, Tulin Akarsu Ayazoglu*

University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Turkey
**Medeniyet University Faculty of Medicine, Department of Anesthesiology and Reanimation, Istanbul, Turkey*

Abstract

Aim: Intensive care unit (ICU) workers have a greater risk of being infected due to procedures requiring intensive contact with the coronavirus disease-2019 (COVID-19) patient. We aimed to explain how we applied the protection of healthcare workers against the contagion of COVID-19 infection in the ICU of a university hospital.

Methods: The study was performed in ICUs of the Goztepe Training Research Hospital with 650 beds which was affiliated to Medeniyet University in Istanbul, Turkey. We recorded the number of COVID-19 patients. We also recorded ICU workers (doctor, nurse, and others), and their working layouts. The frequency of the contagion of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to ICU workers was investigated. We also evaluated precautions for the prevention and evaluated the arrangement of ICUs for COVID-19 patients.

Results: Between March 17th 2020 and May 26th 2020 totaly, a total of 120 hospitalized COVID-19 patients were treated in ICUs. Laboratory confirmed COVID-19 was detected in only one health-care worker in ICUs.

Conclusion: Our experience showed that the correct and proper use of personal protective equipment according to the protocols are effective in protecting ICU workers against the contagion of SARS-CoV-2.

Keywords: COVID-19, SARS-CoV-2, intensive care unit, health-care workers, personal protective equipment

Introduction

Since the first case of coronavirus disease-2019 (COVID-19) was identified in Istanbul city of Turkey on March 9th, 2020, healthcare workers have been battling against the COVID-19 caused by a new type of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). After which despite all the efforts, the number of cases increased exponentially and more than one hundred fifty thousand new cases of COVID-19 were diagnosed until May 19th. Besides that Ministry of Health has been reported that 4199 patients died due to this infection as of May 19th in Turkey (Figure 1).

Healthcare workers are at high risk for the contagion of COVID-19 infection. The National Health Commission of China has been reported that 1,716 (3.8% of laboratory-confirmed cases) health-care workers had been infected with the COVID-19 infection on February 14th 2020 (2). The number of infected health-care workers increased rapidly to 3387, as of 25 February 2020 (3). As of April 30th, The Turkish Minister of Health announced that the number of infected health workers was 7428 (6.18% of laboratory-confirmed cases) (4).

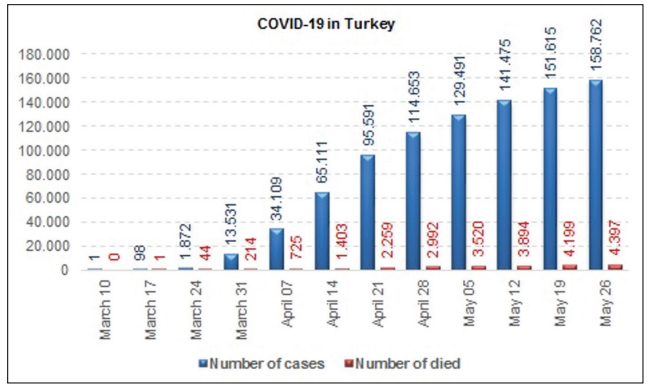

Figure 1. COVID-19 in Turkey
COVID-19: Coronavirus disease-2019

Address for Correspondence: Sinan Uzman, University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Turkey
Phone: +90 505 564 52 71 E-mail: drsinanuzman@yahoo.com ORCID: orcid.org/0000-0003-3166-7302
Received: 01.12.2020 **Accepted:** 28.01.2021

Although there are official recommendations from the World Health Organization (WHO) and other national and international communities to protect healthcare workers from this infection, the facilities and resources required for their implementation may not be sufficient in all centers dealing with the treatment of SARS-CoV-2 infection.

Especially ICU workers are at a greater risk of being infected due to procedures requiring intensive contact such as respiratory therapy, vascular and urinary catheterization and, nursing care with the COVID-19 patient. It has been reported that severe pneumonia with progressive hypoxemia requiring mechanical ventilatory support in the ICU may occur during the course of COVID-19 approximately in 12-17% of patients (5,6). Thereby, in this article, we aimed to explain how we applied the protection of healthcare workers against the contagion of COVID-19 infection in the ICU and to identify healthcare workers infected with COVID-19.

Methods

Study Design

The study protocol was approved by the local hospital ethics committee (date/number: June 3th 2020/0325) and conducted according to the Declaration of Helsinki. The study was performed in the ICUs of the Goztepe Training and Research Hospital with 650 beds which were affiliated to Medeniyet University in Istanbul, Turkey. Before the WHO declared a pandemic on March 11th, 2020, arrangements were performed in the hospital and the admission and triage protocols were established for the confirmed or suspected COVID-19 patients according to the Republic of Turkey Ministry of Health COVID-19 guidelines.

Statistical Analysis

A hospital audit database was used to obtain study data. Data extracted from the audit database were provided using hospital computer software (Nucleus, Monad software, Cankaya, Ankara, Turkey). We recorded the number of COVID-19 patients. We also recorded the ICU workers (physician, nurse, and others) and their working orders. We investigated the frequency of contagion of SARS-CoV-2 to ICU workers in the ICUs and Intermediate Care Unit (IMCU). Also, we evaluated precautions for the prevention and evaluated the arrangement of ICUs for COVID-19 patients.

Intensive Care Unit (ICU) admissions are dependent on the severity of the infection and in accordance with the established criteria such as requiring invasive respiratory support, hemodynamic support with vasoactive drugs, the patients were admitted to our two ICUs with 8 (ICU-I) and 6 (ICU-II) beds. ICU-I and II were on the first and second floor of the emergency building respectively. In addition, a 5-room service (1 bed in each room) was created on the same floor with the ICU-I for the patients who received high-flow nasal cannula (HFCN) oxygen therapy IMCU. Thus, this area was separated from the other parts of the hospital.

Results

Between March 17th 2020 and May 26th 2020 a total of 120 of 871 hospitalized COVID-19 patients were treated in ICUs and IMCU. Laboratory confirmed COVID-19 was detected in only one health-care worker in ICUs from the admission of the first case to the ICU on March 17th, 2020 until May 26th 2020.

A shift work scheduled was prepared for 21 anesthesiologists, 25 residents (21 anesthesiology and 4 internal medicine), 47 nurses, and 19 other personnel (totally 112). ICUs and IMCU were managed by two anesthesiology and reanimation specialist who has an academic degree (associate professor) from Monday until Friday between 08 am and 16 pm during the study period. One of the remaining 19 anesthesiologists worked in shifts (16 pm-08 am from Monday to Friday and 24 hours on the weekend). In each of ICU-I and ICU-II two anesthesia residents and, in the IMCU one of the internal medicine residents served for 24 hours. Sixteen or 24-hour shifts were set up for nurses and other personnel. In each shift, 4 nurses were assigned for ICU-I and, 3 for ICU-II and IMCU. All doctors and nurses were on leave for two or three days after the shift.

Nasopharyngeal and throat swabs were obtained from all ICU workers to perform reverse transcription-polymerase chain reaction (RT-PCR) analysis for SARS-CoV-2 at least once regardless of the presence of symptoms. COVID-19 IgM and IgG dual antibody (Colloidal Gold) rapid test kit (Guanzhou Weimi Bio-Tech Co., Ltd., China) for finger-prick blood samples was used as a screening test for COVID-19. On April 17th, a nurse suffered from fever, sore throat, and cough while on leave and she was diagnosed with COVID-19 confirmed by RT-PCR. She had no respiratory distress and posteroanterior chest radiography was normal. She was isolated at home for 15 days and successfully treated with hydroxychloroquine (2x400 mg loading dose and 2x200 mg for five days) and azithromycin (first day 500 mg, then four days 250 mg).

Discussion

Laboratory confirmed (RT-PCR) COVID-19 was observed in only one of 112 (0.09%) ICU workers. How did we manage to minimize the number of infected ICU workers? For this purpose, we offer the following precautionary

suggestions for the ICU procedures based on available evidence. Furthermore, we share our domestic experiences.

I. Training About COVID-19

While our first COVID-19 patient has not yet been admitted to the ICU, after the WHO declared a pandemic on March 11th, ICU workers consisting of doctors, nurses, and cleaning staff have been trained about the upcoming process by the infection control committee of our hospital. Insufficient attention to personal protection measures at the beginning of the epidemic due to lack of knowledge in Wuhan was the most important reason why healthcare workers get infected (7). It has been reported that the presence of health workers who died or got sick due to COVID-19 and, rumors and misinformation led to an increase in the level of anxiety in healthcare workers and a decrease in the will to work (8). Informing and educating of healthcare professionals about the disease and process was important in terms of applying personal protective measures, relieving their anxiety, and ensuring their motivation.

II. Precautions of Prevention During the Procedures for Respiratory Support

The contagion of the SARS-CoV-2 occurs mainly through respiratory droplets and close contact. Therapeutic interventions for respiratory support including ambu/mask ventilation, endotracheal intubation, non-invasive mechanical ventilation, high-flow nasal catheter therapy, bronchoscopy, and endotracheal suction are aerosol-generating procedures and have a high risk of virus transmission as it increases the risk of direct contact with the droplet (9,10). Personal protective equipment (PPE) (Special work clothes, surgical bonnet, FFP2/N95, latex glove, goggles, face shield, protective clothing, and rubber boot) was used to minimize transmission and it was always available in sufficient numbers. Donning and removing of PPE to manage COVID-19 patients is performed carefully in accordance with the protocols (11).

1. Endotracheal Intubation

We tried to perform endotracheal intubation via a video-guided laryngoscope under elective conditions as much as possible. We developed a transparent fiberglass protective box for tracheal intubation (Figure 2). The patient's airway was evaluated for difficult intubation. We applied preoxygenation for 3 minutes with 100% oxygen. Then we used midazolam 2-3 mg plus fentanyl 50-100 µgr or ketamin 1-2 mg/kg and high doses of rocuronium (1.5 mg/kg) to ensure sedation and muscle relaxation. We performed rapid intubation within 50 seconds following low-pressure mask ventilation. Endotracheal intubations are performed by the most experienced anesthesiologist. Our results showed that all of the endotracheal intubations were smoothly performed on the first attempt. The tube cuff was inflated sufficiently to prevent the droplets from spreading with the patient's exhaled air before the ventilation was initiated.

Figure 2. Protective fiberglass box during the airway intervention

2. HFNC Oxygen Therapy

We applied the HFNC treatment at a rate of 45-60 L/min oxygen [2/fraction of inspired oxygen (FiO_2) between 0.4-0.6]. Cough is a common symptom in COVID-19 patients. Therefore, patients were allowed to wear N95 masks during HFNC oxygen therapy. Furthermore, when applying HFNC, we paid attention to the tight and correct placement of the nasal catheter in order to minimize lateral losses.

3. Endotracheal Aspiration

We used a closed suction system for endotracheal sputum aspiration in patients with invasive ventilation.

4. Invasive Mechanical Ventilation

The type of ventilators available in our ICUs was Servo-i Maquet and Engström Pro. Sterile medical gas was supplied to the ventilator from the central oxygen and air system and, there was no ventilator to use air compressor in our ICUs.

During mechanical ventilation, aerosol particles carrying the virus discharged by the patient's exhaled air and cause pollution of the environment. The condensate which may carry viruses forms in the breathing circuit. Therefore we used a single-use two limbs ventilator circuit with two water traps. We placed virus filters on both the inspiratory and expiratory sides of the breathing circuit which was kept closed during mechanical ventilation. We did not replace the ventilator circuits without any obvious pollution. On the other hand, virus filters were replaced daily. The water accumulated in the water traps as a result of condensation was discharged into a cup containing disinfectant. During the replacement of the ventilator circuit and filters and, discharging of the water traps mechanical ventilator was turned off for eliminating the pollution of the environment by the patient's exhaled air.

5. Weaning and Extubation

Spontaneous breathing trial with T-tube has the risk of aerosols spread and lower success rate of extubation than the pressure support ventilation (PSV) for weaning (12). Therefore, we used to used PSV and continuous positive airway pressure modes for the gradual decrease of withdrawal from ventilatory support during the weaning from mechanical ventilation.

Cough and sputum may occur frequently during the removal of the tracheal tube. We placed an aspiration catheter into the mouth to remove secretions before extubation. To prevent the droplets from spreading, we used a protective box, which was sprayed with a disinfectant on its inner surface during the tracheal extubation, and covered the patient with a disposable bedspread. After extubation, we applied HFNC as described above.

III. Other treatment procedures

Procedures requiring intensive contact with the COVID-19 patient including urinary catheterization, placement of the nasogastric catheter, central venous catheterization, and other vascular procedures were carried out using PPE as in respiratory interventions.

Hydroxychloroquine has *in vitro* activity against the SARS-CoV-2 virus and it decreases viral load in nasopharyngeal swabs. Its antiviral effects may be due to inhibition of virus entry and immune modulation (13-15). Therefore, hydroxychloroquine was considered as a potential drug for the treatment of COVID-19 at the onset of the pandemic (16). Nevertheless, in a systematic review and meta-analysis, it has been reported that hydroxychloroquine does not improve clinical outcomes in COVID-19 (17). Moreover, it has been demonstrated that hydroxychloroquine was not useful as postexposure prophylaxis for COVID-19 (18). However, whether pre-exposure prophylaxis would be beneficial in high-risk populations is a distinct question, with trials ongoing. *In vitro*, it has been showing that hydroxychloroquine may be useful as a prophylactic agent against the SARS-CoV-2 virus especially for high-risk populations such as healthcare workers (19). In our hospital, all ICU workers received hydroxychloroquine phosphate (Plaquenil 200 mg, Sanofi Aventis, Turkey) 400 mg two times a week. We didn't observe any side effects related to hydroxychloroquine phosphate.

Study Limitations

There were several limitations to the present study. The retrospective nature of the study was the first one. Failure to consider other factors such as demographic characteristics, the existence of the concomitant disease, and medical treatment of ICU workers were the other limitations of the study.

Conclusion

Current data showed that approximately 12-17% of COVID-19 patients developed severe pneumonia requiring respiratory support treatment in the ICU (5,6). To the best of our knowledge theretofore it has not been reported the incidence of COVID-19 among ICU workers in the literature. Despite the high risk of contagion during the aerosol-generating respiratory interventions and the other procedures requiring close contact to the patient, the incidence of COVID-19 for our ICUs and IMCU workers was very low. Our experience showed that the correct and proper use of PPE according to the protocols is effective in protecting ICU workers against the contagion of SARS-CoV-2. Moreover informing and educating of healthcare professionals about the disease process and the use of PPE was also important. Although there is no evidence, prophylaxis with hydroxychloroquine may also have been useful.

Authorship Contributions

Concept: S.U., T.A.A., Design: S.U., T.A.A., Data Collection or Processing: T.A.A., Analysis or Interpretation: S.U., T.A.A., Literature Search: S.U., T.A.A., Writing: S.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2021.6538
Med Bull Haseki 2021;59:108-113

Evaluation of the Association between Gastrointestinal Symptoms and Laboratory Outcomes in Hospitalized COVID-19 Patients

Suleyman Ahbab, Fatih Turker, Betul Cavusoglu Turker*, Atay Can Kula, Fatma Pinar Ziyadanoglu, Pelin Acar, Elif Ceren Ak, Raife Dilhan Alcelik, Mufide Aydogan Ahbab**, Hayriye Esra Ataoglu

University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Internal Medicine Clinic, Istanbul, Turkey

**Taksim Training and Research Hospital, Clinic of Internal Medicine Clinic, Istanbul, Turkey*

***University of Health Sciences Turkey, Hamidiye Vocational School of Health Services, Istanbul, Turkey*

Abstract

Aim: The severe acute respiratory syndrome novel corona virus-2 (SARS-nCoV-2) which is an enveloped RNA virus was defined as the cause of Corona Virus Disease-2019 (COVID-19). Gastrointestinal (GI) symptoms can also be observed in COVID-19 patients. This study was performed to evaluate the association between GI symptoms and laboratory results.

Methods: This retrospective study was carried out in the University of Health Sciences Turkey, Istanbul Haseki Health Training and Research Hospital between 11th March and 1st June 2020. This study consisted of a total of 159 patients with COVID-19. COVID-19 infection was defined via a positive nasal and pharyngeal swab test. All symptoms of patients were recorded. Study patients were divided into 2 groups according to the presence of GI symptoms or not.

Results: There were 41 patients in the group with GI and 118 were in the group without GI symptoms. Nausea and/or vomiting were observed in 29, diarrhea in 20 and abdominal pain in 10 patients. Percentages of anosmia (loss of smell sense) and ageusia (loss of taste sense) increased in patients with GI symptoms than the other group ($p=0.005$ and <0.0001). The mean serum aspartate amino transferase (AST) level elevated in COVID-19 patients with GI symptoms ($p=0.022$).

Conclusion: Anosmia and ageusia increased significantly in COVID-19 patients with GI. Serum C-reactive protein and AST levels statistically increased in COVID-19 patients with GI.

Keywords: Gastrointestinal symptoms, SARS-nCoV-2, coronavirus disease-2019, laboratory

Introduction

The severe acute respiratory syndrome novel corona virus-2 (SARS-nCoV-2) which is a single-stranded enveloped RNA virus was declared as the cause of Coronavirus disease-2019 (COVID-19) pandemic by the World Health Organization (1). COVID-19 which first appeared in Wuhan, China continues to affect the world caused deaths of more than 800,000 infected patients globally (2). Respiratory symptoms as cough, expectoration, sore throat and shortness of breath occur commonly in COVID-19 patients and can lead to various clinical results from pneumonia to acute respiratory distress syndrome, respiratory failure and mortality (3). Angiotensin-converting enzyme 2 (ACE2) is a metallopeptidase located on the surface of the cellular membrane and has an important role in the pathogenesis of the infection. SARS-nCoV-2 specifically recognizes and binds to ACE2 by using its spike protein with a high affinity which is responsible for the virus invasion (4). Moreover, ACE2 is expressed in many organs especially in the lung tissue, nasopharyngeal mucosa, small intestine, colon, vascular endothelium and liver (5). In addition to the inflammatory parameters of laboratory analysis, radiological imaging as chest computed tomography (CT) is also a useful way to detect pulmonary

Address for Correspondence: Betul Cavusoglu Turker, Taksim Training and Research Hospital, Clinic of Internal Medicine Clinic, Istanbul, Turkey
Phone: +90 212 909 50 00 E-mail: cavusoglubetul@hotmail.com ORCID: orcid.org/0000-0002-8041-1904
Received 12.10.2020 **Accepted:** 20.01.2021

involvement of the infection. According to recent clinical observations, gastrointestinal (GI) symptoms such as nausea and/or vomiting, abdominal pain and diarrhea may occur in COVID-19 patients without respiratory and other constitutional symptoms (6-8). Patients with GI symptoms may reflect an elevated viral burden in these patients compared to those with only respiratory symptoms (9). It is important to take into account that many COVID-19 patients may present GI symptoms. The intestinal epithelial invasion by SARS-nCoV-2 may result in increased permeability and diminished barrier function with the presence of GI symptoms (9). In this study, it was aimed to better evaluate associations of the clinical characteristics and laboratory results between patients with and without GI symptoms.

Methods

Study Design

This retrospective study was carried out in the internal medicine inpatient clinic of the University of Health Sciences Turkey, Istanbul Haseki Health Training and Research Hospital between 11th March and 1st June 2020. The first official registered COVID-19 case was detected on 11th March 2020 in İstanbul, Turkey. University of Health Sciences Turkey, Istanbul Haseki Health Training Hospital has been designated as one of the pandemic center hospitals in Istanbul by the Turkish Ministry of Health. This study consisted of a total of 159 patients who admitted consecutively and hospitalized in the internal medicine clinic with suspected COVID-19. Patients with a positive clinical evaluation, biochemical tests and chest CT scan results were included in this study. Confirmed cases of COVID-19 infection were defined as with a positive nasal and pharyngeal swab test result from the laboratory (10). University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital's local Ethics Committee approved (registration no: 2020-62) the study design. Data for the study were derived from the electronic management system of the hospital. The database information was anonymized and approved by the ethics committee with no need for consent. GI and other symptoms of the patients on the admission to the hospital were recorded before medical treatment. Other symptoms were fever (≥38 °C), fatigue, muscle soreness, cough, sore throat, shortness of breath, anosmia (loss of smell sense), ageusia (loss of taste sense) and hemoptysis. Patients with GI symptoms defined as those who have at least one of the symptoms; nausea and/or vomiting, abdominal pain and diarrhea (more than 3 times a day with loose stools) without a recent history of antibiotic use. Study patients were divided into 2 groups according to the presence of GI symptoms and compared the laboratory findings. Intensive care unit (ICU) follow-up and mortality were determined as the primary endpoints in this study.

Biochemical Analysis and Radiological CT Imaging

The laboratory-confirmed COVID-19 based on real-time reverse transcriptase polymerase chain reaction assay for nasopharyngeal swab specimens. Complete blood counts, biochemical analysis and chest CT imaging were performed for all patients at the first admittance to the hospital. Complete blood counts were analyzed using the Sysmex XE 2100i device (Japan) by fluorescence flow cytometry. Biochemical parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), amylase, lipase, c-reactive protein (CRP), fibrinogen, D-dimer and ferritin were analyzed by using an Abbot Architect Analyzer System (IL, USA). Chest CT is an important method to detect COVID-19 related pulmonary lesions. Presence of bilateral involvement, ground-glass opacification, consolidation and pleural effusion findings were determined as the important findings on the chest CT scans for the possible pulmonary involvement (11). Chest CT scans were performed by using a 64-detector Philips Brilliance CT device (Philips Medical Systems, Cleveland, Ohio) and pulmonary involvement was examined. Study groups were compared according to the presence of other symptoms, laboratory parameters and chest CT results.

Statistical Analysis

Categorical variables were expressed as numbers and percentages. Study data were presented as the mean ± standard deviation. SPSS 16.0 for Windows was used to perform statistical analysis. The distributions of variables were assessed by using the Kolmogorov-Smirnov z-test. T-tests were used to analyze normally distributed variables, and the Mann-Whitney U test was used to analyze non-normally distributed variables. A p-value less than 0.05 was considered statistically significant.

Results

This study consisted of 159 patients who diagnosed with COVID-19 based on nasopharyngeal swab specimens, biochemical analyses and chest CT image results. Study patients were classified according to their symptom characteristics. There were 41 patients in the group with GI and 118 were in the group without GI symptoms. Nausea and/or vomiting were found in 29 (70.7%), loose stools in 20 (48.8%) and abdominal pain in 10 (24.4%) patients with GI symptoms. A total of 150 patients were recovered, 3 patients were lost and 6 patients were followed up in intensive care unit. The median age of patients with GI symptoms was 57 [minimum-maximum (min: 27-max: 81)] and without GI symptoms was 55

(min: 18-max: 91) years. Percentages of sore throat, anosmia and ageusia sense significantly elevated in patients with GI symptoms than the other group (p=0.035, 0.005 and <0.0001) as indicated in Table 1. The mean serum AST level significantly increased in patients with GI symptoms (p=0.022). Platelet and CRP levels were found to be significantly higher in patients with GI symptoms than those without (Table 2). Although serum ALT and amylase levels increased in patients with GI symptoms than others, no statistical significance was observed. According to the results of chest CT scans, percentage of pulmonary consolidation was found statistically increased in patients with GI symptoms (p<0.0001).

Discussion

GI symptoms are common observed in COVID-19 patients besides respiratory symptoms. These symptoms due to SARS-CoV-2 may be associated with invaded ACE2 expressing enterocytes in the small intestine, ileum and colon. GI system may be a potential route for SARS-CoV-2 infection and can explain the occurrence of GI symptoms (12). However ACE2 receptors are expressed diffusely on the mucous membrane of the whole oral cavity, particularly on the tongue (13), anosmia and ageusia may represent the first or only symptomatic manifestation of COVID-19 in GI system (14). In this study, anosmia and ageusia sense significantly increased in COVID-19 patients with GI symptoms. Likewise, we observed these sensory impairments as complete and sudden onset of anosmia and ageusia in the study patients. Patients with acute onset loss of smell and taste are considered that may have a close relation for concomitant SARS-CoV-2 infection (15). The mechanism of olfaction impairment by COVID-19 is not clarified. The possible hypotheses of anosmia can be related to direct viral damage of the olfactory sensory neurons and systemic inflammation (16-18). Furthermore, SARS-CoV-2 could occupy the taste buds on the tongue accelerating the degradation of the gustatory particles (19). Leichen et al. (20) reported that anosmia and ageusia were independently and strongly associated with a positive COVID-19 test. The recovery of smell and taste senses lasts for the first two weeks after the resolution of COVID-19 (20). In patients with COVID-19, anosmia is not usually accompanied by nasal obstruction unlike other causes of upper respiratory viral infections (21). In addition, ACE2 expression is higher in the small intestine, duodenum and colon. Patients with digestive symptoms have more viruses in the gut-based

Table 1. Comparisons of baseline characteristics and co-morbidities of the study groups

Characteristics	With GI symptoms (n=41)	Without GI symptoms (n=118)	p
Age, median (min-max)	57 (27-81)	55 (18-91)	0.774
Gender (F/M)	28/13	62/56	0.080
Fever†, n (%)	22/41 (53.7%)	54/118 (45.8%)	0.383
Fatigue†, n (%)	23/41 (56.1%)	56/118 (47.5%)	0.130
Muscle soreness†, n (%)	13/41 (31.7%)	22/118 (18.8%)	0.087
Cough†, n (%)	25/41 (61.0%)	61/118 (52.1%)	0.328
Sore throat†, n (%)	11/41 (26.8%)	15/118 (12.7%)	**0.035**
Shortness of breath†, n (%)	15/41 (37.5%)	40/118 (33.9%)	0,679
Anosmia†, n (%)	5/41 (12.2%)	2/118 (1.7%)	**0.005**
Ageusia†, n (%)	8/41 (19.5%)	3/118 (2.6%)	**<0.0001**
Hemoptysis†, n (%)	1/41 (2.4%)	2/118 (1.7%)	0.763
Co-morbidities			
Diabetes mellitus, n (%)	8/41 (19.5%)	40/118 (33.9%)	0.084
Hypertension, n (%)	23/41 (56.1%)	43/118 (37.1%)	**0.034**
Chronic heart disease, n (%)	6/41 (14.6%)	21/118 (18.1%)	0.613
Chronic lung disease, n (%)	4/41 (9.8%)	13/118 (11%)	0.822
Chronic kidney disease, n (%)	1/41 (2.4%)	6/118 (5.1%)	0.477
Hospitalization days, median (min-max)	9 (1-20)	8 (3-28)	0.224
Primary endpoints			0.235
ICU follow up, n (%)	1/41 (2.4%)	5/118 (4.2%)	
Mortality, n (%)	2/41 (4.8%)	1/118 (0.8%)	
Total, n (%)	3/41 (7.3%)	6/118 (5.1%)	

(†Presence of the symptom, ICU: intensive care unit), F: Female, M: Male, n: Number, Min: Minimum, Max: Maximum
(Statistically significant p values expressed in bold and italic)

Table 2. Comparisons of laboratory parameters and chest CT scan results of the study groups			
Parameters (normal ranges)	**With GI Symptoms (n=41)**	**Without GI Symptoms (n=118)**	**p**
Leukocyte (4.2-10.2x10^3/uL)	7.17±5.41	6.97±3.02	0.275
Neutrophil (1.56-6.13x10^3/uL)	4.37±2.30	4.64±2.59	0.550
Lymphocyte (1.18-3.57x10^3/uL)	1.59±0.60	1.64±0.89	0.704
Hemoglobin (12-16 g/dL)	12.81±1.59	12.63±1.96	0.575
Platelets (142-450x10^3/uL)	248.51±112.79	213.20±68.66	***0.019***
MPV (6.8-10.8 fL)	10.50±1.11	10.90±1.18	0.081
CRP (0-5 mg/L)	68.54±77.83	45.62±52.49	***0.037***
Procalcitonin (0-0.06 ng/mL)	0.22±0.87	0.19±0.51	0.844
Fibrinogen (180-350 mg/dL)	382.09±206.00	350.69±221.05	0.366
D-dimer (<0.55 mg/L)	1.71±2.87	1.22±2.79	0.159
Ferritin (11-306 ng/mL)	235.03±223.73	279.37±354.71	0.539
Albumin (35-52 g/dL)	35.70±6.08	36.43±4.49	0.460
LDH (120-247 U/L)	298.84±125.48	253.15±143.00	0.092
AST (<35 U/L)	45.80±46.59	32.27±23.81	***0.022***
ALT (<35 U/L)	36.57±54.56	26.39±21.53	0.093
GGT (<38 U/L)	51.24±47.50	56.23±84.29	0.744
ALP (30-120 U/L)	105.42±141.00	104.01±131.75	0.931
Amylase (28-100 U/L)	92.86±65.29	73.93±55.06	0.089
Lipase (<67 U/L)	46.76±36.52	42.25±41.62	0.325
Chest CT scan findings			
Bilateral involvement, n (%)	35/41 (85.4%)	86/118 (72.9%)	0.106
Ground-glass opacification, n (%)	30/41 (73.2%)	94/118 (79.7%)	0.388
Pulmonary consolidation, n (%)	24/41 (58.5%)	28/118 (23.7%)	***<0.0001***
Pleural effusion, n (%)	1/41 (2.4%)	10/118 (8.5%)	0.190

(MPV: Mean platelet volume, CRP: C-reactive protein, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase, CT: Computed tomography, n: Number of patients)
(Statistically significant p expressed in bold and italic)

on the stool RNA testing of SARS-CoV-2 results and thus potentially greater opportunity to suffer direct damage on the gut mucosa (22).

In this study, serum CRP and AST levels were found statistically higher in patients with GI symptoms than in other patients. Zhang et al. (23) reported elevated liver enzymes in approximately 15-50% of infected patients with COVID-19. Jin et al. (24) demonstrated significantly increased AST levels in COVID-19 patients with GI symptoms as an indicator for liver injury. Elevated ALT levels have also reported without acute liver failure in COVID-19 patients (25). Although there was an increase in serum ALT in patients with GI symptoms, statistical significance could not be achieved in this study. Agarwal et al. (26) reported that liver transaminases elevated mildly in many patients with COVID-19. An increase in the levels of liver enzymes in infected patients may be related to ACE2 receptors located on cholangiocytes and hepatocytes (26). Pancreatic islet cells potentially implicate the high level of ACE2 receptor expression and abnormalities in serum pancreatic enzyme levels may be observed in some cases (27). Although Wang et al. (28) reported serum pancreatic enzyme elevations in 9 of 52 patients with COVID-19, no case was observed with severe pancreatitis. In accordance with Wang et al. (28), serum amylase levels in patients with GI symptoms were found to be elevated compared to other group in this study, statistical significance was not achieved (p=0.089).

Study Limitations

This study has some limitations. First, this study was performed with COVID-19 patients who necessitate to be treated by being hospitalized in the internal medicine clinic. The study was conducted with a limited sample size and limited time interval. It will be beneficial to perform further studies to be conducted with a larger number of participants to verify and relate the results obtained from this study. Serological antibody tests for all participants and virus RNA investigations in the stool for patients with

GI symptoms were not applied. By this, it was unable to evaluate correlations between GI symptoms and viral burden. In addition, the duration of symptoms and transmission ways of the infection could not be clearly obtained for all patients.

Conclusion

GI symptoms are common in COVID-19 patients. Anosmia and ageusia were important findings and observed proportionally higher in patients with GI symptoms at the onset of COVID-19. In addition, serum AST levels were found statistically elevated in COVID-19 patients with GI symptoms than those without. Increased serum AST levels in patients with GI symptoms may be considered as an indicator for the enteric involvement of SARS-Cov-2.

Author Contributions

Concept: S.A., Design: F.T., Data Collection or Processing: P.A., F.P.Z., E.C.A., R.D.A., A.C.K., Analysis or Interpretation: M.A.A., H.E.A., Literature Search: B.C.T., Writing: S.A.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article

Financial Disclosure: The authors received no financial support for the research and/or authorship of this article.

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Original Article

DOI: 10.4274/haseki.galenos.2021.6963
Med Bull Haseki 2021;59:114-121

Noncompliance with Dietary Salt Restriction and Outcomes in Chronic Heart Failure: A Propensity Score Matching Analysis from TREAT-HF Registry

Bihter Senturk, Hakki Kaya*, Ahmet Celik**, Lutfu Bekar***, Hasan Gungor****, Mehdi Zoghi*****, Dilek Ural******, Yuksel Cavusoglu*******, Ahmet Temizhan********, Mehmet Birhan Yilmaz

Dokuz Eylul University Faculty of Medicine, Department of Cardiology, Izmir, Turkey
**Canakkale University Faculty of Medicine, Department of Cardiology, Canakkale, Turkey*
***Mersin University Faculty of Medicine, Department of Cardiology, Mersin, Turkey*
****Hitit University Faculty of Medicine, Department of Cardiology, Çorum, Turkey*
*****Adnan Menderes University Faculty of Medicine, Department of Cardiology, Aydin, Turkey*
******Ege University Faculty of Medicine, Department of Cardiology, Izmir, Turkey*
*******Kocaeli University Faculty of Medicine, Department of Cardiology, Kocaeli, Turkey*
********Eskisehir Osmangazi University Faculty of Medicine, Department of Cardiology, Eskisehir, Turkey*
*********Ankara City Hospital, Clinic of Cardiology, Ankara, Turkey*

Abstract

Aim: To compare chronic heart failure patients with reduced ejection fraction (cHFrEF) who stated to comply with salt restriction in their diets versus those who did not.

Methods: Patients without salt restriction were compared to those with salt restriction regarding HF-related hospitalization (HFrH) and all-cause mortality (ACM) before and after propensity score (PS) matching analysis.

Results: The study included a total of 723 patients. 136 of them stated not to comply with salt restriction, 587 of them stated to comply with salt restriction. More frequent HFrH were observed in patients without salt restriction compared to those with salt restriction (75% vs. 62.9%, p=0.007), though, ACM was similar in both groups (29.4% vs 27.6%, p=0.672). After PS matching, HFrH during follow-up remained more frequent in those without salt restriction compared to those with salt restriction (73.7% vs 59.3%, p=0.019) but ACM was not different in both groups (30.5% vs 29.7%, p=0.887). Noncompliance to dietary salt restriction was found as one of the independent predictors of HFrH.

Conclusion: In cHFrEF outpatients, noncompliance to dietary salt restriction does not seem to increase the risk for ACM but it poses an increased risk for HFrH.

Keywords: Heart failure, reduced ejection fraction, salt restriction, all-cause mortality, hospitalization

Introduction

Heart failure (HF) as a major health problem of the 21st century manifests itself among several disciplines of medicine through its multiorgan interaction. In addition, dietary salt restriction, as a non-pharmacological intervention has been recommended in the guidelines albeit with paucity of strong data until recently (1,2). In the last years, the stronger recommendations of the past have been heavily argued against in the literature (3-5).

Dietary salt restriction with different thresholds is regarded as an inevitable and complementary part of the prevention of hypertension and cardiovascular disease

Yazışma Adresi/Address for Correspondence: Bihter Senturk, Dokuz Eylul University Faculty of Medicine, Department of Cardiology, Izmir, Turkey
E-mail: drbihter@hotmail.com ORCID: orcid.org/0000-0003-3568-4476
Received: 22.01.2021 **Accepted:** 02.03.2021

and hence recommended in such guidelines (6,7). In these guidelines, evidence is relatively well established. However, in the literature, studies evaluating the role of salt restriction in HF are small and vague, though salt restriction is recommended in HF guidelines.

Turkish Research Team in HF (TREAT-HF) is a network which undertakes multicentric observational studies in HF with reduced ejection fraction (HFrEF) among HF centers in Turkey (https://www.treat-hf.com/) (8-10). In our study, we aimed to compare chronic HF patients with HFrEF who stated that they complied with salt restriction in their diets versus those who did not do so.

Methods

Study Design

This study was approved by the Clinical Research Ethics Committee (date: 30.11.2010, number: 2010-01/13). In the TREAT-HF registry, consecutive prospective cohorts for the years 2013, 2014, 2015 (TREAT-HF 1, 2, 3 cohorts) recruiting chronic HFrEF outpatients were addressed. In these cohorts, chronic HFrEF outpatients were administered a questionnaire including demographics, lifestyles, attitudes by an expert after index outpatient visit. One specific question was "Do you undertake salt restriction in your diet?" with no specific threshold along with the response options of "no" and "yes". This is a subgroup analysis from TREAT-HF cohorts with a specific focus on dietary salt restriction.

HFrEF was defined as left ventricular ejection fraction (LVEF) <40% along with HF symptoms as per guidelines recommendations (1,2). Echocardiograms and laboratory data recorded within the last 3 months of index outpatient visit (if there is more than one, the closest one is considered) were considered. Chronic HFrEF was defined as LVEF <40% in conjunction with stable HF symptoms for over one month, lack of hospitalization in previous three months, a stable dose of diuretics for over one month, optimally titrated and stable (minimum one month) doses of guideline-directed medical therapy (GDMT) involving angiotensin-converting enzyme inhibitor&angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists and ivabradine if necessary.

Patient Assessment

All patients were at ACC/AHA Stage C defined as the presence of present or previous symptoms of HF along with structural heart disease. Functional capacities of patients were determined according to New York Heart Association (NYHA) class at time of enrolment regardless of their former status (1). All patients were under chronic outpatient follow-up by HF centers and patients needing parenteral therapy or increase in oral diuretic and/or nitrate therapy while referring to outpatient clinic were not taken into account. HF-related hospitalization (HFrH) during follow-up was recorded when an admitted patient needed parenteral therapy for HF symptoms and signs coupled with a minimum one-day hospitalization, recorded as "Acutely Decompensated Heart Failure" as a primary diagnosis. Patients were monitored for all-cause mortality (ACM) and HFrH and both events were collected every year, and all events were recorded by local investigators. Herein, HFrEF outpatients who responded to the "Do you comply with salt restriction in your diet?" question with "no" (i.e, noncompliance) were compared with "yes" for outcomes including ACM and HFrH during follow-up. A flow chart was provided for the cohort (Figure 1). Since SPSS based propensity score (PS) matching requires the presence of completely filled data set in the database, the whole cohort was narrowed to 723 patients with complete data. set mainly due to the absence of natriuretic peptides (NPs) at index admission (please refer to flow chart), as, NPs are not necessary for the diagnosis of HFrEF according to guidelines (1,2) and are not routinely utilized during follow-up of stable HFrEF outpatients even among expert HF centers at the time of registry.

Statistical Analysis

All statistical procedures were conducted via SPSS software (version 25.0, SPSS Inc., Chicago, IL, institutional software). Continuous variables were expressed as mean ± SD or median (25^{th}-75^{th} percentile) if there is abnormal distribution, and categorical variables as percentages. Comparisons between groups were performed, utilizing the chi-square test for categorical variables, an independent samples t-test for normally distributed continuous variables, and the Mann-Whitney U test when distribution was skewed. A multivariate logistic regression analysis was performed in order to determine the independent predictors for HFrH. The variables with $p<0.1$ obtained from univariate analysis were entered in the multivariable logistic regression model. PS matching extension was provided on top of institutional SPSS 25.0 [Thoemmes, F. (2012). Propensity score matching in SPSS. arXiv:1201.6385 (stat.AP)]. Propensity-based matching was utilized to form paired samples of patients with similar propensity scores and stratified by "yes" or "no" groups according to compliance to salt restriction. The nearest neighbor matching algorithm was used, and covariate adjustment was made for age, coronary artery disease (CAD), diabetes mellitus (DM), NTproBNP, urban life, atrial fibrillation (AF), right ventricular (RV) dilatation, ivabradine use, left atrium diameter according to data provided from the unmatched cohort. A p-value of ≤0.05 was considered statistically significant.

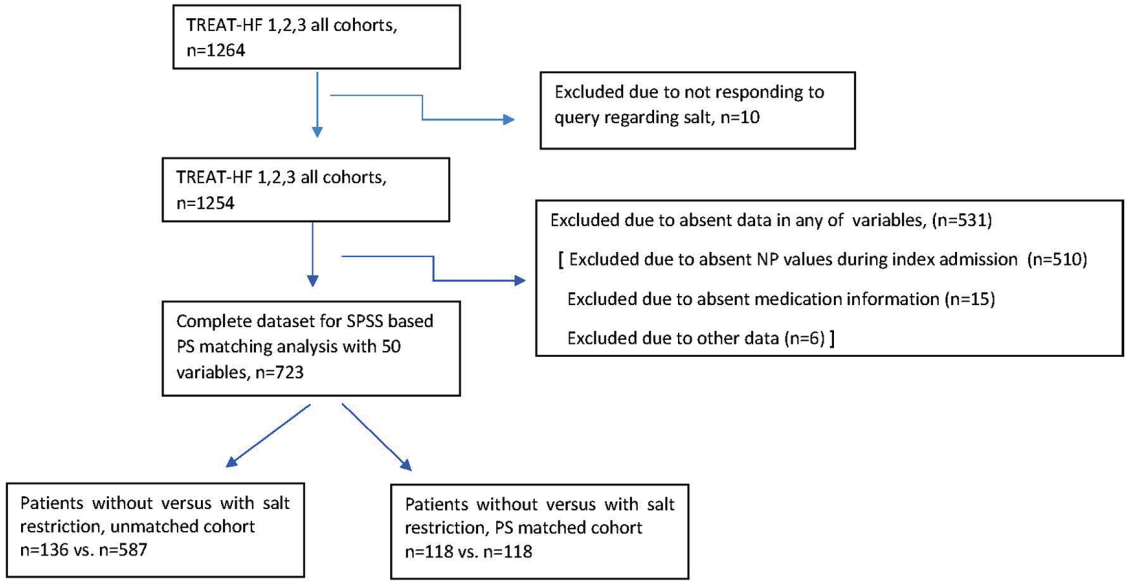

Figure 1: Flow chart of the study
TREAT-HF: Turkish Research Team heart failure, PS: propensity score, NP: Natriuretic peptide

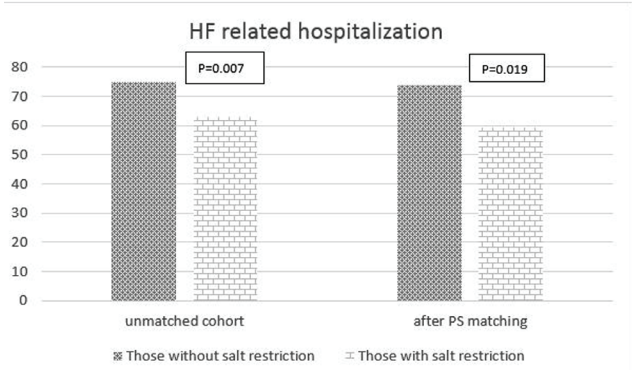

Figure 2: Frequency of HF-related hospitalization in unmatched and matched cohort
HF: Heart failure, PS: propensity score

Results

Mean follow-up of 20.2±11.8 months up to 48 months. Upon creation of unmatched "complete dataset available cohort" for PS matching analysis on SPSS 25.0, there remained 723 chronic HF patients with reduced ejection fraction (cHFrEF) and 136 of them responded with "no" to the question of "Do you comply with salt restriction in your diet?" (i.e, those without salt restriction) and 587 of them responded with "yes" (i.e, those with salt restriction). One-third of the cohort was females in two groups. DM and CAD were less frequent, echocardiographic RV dilatation was more frequent and NTproBNP levels were higher in patients without salt restriction along with more frequent HFrH compared to those with salt restriction (75% vs. 62.9%, p=0.007, Figure 2) as shown on the left panel of Table 1. Of note, ACM on follow-up was similar in both groups in the unmatched cohort (29.4% vs. 27.6%, patients without and with salt restriction respectively, p=0.672). After PS matching, HFrH during follow-up remained more frequent in those without salt restriction compared to those with salt restriction (73.7% vs. 59.3%, p=0.019, Figure 2) and ACM was not statistically different in both groups (30.5% vs. 29.7%, patients without and with salt restriction respectively, p=0.887) (right panel of Table 1).

Patients in the unmatched cohort were also classified into two as those with and without HFrH (Table 2). Upon univariate analysis, multivariable logistic regression analysis was made to obtain independent predictors of HFrH in the unmatched cohort (Table 3). Of note, noncompliance to dietary salt restriction was found as one of the independent predictors of HFrH along with NTproBNP levels, creatinine levels, having NYHA Class III-IV symptoms confirming PS matching analysis.

Discussion

Heart failure is characterized by neurohormonal activation, yielding sodium and water retention, which creates the issue of "congestion" as the major pathophysiology of acute HF syndromes (11). Hence, getting rid of sodium and water in the form of decongestion remains as the principle of therapy in HF (12). In addition, the association of sodium intake and fluid overload in HF brought about non-pharmacological self-care management of chronic HF via salt and fluid restriction in order to minimize the risk of acute decompensations. However, excess salt consumption is not as frequently reported as

Table 1. Comparison of patients with and without dietary salt restriction

Characteristics	Patients without salt restriction, no group n=136	Patients with salt restriction, yes group n=587	p	Patients without salt restriction after PS matching n=118	Patients with salt restriction after PS matching n=118	p after matching
Age (years)	64.6 ±12.2	62.9±12.7	0.130	65.19±11.12	65.19±11.12	1.00
Gender (Female) n (%)	43 (31.6 %)	187 (31.9 %)	0.957	37 (31.4%)	40 (33.9%)	0.781
Urban life n (%)	22 (16.2%)	146 (24.9%)	**0.032** χ^2	20 (16.9%)	25 (21.2%)	0.508
Graduation from university n (%)	6 (4.4%)	42 (7.2%)	0.338	5 (4.2%)	9 (7.6%)	0.409
Hypertension n (%)	48 (35.3 %)	205 (34.9 %)	0.921	42 (35.6%)	38 (32.2%)	0.680
Diabetes mellitus n (%)	24 (17.6 %)	152 (25.9 %)	**0.046** χ^2	21 (17.8%)	25 (21.2%)	0.622
CAD n (%)	48 (35.3 %)	300 (51.1 %)	**0.001** χ^2	43 (36.4%)	43 (36.4%)	1.00
NYHA 3-4 n (%)	61 (44.9 %)	47.5 (47.5 %)	0.634	54 (45.8%)	63 (53.4%)	0.298
AF n (%)	38 (27.95)	130 (22.1%)	0.176	25 (21.2%)	25 (21.2%)	1.00
Heart rate (bpm)	82.26±15.88	82.28±18.7	0.992	81.41±15.55	79.82±16.42	0.447
Laboratory parameters						
BUN (mg/dL)	39 (27-62)	39 (25-57.4)	0.602	39 (27.18-62.25)	41(26-66.23)	0.819
Creatinine (mg/dL)	1.39±0.66	1.35±0.77	0.548	1.40±0.67	1.42±0.77	0.853
Sodium (mmol/L)	137.02±7.17	137.85±4.20	0.666	138.05±4.19	137.61±3.95	0.417
Potassium (mmol/L)	4.55±0.51	4.42±0.59	0.279	4.59±0.46	4.45±0.56	0.212
NT-proBNP (pg/mL)	2225 (836-5935)	1350 (562-3628)	**0.047**[u]	2769 (864-5842)	1862 (675-4453)	0.289
Hb (g/dL)	12.74±2.27	12.51±2.21	0.279	12.62±2.24	12.26±2.12	0.205
Hct (%)	39.39±6.66	38.52±6.25	0.152	39.02±6.57	37.96±6.08	0.199
Echocardiographic parameters						
LA diameter (mm)	45.81±8.29	44.50±6.89	0.055	45.62±8.38	44.29±6.99	0.187
EF (%)	30.84±9.21	31.43±8.04	0.494	31.26±9.16	31.81±8.37	0.628
LVEDD (mm)	57.84±9.31	57.55±8.43	0.709	57.69±9.56	57.33±8.28	0.759
RV dilatation n (%)	64(47.1%)	206 (35.1%)	**0.011** χ^2	54 (45.8%)	47 (39.8)	0.430
SPAP (mmHg)	43.65±13.04	42.57±13.83	0.410	44.29±6.99	43.89±13.1	0.802
Medications						
Beta-blocker n (%)	110 (80.9 %)	485 (82.6 %)	0.620	96 (81.4%)	94 (79.7%)	0.870
ACEI/ARB n (%)	99 (72.8%)	430 (73.3%)	0.915	87 (73.7%)	83 (70.3%)	0.664
MRA n (%)	61 (44.9%)	303 (51.6%)	0.183	56 (47.5 %)	50 (42.4%)	0.513
Daily Loop diuretics n (%)	106 (77.9 %)	430 (73.3%)	0.279	94 (79.7%)	88 (74.6%)	0.439
Ivabradine n (%)	10 (7.4%)	75 (12.8%)	0.077	9 (7.6%)	13 (11%)	0.503
Digoxin n (%)	30 (22.1%)	141 (24%)	0.656	24 (20.3%)	36 (27.1%)	0.284
Outcomes						
HF-related hospitalization n (%)	102 (75%)	369 (62.9%)	**0.007** χ^2	87 (73.7%)	70 (59.3%)	**0.019** χ^2
All-cause death n (%)	40 (29.4%)	162(27.6%)	0.672	36 (30.5%)	35 (29.7%)	0.887

PS: propensity score, CAD: Coronary artery disease, NYHA: New York heart association, AF: Atrial fibrillation, BUN: Blood urea nitrogen, NT-proBNP: N-terminal pro-brain natriuretic peptide, Hb: Hemoglobin, Hct: Hematocrit, LA: Left atrium, EF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, RV: Right ventricular, SPAP: Systolic pulmonary artery pressure, ACEI/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker, MRA: Mineralocorticoid receptor antagonist

χ^2: Chi-square test, n (%); u: Mann-Whitney U tests, median (25^{th}, 75^{th} percentile)

it was thought and nonadherence with medications was more influential in one study (13). Of note, nonadherence was noted in about 10% of patients with acute HF, and these patients had a better prognosis (14). Thereby, risk in relation to excess salt consumption might not strongly exist in the absence of high-quality of evidence as it is hypothetically considered (5). However, there are conflicting opinions in the literature (15). Universal salt reduction has long been recommended in the guidelines (16), largely owing to its proven ability to lower blood pressure, which might be driven by genetic predilection (17) and arterial stiffness in hypertensive population

Table 2. Comparison of cHFrEF patients with and without HF-related hospitalization during follow-up			
Characteristics	**Patients without HF related hospitalization n=252**	**Patients with HF related hospitalization n=471**	**p**
Age (years)	61.82±12.52	63.93±12.64	**0.032** [t]
Gender (Female) n (%)	79 (31.3%)	151 (32.1%)	0.867
Urban life n (%)	64 (25.4%)	104 (22.1%)	0.355
Graduation from university n (%)	18 (7.1%)	30 (6.4%)	0.754
Hypertension n (%)	81(32.1%)	172 (36.5%)	0.253
Diabetes mellitus n (%)	62 (24.6%)	114 (24.2%)	0.928
CAD n (%)	112 (44.4%)	236 (50.1%)	0.160
Dietary salt restriction +/- (%/%)	218/34 (86.5%/13.5%)	369/102 (78.3%/21.7%)	**0.007** χ^2
NYHA Class III-IV n(%)	88 (34.9%)	252 (53.5%)	**<0.001** χ^2
AF n (%)	56 (22.2%)	112 (23.8%)	0.712
Heart rate (bpm)	81.78±17.62	82.55±18.51	0.589
Laboratory parameters			
BUN (mg/dL)	36 (22-52)	41 (27-63)	**0.004**[u]
Creatinine (mg/dL)	1.17±0.61	1.46±0.80	**<0.001**[t]
Sodium (mmol/L)	138.26±4.42	137.67±4.06	0.070
Potassium (mmol/L)	4.50±0.58	4.54±0.57	0.358
NT-proBNP (pg/mL)	778 (342-1919)	2094 (762-4870)	**<0.001**[u]
Hb (g/dl)	13.08±2.08	12.27±2.24	**<0.001**[t]
Echocardiographic parameters			
LA diameter (mm)	44.59±7.47	44.83±7.04	0.667
EF (%)	32.34±8.36	30.76±8.17	**0.014**[t]
LVEDD (mm)	57.22±8.95	57.81±8.40	0.381
RV dilatation n (%)	96 (38.1%)	174 (36.9%)	0.809
SPAP (mmHg)	40.83±13.76	43.82±13.54	**0.005**[t]
Medications			
Beta-blocker n (%)	215 (85.3%)	380 (80.7%)	0.126
ACEI/ARB n (%)	190 (75.4%)	339 (72%)	0.334
MRA n (%)	135 (53.6%)	229 (48.6%)	0.212
Loop diuretics n (%)	176 (69.8%)	360 (76.4%)	0.061
Ivabradine n (%)	32 (12.7%)	53 (11.3%)	0.628
Digoxin n (%)	66 (26.2%)	105 (22.3%)	0.270
Outcome			
All-cause Death n (%)	51 (20.2%)	151 (32.1%)	**0.001** χ^2

cHFrEF: Chronic heart failure with reduced ejection fraction, HF: Heart failure, CAD: Coronary artery disease, NYHA: New York heart association, AF: Atrial fibrillation, BUN: Blood urea nitrogen, NT-proBNP: N-terminal pro-brain natriuretic peptide, Hb: Hemoglobin, Hct: Hematocrit, LA: Left atrium, EF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, RV: Right ventricular, SPAP: Systolic pulmonary artery pressure, ACEI/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker, MRA: Mineralocorticoid receptor antagonist

[t]: Independent sample t-test, mean ± SD: standard deviation; χ^2: Chi-square test, n (%); [u]: Mann-Whitney U tests, median (25^{th}, 75^{th} percentile), SD: Standard deviation

(18). Nevertheless, it was recently shown in the PURE study that moderation of salt intake between 3 g/day-6 g/day was associated with a lower risk of mortality and cardiovascular events compared to either higher or lower levels of salt intake (19). Hence, strict restriction of salt intake does not seem to work in the right direction as expected in overall population. However, HF guidelines adopt salt restriction to a larger extent and recommend salt restriction in the absence of strong data (20). More interestingly, 15 years ago, Alvelos et al. (21) reported in an elegantly designed study that low sodium diet in chronic HFrEF resulted in "activation of anti-natriuretic the antinatriuretic and antidiuretic systems in HF patients". Five years later, Parrinello et al. (22) reported that moderation of sodium intake among HF patients after decompensation was associated with better outcomes compared to low

Table 3. Multivariate logistic regression analysis to predict HF-related hospitalization

	p	OR	95% CI
NTproBNP (pg/mL)	<0.001	1.001	1.000-1.001
Noncompliance with dietary salt restriction	0.046	1.597	1.009-2.527
Creatinine (mg/dL)	0.004	1.701	1.189-2.434
NYHA Class III-IV	0.006	1.631	1.150-2.313

Variables entered in the logistic regression model: Age, NTproBNP, dietary salt restriction, NYHA Class III-IV, BUN, creatinine, Hemoglobin, left ventricular ejection fraction, systolic pulmonary artery pressure, sodium, daily loop diuretic use. NT-proBNP: N-terminal pro-brain natriuretic peptide, HF: Heart failure, NYHA: New York heart association, BUN: Blood urea nitrogen, CI: confidence interval

sodium, which yielded activation of neurohormones and cytokines (23). Later on, Aliti et al. (24) reported that aggressive salt restriction did not enhance weight loss or clinical stability in initial days and concluded that salt restriction in patients with HF was "unnecessary" though, individualized restriction of salt consumption to 5 g/day (moderation) along with fluid restriction might improve signs and symptoms of HF (25). In a more recent paper serially evaluating salt intake of chronic HF patients with food frequency questionnaire, patients were arbitrarily classified into two groups as restricted salt (<2.5 g/day) and unrestricted salt (>2.5 g/day) and it was found that restricted salt intake was associated with poorer outcomes (26). On the contrary, Arcand et al. (27) reported in chronic HF patients that highest tertile of salt consumption (mean 3.8 g sodium/day) was associated with 3.5 times increased risk for mortality during 3-year follow-up. Therefore, in the presence of different thresholds in different studies, it remains to be established how much salt should be regarded as "too much" given that weather, sweating, background salt sensitivity etc. all seem to influence any significant interaction in the body (28). It is interesting to note in one palatability study that chronic HF patients preferred food with a higher concentration of salt more frequently compared to healthy controls (29). This issue was defined as a "hedonic shift" in relation to impaired recognition of salt taste, particularly after acute HF (30). Furthermore, after discharge from the hospital, the educated behavioral pattern of HF patients fora low sodium diet has recently been shown to decrease significantly in 3 months (31). Hence, it may be reasonable to individualize non-pharmacological management, particularly salt intake and to avoid strict numeric thresholds since the majority of these patients have altered sensation and does not follow salt restriction soon after hospitalization, and then, the best strategy might be to let the patient decide according to his/her palatability. Of note, Sodium-HF trial is expected to provide scientific evidence to strict salt restriction in patients with chronic HF, as it evaluates the efficacy of strict dietary sodium reduction (<1.5 g/day) in comparison to usual care for patients with chronic HF (32).

In the current analysis enrolling chronic HFrEF patients from expert HF centers in Turkey, we found an increased risk for HFrH in those without salt restriction, along with no increased risk for ACM, though, "no" group, i.e., those without salt restriction were, less frequently in urban life, higher N-terminal pro-brain natriuretic peptide, more frequent RV dilatation on echocardiogram in the whole cohort. Upon creation of an unmatched cohort with the complete dataset, similar results were obtained. Then, PS matching analysis in SPSS along with adjustment for covariates resulted in more HFrH in those without salt restriction along with no difference in ACM on follow-up, which is discrepant with the recent data Doukky R and coworkers (26) though not fully supporting the data Arcand and coworkers (27), since we did not observe any negative or positive signal with regard to ACM, However, HFrH was influenced by salt restriction in both analyses. If our study had assessed cardiac deaths in addition to ACM, perhaps cardiac deaths would be found to be more common in patients without salt limitation. We found ACM was more frequent in patients with HFrH. We think this significant difference may be due to cardiac deaths.

Study Limitations

Several confounders might have been missed in this study. First of all, "no" response might not mean consistent "no" or vice versa during follow-up. Hence, many patients might have crossed to "no" group from "yes" group according to patients' congestion status as it is not easy to keep up with salt restriction continuously, and hence, any potential benefit with regard to ACM might have been missed. Furthermore, only ACM was assessed; cardiac deaths were not separately assessed in our study. In the cohort, the "no" group was smaller. Since the centers participating in the TREAT-HF cohorts were expert HF centers in Turkey, there was a bias for stronger motivation for non-pharmacological interventions compared to overall physician attitude. However, initial enthusiasm for salt restriction decreased in the literature during the enrolment phase of the registry, hence changing environment might have diluted the effect of the findings. Besides, there might be other reasons for not complying with salt restriction such as previous hyponatremia. GDMT use was evaluated only at baseline, however, any improvement in GDMT during follow-up and better adherence to GDMT could potentially alter prognosis. Since the patient cohort was made up of relatively stable and chronic outpatients with HFrEF and without recent decompensation, there might have been a selection bias for excluding HFrEF

patients who might benefit from salt restriction. Hence, the potential role of the salt restriction in patients with more progressive disease, more rapid course or more fluctuating course remains still remains to be established. Besides, the NYHA Class IV group was small and was mainly made up of ambulatory patients since salt restriction might have some value in these patients. Diagnosis of HFrH was not adjudicated independently and some events outside the participant hospital might have been underestimated since some HF-related events might have been missed, at least as the primary diagnosis, in other hospitals. Last but not least, relying on a qualitative measure rather than measuring urine sodium or a specific food questionnaire could be a major limitation. However, urine sodium excretion is determined by individual status with large inter-individual variations and is questionable in the setting of chronic diuretic use; hence it is not a simple biomarker (33).

Conclusion

"Declaring" noncompliance with dietary salt restriction was associated with increased HFrH risk in chronic HFrEF outpatient population, though, ACM remained unaffected.

Authorship Contributions

Concept: B.S., H.K., A.C., L.B., H.G., M.Z., D.U., Y.C., A.T., M.B.Y., Design: B.S., L.B., H.G., D.U., Y.C., A.T., M.B.Y., Data Collection or Processing: B.S., H.K., A.C., L.B., H.G., M.Z., D.U., Y.C., A.T., M.B.Y., Analysis or Interpretation: B.S., L.B., H.G., D.U., Y.C., A.T., M.B.Y., Literature Search: B.S., H.K., A.C., L.B., H.G., M.Z., D.U., Y.C., A.T., M.B.Y., Writing: B.S., M.B.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2021.6813
Med Bull Haseki 2021;59:122-127

A Different Obturator Nerve Block Approach Using Nerve Stimulation Device Under Fluoroscopy Guidance in the Transurethral Resection of Lateral Bladder Wall Tumors

Cuneyd Sevinc, Tahir Karadeniz*

Istinye University Faculty of Medicine, Department of Urology, Istanbul, Turkey
**Ulus Liv Hospital, Clilnic of Urology, Istanbul, Turkey*

Abstract

Aim: This study aims to define the efficacy and safety of a different obturator nerve block technique using fluoroscopy and nerve stimulation device during transurethral resection of bladder tumor (TUR-BT).

Methods: Sixty patients with lateral bladder wall tumors who had TURBT were retrospectively analyzed for the formation of obturator reflex. Thirty patients received spinal anesthesia (SA) and 30 patients received SA combined with an obturator nerve block (ONB). ONB was performed in the lithotomy position. A percutaneous needle was advanced to the superolateral portion of the obturator foramen under fluoroscopic guidance. The nerve was localized with a nerve stimulation device and 5 mL of 2% prilocaine was injected to perineural area. Additionally, the tumor base was marked intravesically by resectoscope with fluoroscopy and 5 mL of %2 prilocaine was administered to nearby tissue. Obturator reflex formation reflex-related related complications were compared between the two groups.

Results: The results of our study yielded a statistically significant difference in the favor of ONB compared to SA alone for the occurrence of obturator reflex (13% vs 43%, p=0.020), bladder perforation (0% vs 23.3%, p=0.002), and absence muscle tissue in the pathological specimen (10% vs 40%, p=0.01).

Conclusion: ONB with the help of a nerve stimulation device, directed by fluoroscopy is effective to prevent obturator reflex and related complications.

Keywords: Fluoroscopy, obturator nerve, reflex, urinary bladder neoplasms

Introduction

Transurethral resection of bladder tumors (TURBT) is the first step for the diagnosis and treatment of bladder cancer (1). TURBT aims to remove all visible tumors in the bladder together with the underlining muscle tissue. Complete resection of the tumor for appropriate staging and further treatment planning is crucial for bladder cancer (2). However, nearly 50% of all bladder tumors are located at the lateral bladder wall where the risk for obturator reflex-related muscular jerk exists (3). The obturator reflex is one of the most serious complications of TURBT which can cause perforation of the bladder wall, increase the risk of TUR syndrome, lead to incomplete tumor resection, tumor dissemination and hemorrhage (4). Obturator reflex is reported to occur in 20% to 55% of patients during resection of lateral bladder wall tumors (5,6). The cause of this muscle reflex is the proximity of the obturator nerve to the posterolateral thigh. To prevent adductor muscle contraction, the use of muscle relaxants under general anesthesia is usually sufficient. However, in cases where spinal anesthesia (SA) is preferred, obturator nerve blockade (ONB) is reported to be necessary and useful to prevent this undesired event (7). Other precautions to prevent ONB are incomplete bladder filling, using low

Yazışma Adresi/Address for Correspondence: Cuneyd Sevinc, Istinye University Faculty of Medicine, Department of Urology, Istanbul, Turkey
Phone: +90 533 557 56 96 E-mail: cuneydsevinc@yahoo.com ORCID: orcid.org/0000-0002-6321-5143
Received: 13.12.2020 **Accepted:** 07.02.2021

electrical current and intermittent resection of the tumor (6,7).

The complicated anatomical structure of the region and the difficulty of approaching to nerve trace makes it often difficult for many urologists to use ONB in daily practice (3,8). ONB is usually performed by anesthesiologists with the guidance of ultrasound in the supine position (4,5).

In this study we try to define a urologist friendly technique to perform ONB as urologists are familiar to target a needle with the aid of fluoroscopy. Additionally a nerve stimulation device further increases the accuracy of the procedure.

Methods

Study Design

In this study, was approved by, and ethics committee approval was obtained from Istınye University Clinic Researches Ethics Committee (no: 2017-KAEK-120, decision no: 2/2020.K-085).

Overall, 134 patients undergone TUR-bladder tumor (BT) from January 2015 to December 2018 as part of their routine medical care were evaluated. Of these, sixty patients with an inferolateral bladder wall tumor had undergone TUR BT with SA or SA with ONB were enrolled into the study. Patients using neurological medications or having neurologic deficits and patients who are not eligible for SA were excluded from the study. Thirty patients in the study group were operated with the ONB technique (ONB group). And 30 patients who were operated under SA without nerve block (SA group) were included as control group.

Data of the patients was prospectively collected as the policy of our institution and was retrospectively evaluated from the electronic database of our clinic. A specific matching procedure was not performed.

For each group, age, sex, tumor size, localization of the tumor, stage, grade, presence of obturator reflex, bladder perforation, hemorrhage, major complications, presence or absence of muscle tissue in pathology specimen, complete or incomplete resection status, and operation time were evaluated. In case of full thickness bladder perforation, the procedure was quitted after bleeding control. Severe bleeding was controlled endoscopically, and the procedure was postponed for another session. Complications were recorded according to the Clavien classification system (9). For the ONB group, fluoroscopy time and time spent for ONB was also evaluated. For patients who had no muscle tissue on pathologic evaluation and who had high-grade tumor or tumor size larger than 3 cm, a second TUR BT was performed.

Obturator Nerve Block Technique

Under the guidance of fluoroscopy (General Electric GE OEC Brivo 850), ten cm Teflon-insulated needle (21G Stimuplex A, B. Braun Melsungen AG, Germany) allowing both current transfer into deep tissues and application of local anesthesia through its channel, was inserted below the inguinal ligament, lateral to the pubic tubercle and advanced through the superolateral portion of the obturator foramen (Image 1, Image 2). For better localization of the obturator nerve, a nerve stimulation device (Stimuplex HNS 12, B. Braun Melsungen AG, Germany) was used. The nerve stimulator adjusted to 2 mA electric current. Adductor muscular contractions were observed when the needle was around 4-6 cm

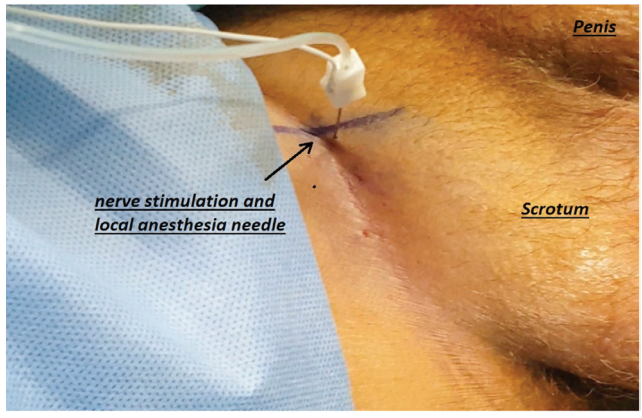

Image 1. Insertion of the nerve stimulation and local anesthesia needle

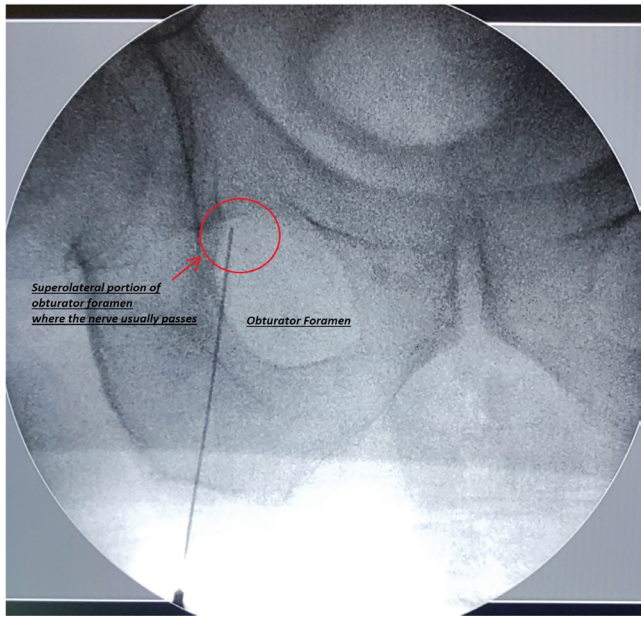

Image 2. Targeting obturator nerve at superolateral position of obturator foramen

depth in all cases. The setting was reduced to 0.5-0.2 mA for the precision of the localization. When the position of the obturator nerve was confirmed with muscle jerks at low stimulation current, 5 mL of 2% prilocaine was administered. This resulted in the immediate cessation of the adductor muscle jerks.

After the first injection, the resectoscope was placed inside the bladder to the possible resection sites where obturator reflex can be triggered (in most cases at the base of the tumor at the lateral bladder wall). The position of the resectoscope was identified under fluoroscopic view and local anesthesia needle was re-advanced to that space (Image 3). After negative aspiration, 5 mL of 2% prilocaine was administered as close as possible to the tip of the resectoscope. In the control group, no additional procedure was done after spinal anesthesia.

TUR BT Technique

All of the patients underwent SA as the first step. Standard preparation and dressing for operation were completed with the patient in the lithotomy position. The procedure began with routine cystoscopy. Localization of the tumor at the lateral bladder wall was confirmed. The number and size of the tumor were noted. The operation was performed using a bipolar resectoscope of Olympus ESG-400 plasma kinetic U-shaped cutting loop with 120V cutting/80V coagulation settings with normal saline for irrigation.

Statistical Analysis

Chi-square and Fisher's Exact test was used to compare perioperative categorical variables as gender, tumor stage, obturator reflex formation, incomplete resection, bladder perforation and absence of muscle tissue on pathological examination between the two groups. Mann-Whitney U test was performed to determine the association between the two groups and perioperative continuous variables as age, fluoroscopy time, ONB time, OT time, tumor size. A p value of <0.05 was defined as statistically significant.

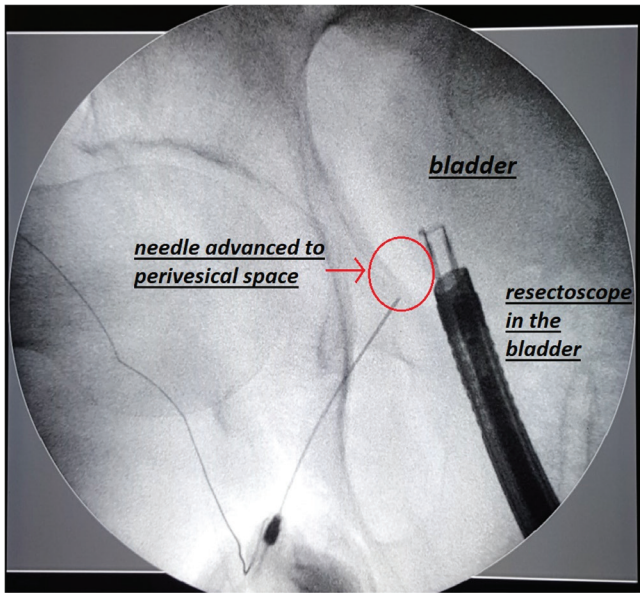

Image 3. Advancement of the needle to perivesical space nearby the tumor base

Results

The mean age and gender of the patients were similar for both groups. There was no statistical difference between the groups regarding tumor size, tumor grade and stage (Table 1).

Operative outcomes are summarized in Table 2. Obturator reflex was statistically significantly lower in the ONB group 4/30 (13%) than in the SA group 13/30 (43%) (p=0.020). For patients whom the obturator reflex occurred, the procedures could be completed with slight muscular jerks in all patients of the ONB group, whereas complete tumor resection was impossible because of excessive bleeding or deep bladder wall perforation in 4 (13%) procedures of the SA group. This parameter revealed no significant difference between the groups (p=0.112).

There was one patient with subserosal bladder perforation (3.33%) in the ONB group. In the SA group, different degree of bladder perforations (2 full-thickness, 5 subserosal) were observed in 7/30 of the cases (23.3%). This parameter yielded a statistically significant difference (p=0.02). In terms of hemorrhage, no statistically significant difference was defined between the ONB (n=0, 0%) group and the SA group (n=30, 10%) (p=0.237). The absence of muscular tissue in the final pathological analysis was determined in 3 cases (10%) in the ONB group and 12 cases (40%) in the SA group. The difference was statistically significant (p=0.001).

There were no major surgical complications in both groups. The duration of the operation was not

Table 1. Patients' characteristics

	Group ONB (n=30)	Group SA (n=30)	p
Age (years), mean ± SD	65.1±12	64.3±9.8	0.43
Gender (male/female)	20/10	22/8	0.78
Tumour size, (cm), mean ± SD	2.66±1.9	2.53±1.6	0.21
Tumour Stage, n (%)	-	-	0.97
Ta Low Grade	16 (53.3%)	14 (46.6%)	-
Ta High Grade	3 (10%)	3 (10%)	-
T1 Low Grade	2 (6.6%)	3 (10%)	-
T1 High Grade	6 (20%)	6 (20%)	-
T2 High Grade	3 (10%)	4 (13.3%)	-

ONB: Obturator nerve block, SA: Spinal anesthesia, SD: Standard deviation

statistically significantly different between the two groups (p=0.45). The average time for administration of ONB and for fluoroscopy was 7.2 minutes and 14.5 seconds, respectively. The postoperative evaluation did not reveal any local anesthesia-related complications such as seizure, bradycardia, anaphylaxis, or dysrhythmia.

Table 2. Intraoperative findings

	Group ONB (n=30)	Group SA (n=30)	p
Operation time, (minutes), mean ± SD	48.3±6.9	49±7	0.45
Obturator nerve block time, (minutes)	7.2	-	-
Floroscopy time, (seconds)	14.5	-	-
Obturator reflex formation, n (%)	4 (13%)	13 (43%)	0.020*
Incomplete resection, n (%) due to bladder perforation due to severe bleeding	0 (0%) - -	4 (13%) 2 (6.5%) 2 (6.5%)	0.112 - -
Bladder perforation, n (%) Subserosal Full-thickness	1(3.3%) 1(3.3%) -	7 (23.3%) 5 (16.6%) 2 (6.6%)	0.002** - -
Hemorrhage, n (%)	0 (0%)	3 (10%)	0.237
Absence of muscle tissue in pathology, n (%)	3 (10%)	12 (40%)	0.001***

*Obturator reflex formation was significantly lower in the ONB group with Fisher's Exact test
**Bladder perforation was significantly lower in the ONB group with Fisher's Exact test
***Absence of muscle tissue in pathology was significantly lower in the ONB group with Fisher Exact test. ONB: Obturator nerve block, SA: Spinal anesthesia, SD: Standard deviation, n: Number

Discussion

BTs are located on the lateral bladder wall in nearly 50% of the cases (3). The risk of occurrence of obturator reflex is reported as 20% to 55% in these cases (4-6). This may cause unwanted contractions in thigh muscles which may result in some serious complications changing from slight bladder perforation to injuries of the adjacent iliac vessels (4-8,10). There are also reports for the probability of extravesical tumor spillage and extreme bleeding which may prevent proper tumor resection or sometimes even completion of the procedure (11,12). Extravesical tumor spillage can lead to requirement for more radical treatment modalities (13).

Resection of the tumor under general anesthesia with active use of muscle relaxants may be the most effective way of preventing the obturator nerve reflex (4). There are some reports which showed that even under general anesthesia obturator reflex may happen (14). If SA is preferred, there are some precautions in the literature to prevent the obturator reflex. Resection in a half-filled bladder, using intermittent or low energy settings, and bipolar cauterization are some of these (6,7,15). The safest method to prevent the reflex for patients with SA is reported to be the application of obturator nerve block (4,5,11,14,15).

Many studies are reporting safe and efficient techniques for ONB (16). Using anatomical landmarks or ultrasonography was found to be efficient to localize the obturator nerve. Feigl et al. (8) defined detailed anatomical landmarks for the perfect application of the needle on a detailed evaluation in cadaveric samples. Shah et al. (17) reported the use of nerve stimulation devices increases the success rate of ONB from 76% to 90% and decreases the procedure time 50%.

Khorrami et al. (18) reported a transvesical application of ONB for urologists. They used a long nerve stimulating needle which they advanced through the working channel of a cystoscope, puncturing the bladder mucosa and transpassing bladder wall layers lateral to the ureteric orifice. They secured the position of the obturator nerve with a nerve stimulation device and used the same needle to apply local anesthesia around the nerve fiber. A few years later they reported their technique was also effective without the use of nerve stimulating device. They used intravesical anatomical landmarks and injected the local anesthetic to three separate points between the ureteric orifice and bladder neck at equal distances (19). Today ONB procedure is still not widely accepted among urologists. This may be because of the complexity of the defined anatomical landmarks for the application of the nerve block or the need for ultrasonography or puncturing of bladder mucosa to find the exact position of the nerve. Additionally, most of the studies were conducted by experienced anesthesiologists (4,14,17).

In our study, we tried to define a urologist friendly technique. We used fluoroscopy to localize the obturator foramen and obturator nerve which passes from the superolateral part of the obturator foramen. Nerve stimulation device which was recommended to improve the success of the obturator nerve block was used to confirm the precise localization of the nerve.

After the first injection was completed, we made a second injection to the perivesical space that was localized with the help of a resectoscope inside the bladder. We either tried to mark the riskiest point that will trigger the obturator reflex, or we placed the resectoscope to the tumoral base that resection will be made. This place is visualized by fluoroscopy and the local anesthesia needle was advanced closer to that area. The second injection was used because our previous experiences showed us obturator block was sometimes ineffective with the block of the obturator nerve at a single site. This failure may be

related to the possible presence of accessory obturator nerve (5,8). To overcome the risk of the obturator nerve anatomical variations we decided to perform a perivesical anesthetic block. In this way the block was made to the surrounding tissue of resection site independent from the route of nerve. Perivesical local anesthetic application was also used by Khorrami et al. (18) and proven to be effective (19). Our study confirmed the same findings but even proposed a wider range of freedom of selecting the injection site compared to intravesical application route used by Khorrami et al. (18) as our technique has the advantage for the surgeon to perform the block when the patient is in the lithotomy position, it is possible to repeat the injection throughout the operation if needed. Additionally, this technique enables to perform the block not before but during the operation if a previously unexpected lateral bladder wall tumor is observed intraoperatively or muscular jerk occurs during the resection.

Bladder perforation may be one of the most serious complications caused by obturator jerk. This has the potential to cause dissemination of tumor cells or sometimes inability to complete the resection. In a large series reported by Collado et al. (12), 2821 patients who had superficial BT were evaluated and it was found that 36 patients (1.3%) had bladder perforation, of which 30 were extraperitoneal and six were intraperitoneal. Four of them required open correction. In the literature, ONB was reported to decrease bladder perforation significantly (5,11,15). These results were concordant with our findings. Although we experienced slight obturator jerk in 4 cases, all these 4 cases were completed with careful low energy intermittent resection as recommended in previous studies (20,21). However, for patients in whom ONB was not performed 4 procedures could not be completed due to full-thickness bladder perforation and severe bleeding. We think this finding is remarkable. The presence of muscular tissue in the final pathological analysis is an important issue. Our study revealed higher complete resection rates and higher detrusor muscle rates on pathologic specimens in patients who underwent ONB. Like our study, Erbay et al. (22) reported that complete tumor resection and the presence of detrusor muscle tissue in the pathological specimen ratios were significantly higher in ONB applied patients. They also concluded that the postoperative recurrence of BT was found to be significantly higher in the non-ONB group (22). This seems to be an important advantage of ONB.

Urologists are well adapted to use fluoroscopy from endourologic procedures. Although our technique may be criticized as it causes exposition of radiation which is not necessary in a TUR BT operation, we calculated average fluoroscopy time as 14.5 seconds. There are studies reporting the average ureteric stone procedures fluoroscopy time to be 78 seconds (23). More recent studies are reporting 34.86 seconds covering all urological procedures and they mention the average use of fluoroscopy by endourology trained faculty is 68.35 seconds (24). Although our procedure needed far less radiation exposure duration, we still had strict adherence to the ALARA principle (as low as reasonably achievable). Compared with other obturator nerve block techniques, this block is encouragingly fast and easy to perform. The advantage of lithotomy position enables the application of the ONB not as a routine but on-demand which is either the presence of a tumor on the lateral wall or facing an unexpected reflex throughout the procedure.

Study Limitations

The retrospective design and the low patient number of the study is a weakness. A prospective randomized study with a higher patient population seems to be essential to provide more reliable information. Direct comparison with ultrasound-guided nerve block techniques would provide better information about the efficacy of the technique. Furthermore, a comparison with patients who underwent general anesthesia for this kind of bladder cancer would be useful.

Conclusion

This study defines a different obturator nerve block technique which enables urologists to perform the procedure during the operation without changing the position of the patient. Easy orientation with fluoroscopy guidance and using lithotomy position seem to be the main advantages. Further studies are required to determine the relative efficacy and safety of this technique to previously described approaches.

This study showed that SA combined with ONB prevents the obturator reflex during TUR BT, reduces the risk for bladder perforation and is associated with higher muscle tissue rates on the pathological specimens. Routine application of ONB along with SA during such operations may provide a better operative outcome.

Authorship Contributions

Concept: C.S., T.K., Design: C.S., T.K., Data Collection or Processing: C.S., Analysis or Interpretation: C.S., T.K., Literature Search: C.S., Writing: C.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2021.6429
Med Bull Haseki 2020;58:128-132

Efficacy and Safety of Percutaneous Endoscopic Gastrostomy in Elderly Patients Aged Over 65: A Tertiary Center Long-term Results

Mustafa Zanyar Akkuzu, Orhan Sezgin, Enver Ucbilek, Ferzan Aydin, Hatice Rizaoglu Balci, Serkan Yaras, Osman Ozdogan, Fehmi Ates, Engin Altintas

Mersin University Faculty of Medicine, Department of Internal Medicine and Gastroenterology, Mersin, Turkey

Abstract

Aim: Percutaneous endoscopic gastrostomy (PEG) is a method that can be applied for nutritional purposes in patients who cannot be fed orally for various reasons but whose gastrointestinal system functions are normal. In this study, we aimed to determine the etiological causes and long-term outcomes (efficacy, safety, lifespan) of PEG in patients over 65 years of age.

Methods: The data of patients aged 65 years or older who had PEG in our unit between 2015 and 2019 were analyzed retrospectively. The demographic information of the patients, the units they are being followed in, the underlying diseases, additional diseases, if any, complications-related to the procedure and the average life span were evaluated.

Results: During this period, 140 patients had been PEG inserted. 51% of patients were male and the average age was 73.7±9.2 years, and the average age of women was 76±7.2 years. The most frequent cause of PEG insertion is a neurological disease. PEG insertion was the most common in cerebrovascular events, with a rate of 39%. PEG was implanted in 30% for Alzheimer's disease, and 14% for malignant reasons. 28% of the patients lived less than a month. In total, 76% of patients died. The average life expectancy of patients who died after PEG was 221.3±330.7 days.

Conclusion: PEG is the gold standard in patients with normal gastrointestinal system functions in long-term enteral nutrition. However, in patients with a life expectancy of less than 1 month, the decision to place PEG or not should be made carefully.

Keywords: Percutaneous endoscopic gastrostomy, indication, complication, nutrition, senility

Introduction

Initially developed by Gauderer and Ponsky in 1980, Percutaneous endoscopic gastrostomy (PEG) is a method that can be applied for nutritional purposes in cases who have healthy gastrointestinal system functions but cannot feed orally for various reasons (1). Today, it is particularly used in patients who demonstrate insufficient oral intake, receive nasogastric tube feeding, at high risk of aspiration pneumonia and mostly in patients who have chronic neurological diseases (2). With being a surgical procedure, gastrostomy tube placement can be carried out under general anesthesia and morbidity rates ranging from 6 to 25% have been reported (3). However, PEG insertion is a cheaper, more practical and less risky method compared to surgical gastrostomy since it can be performed under local anesthesia and intravenous sedation even without the use of the endoscopy unit.

Enteral feeding has multiple advantages over parenteral feeding in patients who need long-term nutrition support, such as being more economical, easier and more convenient, requiring no central venous route, protecting the intestinal flora, preventing mucosal atrophy, reducing bacterial translocation, and maintaining intestinal immune response. Long-term use of nasogastric, nasodudenal and nasojejunal methods in patients undergoing prolonged enteral feeding has various complications such as nasopharyngeal discomfort, nasal erosion, acute otitis media, acute sinusitis, pharyngeal ulcer, esophagitis, esophageal ulcer, esophageal perforation, gastric erosion and ulceration (4,5).

Yazışma Adresi/Address for Correspondence: Mustafa Zanyar Akkuzu, Mersin University Faculty of Medicine, Department of Internal Medicine and Gastroenterology, Mersin, Turkey
Phone: +90 324 241 00 00 E-mail: zanyarakkuzu@gmail.com ORCID: orcid.org/0000-0002-9908-6881
Received: 23.07.2020 **Accepted:** 03.02.2021

In this study, we aimed to determine the etiological causes and long term outcomes (efficacy, safety, lifespan) of PEG in patients over 65 years of age.

Methods

Study Design

In this study, the data of geriatric patients aged 65 and over who had a PEG tube inserted at the clinic between 2015 and 2019 were analyzed retrospectively. Study data were collected from the endoscopy unit's data bank and patient files. Informed consent forms were obtained from all patients or relatives before procedures. Nurture Ethics committee approval was obtained for our study from the Mersin University Medical Faculty ethics committee on 22.01.2020 (resolution no: 56).

PEG Technique

Prior to the procedure, patients underwent an endoscopy to evaluate whether there were any anatomical pathologies in the stomach or duodenum that may obstacle PEG procedure. All PEG procedures were performed using sedation with local nasopharyngeal lidocaine and parenteral midazolam and, when required, under general anesthesia in some patients in the endoscopy unit with antibiotic prophylaxis, after the oral intake was stopped for a minimum of 6 hours. The patients were monitored and some patients who needed oxygen supplements were delivered. PEG tube was placed in all patients using the "Pull Technique (Gauderer Ponsky)" (1). Accompanied by two physicians and nurses, one of whom performed the endoscopic procedures, another performed PEG insertion in the epigastric site. The procedure was performed in compliance with the sterilization policy and the ideal antrum-corpus junction was detected using finger palpation with the endoscopic light that is visible through the skin. Flexible gastroscope (different brands) and various types of commercially available 16-20 Fr PEG sets were used. After the procedure, the patients' relatives who would nurture the patient were provided with detailed information about enteral nutrition, tube cleaning, and cleaning of surrounding tissue. Feeding through the gastrostomy was initiated approximately 4 hours after the procedure. Polymeric enteral nutrition formulas were used in the nutritional treatment of patients.

Statistical Analysis

The statistical analysis was carried out using SPSS version 21.0 software. Patients' data were given as mean ± standard deviation, while categorical data as percentage.

Results

A total of 140 patients included in the study. Of our patients, 72 (51%) were male and 68 (49%) were female. The average total age was 74.5±8.4 years.

The top three departments that referred the patients to our clinic for PEG insertion was neurology, which ranked first with 116 (83%) patients, followed by medical oncology [14 (10%) patients], and otorhinolaryngology clinic [5 (3.5%) patients], respectively. All clinics are shown in detail in Table 1.

When we examined the reasons for PEG insertion; cerebrovascular events were the leading cause in 55 (39%) patients. PEG was inserted in 42 (30%) patients due to Alzheimer and dementia, 14 (10%) due to Parkinson's disease, 6 (4.3%) patients due to amyotrophic lateral sclerosis (ALS), and 3 (2%) patients due to cerebral palsy. PEG insertion was carried out due to malignant reasons in 14.3% of the patients. Further information and additional associated diseases are given in Table 1.

During PEG insertion, there were no acute complications associated with upper gastrointestinal system endoscopy and PEG insertion. During follow-up, the tubes of 33 (23.5%) patients were dislodged and replaced on standard PEG replacement time due to puncture and wear (Table

Table 1. Patient characteristics

	Parameters	**Number (%)**
	Mean age	
Male	73.7±9.2	72 (51)
Female	76±7.2	68 (49)
Total	74.5±8.4	140 (100)
Clinics where cases referred	Neurology	116 (83)
	Medical oncology	14 (10)
	Otorhinolaryngology	5 (3.5)
	Neurosurgeon	3 (2)
	General surgery	2 (1.5)
Etiology	Cerebrovascular diseases	55 (39)
	Dementia and Alzheimer's disease	42 (30)
	Parkinson's disease	14 (10)
	Amyotrophic lateral sclerosis	6 (4.3)
	Cerebral palsy	3 (2)
	Esophageal tumor	4 (2.9)
	Laryngeal cancer	4 (2.9)
	Other malignancies (Lung 3, tongue tumor 3, tongue tumor 3, colon 2, brain 1, malignant melanoma 1)	12 (8.5)
Additional diseases	Essential hypertension	26 (18.5)
	Diabetes mellitus	15 (11)
	Coronary artery disease	15 (11)
	Chronic kidney disease	5 (3.5)
	Chronic obstructive pulmonary disease	4 (3)
	Chronic atrial fibrillation	3 (2)

2). Five (3.5%) patients developed purulent discharge and abscess at the PEG site after an average of 268±100 days. It was treated with local treatment and antibiotic use, and then catheter was replaced. Local bleeding developed at the PEG site in 3 (2%) patients, because they pulled the PEG catheters themselves. It was brought under control with a local compression. The buried bumper syndrome also occurred in these patients and afterward, they were treated. In one patient (0.7%), peritonitis developed due to the leakage around the PEG site and the patient died despite having a surgical operation in the follow-up. One hundred seven patients (76.5%) did not develop complications and/or did not show up for PEG tube replacement: 22 patients had a new PEG tube inserted in the last 6 months and 11 of them were alive. In addition, there was no problem developed among the living: a total of 96 patients died during the period, including 62 patients in less than six months. However, there were no complications associated with PEG.

One hundred ten (76%) of the patients died and 30 (24%) were still alive. The mean age of the living was 72.7±7.3 years. The average life span of the deceased patients after PEG insertion was 221.3±330.7 days and their mean age was 74.5±8.5 years. When we examined all the deceased patients, cerebrovascular diseases ranked first with 44 patients. There were 28 Alzheimer patients, 12 with Parkinson's disease, 3 with ALS, 3 with cerebral palsy and 18 with malignant diseases. While the mean time of death in patients with malignant diseases was 206±282 days, the mean time of death in neurological events were 223±340 days.

A total of 70 (50%) patients lived less than six months. Forty (28%) of these patients also survived for less than a month. The mean age of patients surviving less than one month was 76±8.7 years and the average life span was 15.5±8.2 days. The mean age of all patients who lived less than six months was 75.6±8.6 years and the mean life span was 51.3±55.6 days (Table 2).

Table 2. Complications and life span

	Parameters	Number (%)
PEG complications	Natural causes such as puncture and wear on the PEG tube, normal replacement time	24 (17)
	Drainage, abscess, infection at PEG site	5 (3.5)
	Local bleeding as a result of buried PEG or patients pulling PEG tube themselves	3 (2)
	Peritonitis due to leakage around PEG site	1 (0.7)
	Total complication	33 (23.5)
	Recently deceased or newly inserted PEG tube	107 (76.5)
Life span of cases	Total living patient Mean age 72.7±7.3	30 (24)
	Total deceased patient Mean age 74.5±8.5 Mean life span 221.3±330.7 days	110 (76)
	Life span less than 1 Month mean age 76±8.7 Mean life span 15.5±8.2 days	40 (28)
	Life span less than 6 months Mean age 75.6±8.6 Life span 51.3±55.6 days	70 (50)

PEG: Percutaneous endoscopic gastrostomy

Discussion

Providing nutritional support for patients is one of the most important points of treatment. PEG has also been a milestone for nutritional support in patients who have a healthy gastrointestinal tract but cannot feed orally. Enteral feeding via PEG should generally be used in patients who cannot take it orally for more than 1 month. The need for PEG is higher in elderly patients, as neurological complications and frequency of malignancy increase exponentially with age. In our study, gastrointestinal tract continuity was normal in all patients who underwent PEG. We did not confront technical difficulties and complications during the application.

It is found that the patients having a PEG tube inserted mostly had neurological problems (86%). This was followed by patients with tumors. Therefore, neurology (83%) was the first among the departments that referred patients for PEG insertion. Oncology ranked second with a frequency of 10%. Cerebrovascular diseases were in the first place among neurological diseases that require PEG insertion. Dementia, Alzheimer's disease and Parkinson's disease were also among the common reasons. The results of our study were generally compatible with the large series published across the world and in our country (6-9). Our observations show that neurologists are conscious of and work in harmony with PEG application.

Contraindications for PEG include previous abdominal operation, coagulopathy, morbid obesity, presence of severe ascites, peritonitis, peritonitis carcinomatosa, laryngeal or esophageal obstructions (10,11). None of our patients had contraindication for PEG insertion.

While 30-day mortality rates after the PEG procedure were 8-20% (12-14) in foreign series, the mortality rate was reported as 10-26.8% (10,15) in our country. Late mortality rates were reported as 15.7-67% (10,16). A study conducted by Malmgren et al. (16) reported the 6 month mortality rate as 56%, while a study by Ermis et al. (10) reported 30%. In our group, 76% of the patients who underwen PEG insertion died. The average life span of the

deceased after PEG insertion was 221.3±330.7 days. Our one-month mortality rate was 28% and 6 month mortality rate was 50%.

Eighteen out of 20 patients with malignancy died at follow-up, and the life span of this group was 206±282 days. The mean age of patients with malignancy was 67.9±5.5 years. We believe that decision-making process for nutrition, especially in cancer patients, should be carried out for each individual, taking into account the patient's symptoms, performance status, estimated life expectancy, and the willingness or preferences of the patients in particular. Approximately one-third of our patients died within 1 month. Placing a PEG tube in patients whose life expectancy is considered to be less than 1 month is a case that needs special consideration. If required, nasogastric or parenteral feeding can be done during this period. Thus, patients can elude unnecessary risks and expenditures. The fact that our patients were old and that they had concomitant diseases had a significant effect on the life span of our patients. Most of our patients who developed complications were older men.

In the literature, 1-3% of deaths were reported to be associated with the PEG procedure (17-21). In our study, there was a procedure-related death in 1 (0.7%) patient. Peritonitis due to leakage around the PEG tube resulted in the patient's death despite surgery.

Over time, the PEG tube may harden, become colored, develop irregular torsion, and an unpleasant odor may occur. Tubes must be replaced when they begin to cause problems such as barriers limiting the feeding, breaks or leaks (22). PEG replacement was done in 23.5% of all our patients. In 17% of those patients, PEG replacement was done for reasons such as puncture and wear on the PEG tube. Since the need for nutrition through PEG tube remained for some of our patients, PEG catheters were regularly replaced. PEG complications were also the cause in 6.5% of our patients that led to catheter replacement.

Complications related to the procedure can be observed during or after the PEG procedure. PEG-related complications include peristomal pain, wound infection, abscess, necrotizing fasciitis, bleeding, pneumoperitoneum, colon or small bowel perforation, splenic or liver laceration, intraperitoneal hemorrhage, buried bumper syndrome and gastroparesis, aspiration and diarrhea. In the literature, procedure-related mortality rate is reported as 1-3%, major complication rate is 6%, and minor complication rate is between 12% and 55% (23). In accordance with the literature, a total of 6.5% of complications developed in our cases.

PEG-related wound infections occur in 5-25% of patients. Usually, significant erythema, tenderness and purulent exudate develop in the PEG area (24). In 3.5% of our patients, wound infection such as discharge and abscess developed at the PEG site. All our patients received prophylactic antibiotics. There is consensus in the literature on the use of antibiotic prophylaxis for PEG, and antibiotic prophylaxis significantly reduces the PEG tube insertion site infections (25,26). In the case of infection, appropriate antibiotic therapy and local antiseptic and frequent dressing changes can help treat minor infections (27,28). In our patients who developed an infection, PEG tube was replaced after the infection treatment.

Bleeding is a rare, often early complication after PEG placement. It may be hematoma or melena or unexplained anemia, hypotension. Buried PEG bumper syndrome as a different complication is potentially serious and occurs in roughly 1% of patients underwent PEG tube insertion. The internal support (bumper) moves through the gastrostomy tract in the stomach and abdominal wall to the surroundings and settles anywhere along the way (24). Even if asymptomatic, a buried bumper should be removed after diagnosis because continuous migration of the bumper may cause bleeding, perforation, peritonitis and death, eventually (29). 2% of our patients had buried PEG and bleeding was observed at the local PEG site as a result of pulling PEG tubes. However, this was treated with the interventions.

Gastrointestinal complications may include diarrhea, nausea, vomiting or insufficiency, aspiration, obstipation, cramps and bloating. Necessary symptomatic treatment such as appropriate nutritional feeding and prokinetics should be given. The best way to prevent long-term complications is to provide good care at home with detailed information given to the patient relatives. We believe that it is very important to follow up these patients at home and in the hospital by a specialized nutrition team.

Study Limitations

The limitation of our study was that it was retrospective. Therefore, we could only access the long-term follow-up and complications of the patients from the hospital data system.

Conclusion

The PEG tube insertion is an affordable, safe and practical feeding method that can be inserted in a short time, applied even at the bedside, has low morbidity and mortality rates, and shortens hospital stay. In patients whose life expectancy is considered to be less than 1 month, it is necessary to consider their special conditions to make a decision.

Authorship Contributions

Concept: M.Z.A., O.S., Design: M.Z.A., O.S., Data Collection or Processing: F.A., H.R.B., S.Y., O.O., Analysis or Interpretation: F.A., E.U., E.A., Literature Search: M.Z.A., S.Y., E.U., O.O., Writing: M.Z.A., O.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2021.6749
Med Bull Haseki 2021;59:133-138

The Effect of Chronic Glucocorticoid Exposure on Brown Adipose Tissue in Cushing's Disease

Alev Selek, Mehmet Sozen, Berat Furkan Cayir*, Ilhan Tarkun**, Berrin Cetinarslan, Zeynep Canturk, Emre Gezer, Damla Koksalan

Kocaeli University Faculty of Medicine, Department of Endocrinology and Metabolic Diseases, Kocaeli, Turkey
**Ozalp State Hospital, Clinic of Internal Medicine, Van, Turkey*
***Anadolu Medical Center, Endocrinology and Metabolic Diseases, Kocaeli, Turkey*

Abstract

Aim: In this study, we aimed to evaluate the levels of brown adipose tissue markers uncoupling protein-1 (UCP-1), irisin, bone morphogenetic protein-7 (BMP-7) and PR-Domain Zinc Finger Protein-16 (PRDM-16) in Cushing's disease (CH) with hypercortisolism.

Methods: The study was conducted prospectively with 48 CH patients and 40 healthy volunteers between 2018 and 2019. Two cc of peripheral blood taken from the participants was centrifuged and stored at -80 °C degrees. Cushing's syndrome was excluded by performing 1 mg dexamethasone suppression test in the control group. Blood samples were analyzed by Enzyme-linked Immunosorbent Assay method.

Results: The patient group included 11 males (22.9%), 37 female (77.1%); 9 male (22.5%) and 31 females (77.5%) in the control group. Body mass index was 31.29±5.76 kg/m^2 in the patient group and 33.42±3.11 kg/m^2 in the control group. PRDM-16, Irisin, BMP-7, UCP-1 levels were not significantly different between the two groups. While there was a positive correlation between serum cortisol and irisin, a negative correlation was observed between urinary free cortisol and UCP-1.

Conclusion: These data suggest that long-term exposure to high doses of glucocorticoids in CH patients causes loss of adipose tissue functionality and development of resistance *in vivo*.

Keywords: Cushing's disease, glucocorticoid, brown fat tissue, UCP-1, irisin, BMP-7, PRDM-16

Introduction

Cushing syndrome (CS) results from long-lasting and inappropriate exposure to excessive concentrations of free glucocorticoids in the bloodstream. It leads to many comorbid conditions including chronic hypercortisolism, obesity, hypertension, diabetes, dyslipidemia and cerebrovascular diseases (1). Adipose tissue plays a central role in the interaction between nutrition, energy balance and human health. White adipose tissue (WAT) stores the energy, whereas brown adipose tissue (BAT) distributes the energy. With the discovery of BAT that has a high metabolic activity by functional imaging methods, research on importance of BAT has been increasing (2). Uncoupling protein-1 (UCP-1) is localized in the inner membrane of mitochondria of BAT cells and leads to a very high amount of fatty acid oxidation that directly produces heat through annihilation of the negative feedback inhibition on the mitochondrial Krebs cycle executed by high adenosine triphosphate and/or low adenosine diphosphate levels (3). In studies, several mediators which regulates UCP-1 expression and are involved in differentiation of BAT, including irisin, bone morphogenetic protein-7 (BMP-7) and PR-Domain Zinc Finger Protein-16 (PRDM-16), have been described (4-6).

Knowledge on effect of glucocorticoids on functions of BAT in humans is insufficient. Glucocorticoids have

Address for Correspondence/Yazışma Adresi: Mehmet Sozen, Kocaeli University Faculty of Medicine, Department of Endocrinology and Metabolic Diseases, Kocaeli, Turkey
Phone: +90 505 823 50 44 E-mail: mehmetsozen07@gmail.com ORCID: orcid.org/0000-0002-8428-1115
Received/Geliş Tarihi: 27.11.2020 **Accepted/Kabul Tarihi:** 03.02.2021

been shown to inhibit the reaction of adipocytes in human BAT cultures to adrenergic stimulation *in vitro* (7). While glucocorticoids alter the brown preadipocyte tissue, it suppresses UCP-1 expression and activity in brown adipocytes. In animal trials, lipid deposition in BAT increases with the administration of glucocorticoids, whereas thermogenic activity and production of UCP-1 are decreased (8).

In our study, it was aimed to evaluated levels of UCP-1, irisin, BMP-7 and PRDM-16, which are considered as markers for brown adipose tissue, in Cushing's disease (CH) cases with hypercortisolemia.

Methods

This study was approved by Kocaeli University Ethics Committee on Noninvasive Clinical Research with the project number KU GOKAEK 2018/274 on 27.10.2018. For the clinical prospective study in which the levels of UCP-1, irisin, BMP-7 and PRDM-16, which are considered as markers for brown adipose tissue, were evaluated in CH cases, 48 patients diagnosed with CH who were being followed-up between 15.11.2018 and 01.04.2019 in Kocaeli University Department of Endocrinology and Metabolism. As a control group, 40 volunteers at 30-60 years of age who were overweight or obese, screened for CH and found to be negative, had normal glucose tolerance and had not used any hormone therapy for last 6 months were recruited. Data of those with CH and volunteers were obtained from the hospitals' automation system and patients' files.

Those who were on an insulin or incretin-based therapy had a chronic inflammatory disease, had an active malignancy, used steroids for a long period of time before 6 months, were using a medication that may influence energy homeostasis and had renal or liver dysfunction were excluded from the study.

Of the volunteers and the patients diagnosed with CH included in the study; 2 cc of blood were taken in a dry tube after obtaining informed consent. Bloods taken were centrifuged at a speed of 3,000 rpm for 15 minutes and the plasmas were stored at -80 degrees on the same day. In addition, patients' anthropometric and demographic characteristics, as well as history of drug use and smoking were also recorded. The volunteers included in the control group underwent 1 mg DST screening test and CS was excluded.

UCP-1, irisin, PRDM-16 and BMP-7 were analyzed by using the brand elabscience commercial kits in the Radim Diagnostics Rome (Italy) device with Enzyme-linked Immunosorbent Assay method in Kocaeli University Faculty of Medicine Biochemistry Research Laboratory. The unit was determined to be ng/mL.

Statistical Analysis

Statistical evaluation was performed by using the IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) package program. Conformity to normal distribution was evaluated with Kolmogorov-Smirnov test. Numerical variables exhibiting normal distribution were given as mean ± standard deviation and those not exhibiting normal distribution as median (25^{th}-75^{th} percentiles), whereas the categorical variables, however, were given as frequency (percentage). Intergroup difference was determined by using student t-test for numerical variables exhibiting normal distribution and using Mann-Whitney U test for numerical variables not exhibiting normal distribution. Correlations between categorical variables were evaluated by using chi-squared analysis. For analysis of correlations between numerical variables, Spearman correlation analyses were used, as assumption of normal distribution could not be made. Considering the factors with an impact on the study, moderator analysis was used and the corrected values of the markers were interpreted again. For testing bidirectional hypotheses, a $p<0.05$ was considered sufficient for statistical significance.

Results

For the study, 48 patients diagnosed with CH (37 female, 11 male) and 40 volunteers (31 female, 9 male) as a control group were recruited. The mean age of the groups was similar. General characteristics and laboratory values of the patient and control groups are represented in Table 1.

When the markers for BAT were compared between the patient and control groups, the markers PRDM-16, irisin, BMP-7 and UCP-1 were determined to be similar between both groups (Table 2).

By using the moderator analysis in our analysis as weight and body mass index (BMI) were included as the factors influencing BAT, corrected values of markers of both groups were re-calculated in accordance with weight and BMI and then compared again, and the results were found to be similar between both groups ($p>0.05$).

When the group with CH was evaluated in itself, it was determined that 19 (40.4%) had a macroadenoma and 28 (59.6%) a microadenoma. While 82% of patients underwent early remission, the disease persisted in 18% of patients. Furthermore, during their 6-year follow-up, 23% of the diagnosed patients were found to have a recurrence and 77% continued to be in remission.

Data on effects of the size adenomas, time to postoperative remission and rate of recurrence on markers for BAT are represented in Table 3.

A positive correlation was observed between preoperative basal cortisol and night-time cortisol

and irisin, among the markers for BAT, and a negative correlation was observed between urinary free cortisol (UFC) and UCP-1 (Table 4).

By dividing the patient group as those with a BMI under 30 and over 30, irisin, PRDM-16, UCP-1 and BMP-7 were compared. BMP-7 was determined to be higher in the group with a BMI >30 (p<0.05). No significant difference was detected for other markers for BAT (p>0.05). In the comparison by triglyceride (TG) levels, PRDM-16 and BMP-7 were determined to be higher in patients with a TG <150 (p<0.05). No significant difference was determined between HbA1c and markers for BAT (p>0.05).

Discussion

CS indicates pathological hypercortisolism as a result of excessive adrenocorticotropic hormone (ACTH)

Table 1. Characteristics of the patient and control groups

	Patient group	Control group	p
Female (n) (%)	37 (77.1%)	31 (77.5%)	>0.05
Male (n) (%)	11 (22.9%)	9 (22.5%)	>0.05
Age (years) (mean ± SD)	44.04±13.79	45.30±9.31	>0.05
Weight (kg) (mean ± SD)	82.47±13.13	89.51±11.26	<0.05
BMI (kg/m²) (mean ± SD)	31.29±5.76	32.4±3.11	<0.05
HbA1c (%)	6.3 (5.7-6.8)	5.6 (5.3-5.9)	<0.05
CRP (mg/L)	0.73 (0.4-1.2)	0.53 (0.3-0.9)	>0.05
Triglyceride (mg/dL) (mean ± SD)	190.5±80	83.5±49.2	<0.05
HDL (mg/dL) (mean ± SD)	48.5±15.5	51.3±10.7	>0.05
LDL (mg/dL) (mean ± SD)	125.1±27.5	134.6±27.9	>0.05
25-OH (mg/mL) (mean ± SD)	15.3±7.83	17.9±8.31	>0.05

Independent samples t-test
BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, CRP: C-reactive protein, 25-OH: Vitamin D, SD: Standard deviation

Table 2. Comparison of the patient and control groups for markers for BAT

	Patient group	Control group	p
UCP-1 (ng/mL)	1.4±1.09	1.3±0.74	>0.05
İrisin (ng/mL)	3.2±0.8	2.7±1.16	>0.05
BMP-7 (ng/mL)	148.1±97.9	158.8±84.78	>0.05
PRDM-16 (ng/mL)	207.6±136.3	306.9±308.6	>0.05

UCP-1: Uncoupling protein-1, BMP-7: Bone morphogenetic protein-7, PRDM-16: PR-Domain Zinc Finger Protein-16, BAT: Brown adipose tissue

Table 3. Correlation of size of adenoma, time of remission and rate of recurrence with markers for BAT in the patient group

	Recurred	Not recurred	Those with early remission	Those without early remission	Microadenoma	Macroadenoma
İrisin (25%-75%)	3.6 (3.1-3.7)	3.7 (2.2-3.7)	3.7 (2.6-3.7)	3.7 (3.7-3.7)	3.7 (2.29-3.7)	3.7 (3.5-3.7)
p	>0.05		>0.05		>0.05	
UCP-1(25%-75%)	0.79 (0.43-1.12)	0.91 (0.56-2.43)	1.12 (0.55-2.36)	2.5 (0.5-2.7)	1.68 (0.61-2.6)	1.01 (0.49-1.27)
p	>0.05		>0.05		<0.05	
PRDM-16 (25%-75%)	180 (146-263)	153 (138-217)	157 (142-281)	164 (132-195)	160 (140-240)	152 (138-197)
p	>0.05		>0.05		>0.05	
BMP-7 (25%-75%)	98.9 (60-135)	104 (67-240)	127 (72-210)	217 (77-350)	157 (67-242)	86 (65-177)
p	>0.05		>0.05		>0.05	

Spearman correlation analyses
UCP-1: Uncoupling protein-1, BMP-7: Bone morphogenetic protein-7, PRDM-16: PR-Domain Zinc Finger Protein-16, BAT: Brown adipose tissue

Table 4. Correlation analysis of markers for BAT and hormones in the patient group								
	Basal ACTH		Basal cortisol		Night-time cortisol		Urinary free cortisol	
	r	p	r	p	r	p	r	p
irisin	0.041	0.783	0.328	0.024	0.375	0.019	0.143	0.411
UCP-1	-0.09	0.546	0.145	0.331	-0.079	0.633	-0.391	0.020
PRDM-16	-0.124	0.405	-0.097	0.518	0.155	0.346	-0.004	0.984
BMP-7	-0.164	0.272	0.094	0.528	-0.082	0.621	-0.239	0.167

Spearman correlation analyses
UCP-1: Uncoupling protein-1, BMP-7: Bone morphogenetic protein-7, PRDM-16: PR-Domain Zinc Finger Protein-16, ACTH: Adrenocorticotropic Hormone

production or autonomous adrenal cortisol production. Adrenocorticotropic hormone -dependent cortisol excess due to a pituitary adenoma is called CH and it accounts for 80% of endogenous CS. CS is associated with hypertension, diabetes, coagulopathy, cardiovascular diseases, infections and fractures, all of which may lead to significant morbidity and mortality (9).

Glucocorticoids are an important part of human and animal physiology as a modulator of inflammation and glucose homeostasis, mainly during the stress response. Furthermore, glucocorticoids have been found to play a significant role in energy homeostasis and physiology of adipose tissue over the years (10). Abnormal levels of circulating glucocorticoids directly affect the physiology of WAT at both cellular and molecular level, stimulating adipogenesis and leading to enlargement of adipose tissue (11). Observed importance of the need for glucocorticoids for WAT function has led to foresight that glucocorticoids may also modulating BAT function. In fact, BAT has also been shown to be a target organ for glucocorticoids in early studies (12). Similar to effect on WAT, glucocorticoids may induce lipid deposition in BAT and this may reflect an impaired UCP-1-related thermogenic capacity. If excessive exposure to glucocorticoids suppresses BAT thermogenesis, this may reduce dietary thermogenic energy expenditure and it has been suggested that this may contribute to the development of glucocorticoids-induced obesity in mice and humans (13).

In this study, it was aimed to demonstrate alterations in UCP-1, irisin, PRDM-16 and BMP-7, which are considered to be markers for BAT, in CH that is a hypercortisolemic condition compared to healthy volunteers, under the light of the data obtained from *in vivo* and *in vitro* studies.

Activity of the hypothalamic-pituitary-adrenal axis has an impact on production and secretion of glucocorticoids. Glucocorticoids may modulate UCP-1-induced thermogenesis in BAT. High levels of ACTH appear to up-regulate UCP-1 transcription in vitro. Accordingly, an increase in UCP-1 mRNA and UCP-1 protein levels after treatment with ACTH was determined in studies on cultured adipocytes (14,15). ACTH-induced up-regulation of UCP-1 levels most likely occurs via activation of Gs-cAMP-protein kinase A (PKA) signaling following binding of ACTH to the cognate melanocortin 2 receptor (16). When exposed to a stress factor, while circulating glucocorticoids levels increase after 20 minutes, circulating ACTH levels increase much more rapidly. Therefore, ACTH may initially promote the activity of BAT, and this effect may then be suppressed with an increase in glucocorticoids. However, ACTH concentrations used in animal studies are at least 5-fold higher than the maximal physiological ACTH concentration in case of stress (15,17,18). Because effects of ACTH on BAT are dose-dependent and they occur at these supraphysiological doses, it is unlikely for ACTH-induced activation of UCP-1-induced thermogenesis to be related under physiological conditions (19). In our research, serum basal ACTH levels were found to have no effect on BAT. This, in turn, supports the idea in the literature that exposure to ACTH at physiological doses has no significant effect on BAT.

First clues for a potential association between glucocorticoids and BAT function were obtained from studies on adrenalectomized rats. The researchers observed that there was a significant reduction in lipid stores in BAT in adrenalectomized rats and mice as earlier as 1949 (20). In such adrenalectomized rodents, regaining of lipid stores after glucocorticoid injection indicates that the effect of adrenalectomy on BAT actually results from absence of glucocorticoids (21). Based upon this, in earlier studies, the hypothesis that adrenalectomy inhibits glucocorticoids-induced suppression of BAT thermogenesis and, thusly, increases energy expenditure and reduces the incidence of obesity was proposed (22). Therefore, consistent with this, BAT function may be clearly suppressed in presence of glucocorticoids. In animal studies, chronic glucocorticoid treatment has been reported to cause deep lipid deposition in BAT and a reduction in UCP-1 mRNA and UCP-1 protein levels (8,14). However, there also are studies which did not found any alteration in BAT UCP-1 protein levels or UCP-1-induced thermogenic capacity (23). Direct human studies on effects of glucocorticoids on BAT are very limited due to challenges in sample tissue collection. Nevertheless, there are indicators demonstrating a suppressive effect of glucocorticoids on BAT in humans. In retroperitoneal

adipose tissue analysis of 57 patients, the intensity of BAT in patient groups with cortisol-secreting adenomas and secondary hypercortisolism was found to be lower compared to those with aldosterone-secreting adenomas, pheochromocytomas and nonfunctional adenomas (24). Again in this study, a negative correlation was also determined between UFC level and retroperitoneal UCP-1 expression. Similarly, a negative correlation was also determined between the group with UFC and UCP-1 in the group with CH in our study.

The intensity of BAT is reduced in individuals on chronic glucocorticoids compared to matched controls (25). In a study by which effects of glucocorticoids on human BAT in vitro, UCP-1 levels were found to be up-regulated in presence of 10 μM dexamethasone in supraclavicular human brown adipocyte cultures that differentiated for 9 days (7). However, the duration of exposure to glucocorticoids influences *in vitro* experimental results. For instance, while a 24-hour treatment with 100 nM cortisol increases basal UCP-1 expression in human adipocytes, a 48-hour treatment with the same dose of cortisol does not do so. Furthermore, while a 24-hour treatment with 1 μM cortisol does not influence UCP-1 gene expression, a 48-hour treatment with 1 μM reduces basal UCP-1 mRNA levels (25). In our study, no difference in markers for BAT was determined between those with CH and healthy volunteers. UCP-1 and BMP-7 were increased in correlation with cortisol in CH patients. The reason for this may be interpreted as that long-lasting exposure to high-dose glucocorticoids leads to loss of functioning of adipose tissue in CH patients and to high levels of markers by causing an *in vivo* resistance.

İrisin, a thermogenic adipomyokine cleaved from Fibronectin type III domain-containing protein 5, plays a role in browning of the adipose tissue. İrisin facilitates glucose uptake by skeletal muscles, improves hepatic glucose and lipid metabolisms and has a positive effect on hyperlipidemia and hyperglycemia caused by obesity and metabolic syndrome, thereby acting as an insulin-sensitizing hormone (26). In a study where irisin levels were examined in 40 BAT-positive and 40 BAT-negative women determined by using 18F-florodeoxyglucose positron emission tomography, no difference was observed between the groups (27). In a study on those with CH, circulating irisin levels were determined to be lower compared to controlled CH group (in postoperative 1st year) and the control group (28). In our study, no significant difference in irisin levels was found between the patient and control groups ($p>0.05$).

Targeting brown fat in order to increase energy expenditure and promote negative energy balance has been a strategy being sought for a long period of time for the prevention and treatment of obesity (29). In previous studies, UCP-1 deficient mice exhibited increased an increasing susceptibility to diet-induced obesity (30). In a study conducted with obese individuals, *PRDM-16* gene polymorphism was observed to be a risk factor for obesity (31). BMP-7, a member of transforming growth factor-β superfamily is known for with its osteogenic properties and plays a role induction, development and regulation of adipocytes, especially BAT (32). In our study, the patient and control groups were similar in terms of weight and BMI. In the patient group, BMP-7 was found to be higher in patients with a BMI <30 kg/m^2 compared to those with a BMI >30 kg/m^2 ($p<0.05$). This is thought to be associated with mechanisms of resistance due to chronic glucocorticoid exposure.

Study Limitations

One of them is conduction of the study with a relatively small sample size. In addition, CH is usually late-diagnosed unless it has an aggressive course and how long the patients are exposed to increased endogenous glucocorticoid levels cannot be clearly estimated.

Conclusion

Studies on the association between glucocorticoids and BAT function have been carried on for years. Data obtained from animal studies have developed an interest in the physiology of BAT in humans. However, due to technical challenges, data from human studies are limited. In this study, we aimed to evaluate the association between CH and BAT via irisin, UCP-1, PRDM-16 and BMP-7. In CH, results similar to those in healthy volunteers were obtained. A positive correlation was observed between serum cortisol and irisin, whereas a negative correlation was observed between urinary cortisol and UCP-1. Studies with larger groups will provide obtaining clear data on BAT function in CH.

Authorship Contributions

Concept: A.S., I.T., B.C., Design: A.S., I.T., B.C., Data Collection or Processing: B.F.C., D.K., E.G., Analysis or Interpretation: A.S., M.S., Z.C., Literature Search: B.F.C., M.S., Writing: A.S., M.S., B.F.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This work was supported by Kocaeli University Scientific Research Projects Coordination Unit (2018/067HD).

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Original Article

DOI: 10.4274/haseki.galenos.2021.6799
Med Bull Haseki 2021;59:139-144

Can Subclinical Inflammatory Markers Predict Birth Time and Birth Weight in Hyperemesis Gravidarum?: A Comparative Study and Comprehensive Current Literature Review

Melike Demir Caltekin, Ibrahim Caltekin*, Taylan Onat, Demet Aydogan Kirmizi, Emre Baser, Serenat Eris Yalcin**, Mustafa Kara***, Ethem Serdar Yalvac

Yozgat Bozok University Faculty of Medicine, Department of Obstetrics and Gynecology, Yozgat, Turkey

**Yozgat Bozok University Faculty of Medicine, Department of Emergency Medicine, Yozgat, Turkey*

***University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinic of Obstetrics and Gynecology, Antalya, Turkey*

****Kırsehir Ahi Evran University Faculty of Medicine, Department of Obstetrics and Gynecology, Kırsehir, Turkey*

Abstract

Aim: To evaluate subclinical inflammatory markers in hyperemesis gravidarum (HEG) cases and to determine the relationship of these markers with the gestational age at delivery and birth weight in pregnant women with HEG.

Methods: Fifty-two patients who presented to our hospital between 1 May 2017 and 1 September 2019 with HEG and 60 pregnant women as the control group were included in this retrospectively designed study. The relationship of subclinical inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the lymphocyte-to-monocyte ratio (LMR) with HEG, and their relationship with birth week and birth weight in HEG cases were examined.

Results: In HEG cases, NLR and PLR values were higher (p=0.006 and p=0.004, respectively), whereas LMR values were lower (p<0.001). In HEG cases, gestational age at delivery had a negative correlation with NLR and PLR and positive correlation with LMR (r=-0.567, p<0.001; r=-0.322, p=0.02, and r=0.279 p=0.045, respectively). In addition, NLR and PLR had negative correlations with birth weight (r=-0.582, p<0.001; r=-0.302, p=0.029, respectively).

Conclusion: While NLR and PLR values increase in HEG cases, LMR value decreases. It has been determined that varying rates of subclinical inflammatory markers in HEG are associated with preterm birth week and low birth weight.

Keywords: Hyperemesis gravidarum, subclinical inflammation, birth weight

Introduction

Hyperemesis gravidarum (HEG) is a clinical condition that leads to severe nausea, vomiting, weight loss, and electrolyte imbalances in pregnancy, and in some cases, hospitalization is required (1). However, there is no consensus with definitive diagnostic criteria that can define this presentation and multifactorial effects have been mentioned in the etiology (2). HEG may be associated with maternal and fetal poor outcomes and it remains to be the leading cause of hospital admissions and hospitalizations in early pregnancy weeks (3,4).

There are no markers in use to diagnose HEG or to determine the severity of the disease (1). However, it has been stated that inflammation plays an effective role in HEG, and many inflammatory markers play a role in the determination of this process (5). Subclinical inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the lymphocyte-to-monocyte ratio (LMR) are used in other inflammatory diseases in the determination of the disease activity and severity and in making the diagnosis (6-8). In addition, C-reactive protein (CRP) levels may increase in

Yazışma Adresi/Address for Correspondence: Melike Demir Caltekin, Yozgat Bozok University Faculty of Medicine, Department of Obstetrics and Gynecology, Yozgat, Turkey
Phone: +90 354 212 70 50 E-mail: melike_deu@hotmail.com ORCID: orcid.org/0000-0001-8797-7794
Received: 11.12.2020 **Accepted:** 30.01.2021

HEG, where inflammatory mechanisms play a critical role in pathophysiology (9). Just like CRP, NLR and PLR, which are important subclinical inflammatory markers, have also been found to be increased in HEG (10). Also, systemic inflammatory markers are independent determinative markers for systemic endothelial dysfunction (11). It has been determined in different pregnant groups that these markers can be predictors for both low neonatal birth weight and preterm birth week (12).

In this study, it was aimed to evaluate subclinical inflammatory markers in pregnant women with HEG and to determine the relationship of these markers with the birth week and birth weight.

Methods

The ethics committee approval of the study was given by the university's local ethics committee (protocol number: 2020-KAEK-189_2020.05.19_20) and the principles of the Helsinki Declaration were followed during the study. The study was conducted in a tertiary center and the data of the patients were obtained from the electronic medical records of the hospital. Fifty-two patients who presented to our hospital with HEG between May 1st 2017 and September 1st 2019 and 60 pregnant women as controls were included in this retrospectively designed study. The patients in the study group and the control group were compared in terms of demographic data, gestational characteristics, and inflammatory markers. A power analysis was conducted using the GPower version 3.1.7 software based on the findings of comparable studies (13). An effect size of 0.73 was used with a power set at 0.95 and alpha at 0.05 to determine that an n=50 sample size was required in each group.

The demographical and clinical characteristics of the pregnant women who applied to the clinic with symptoms of HEG such as age, gestational age at the time of admission, gravidity, parity, birth weight, and the weight gained during pregnancy were determined. The height, the weight, clinical status and clinical course, blood samples, the files, and electronic records of pregnant women were examined, subclinical inflammatory markers such as NLR, PLR, and LMR were determined and body mass index (BMI) was calculated from body weight/height^2 (kg/m^2). The blood values of HEG cases were calculated from the results of blood samples taken at the time of the presentation where the most severe symptoms were seen, before hospitalization and hydration. Blood samples taken from healthy pregnant women without HEG in the first trimester were used in the study for control purposes. The relation of subclinical inflammatory markers with HEG and their relationship with preterm birth week and LBW in HEG cases were also investigated.

The pregnant women who were under 18 years of age, who had multiple pregnancies, smoking history, thyroid disease, BMI of >35 kg/m^2, gastrointestinal system disease, chronic liver disease, diabetes mellitus, metabolic syndrome, deep vein thrombosis, rheumatic disease, an inflammatory disease that may affect hematological inflammatory parameters were all excluded from our study (n=6). In addition, patients with conditions such as previous preterm birth, premature rupture of the membranes, and pre-eclampsia that may cause LBW and early gestational week were also excluded from the study (n=4). Patients who had missing data and whose blood sample results were inaccessible were also not included in the study (n=6). A total of 16 pregnant women with HEG were excluded. Considering these features, pregnant women who did not have any chronic or inflammatory disorders and who had the same demographic characteristics as the study group were determined as the control group.

Evaluation of HEG

A pregnant woman who had more than 2 severe vomiting episodes, the presence of ketonuria in a random urine sample, and weight loss of more than 5% of body weight was diagnosed with HEG (14).

Laboratory Analysis

Hematological parameters were studied within the first hour to prevent errors in parameters from blood samples taken in tubes containing Ethylenedinitrile-tetraacetic acid with the XN-1000 hematology analyzer (Sysmex Corporation, Kobe, Japan) device. NLR, PLR, and LMR values were calculated from the obtained complete blood count (CBC) values. NLR was calculated as the absolute neutrophil count divided by the lymphocyte count. PLR was calculated as the absolute platelet count divided by the lymphocyte count. LMR was calculated as the absolute lymphocyte count divided by the monocyte count.

Statistical Analysis

Statistical Package for Social Sciences (Inc; Chicago, IL, USA) version 20.0 software was used to analyze the data. HEG and control patients' values were determined using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to evaluate whether they were normally distributed or not. The independent sample t-test was used to compare continuous variables with normal distributions and the Mann-Whitney U test was used to compare variables with non-normal distributions. The chi-square test or Fischer's Exact test (when chi-square test assumptions did not hold due to low expected cell counts), where appropriate, was used to compare the proportions in different groups. Analysis results of different variables were given as mean

± standard deviation, median (minimum-maximum), and n (%). Receiver operating characteristic (ROC) curve analysis was used to identify the optimal cut-off values of NLR, PLR, and LMR in order to diagnose HEG with maximum sensitivity and specificity. Spearman correlation analysis was used for the evaluation of a possible correlation between different variables. A value of $p<0.05$ was accepted as statistically significant.

Results

The demographic and clinical characteristics of the patient and the control groups are shown in Table 1. HEG cases were found to have earlier birth weeks than the control group ($p<0.001$). Also, when the weight gained during pregnancy was examined, it was found that this value was lower in HEG cases ($p<0.001$). It was determined that 61.5% of the pregnant women who were hospitalized due to hyperemesis presented to the emergency department and 38.5% presented to the outpatient clinic. The mean hospitalization week of the pregnant women with HEG was 9.6±2.4. The average length of hospital stay was determined as 3.1±2 days.

The evaluation of subclinical inflammatory markers and hematological values for both groups are shown in Table 2. In HEG cases, NLR and PLR values were higher ($p=0.006$, $p=0.004$, respectively), whereas LMR values were found to be lower ($p<0.001$).

Table 1. The demographic and clinical characteristics of the patient and control groups

		Hyperemesis (n=52)	Control (n=60)	p
Age		28 (19-39)	30 (21-37)	0.131**
Gravidity		2 (1-6)	3 (1-6)	0.085**
Parity		1 (0-4)	1 (0-4)	0.080**
BMI (kg/m^2)^		26.5±4.36	27.3±3.41	0.288*
Birth weight (g)^		3060±321	3265±414	0.004*
Gestational age at delivery		38 (34-42)	39 (35-42)	<0.001**
Weight gained during pregnancy		11 (4-18)	13 (7-22)	<0.001**
Apgar 1. min	<7	3 (5.8%)	4 (6.7%)	0.845***
	≥7	49 (82.7%)	56 (93.3%)	
Apgar 5. min	<7	1 (1.9%)	2 (3.3%)	0.641***
	≥7	51 (98.1%)	58 (96.7%)	
Neonatal gender	Male	21 (40.4%)	31 (51.7%)	0.315***
	Female	31 (59.6)	29 (48.3%)	
Mode of delivery	Vag.delivery	25 (%48.1)	24 (40%)	0.504***
	C-section	27 (%51.9)	36 (60%)	

^ Values are given as mean ± standard deviation; others are given as median (minimum-maximum), *Independent simple *t*-test, **Mann-Whitney U test, ***Chi-square test. Values in bold represent statistically significant outcomes. BMI: Body mass index, Vag.delivery: Vaginal delivery, C-section: Caesarean section

In Table 3, the correlation analysis of HEG cases with birth week, baby birth weight, 1st and 5th minute Apgar scores and urine ketone level, hospitalization time, and subclinical inflammatory markers are shown. In HEG cases, birth week had negative correlations with NLR and PLR and a positive correlation with LMR ($r=-0.567$, $p<0.001$; $r=-0.322$, $p=0.02$, and $r=0.279$ $p=0.045$, respectively). In addition, NLR and PLR had negative correlations with birth weight ($r=-0.582$, $p<0.001$; $r=-0.302$, $p=0.029$, respectively).

ROC analysis of subclinical inflammatory markers for HEG cases is shown in Figure 1. In HEG cases, a 3.65 cut-off value was found with 61.5% sensitivity and 55% specificity for NLR, a 113.24 cut-off value was found with 71.2% sensitivity and 60% specificity for PLR, and a 3.15 cut-off value was found with 66.7% sensitivity and 69% specificity for LMR.

Discussion

In pregnant women who had symptoms of HEG, NLR and PLR values were found to be higher whereas LMR values were lower. Besides, it was determined that the baby birth weight, birth week, and weight gained during pregnancy were lower in HEG cases. In addition, as a result of this study, it was determined that in pregnant women with HEG there was a correlation between subclinical markers and the birth weight and the birth weeks of babies.

Table 2. The comparison of the subclinical inflammation marker values between HEG patients and controls

	Hyperemesis (n=52)	Control (n=60)	p
Hb (g/dL)^	12.3±1.7	12.2±1.4	0.879*
NEU (×10^3/uL)	7.1 (4.08-12.76)	6.7 (3.53-12.30)	0.088**
LYM (×10^3/uL)	1.7 (0.4-3.2)	2.1 (1.1-5)	0.015**
Monocyte (×10^3/uL)	0.7 (0.4-1.2)	0.5 (0.1-1)	<0.001**
PLT (×10^3/uL)	245 (122-408)	214.5 (132-668)	0.103**
NLR	4.1 (2-15.7)	3.5 (1.4-7.4)	0.006**
PLR	134 (52.7-655.8)	105.6 (49.6-286.7)	0.004**
LMR	2.5 (0.4-7)	3.7 (1.8-13.4)	<0.001**

^Values are given as mean ± standard deviation; others are given as median (minimum-maximum), *Independent simple t-test, **Mann-Whitney U test. Values in bold represent statistically significant outcomes.
Hb: Hemoglobin, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, NEU: Neutrophil count, LYM: Lymphocyte count, PLT: Platelet count, HEG: Hyperemesis gravidarum

Table 3. The correlation of the birth week the birth weight APGAR 1. min and APGAR 5. min with urine ketone level length of hospital stay NLR PLR LMR in the HEG group

	Gestational age		Birth weight		APGAR 1. min		APGAR 5. min	
	r	p	r	p	r	p	r	p
Urine ketone level	-0.173	0.22	-0.057	0.688	-0.095	0.504	-0.102	0.470
Length of hospital stay	-0.241	0.085	-0.185	0.188	-0.149	0.293	-0.164	0.244
NLR	-0.567	**<0.001**	-0.582	**<0.001**	0.239	0.088	0.190	0.177
PLR	-0.322	**0.02**	-0.302	**0.029**	0.201	0.153	0.257	0.066
LMR	0.279	**0.045**	0.253	0.071	-0.073	0.606	0.014	0.922

r: Sperman's rho, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio

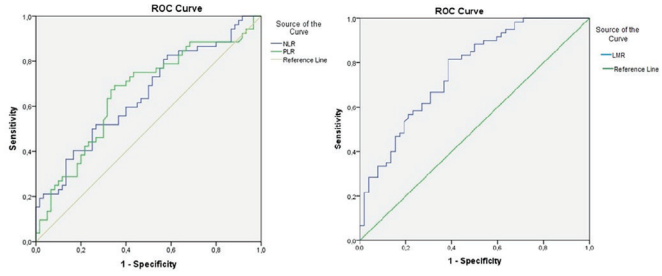

Figure 1. Receiver operating characteristic curves of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio according to the presence of hyperemesis gravidarum

LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio

The etiology of many diseases has been investigated in gynecology and obstetrics practice and it has been determined that inflammatory events play a key role in cases such as polycystic ovarian syndrome, ovarian hyperstimulation syndrome, and pregnancy hypertension (12,15,16). Although there is no test or marker that can fully reveal the mechanisms of HEG formation, the early determinants of inflammation such as interleukin (IL-6) and tumor necrosis factor-α were high in HEG cases which indicates an inflammatory condition. Besides, the determinants such as NLR, PLR, and CRP were found to be high in HEG (17), and this has been supported by many studies (13,18). In accordance with these results, in our study, it was determined that there was a decrease in LMR levels, which is another inflammatory indicator, as well as increased NLR and PLR levels in HEG cases.

In our study, the neonatal birth weight of the babies of women with HEG was found to be lower than the control group. Neonatal birth weight is affected by fetal, maternal, and placental factors. In addition, endothelial damage, thrombosis, and inflammation have been shown to constitute the main injury through mechanisms in which inflammatory cells play a role in many diseases. Besides, it has been reported that neonatal birth weight is associated with NLR and PLR (19). In our study, it was determined that there was a negative correlation between increased NLR and PLR levels, which are inflammatory parameters, and birth weight in HEG cases, and a negative correlation between LMR levels and birth weight.

Low birth weight (LBW) constitutes an increased risk for perinatal mortality and morbidity (20). HEG is known to be associated with neonatal outcomes such as preterm labor, LBW, and placental dysfunctions such as miscarriage and stillbirth (21,22). However, in our study with pregnant women with similar demographic characteristics, it was ensured that LBW in HEG cases could have been predicted with subclinical inflammatory markers.

In HEG cases, the relationship between ketonuria levels and inflammatory parameters have been previously studied, but similar to our study, no significant correlation was found between inflammatory markers (23). Vikanes et al. (24) determined that the 1st minute Apgar scores of <7 were less common in HEG cases, and both Kuru et al. (25) and Vikanes et al. (24) have identified the 5th minute Apgar scores of <7 as insignificant in cases of HEG.

The correlation of 1st and 5th minute Apgar scores with inflammatory markers was previously investigated in patients with pregnancy hypertension, but no correlation was observed (12). Similarly, in our study, there was no correlation between NLR, PLR, and LMR with 1st and 5th minute Apgar scores in HEG cases. When the 1st and 5th minute Apgar scores were examined, it was observed that there was no significant difference between pregnant women with HEG and the control group, especially in terms of the score being <7. These results indicate that there is no difference between HEG cases and normal pregnant women in terms of fetal well-being.

In a cohort study by Vandraas et al. (26), it was found that the risk of developing preterm delivery below 32 weeks was lower in pregnant women with HEG, but there was a 0.5 day shortening in the gestational period. In another study evaluating pregnant women with HEG and normal pregnant women, it was found that HEG did not change the birth week and delivery type (vaginal delivery, cesarean delivery) (27). In our study, no difference was detected in terms of delivery type, but it was determined that the gestational week of pregnant women with

HEG was on average 1 week earlier. It was found that inflammatory markers were correlated with this condition. Vogel et al. (28) reported the relationship between the second trimester inflammatory markers with preterm labor. In our study, it can be concluded that the process leading to birth in pregnant women with HEG might be somewhat shorter.

Contrary to our findings, Kuru et al. (25) reported that HEG was not associated with adverse pregnancy outcomes such as LBW and preterm gestation. This difference may be due to the fact that our study was conducted with a relatively small population or that our patients with HEG consisted of patients with more severe symptoms. Perhaps, if we had classified pregnant women with HEG according to their symptoms or included a third group of pregnant women diagnosed with HEG with normal laboratory parameters, we could clarify whether the association of inflammatory parameters with preterm delivery and LBW was due to HEG or variable blood parameters.

Theoretically, increased hemoconcentration due to vomiting can be expected in patients with HEG. Cintesun et al. (23) found that hematocrit and platelet levels did not change in HEG patients (23). These findings were similar in our study. The degree of hemoconcentration can be masked by the physiological decrease in the hematocrit and platelet levels that normally occurs during pregnancy.

There are some limitations to our study. Our main limitation is the low number of patients because our study was conducted as a single-centered study. Also, the fact that our study was designed retrospectively constitutes another limitation. However, in our study, identifying similar demographic and clinical peer groups in both pregnant women with HEG and the control group enabled our evaluations to be healthy.

Conclusion

In conclusion, high NLR, PLR, and low LMR values in pregnant women with HEG can be a warning for LBW and preterm birth week. In this respect, there is a need for a larger series of studies to be conducted prospectively.

Authorship Contributions

Concept: M.D.C., Design: M.K., E.S.Y., Data Collection or Processing: I.C., S.E.Y., Analysis or Interpretation: T.O., Literature Search: D.A.K., E.B., Writing: M.D.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2021.6871
Med Bull Haseki 2021;59:145-151

Evaluation of Cervical Lymphadenopathy in Children: Is Epstein-Barr Virus Infection Predictable?

Nurhayat Yakut, Eda Kepenekli

Marmara University Faculty of Medicine, Department of Pediatric Infectious Diseases, Istanbul, Turkey

Abstract

Aim: The aim of this study was to evaluate the paediatric patients with cervical lymphadenopathy (LAP) and to compare the clinical and laboratory features between Epstein-Barr virus (EBV) infections and the other aetiologies.

Methods: We conducted a retrospective, single-center study of paediatric patients with cervical LAP from a tertiary care hospital in Turkey between October 2017 and March 2020. The medical records including demographic information, clinical features and laboratory results were collected from paediatric patients with cervical LAP. Patients were divided into two groups according to whether the aetiology of LAP was EBV infection or the others. Clinical and laboratory findings were compared between the two groups.

Results: A total of 175 patients included in the study. Nonspecific lymphadenitis was the most common diagnosis occurring at a rate of 54.3%. EBV infection was responsible for 17.1% of all causes. The presence of fever, white blood cell (WBC) and lymphocyte count were significantly higher and LAP size was significantly larger in patients with cervical LAP caused by EBV infection.

Conclusion: Fever, elevated WBC and lymphocyte count may be predictors for EBV infection in children with cervical LAP. In patients who had these features, serological tests for EBV could make a significant contribution to reach an accurate diagnosis without wasting time.

Keywords: Cervical LAP, children, EBV infection

Introduction

Cervical lymphadenopathy (LAP) is commonly defined as cervical lymph nodes measuring more than 1 cm in diameter is a common finding on physical examination in children and creates parental anxiety. The prevalence rate is about 38% to 45% of otherwise healthy children (1,2). There are too many conditions in the differential diagnosis of cervical LAP. Although the most common causes are bacterial and viral infectious diseases resulting in reactive hyperplasia, malignancies, congenital abnormalities and autoimmune diseases can also be the reason (3,4). One of the primary infectious causes of cervical LAP is Epstein-Barr virus (EBV) infection usually appears in early childhood in developing countries like our country (5). More serious disorders such as malignancy should be excluded rapidly in order to avoid unnecessary investigations and to relieve the parent. The aim of this study was to investigate the demographic, clinical and laboratory characteristics, treatment, and outcomes in children with cervical LAP and to compare the clinical and laboratory features between EBV infections and the other aetiologies.

Methods

Study Design and Data Collection

This study was conducted with the approval of the Marmara University Clinical Research Ethics Committee of our hospital (date: January 3rd 2020 and decision no: 09.2020.6).

A retrospective single-center study was conducted of paediatric patients with cervical LAP at outpatient clinic and ward of paediatric infectious diseases of tertiary care hospital in Turkey. The medical records were collected from paediatric patients with cervical LAP in our hospital, between October 2017 and March 2020. The following demographic information, clinical features, laboratory results and management data were collected

Yazışma Adresi/Address for Correspondence: Nurhayat Yakut, Marmara University Faculty of Medicine, Department of Pediatric Infectious Diseases, Istanbul, Turkey
Phone: +90 216 657 0606 E-mail: nurhayatyakut@gmail.com ORCID: orcid.org/0000-0002-6383-0568
Received: 01.01.2021 **Accepted:** 04.02.2021

retrospectively: age, gender, LAP size and location, duration of symptoms and antibiotic therapy, previous use of antibiotic therapy, duration of hospital stay, surgical drainage, ultrasonography, computed tomography, magnetic resonance imaging, complete blood count, C-reactive protein, lactate dehydrogenase (LDH), uric acid level, liver function tests, excisional biopsy and final diagnosis.

Definitions

Enlarged >10 millimeters lymph nodes in the cervical region were accepted as cervical LAP.

The diagnosis of primary EBV infection was confirmed in the presence of IgM antibodies to EBV viral capsid antigen.

Statistical Analysis

Data were entered into Microsoft Office Excel 2010 (Microsoft, Redmond, WA, USA). The statistical analysis was performed using SPSS version 22.0 (IBM, SPSS). Normally distributed data were assessed using means and the Student's t-test. The significance of the nonparametric data was assessed using the Mann-Whitney U test. The statistical significance of the dichotomous outcomes was determined using the chi-square test, Fisher's Exact test, the Fisher-Freeman-Halton test, and Yates's continuity correction. A multivariate logistic regression analysis was performed. A p-value of <0.05 was considered statistically significant.

Results

A total of 175 children with cervical LAP were examined in our hospital between October 2017 and March 2020. Among the 175 patients, 133 (76%) had received antibiotics before admission. Surgical drainage was who performed in 40 patients (22.8%). At least one pathogen was identified in 32 of 40 (80%) patients performed surgical drainage. *Staphylococcus aureus* was the most common organism isolated in 10 (31.2%) patients, followed by *Streptococcus viridans* in 8 patients (25%) and *Streptococcus pyogenes* in four patients (12,5%). Lymph node excisional biopsy was performed in 27 (15.4%) patients. The results of biopsies were as follows: 16 patients (59.2%) of reactive lymphadenitis, 7 patients of necrotizing granulomatous lymphadenitis, three patients of Hodgkin's lymphoma and one patient of nasopharyngeal carcinoma. The most common cause of cervical LAP was nonspecific lymphadenitis in 95 (54.3%) patients. In 30 patients (17.1%), a diagnosis of EBV infection was performed.

The mean white blood cell (WBC) count at the time of admission was 12014.29±5759.29 (range, 2500-38200) /mm^3. The most LAP localization was the right cervical region in 63 (36%) patients and 53 (30.3%) patients had cervical LAP bilaterally. The patient characteristics are summarised in Table 1.

Patients were divided into two groups; patients with cervical LAP caused by EBV infection (Group 1; n=30), and patients with cervical LAP caused by the other aetiologies (Group 2; n=145). Clinical and laboratory findings were compared between the two groups. The male/female ratio was similar between the two groups. Duration of symptoms, antibiotic therapy and hospital stay of the patients were significantly shorter in Group 1 ($p<0.05$).

The prevalence of fever, tonsillopharyngitis and hepato/splenomegaly was found significantly higher in Group 1. Patients with EBV infection had a lower percentage of hospitalization and antibiotic use ($p<0.05$). According to the univariate analysis, the following laboratory values were significantly higher in Group 1: lymphocyte, granulocyte, WBC count, alanine aminotransferase, aspartate aminotransferase and LDH ($p<0.05$). Mean lymph node size was 4.32±0.84 cm in Group 1 and 2.87±0.49 cm in Group 2. Lymph node size in Group 1 was significantly larger than Group 2 ($p<0.05$) (Tables 2, 3).

In the multivariate analysis, we detected that WBC, lymphocyte count and prevalence of fever were significantly higher [odds ratio (OR)=1.000; 95% confidence interval (CI): 0.999-1.000, OR=1.001; 95% CI: 1.000-1.002, OR=51,591; 95% CI: 2.225-1169,919, respectively], and lymph node size was significantly larger (OR=30,562; 95% CI: 4.346-214,925) in Group 1 (Table 4).

Discussion

Cervical LAP is one of the most common problems in children. It creates anxiety in parents with diverse aetiologies including malignancy (6). EBV infection is also in the differential diagnosis (7). In this study, we tried to investigate pediatric cervical LAP characteristics and detect the difference of cervical LAP caused by EBV from the other aetiologies.

In this study, we detected that among the 175 patients, 108 (61.7%) were male. Similar to our study, previous studies report that cervical LAP is more likely to be seen in boys (8,9). The spectrum of clinical manifestations and findings can vary according to aetiology. A retrospective study by Aykac et al. (4) conducted on children reported that the most frequent symptoms and findings were fever (45.3%), tonsillopharyngitis (53%) and hepatomegaly (10.3%). In another study conducted on Sudanese children with cervical LAP, Bilal et al. (10) reported that the most common clinical examination findings were fever (71.3%), cough (57%), weight loss (55%) and sore throat (46.2%). One of the important reasons for cervical LAP is dental caries resulting in odontogenic infections. Our

Table 1. The demographic and clinical characteristics of the patients			
		Min-Max	**Mean ± SD (median)**
Age (years)		0.2-18	6.56±4.48
Duration of symptoms $_{(median)}$		2-120	12.42±13.11 (10)
Duration of antibiotic therapy (day) $_{(median)}$		0-28	10.36±7.45 (10)
Duration of hospitalisation $_{(median)}$		0-29	5.11±7.07 (0)
LAP size (cm)		2-6	3.12±0.78 (3)
		n	**%**
Gender	Female	67	38.3
	Male	108	61.7
Clinical symptoms and findings	Fever	55	31.4
	Tonsillopharyngitis	27	15.4
	Limited neck mobility	20	11.4
	Tooth decay	25	14.3
	Odynophagia	5	2.9
	Hepato/splenomegaly	12	6.9
Prior antibiotic treatment	No	42	24
	Yes	133	76
Final diagnosis	Pharyngotonsillar infections	10	5.7
	Odontogenic infections	24	13.7
	Non-specific lymphadenitis	95	54.3
	Epstein-Barr virus infection	30	17.1
	Tularemia	3	1.7
	Cat-scratch disease	2	1.1
	Tuberculous lymphadenitis	7	4
	Nasopharyngeal carcinoma	1	0,6
	Hodgkin lymphoma	3	1.7
Hospital unit	Outpatient	94	53.7
	Inpatient	81	46.3
Excisional biopsy	No	148	84.6
	Yes	27	15.4
Antibiotic treatment	No	50	28.6
	Ampicillin-sulbactam	47	26.9
	Ampicillin-sulbactam + clindamycin	24	13.7
	Others	54	30.9
C-reactive protein, mg/dL	Negative (<3 mg/dL)	82	46.9
	Positive (>3 mg/dL)	93	53.1
Imaging modalities	Ultrasound imaging	113	64.6
	Computed tomography	4	2.3
	USG + CT	37	21.1
	USG + Magnetic resonance imaging	15	8.6
	USG + CT + MRI	6	3.4
LAP localization	Right	63	36
	Left	59	33.7
	Bilateral	53	30.3

LAP: Lymphadenopathy, USG: Ultrasound imaging, CT: Computed tomography, MRI: Magnetic resonance imaging, Min-Max: Minimum-maximum, SD: Standard deviation

results about the reason for cervical LAP are similar to previous studies.

Several studies confirmed that clinical symptoms and findings lasting more than four weeks may indicate increased risk for malignancy (8,11,12). In accordance with previous studies, we detected that the mean duration of symptoms was 12.42±13.11 and only four patients were diagnosed with malignancy. These results suggest that patients with persistent cervical LAP and chronic symptoms may present malignancy and further evaluation may be required for these patients.

Cervical LAP frequently represents a transient response of lymphatic tissue to a benign local or generalized infection, but it can also rarely be caused by other more significant pathology such as malignancy. The most common cause of cervical LAP in children is reactive hyperplasia secondary to known or unknown infectious agents (12). A systematic review of 2687 cervical LAP in paediatric patients showed that the most common cause was nonspecific benign etiology occurring at a rate of 67.8% (13). In another study, Indolfi et al. (14). reported that among 392 paediatric patients with head and neck LAP, 220 patients (56.1%) had a history of infection and 101 patients (24.9%) nonspesific reactive lymphadenitis. Similarly, we found that nonspecific lymphadenitis was the most common cause of cervical LAP.

Bacterial infections resulting in cervical LAP range from aerobic and anaerobic to mycobacterial infections. The most commonly reported microorganisms isolated from suppurative cervical LAP are *Staphylococcus aureus*, followed by group A streptococcus (*Streptococcus pyogenes*) and anaerobic bacteria (12,15). Indolfi et al. (14) reported that the most frequently isolated pathogen was S. pyogenes in 31 patients (22.9%), followed by *S. aureus* in 10 patients (7.4%). In accordance with the previous reports, the most commonly isolated pathogen in our study was *S. aureus. S. viridans* was the second most common microorganism. Compared with other studies, we detected a higher incidence of *S. viridans*. The reason for this can be explained by the high number of patients with dental caries.

Table 2. Comparison of patient characteristics of the two groups by univariate analysis

		EBV lymphadenitis (Group 1)	Other aetiologies (Group 2)	p
		Mean ± SD (median)	Mean ± SD (median)	
Age (years)		5.77±4	6.73±4.57	[1]0.286
Duration of symptoms (median)		7.23±5.2 (6)	13.5±13.98 (10)	[2]0.002*
Duration of antibiotic therapy (day) (median)		1.33±3.46 (0)	12.23±6.64 (14)	[2]0,000*
Duration of hospitalization (median)		1.27±2.49 (0)	5.91±7.44 (2)	[2]0.001*
		n (%)	n (%)	
Gender	Female	7 (23.3%)	60 (41.4%)	[3]0.100
	Male	23 (76.7%)	85 (58.6%)	-
Clinical symptoms and findings	Fever	23 (76.7%)	32 (22.1%)	[3]0.000*
	Tonsillopharyngitis	17 (56.7%)	10 (6.9%)	[4]0.000*
	Limited neck mobility	5 (16.7%)	15 (10.3%)	[4]0.241
	Tooth decay	0 (0%)	25 (17.2%)	[4]0.006*
	Odynophagia	1 (3.3%)	4 (2.8%)	[4]0.614
	Hepato/splenomegaly	12 (40%)	0 (0%)	[4]0.000*
Prior antibiotic treatment	No	15 (50%)	27 (18.6%)	[3]0.001*
	Yes	15 (50%)	118 (81.4%)	-
Surgical drainage	No	29 (100%)	105 (72.4%)	[3]0.003*
	Yes	0 (0%)	40 (27.6%)	-
Positive culture	No	14 (100%)	61 (65.6%)	[4]0.005*
	Yes	0 (0%)	32 (34.4%)	-
Hospital unit	Outpatient	23 (76.7%)	71 (49%)	[3]0.010*
	Inpatient	7 (23.3%)	74 (51%)	-
Excisional biopsy	No	30 (100%)	118 (81.9%)	[4]0.005*
	Yes	0 (0%)	27 (18.1%)	-

[1]Student t-test, [2]Mann-Whitney U Test, [3]Yates's continuity correction, [4]Fisher's Exact Test, EBV: Epstein-Barr virus

Table 3. Comparison of patient characteristics and laboratory findings of the two groups by univariate analysis				
		EBV lymphadenitis (Group 1)	Other aetiologies (Group 2)	p
		Mean ± SD	Mean ± SD	
White blood cells/mm^3		14546.67±6702.07 (12800)	11490.34±5424.14 (10400)	[1]0.009*
Hemoglobin, g/dL		11.91±1.48 (11.7)	11.64±1.38 (11.6)	[1]0.595
Alanine aminotransferase, IU/L		117.67±125.68 (67.5)	23.4±32.93 (15)	[1]0.000*
Aspartate aminotransferase, IU/L		112.63±112.56 (73)	35.66±32.39 (29)	[1]0.000*
Uric acid mg/dL		3.64±1.06 (3.5)	3.37±1.05 (3.2)	[1]0.180
Lymphocytes/mm^3		8593.33±4083.35 (8500)	3693.79±1723.58 (3400)	[1]0.000*
Granulocytes before treatment/mm^3		4036.67±2725.04 (3300)	6428.28±4902.21 (5300)	[1]0.001*
Granulocytes after treatment /mm^3		3166.67±1577.94 (3050)	3736.57±2116.47 (3400)	[1]0.115
Lactate dehydrogenase, IU/L		408.8±200.2 (352.5)	270.51±101.09 (259)	[1]0.000*
LAP size (cm)		4.32±0.84 (4.5)	2.87±0.49 (3)	[1]0.000*
		n (%)	n (%)	
Antibiotic treatment	No	27 (90%)	23 (15.9%)	[2]0.000*
	Ampicillin-sulbactam	1 (3.3%)	46 (31.7%)	-
	Ampicillin-sulbactam+ Clindamycin	0 (0%)	24 (16.6%)	-
	Others	2 (6.7%)	52 (35.9%)	-
C-reactive protein, mg/dL	Negative (<3 mg/dL)	15 (50%)	67 (46.2%)	[3]0,859
	Positive (>3 mg/dL)	15 (50%)	78 (53.8%)	-
Imaging modalities	Ultrasound imaging	27 (90%)	86 (59.3%)	[4]0.033*
	Computed tomography	0 (0%)	4 (2.8%)	-
	USG + CT	3 (10%)	34 (23.4%)	-
	USG + MRI	0 (0%)	15 (10.3%)	-
	USG + CT + MRI	0 (0%)	6 (4.1%)	-
LAP localization	Right	6 (20%)	57 (39.3%)	[2]0.000*
	Left	4 (13.3%)	55 (37.9%)	-
	Bilateral	20 (66.7%)	33 (22.8%)	-

[1]Mann-Whitney U Test, [2]Chi-square test, [3]Yates's continuity correction, [4]Fisher Freeman Halton Test, LAP: Lymphadenopathy, USG: Ultrasound imaging, CT: Computed tomography, MRI: Magnetic resonance imaging, SD: Standard deviation, EBV: Epstein-Barr virus

Table 4. Multivariate logistic regression analyses of predictor for EBV lymphadenitis			
	OR	95% CI	p
White blood cells	1.000	0.999-1.000	0.034*
Lymphocytes	1.001	1.000-1.002	0.001*
LAP size	30.562	4.346-214.925	0.001*
Fever	51.591	2.225-1169.919	0.013*
Constant	0.000	-	0.000*

EBV: Epstein-Barr virus, OR: Odds ratio, CI: Confidence interval, LAP: Lymphadenopathy

Many viruses, including EBV, may cause a self-limited and uncomplicated cervical LAP in children. In large cohort studies with paediatric patients, rate of cervical LAP caused by EBV was reported as 15% Abdel-Aziz et al. (7), 8.8%, % by Deosthali et al. (13) and 32.7% by Sarsu et al. (16) In addition, Bozlak et al. (9) and Indolfi et al. (14) demonstrated that EBV was responsible for 27% and 29.6 of infectious causes of cervical LAP, respectively. A cross-sectional study by Bilal JA conducted on 82 children with cervical LAP reported that EBV infection was diagnosed in 13 (15.9%) patients (17). These different rates can be caused by different study designs, including different geographic regions and age groups. In our study, EBV infection was serologically diagnosed in 30 (17.1%) patients with cervical LAP.

Determining diagnostic pathway for patients with cervical LAP is difficult because of broad differential diagnoses. The differential diagnosis of cervical LAP includes many viral infectious diseases such as EBV infection. Some symptoms and findings may guide the differential diagnosis. A recent history of upper respiratory tract infection, dental caries and fluctuation suggest a reactive process (18,19). Weight loss, lymph nodes more than 2.5 cm in size being hard and fixed to the underlying tissue, multiple sites of LAP have been

associated with a higher risk of malignancy (20-23). We think that determining clinical and laboratory predictors of EBV may be helpful to differential diagnosis and prevent unnecessary investigations and medical procedures. In this study, we found that WBC, lymphocyte count, liver enzymes, prevalence of fever, tonsillopharyngitis and hepato/splenomegaly were significantly higher and LAP size was significantly larger in children with cervical LAP caused by EBV than the other aetiologies. These results are similar to previous studies conducted on children with cervical LAP (7,17,24-27). When patients have these symptoms or findings, a serologic assay for EBV may be warranted to help with the diagnostic evaluation on the first step.

Study Limitations

The important limitations of this study were its retrospective, single-center design and relatively small sample size.

Conclusion

Our study determined that there were independent association between fever, elevated WBC, lymphocyte count, lymph node size and cervical LAP caused by EBV infection. The presence of these features may be warning sign for EBV and serological tests for EBV specific IgM and IgG antibodies can take place in the first step for differential diagnosis in these patients.

Authorship Contributions

Concept: N.Y., E.K., Design: N.Y., E.K., Data Collection or Processing: N.Y., Analysis or Interpretation: N.Y., E.K., Literature Search: N.Y., Writing: N.Y., E.K.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: No financial support was received.

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Original Article

DOI: 10.4274/haseki.galenos.2021.6491
Med Bull Haseki 2020;58:152-158

Relationship Between Clinical Disease Characteristics and Acute and Structural Changes in Sacroiliac Magnetic Resonance Imaging in Patients with Newly Diagnosed Axial Spondyloarthritis

Mustafa Corum, Tugba Aydin

Istanbul Physical Medicine and Rehabilitation Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Istanbul, Turkey

Abstract

Aim: The association between acute and structural lesions on magnetic resonance imaging (MRI) of the sacroiliac joint (SIJ) with clinical and laboratory features has not been fully investigated. This study aimed to compare the clinical and laboratory features of patients diagnosed with axial spondyloarthritis (axSpA) with and without inflammation or structural lesions in SIJ MRI.

Methods: Eighty four patients diagnosed with axSpA between June 2019 and June 2020 were retrospectively examined. Patients' medical records, laboratory data and MRI findings were collected. Inflammation was measured by C-reactive protein levels and erythrocyte sedimentation rate (ESR) (Westergren method, 0-20 mm/h). Moreover, the Spondyloarthritis Research Consortium of Canada MRI index was used to assess inflammation and structural changes of the SIJ.

Results: ESR values were statistically significantly different in patients with SIJ backfill and ankylosis (p=0.013 and p=0.016, respectively) and symptom duration in patients with SIJ erosion and ankylosis (p=0.048 and p=0.049, respectively) compared to those without. Morning stiffness was the only IBP characteristic which had a significant correlation with the presence of SIJ ankylosis (p=0.048, r=-0.218).

Conclusion: Clinical and laboratory characteristics in axSpA patients are associated with chronic structural lesions rather than inflammation signs in SIJ MRI.

Keywords: Back pain, inflammation, sacroiliac joint, spondyloarthritis

Introduction

Axial spondyloarthritis (axSpA) is a group of chronic inflammatory rheumatic diseases involving ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis, arthritis associated with inflammatory bowel disease and undifferentiated SpA (1). Genetics, environmental factors and immune-mediated mechanisms contribute to axSpA pathogenesis; however, its etiology is indefinite (2-4).

The modified New York criteria include only the presence of structural damage to sacroiliac joints (SIJ) in plain radiography; therefore, it can diagnose only advanced diseases (2). Because of the slow development of radiographic changes, only 70% of axSpA patients can meet the modified New York criteria after 5 years of symptoms (5). To facilitate early diagnosis and treatment of axSpA, the following criteria have been added to the classification of the Assessment of Spondyloarthritis International Society (ASAS): the presence of sacroiliitis on magnetic resonance imaging (MRI), radiographs along with a SpA characteristic or positivity of human leukocyte antigen B27 (HLA B27) along with two SpA characteristics in patients with chronic back pain aged <45 years (6). AxSpA treatment is aimed at early intervention during the disease course, when the response to treatment is at its

Address for Correspondence: Mustafa Corum, Istanbul Physical Medicine and Rehabilitation Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Istanbul, Turkey
Phone: +90 555 874 59 19 E-mail: mustafacorum@gmail.com ORCID: orcid.org/0000-0001-6720-4452
Received: 19.08.2020 **Accepted:** 03.02.2021

peak in the period before the occurrence of radiographic sacroiliitis (7).

Therefore, MRI is an important tool for SpA diagnosis because it can identify inflammation before the detection of structural radiographic changes (8). Furthermore, MRI scans can provide additional important objective information about treatment effectiveness (9). Bone marrow oedema (BME) of SIJ is a well-known inflammatory lesion in SIJ and can progress to chronic lesions such as BME, subchondral sclerosis, erosions, fat metaplasia and ankylosis (10,11).

Inflammatory back pain (IBP) is a chronic lower back pain which usually begins during young adulthood, improving by exercise and worsening with immobility and associated with morning stiffness. The presence of IBP characteristics, an important component of the ASAS classification criteria, has been specifically indicated for the diagnosis of axSpA in patients with chronic back pain (12). While the prevalence of IBP ranges between 5.0% and 6.0% among adults aged 20-69 years, the prevalence of SpA is estimated to be between 0.4% and 1.3% (13,14). This suggests that IBP characteristics can be common components of lower back pain due to many different diseases.

Therefore, this study aimed to determine which IBP parameters and disease characteristics are associated with acute (active inflammation) and/or chronic structural MRI changes in SIJ during the initial diagnosis of axSpA.

Methods

Study Design

The ethical approval was obtained from Bakirkoy Sadi Konuk Training and Research Hospital Ethics Committee (no: 2020/308). The study was conducted in accordance with the Helsinki Declaration and allowed the retrospective data collection, analysis of laboratory and MRI examinations and conducting phone calls.

The medical records of 110 patients with IBP, who were admitted to our department, were retrospectively examined and 84 patients newly diagnosed axSpA according to the ASAS criteria (1) upon their admittance to the outpatient clinic of Physical Medicine and Rehabilitation between June 2019 and June 2020 were included in the study. The medical records of the patients were obtained from the hospital database.

The inclusion criteria included meeting ASAS classification criteria [imaging criteria, sacroiliitis on imaging and ≥1 SpA feature and clinical criteria, positive HLA-B27 and ≥2 other SpA features] for axSpA as a result of retrospective examination of the patients' medical records, being diagnosed for the first time and obtaining the first MRI findings and laboratory data in our hospital. Also, patients were included aged between 18 and 65 years, had symptoms for >3 months and had initial diagnosis in our hospital. Exclusion criteria were the inability to contact with patients and incomplete data regarding symptoms.

Clinical and Laboratory Assessment

IBP parameters include pain duration of >3 months, pain during the second half of the night, morning stiffness, reduced pain with exercise and the onset of symptoms before 40 years of age. The IBP parameters were scored with "yes=1", "no=0", and the total IBP score (0-5) was calculated. Moreover, demographic data such as gender, age and symptom duration were recorded.

C-reactive protein (CRP) (immunoturbidimetric method, 0-0.5 mg/L) and erythrocyte sedimentation rate (ESR) (Westergren method, 0-20 mm/h) levels were measured. CRP level of >0.5 mg/L and ESR level of >20 mm/h were defined as elevated CRP and ESR levels, respectively.

MRI Assessment

MRI examinations were performed on a 1.5 Tesla unit (MAGNETOM Aera; Siemens Healthcare, Erlangen, Germany) with a whole-body surface coil system in the supine position. All sequences were obtained using 12-15 semi-coronal slices with a thickness of 4 mm in the coronal oblique plane parallel to the long axis of the sacrum. The imaging protocol included T1-weighted spin-echo (T1W/SE) pulse sequence, T2-weighted turbo spin-echo (T2W/TSE) sequence and short-tau inversion recovery (STIR) sequences. All images were evaluated by an experienced radiologist based on the ASAS classification criteria and the Spondyloarthritis Research Consortium of Canada (SPARCC) classification. The SPARCC scoring was used in the inflammatory and structural evaluation of SIJ (15).

An inflammatory lesion is defined as an increased bone marrow signal of either the iliac or sacral bones on the STIR sequence (Figure 1). The T1WSE MRI sequence may reveal a lesion in bone marrow adjacent to the subchondral bone, termed fat metaplasia characterized by a homogeneous increase in marrow signal, indicative of lipid accumulation and a distinct border (Figure 2A). Erosion is considered present when there is a breach in the cortical bone of either the iliac or sacral bones, which appears dark on both T1W/SE and STIR sequences, together with loss of the bright signal from the adjacent marrow matrix on T1W/SE MRI (Figure 2A). New tissue growth in erosive regions with the same signal intensity as fat metaplasia in T1W/SE MRI is called backfill (Figure 2B). Also, ankylosis is defined as a bone marrow signal on the T1W/SE sequence extending between the sacral and iliac bone marrow with a full-thickness loss of the dark

appearance of the iliac and sacral cortical bone (Figure 2B).

The SPARCC inflammation score was based on the assessment of all signal changes in the sacrum until the iliac bone and sacrum foramina in the STIR sequence in six consecutive semi-coronal slices covering the cartilaginous part of the joint from posterior to anterior regions. Each SIJ is divided into 4 quadrants (upper and lower iliac and upper and lower sacral), each of which was evaluated separately. For the calculation of the SPARCC score of active inflammatory changes, the presence of hyperintensity lesions in the STIR sequence in each of these 4 quadrants was recorded in each of the 6 segments (0=normal signal, 1=present lesion of increased intensity). Moreover, an additional point was given to the presence of an intense signal in the lesion in the 6 segments of each quadrant or the presence of a lesion with a depth of ≥1 cm (maximum total score=72) (16). SPARCC MRG SIJ structural score allows T1W/SE sequence MRI assessment of the presence of fat metaplasia, erosion, backfill and ankylosis. Five consecutive semi-coronal slices were evaluated from the posterior to the anterior regions, beginning from the transitional slice which is the first ligamentous cartilage slice. Each erosion and fat metaplasia was scored in total between 0-40 for 5 segments in 4 quadrants in SIJ, 0-8 per segment, whereas each backfill and ankylosis was scored a total of 0-20 for 5 segments, 0-4 per segment in 2 halves (upper versus lower) (11).

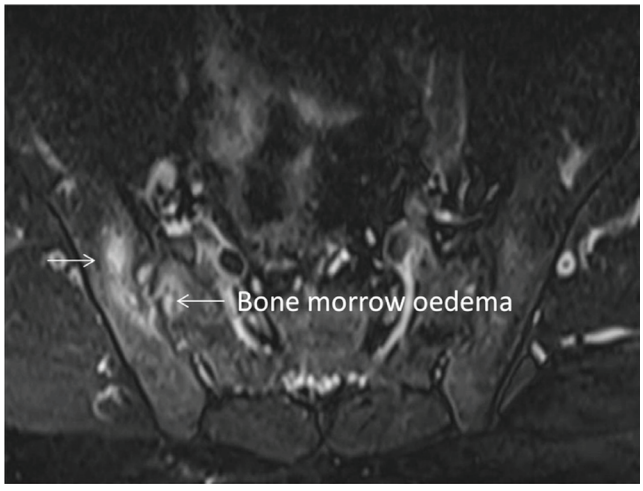

Figure 1. MRI findings of inflammatory lesions in the STIR sequence of SIJ
MRI: Magnetic resonance imaging, SIJ: Sacroiliac joint, STIR: Sequence and short-tau inversion recovery

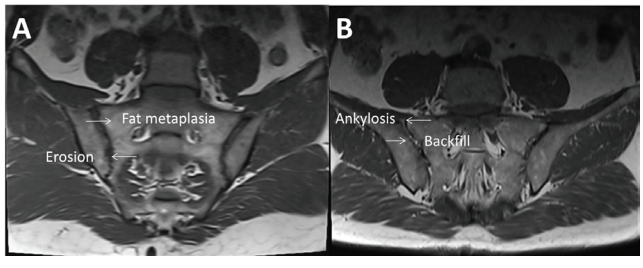

Figure 2. MRI findings of structural lesions in the T1W/SE sequence of SIJ. A) fat metaplasia and erosion B) backfill and ankylosis
MRI: Magnetic resonance imaging, SIJ: Sacroiliac joint, T1W/SE: T1-weighted spin-echo

Statistical Analysis

The Statistical Package for the Social Sciences (Version 22.0, IBM Corp., Armonk, NY, USA) was used to analyze the data. The descriptive statistics of the data were expressed in mean values and standard deviation for continuous variables, and in counts and percentages for categorical variables. The Shapiro-Wilk test was used to determine whether the normal distribution was present. Spearman's correlation test was performed to analyze the relationship between IBP parameters, inflammation and structural lesions in SIJ. Differences in demographics and baseline disease characteristics were analyzed by the presence or absence of SIJ BME (≥2 or 0<2) and by the separate presence or absence of any structural lesions (> or=0). These analyses were performed using the Mann-Whitney U test. Statistical significance was considered at $p<0.05$.

Results

Demographic, clinical, laboratory and SIJ MRI findings of patients are summarized in Table 1. A total of 84 patients were diagnosed with axSpA (35 females, 49 males; mean age 29.4±5.0 years) and were included in the final analysis after exclusion of 26 patients due to inadequate clinical data and unwillingness to participate. The mean duration of symptoms for these patients was 3.3±2.3 years. CRP elevation was detected in 18/84 patients (21.4%) and erythrocyte sedimentation rate (ESR) elevation in 7/84 patients (8.3%), whereas the mean CRP and ESR values were 0.5±1.0 mg/L and 8.0±7.8 mm/h, respectively. A total of 73/84 patients (86.9%) had acute inflammation in the MRI, whereas certain patients had structural fat metaplasia (72/84, 85.7%), erosion (78/84, 92.8%), backfill (74/84, 88.0%) and ankylosis (69/84, 82.1%).

Table 2 shows the demographic and baseline disease characteristics in patients with BME (score ≥2) and without BME (score <2) in SIJ MRI and the presence (score >0) or absence (score=0) of structural lesions. Similar differences were observed in demographic and basic disease characteristics when SIJ was characterized by the presence or absence of BME ($p>0.05$). When it

was characterized by patients with and without structural lesions in SIJ, the symptom duration was slightly statistically longer in SIJ erosion and ankylosis (p=0.048 and p=0.049, respectively). The ESR values were statistically significant differences in SIJ backfill and ankylosis (p=0.013 and p=0.016, respectively).

The association of different IBP characteristics with MRI findings (BME and structural lesions) is detailed in Table 3. Morning stiffness showed a slightly significant correlation with the presence of SIJ ankylosis (p=0.048, r=-0.218), there was no significant correlation between other IBP characteristics and acute and structural lesions in SIJ MRI.

Discussion

Table 1. Demographics and SPARCC score of SIJ inflammation and structural lesions of the 84 patients with axial spondyloarthritis

Characteristics	Mean ± SD or n (%)
Age, years	29.4±5.0
Gender, female/male	35 (41.7)/49 (58.3)
Duration of symptoms, years	3.3±2.3
CRP, mg/L	0.5±1.0
CRP elevation, yes/no	18 (21.4)/66 (78.6)
ESR, mm/h	8.0±7.8
ESR elevation, yes/no	7 (8.3)/77 (91.7)
Inflammatory back pain score (0-5)	4.0±0.7
SPARCC score of BME (0-72)	18.4±14.7
SPARCC score of fat metaplasia (0-40)	13.0±9.3
SPARCC score of erosion (0-40)	13.1±9.1
SPARCC score of backfill (0-20)	7.2±5.4
SPARCC score of ankylosis (0-20)	8.0±5.7

Means (SD) is given for continuous variables; n (%) is given for categorical data. SD: Standard deviation, SPARCC: SPondyloArthritis Research Consortium of Canada, BME: Bone marrow edema, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SIJ: Sacroiliac joint

This study compares age, pain duration, inflammatory markers (CRP and ESR), IBP characteristics and patients with and without acute and structural lesions of SIJ MRI during the initial diagnosis of axSpA; thus, the study evaluates the relationship between the disease characteristics and SIJ MRI signs. According to the results of our study, the mean ESR values were higher than those in patients with SIJ backfill and ankylosis lesions and mean symptom duration was longer in patients with SIJ erosion and ankylosis lesions than those who did not. Furthermore, morning stiffness was the only IBP characteristic that had a significant correlation with the presence of ankylosis.

Although IBP characteristics are included in different diagnostic criteria used in both research and clinical practice for the diagnosis of axSpA, the strength of the relationship between IBP characteristics and the presence of axSpA disease is controversial (11). Although the underlying pathogenesis of IBP is not fully understood, it is believed that the inflammation in the MRI in SIJ and surrounding structures clinically represents IBP (17). However, studies have demonstrated that the acute lesion rate in SIJ MRI in patients with IBP characteristics is between 26% and 41% (18, 19). Therefore, Braun et al. (20) emphasized that only IBP characteristics of limited value for the axSpA diagnosis and that imaging with IBP parameters or combination with other diagnostic criteria parameters can be useful. However, the relationship between acute and structural lesions in SIJ MRI and IBP has been investigated in a limited number of studies. Kivity et al. (17) examined the relationship between acute and structural sacroiliitis in MRI with IBP features and revealed ta significant correlation between BME with night pain and morning stiffness, as well as the relationship between nocturnal pain with structural lesions. Because of the connection between IBP features and the acute inflammation in SIJ MRI in the aforementioned study, it has been emphasized

Table 2. Demographics and baseline disease characteristics according to the presence or absence of SIJ inflammation and structural lesions

	SPARCC SIJ BME			SPARCC SIJ Fat metaplasia			SPARCC SIJ Erosion			SPARCC SIJ Backfill		SPARCC SIJ Ankylosis				
	≥2 n=73	<2 n=11	p	>0 n=72	0 n=12	p	>0 n=78	0 n=6	p	>0 n=74		0 n=10	p	>0 n=69	0 n=15	p
Age, years	29.0±5.1	31.6±2.5	0.141	29.3±5.2	29.3±5.3	0.928	29.0±5.0	33.0±3.2	0.062	29.1±5.0		31.0±4.0	0.304	29.3±4.9	29.5±5.3	0.656
Symptom duration, years	3.6±2.6	3.2±2.2	0.829	4.2±2.7	3.1±2.2	0.127	5.5±3.3	3.1±2.1	0.049*	4.3±3.1		3.1±2.1	0.254	4.2±2.5	3.1±2.2	0.048*
CRP, mg/L	0.5±1.1	0.4±0.2	0.083	0.6±1.1	0.2±0.0	0.522	0.5±1.1	0.2±0.0	0.663	0.6±1.1		0.2±0.0	0.205	0.5±0.8	0.7±1.9	0.202
ESR, mm/h	7.9±8.2	8.3±6.2	0.392	8.3±8.1	5.8±5.4	0.283	8.2±8.0	5.0±4.6	0.226	8.5±8.0		3.8±3.7	0.013*	8.8±8.2	4.0±3.1	0.016*
Inflammatory back pain score	4.2±0.4	4.0±0.7	0.346	4.0±1.0	4.0±0.6	0.749	4.3±0.5	4.0±0.7	0.353	4.4±0.5		4.0±0.7	0.109	4.3±0.6	3.9±0.74	0.101

Values are mean ± standard deviation. Ps were calculated using Mann-Whitney U test. SPARCC: SPondyloArthritis Research Consortium of Canada, SIJ: Sacroiliac joint, BME: Bone marrow edema, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

Table 3. Correlation between inflammatory back pain features, the presence of bone marrow edema and structural lesions on MRI of the SIJ

IBP feature	SPARCC SIJ BME	SPARCC SIJ Fat Metaplasia	SPARCC SIJ Erosion	SPARCC SIJ Backfill	SPARCC SIJ Ankylosis
Night pain	p=0.938, r=-0.009	p=0.178, r=0.149	p=0.361, r=0.101	p=0.936, r=0.009	p=0.413, r=0.090
Duration above 3 months	p=0.188, r=-0.098	p=0.355, r=0.046	p=0.264, r=-0.070	p=0.286, r=0.063	p=0.449, r=0.014
Morning stiffness	p=0.197, r=-0.142	p=0.270, r=0.122	p=0.059, r=-0.207	p=0.275, r=-0.121	p=0.048*, r=-0.218
Improvement with exertion	p=0.914, r=-0.014	p=0.101, r=-0.180	p=0.806, r=-0.027	p=0.214, r=-0.137	p=0.114, r=-0.174
Began before the age of 40	p=0.584, r=-0.061	p=0.564, r=-0.064	p=0.696, r=-0.043	p=0.604, r=-0.057	p=0.235, r=0.131

Spearman correlation was tested. IBP: Inflammatory back pain, SPARCC: SPondyloArthritis Research Consortium of Canada, SIJ: Sacroiliac joint, BME: Bone marrow edema, MRI: Magnetic resonance imaging

that physicians can reduce the disease progression with early treatment by encouraging the evaluation of SIJ MRG in patients with IBP characteristics. However, Arnbak et al. (21) examined the relationship between IBP characteristics and MRI findings in the spine and SIJ and they found a higher association between night pain and SIJ sclerosis and found that structural changes are more consistently related with pain characteristics than BME findings are associated with active inflammation. Similarly, when we compare MRI examinations based on SPARCC scoring and IBP characteristics based on anamnesis in our study, we found that morning stiffness was significantly correlated with the presence of ankylosis. The contradictory study results suggest that there is a weak correlation between the acute or structural findings of the axSpA-related MRI and IBP parameters, but a more consistent correlation between structural findings and IBP can be attributable to the fact that chronic MRI manifestations represent a more severe inflammatory process. Moreover, during the diagnoses made herein, we found that most patients had a high total IBP score (mean score; 4.0±0.7), whereas there was no difference in the total IBP score of patients with and without acute or structural lesions in SIJ MRI.

The current approach to axSpA treatment is to intervene at disease onset, in which the response to treatment is the greatest before the appearance of radiographic sacroiliitis (22). Therefore, it is important to demonstrate inflammation with MRI before the detection of radiographic changes and identify patients with axSpA with a higher risk of progression to AS. Blachier et al. (23) showed that structural radiological lesions in early axSpA were positively correlated with the CRP level and active inflammation seen in the MRI of SIJ. A recent study by Min et al. (24) found that has a higher CRP level and ESR than non-radiographic axSpA. Similarly, ESR levels were found to be significantly higher in axSpA patients with structural lesions (backfill and ankylosis) in our study. The aforementioned findings support that the acute inflammatory condition is more common in AS patients in terms of biochemical parameters and MRI findings compared to non-radiographic axSpA. Although the severity of sacroiliitis was not evaluated radiographically in our study, the mean basal SIJ MRG inflammation score was 18.4 according to the SPARCC scoring and higher than the previously reported values in non-radiographic axSpA studies (7.4 and 10.0, respectively) (25,26). Again, the mean basal SIJ MRI inflammation score in our study was >14.0 which was same as the score in the group of AS patients in the study by Min et al. (24), and this difference might be attributable to the inclusion of more patients with advanced structural lesions (presence of SIJ ankylosis is 82.1%). This, in turn, supports studies in which the severity of sacroiliitis on plain radiography was positively correlated with the inflammatory score of SIJ MRI. Moreover, the symptom duration in non-radiographic axSpA and AS in the study by Min et al. (24) was 1 and 2 years, respectively and the symptom duration in our study was 3.3 years; the symptom duration was significantly longer in patients with SIJ erosion and ankylosis than those who did not which may be another reason for the large number of structural lesions in our study.

SIJ radiography is recommended as the first imaging modality to diagnose sacroiliitis as part of axSpA. Since it can be identified even in patients whose structural lesions are radiographically normal on SIJ MRI, it is better to use MRI instead of radiography to identify structural lesions as well as inflammation because MRI has higher sensitivity than radiography. Indeed, BME is evident on MRI several years prior to the development of structural changes visible on radiograph (27). Structural lesions are also generally not observed on radiographs for more than five years from the onset of the disease (28). In addition, as shown in our study, clinical and laboratory characteristics have been determined to be associated with advanced structural lesions. In conclusion, MRI can identify patients who can avoid further radiographic progress with early detection of the acute and early-stage structural lesions in SIJ and diagnostic abilities of SpA can be enhanced by adding MRI in the diagnostic workup.

Study Limitations

Our research has certain limitations. First, since the patients in our study were admitted to the Physical Medicine and Rehabilitation outpatient clinic, this group might include patients with advanced MRI lesions. Second, the severity of sacroiliitis was not evaluated radiographically due to the lack of plain radiographical images of the patients. Third, because it was a retrospective examination, it contains only basic data and information indicating the activity of the disease, such as Bath AS Disease Activity Index, is missing. Finally, the high level of intra-reader variability cannot be ignored because the MRI assessment and calculation of SPARCC scores were performed by a single radiologist.

Conclusion

According to the results of this study, ESR values and symptom duration are statistically higher in axSpA patients with structural lesions in SIJ MRI than those who did not and morning stiffness was significantly correlated with the presence of ankylosis. In our study, clinical and laboratory characteristics were associated with structural lesions rather than acute inflammation in MRI findings. Further research is needed to correlate specific MRI findings with clinical disease characteristics.

Acknowledgements

The authors thank Deniz Yakar Mutlu for MRI assessments in this study.

Authorship Contributions

Concept: M.C., Design: M.C., T.A., Data Collection or Processing: M.C., T.A. Analysis or Interpretation: T.A. Literature Search: T.A. Writing: M.C.

Conflict of Interest: This study was conducted as a master's thesis. The authors confirm that this article's content has no conflicts of interest.

Financial Disclosure: The authors declared that this study received no financial support

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Original Article

DOI: 10.4274/haseki.galenos.2021.6972
Med Bull Haseki 2021;59:159-166

Do Inner Ear and Mastoid Bone Structural Variations Have a Determining Role on Vestibular Symptoms of Migraine?

Zehra Cinar, Cigdem Kalaycik Ertugay, Ozgür Yigit, Yesim Karagoz*, Osman Ozgur Yalin**

University of Health Sciences Turkey, Istanbul Training and Research Hospital, Clinic of Otorhinolaryngology Head and Neck Surgery, Istanbul, Turkey

**University of Health Sciences Turkey, Istanbul Training and Research Hospital, Clinic of Radiology, Istanbul, Turkey*

***University of Health Sciences Turkey, Istanbul Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey*

Abstract

Aim: To investigate the possible relationship between morphological changes caused by anatomical structural differences and functional impairment in Vestibular migraine (VM) and Chronic Migraine (CM) disease.

Methods: A total of 44 patients (VM group; 23 and CM group; 21) included in the study. The medical records of patients with CM and VM between 2016-2018 were retrieved from the digital database of the otorhinolaryngology and neurology clinics. The mastoid bone and inner ear measurements in temporal bone high resolution computed tomography and inner ear magnetic resonance imaging were performed in our study. The two groups were compared radiologically.

Results: Right cochlear height in the VM group was significantly higher than the CM group. The left vestibular height in the VM group was significantly higher than the CM group.

Conclusion: The reason why not all patients with CM have vestibular complaints may be due to some differences in the inner ear anatomical structure.

Keywords: Vertigo, migraine disorders, cochlea, vestibule, labyrinth, ear, inner, mastoid

Introduction

Migraine is a specific neurological disease and diagnosis is made according to the widely accepted International Classification of Headache Disorders 3rd Edition (ICHD-3). If the attack frequency is more than 15 days per month for more than three months, it is diagnosed as chronic migraine (CM) (1,2). Vestibular migraine (VM) is one of the most common causes of episodic vertigo in adults and children (3). The diagnostic criteria for VM were proposed by Neuhauser in 2001 and revised by the Bárány Neuro-Otology Society in 2012, and diagnostic criteria were established in 2013 with the International Headache Society. Accordingly, the diagnostic criteria combine the typical signs and symptoms of migraine with vestibular symptoms lasting 5 minutes to 72 hours and exclusion of other causes of headache (4). Vestibular migraine is considered as the second most common cause of vertigo (5).

Based on the idea of possible similar pathophysiology, the literature focused on the differential diagnosis of Meniere's Disease and VM (6-8). On the other hand, there are few studies comparing CM and VM radiologically and clinically. Carvalho et al. (9) investigated the relationship between vestibular symptoms and migraine subtypes, and detected a greater frequency of vestibular symptoms in CM patients. However, we do not know the reason for not having vestibular complaints in all migraine patients. Some reports showed radiological increased activity

Yazışma Adresi/Address for Correspondence: Zehra Cinar, University of Health Sciences Turkey, Istanbul Training and Research Hospital, Clinic of Otorhinolaryngology Head and Neck Surgery, Istanbul, Turkey
Phone: +90 212 459 60 00 E-mail: drzehradonmez@hotmail.com ORCID: orcid.org/0000-0002-5027-4750
Received: x24.01.2021 **Accepted:** 05.03.2021

involvement in some regions of the brain in patients with VM (10,11). Based on this information, we hypothesized that the reason might be several anatomical differences. Nevertheless, there is a lack of literature about this issue.

Based on these facts, the mastoid bone and inner ear measurements in temporal bone high resolution computed tomography (HRCT) and inner ear magnetic resonance imaging (MRI), as well as measurements of the internal acoustic canal (IAC) and cranial nerves in it were performed in our study. Both groups were compared radiologically. This study aims to reveal the possible relationship between morphological changes caused by anatomical structural differences and functional impairment in these two diseases.

Main points

CM is a frequent neurological disease. VM has the typical signs and symptoms of CM combined with vestibular symptoms. In the current study right cochlear height in the VM group was significantly higher than the CM group ($p<0.05$). The left vestibular height in the VM group was significantly higher than the CM group ($p<0.05$). The reason for not having vestibular complaints in all CM patients might be several anatomical differences. This is the first study that investigated the inner ear and mastoid bone anatomical variations between VM and CM.

Methods

For this study, the approval was obtained from the local ethics committee of a tertiary hospital on 09.03.2018 (Decision number: 1198). This study was a retrospective comparative study conducted using the medical records of patients diagnosed with VM and CM disease. So informed consent was not taken.

Study Design

This research is a retrospective comparative study conducted by accessing the medical records of patients with CM diagnosis who were followed up and treated in the neurology clinic and the patients diagnosed with VM who were treated and followed up in the tertiary hospital Otorhinolaryngology-Head and Neck Surgery Clinic and Neurology Clinic between 2016-2018. The medical records of patients were retrieved from the digital database of the otorhinolaryngology and neurology clinics.

Patient Selection

The patients were evaluated by neurologists and headache specialists from the tertiary hospital Neurology Clinic and Vertigo Clinic of Otorhinolaryngology-Head and Neck Surgery Clinic and diagnosed with VM and CM according to ICHD-3 diagnostic criteria (1).

A neurology specialist who worked in the headache outpatient clinic made full neurological examinations, and differential diagnosis of CM and VM. An otolaryngologist evaluated these patients in the vertigo outpatient clinic and performed detailed otomicroscopic and vestibular examinations by using videonystagmography. The differential diagnosis of Meniere's disease, benign paroxysmal positional vertigo and other possible etiologies and related conditions of vertigo were made by the consensus of otolaryngologist, neurology specialist and radiologist.

Patients who had an ongoing infection, were pregnant, had autoimmune disorders, history of the previous otologic and cranial surgery, Meniere's disease, benign paroxysmal positional vertigo-like dizziness pathology, chronic neurophysiological disease, psychiatric pathology-related headache, patients who were <18 and >65 years old were excluded.

All patients were examined in terms of clinical characteristics such as disease duration, headache characteristics, pain localization, attack frequency, use of analgesics, and treatment options by a neurologist who worked in the headache clinic. Pain severity was evaluated with the visual analog scale. Also, the migraine disability assessment scale and the beck depression scale were filled out by the patients, and allodynia was evaluated using the Turkish version of the validated 12-item allodynia symptom checklist (12).

Migraine, VM and CM diagnoses were made by an experienced neurologist based on ICHD-3 diagnostic criteria (1). Patients with secondary headaches and other primary headache disorders were excluded. Other vestibular causes that could accompany VM were excluded by otolaryngological examination and audio-vestibular tests performed by the relevant specialists.

Computed Tomography Parameters and Data Analysis

Measurements of the labyrinth performed with temporal bone HRCT sections were determined using the methods described in the literature on the raw images and the constructed images created by the relevant researcher at the workstation (13-16). These measurements were chosen because previous studies have demonstrated their utility in identifying detailed inner ear abnormalities (14-19).

Temporal bone HRCT examinations were performed on the patients with a multi-detector CT unit (Philips Ingenuity 128 CT scanner, Philips Healthcare, Cleveland, OH) in the radiology clinic of our hospital. The tube voltage and current were 140 kV and 124 mAs; field-of-view was in the range of 22-24 cm. While the patient was in the supine position, axial sections with a slice thickness of 0.625 mm parallel to the orbitomeatal line were taken with 0.33 mm increments without overlap in the bone algorithm. At the workstation (GE Healthcare advantage workstation 4.3,

Milwaukee, WI), raw data were reconstructed, and the radiologist performed inner ear and IAC measurements. CT measurements performed in this study were: Cochlear width and height, vestibular length and height, IAC proximal, mid and distal heights, IACl ength cochlear apertura diameter, vestibular apertura diameter, distance between the tegmen-mastoid tip, the distance between sigmoid sinus anterior wall - external acoustic meatus, the distance between petrous apex - mastoid aditus medial wall. (Figure 1)

Magnetic Resonance Imaging Parameters and Data analysis

Due to the long and not always planar course extending from the brainstem to the cerebellopontine angle and from there to the fundus of the IAC, reconstruction of the nerve diameters and cross-sectional areas at varying levels is required in the evaluation of cranial nerves (20).

3D T2A-weighted raw images for temporal bone and cerebellopontine angle (SPA) taken with the routine protocol (TR: TE: FA: 0,7 mm slice thickness, 256x128 matrix) in MRI unit (1.5 T GE Healthcare Signa Hdxt, Milwaukee, WI) were transferred to the workstation (GE Healthcare advantage workstation 4.3, Milwaukee, WI). In the reconstructed and sagittal-oblique angled projections, nerve traces were visualized in sections perpendicular to the neural structures within the IAC. Ellipsoid or circular shaped surface areas of the nerve structures from the SPA system were tried to be measured from the same levels bilaterally. MRI measurements performed in this study were: Vestibulocochlear complex cross-sectional surface area (CSA), facial nerve CSA (cerebellopontin angle), superior and inferior vestibular nerves CSA's, IACcochlear nerve CSA (Figure 2).

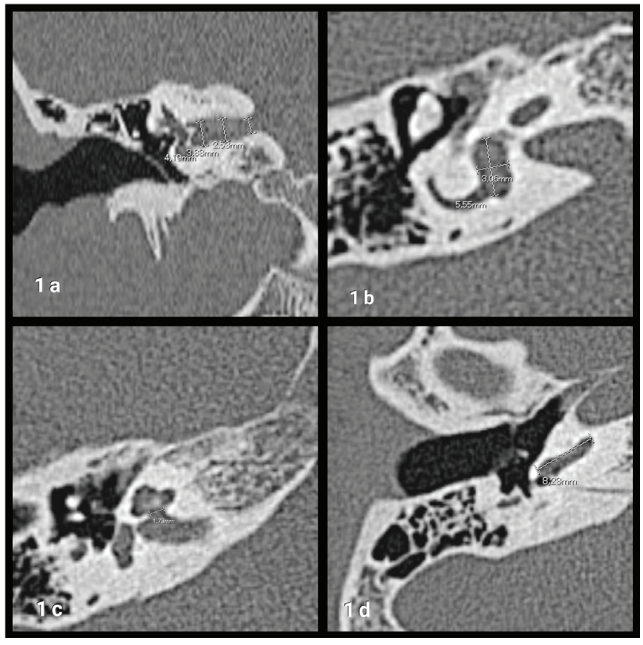

Figure 1. a. Proximal, middle and distal internal acustic canal height measurements in coronal multiplanar reconstruction image on temporal bone HRCT. b. Vestibule measurements in the axial section on HRCT. c. Cochlear nerve bone canal measurement on HRCT. d. Cochlear width measurement on HRCT
HRCT: High resolution computed tomography

Statistical Analysis

Statistical analyzes were made with the SPSS version 26.0 program. Compliance of quantitative variables to normal distribution was examined by histogram graphics and the Kolmogorov-Smirnov test. Mean, standard deviation, and median values were used while presenting descriptive analyzes of age, CT and MRI results. When comparing gender ratios between CM and VM groups, the Chi-square test was used. Age, CT and MRI results were compared between CM and VM groups using the Mann-Whitney U test. The situations where the p-value was less than 0.05 were evaluated as statistically significant results.

Results

Twenty-three patients (15 women, 8 man; mean age 40.7± standard deviation 12.8, a total of 46 ears) diagnosed with VM and 21 patients diagnosed with CM headache (18 women, 3 men, mean age 40.7±

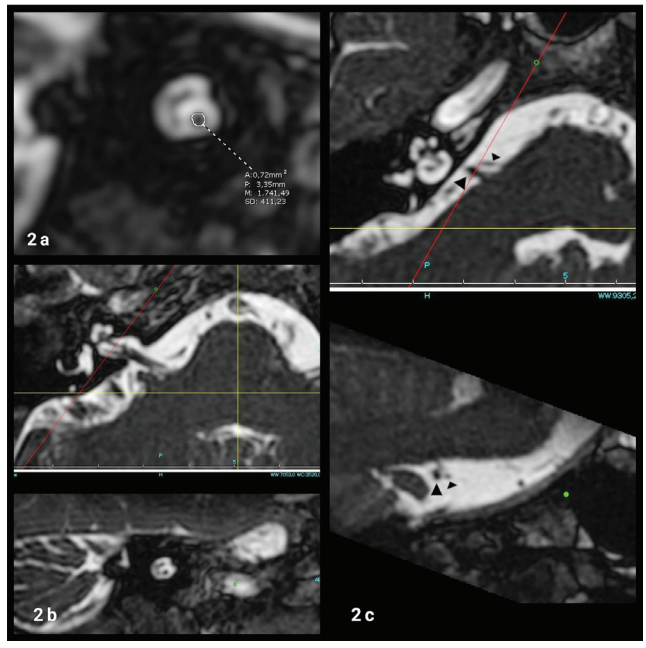

Figure 2. a. Cochlear nerve measurements in sagittal MPR FIESTA image (free-hand method) on MRI. b. Cochlear nerve in axial and sagittal MPR FIESTA image on MRI. c. Right vestibulocochlear complex (large arrowhead) and facial nerve (small arrowhead) on the axial and sagittal, oblique MPR images at the level of the brainstem on MRI
MRI: Magnetic resonance imaging, MPR: Multiplanar reconstruction

standardeviation 12.6, a total of 42 ears) were included in the study.

The age and gender distribution of the patients in the CM group and the VM group did not differ significantly (p>0.05) (Table 1).

Computed Tomography Findings

There was no statistically significant difference between CM and VM groups in terms of the right side of cochlear width; vestibular length and height; IAC proximal, mid-, and distal height; right IAC length; cochlear and vestibular aperture diameters (p>0.05). Additionally, the distances between the right side of tegmen- mastoid tip, sigmoid sinus anterior wall - external acoustic meatus, and petrous apex-mastoid aditus medial wall did not differ significantly (p>0.05) in the CM group and the VM group. However, right cochlear height in the VM group was significantly higher than the CM group (p<0.05) (Table 2).

There was no statistically significant difference between CM and VM groups in terms of the left side of cochlear width; vestibular length; IAC proximal, mid-, and distal height; right IAC length; cochlear and vestibular aperture diameters (p>0.05). Additionally, the distances between the left side of tegmen-mastoid tip, sigmoid sinus anterior wall - external acoustic meatus, and petrous apex-mastoid aditus medial wall did not differ significantly (p>0.05) in the CM group and the VM group. However, the left side of cochlear and vestibular heights in the VM group was significantly higher than the CM group (p<0.05) (Table 2).

Magnetic Resonance Imaging Findings

The right side CSA of vestibulocochlear complex, facial nerve, superior vestibular nerve, inferior vestibular nerve, and cochlear nerve did not differ significantly (p>0.05) in CM group and VM group (Table 3).

The left side CSA of vestibulocochlear complex, facial nerve, superior vestibular nerve, inferior vestibular nerve, and cochlear nerve did not differ significantly (p>0.05) in CM group and VM group (Table 3).

Discussion

This research is the first study evaluating the anatomical structural differences of the inner ear and mastoid bone in CT examination between VM and CM headache, and the 7th and 8th nerves in MRI. In our study, no significant difference was found in CT measurements, between the VM group and CM group in terms of HRCT findings except for cochlear and vestibular heights. Statistically significant difference was found in cochlear and vestibular height in the VM group compared to the CM group. However, these differences were only in the right or left ears and not both. In MRI, no significant anatomical differences were found between the two groups.

Manzari L stated that VM and motion sickness was the most common accompanying diagnosis in patients who were found to have unilateral and bilateral large vestibular aqueduct on CT imaging (21).

Since the large vestibular aqueduct is a finding that can also be seen in Meniere's disease, some studies have been conducted to determine possible radiological differences between VM and Meniere's disease, and endolymphatic hydrops has been tried to be shown (7,22,23).

Sun et al. (22) evaluated the usability of MRI for the investigation of endolymphatic hydrops in patients with definite or possible VM and Meniere's disease. Although varying degrees of cochlear and vestibular hydrops were observed in the affected ears of patients with Meniere's disease, suspicious cochlear hydrops was observed in patients with VM however vestibular hydrops was not found (22).

Nakadaka et al. (23) compared to the size of the cochlear and vestibular endolymphatic space between VM and Meniere's disease patients and no vestibular hydrops was observed except in 2 patients in the VM group. However significant vestibular hydrops was observed in all patients with Meniere's disease (23).

As an interesting result, Gurkov et al. (7) found cochlear and vestibular endolymphatic hydrops in some VM patients. It has been stated that locally developed inner ear MRI can be useful in the diagnosis of patients with suspected VM (7).

Due to the detection of the large vestibular aqueduct and possible hydrops in the radiological examinations of patients with VM, some studies have been conducted to investigate the difference between VM and Meniere's disease (5,22,23). Krombach G et al. (24) investigated anatomical differences by CT in Meniere's patients. They found that the vestibular aqueduct was shorter and narrower and the left cochlear

Table 1. Age and gender distribution of patients in the chronic migraine group and the vestibular migraine group

		Chronic migraine				Vestibular migraine				p	
	Mean ± SD n-%			Medyan		Mean ± SD n-%		Medyan			
Age		40.7	±	12.6	45.0	40.7	±	12.8	44.0	0,962	m
Gender	Female	18		85.7%		15		71.4%		0,117	X^2
	Male	3		14.3%		8		38.1%			

m Mann-Whitney u test/ X^2 Chi-square test, SD: Standard deviation

height was significantly higher in Meniere's patients compared to the control group (24). Similarly, a significant difference was found in cochlear height and vestibular height in the VM group compared to the CM group in our study. The importance of morphological observations can be predicted after the final clarification of VM pathogenesis; however, anatomical observations can provide valuable clues regarding the pathogenesis of the disease. It is not yet clear that the VM is a physiopathologically and anatomically completely different entity from Meniere's disease. When viewed from this aspect, we observed in our study that there were anatomical differences in the inner ear similar to Meniere's patients.

The number of studies investigating the differences between CM and VM is limited in the literature (10,25-28). Besides that, possible anatomical differences in the inner ear and mastoid antrum of patients with VM and CM and in the IAC and the nerves within it have not been investigated before.

MRI can also help us to understand the morphological differences and pathogenesis between VM and CM headaches. In previous studies, hypermetabolism was detected in functional imaging of the brain, during and between migraine attacks. In functional MRI, signal changes due to activity involvement were encountered

Table 2. Comparison of computed tomography measurements of right and left inner ear and mastoid bone between the chronic migraine group and the vestibular migraine group

	Chronic migraine				Vestibular migraine				p	
	Median ± SD			Median	Mean ± SD			Medyan		
Left (CT)										
Cochlear width	9.20	±	0.66	9.29	8.98	±	0.57	9.03	0.318	m
Cochlear height	3.41	±	0.35	3.37	3.64	±	0.40	3.65	0.040	m
Vestibular length	5.66	±	0.48	5.66	5.68	±	0.39	5.60	0.906	m
Vestibular height	2.96	±	0.51	3.10	3.20	±	0.39	3.20	0.124	m
IAC proximal height	4.31	±	0.80	4.20	4.49	±	0.99	4.52	0.549	m
IAC mid height	4.68	±	0.81	4.77	4.78	±	0.93	4.51	0.897	m
IAC distal height	4.49	±	0.59	4.41	4.67	±	0.79	4.85	0.391	m
IAC length	10.9	±	2.0	10.9	10.3	±	2.1	9.9	0.188	m
Cochlear apertura diameter	2.19	±	0.29	2.20	2.12	±	0.38	2.15	0.716	m
Vestibular apertura diameter	0.92	±	0.24	0.87	0.90	±	0.29	0.86	0.751	m
Distance between tegmen-mastoid tip	36.5	±	3.8	36.5	36.2	±	4.6	36.0	1.000	m
Distance between sigmoid sinus anterior wall - external acoustic meatus	12.4	±	4.5	13.0	11.7	±	2.7	11.2	0.206	m
Distance between petrous apex-mastoid aditus medial wall	29.4	±	13.1	34.9	35.0	±	2.3	35.1	0.664	m
Right (CT)										
Cochlear width	9.10	±	0.56	9.21	9.06	±	0.48	9.01	0.716	m
Cochlear height	3.45	±	0.32	3.41	3.73	±	0.29	3.78	0.002	m
Vestibular length	5.58	±	0.39	5.50	5.63	±	0.42	5.65	0.526	m
Vestibular height	3.09	±	0.37	3.16	3.39	±	0.27	3.44	0.014	m
IAC proximal height	4.05	±	0.81	3.90	4.24	±	1.01	4.18	0.638	m
IAC mid height	4.68	±	0.92	4.48	4.77	±	1.16	4.40	0.934	m
IAC distal height	4.60	±	0.67	4.52	4.59	±	0.67	4.61	0.991	m
IAC length	10.4	±	2.1	10.5	9.9	±	2.0	9.9	0.250	m
Cochlear apertura diameter	2.05	±	0.29	2.11	2.13	±	0.38	2.15	0.581	m
Vestibular apertura diameter	0.91	±	0.31	0.77	0.98	±	0.26	0.86	0.209	m
Distance between tegmen-mastoid tip	35.6	±	3.9	35.6	37.2	±	4.9	38.1	0.189	m
Distance between sigmoid sinus anterior wall - external acoustic meatus	12.9	±	2.6	13.0	12.5	±	2.6	12.3	0.557	m
Distance between petrous apex- mastoid aditus medial wall	36.3	±	2.4	36.4	36.0	±	5.0	35.3	0.177	m

m Mann-Whitney U test, IAC: Internal acoustic canal, SD: Standard deviation, CT: Computed tomography

in the thalamus and occipital lobes of patients with VM (10,25).

Wang et al. (26) investigated the differences in cerebral gray matter in CM patients without aura, VM and healthy controls. The gray matter volume of some brain regions of patients with VM was found to be significantly greater than the other two groups (26).

Zhe et al. (28) compared the healthy control group and VM group and examined structural cortical changes with MRI. Interestingly, they found that the volume of gray matter decreased in the different brain regions in the VM group compared to the control group (28).

In our study, no significant anatomical structure differences were found in the MRI of 7th and 8th nerves between both groups.

In a CT study, it was shown that the morphometric anatomy of the semicircular canals was compatible with the movement pattern. It has been stated that the diameter of the semicircular canals is more important than the radius of curvature and the height, width and length of the semicircular canals (29).

It has been shown that there is a high level of morphological variation in the bony labyrinth of the inner ear, especially in the shape, size, and angles of the semicircular canals, between very slow-moving sloth species and much faster moving species (30).

Are the different movement patterns in different species a consequence of this anatomical structural difference or have the inner ear anatomies adapted to the modality of movement phylogenetically over time because they act differently? Unlike healthy individuals, do minimal anatomical differences lead to significant balance and movement disorders in Meniere's disease, VM and other vertiginous diseases? All these issues need to be illuminated with further comprehensive studies.

Study Limitations

There were 13 structural comparisons and right and left ears were compared separately but some differences were only in the right or left ears and not both, which is the most weak part of the present study. We thought that the reason might be the small sample. Therefore, the small number of patients and radiological and clinical long-term follow-up failure are the limitations of this study. There is a need for more comprehensive studies to be conducted with a much larger number of patients on whether minor anatomical structural differences cause major functional debility and taking the early and long-term follow-up results into account.

On the other hand, another limitation of this study is that an audiometric evaluation was not performed to consider the presence of low frequency sensorineural hearing loss, which helps in the differential diagnosis of Meniere's disease in the patient group diagnosed with vestibular migraine. However, it should not be neglected that permanent hearing loss in Menier's disease occurs after repeated attacks over time. Hearing status should be evaluated in patients with long-term follow-up to investigate the possibility of VM being a variant of Menier's disease. The follow-up period in this study was limited to 3 years and this is one of the limitations of our study. We need to evaluate the long-term hearing status in patients with VM in future studies.

Conclusion

A significant difference was found in cochlear and vestibular heights of the right or left ears in the VM group

Table 3. Comparison of magnetic resonance imaging measurements of the right and left inner ear, internal acoustic canal and neural structures in the chronic migraine group and the vestibular migraine group

	Chronic migraine				Vestibular migraine				p	
	Mean ± SD			Median	Mean ± SD			Median		
Left (MRI)										
Vestibulocochlear complex CSA	2.83	±	0.65	2.76	2.86	±	0.42	2.81	0.549	m
Facial nerve CSA (CPA)	0.97	±	0.33	0.93	1.19	±	0.41	1.09	0.076	m
Superior vestibular nerve	0.64	±	0.20	0.60	0.66	±	0.23	0.65	0.897	m
Inferior vestibular nerve	0.41	±	0.16	0.33	0.43	±	0.15	0.43	0.533	m
IAC cochlear nerve	1.07	±	0.31	0.96	1.02	±	0.41	0.88	0.301	m
Right (MRI)										
Vestibulocochlear complex CSA	2.93	±	0.57	2.85	2.85	±	0.56	2.81	0.760	m
Facial nerve CSA (CPA)	0.87	±	0.31	0.73	0.96	±	0.22	0.95	0.076	m
Superior vestibular nerve	0.67	±	0.23	0.63	0.65	±	0.26	0.59	0.672	m
Inferior vestibular nerve	0.38	±	0.12	0.35	0.43	±	0.19	0.38	0.580	m
IAC cochlear nerve	1.00	±	0.25	0.89	0.93	±	0.24	0.95	0.341	m

m: Mann-Whitney U test, SD: Standard Deviation, CPA: Cerebellopontine angle, IAC: Internal acoustic canal, CSA: Cross-sectional surface area, MRI: Magnetic resonance imaging

compared to the CM group. There may be a relationship between the morphological changes caused by anatomical structural differences between CM and VM and functional impairment. As the differences were not found in both ears, future studies with larger samples should be performed.

Author Contributions

Concept: Z.C., C.K.E., O.Y., Y.K., O.O.Y., Design: Z.C., C.K.E., O.Y., Y.K., O.O.Y., Data Collection or Processing: Z.C., C.K.E., O.Y., Y.K., O.O.Y., Analysis or Interpretation: Z.C., C.K.E., O.Y., Y.K., O.O.Y., Literature Search: Z.C., C.K.E., O.Y., Y.K., O.O.Y., Writing: Z.C., C.K.E., O.Y., Y.K., O.O.Y.

Funding and support: This research received no specific grant from any funding agency in public, commercial or not-for-profit sectors.

Conflict of interests: The authors declare that there is no conflict of interest.

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Original Article

DOI: 10.4274/haseki.galenos.2021.6465
Med Bull Haseki 2020;59:167-71

Evaluation of Quality of Life and Anxiety Disorder in Children and Adolescents with Primary Headache

Rabia Gokcen Gozubatik-Celik, Musa Ozturk

University of Health Sciences Turkey, Bakirkoy Prof Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey

Abstract

Aim: To investigate the effect of coexistence of primary headache with depression, anxiety, and anxiety disorder on patients' quality of life and the variability of this effect according to the types of primary headache in children and adolescents with primary headache.

Methods: A total of 61 patients [29 migraines, 32 tension-type headaches (TTH) patients] and 31 healthy controls were included in the study. Multiple measures including the Screen for Child Anxiety-Related Disorders, the Children's Depression Inventory (CDI), the Pediatric Quality of Life Inventory, and the Visual Analogue Scale were administered to each participant on a voluntary basis for the establishment of the diagnosis.

Results: Mean age was 12.0±2.3 years in migraine patients, 13±4.3 years in TTH patients, and 12.4±2.1 years in the control group. The mean anxiety score was 32.0±3.1, 16.0±2.5, and 8.0±1.3, respectively. The anxiety scores were significantly higher in the patient groups compared to the control group ($p<0.001$) and were higher in migraine patients compared to TTH patients and the control subjects ($p<0.001$). The mean CDI scores of migraine and TTH patients were 22.0±2.7 and 26.0±4.3, respectively ($p=0.439$). In the control group, this score was 10.0±4.0 and it was significantly lower than those of patient groups ($p=0.002$). Mean quality of life score was 59.31±13.5 in migraine patients, 62.08±21.2 in TTH patients, and 86.83±31.7 in the control subjects. Quality of life scores were significantly lower in the patient groups compared to the control group ($p<0.001$).

Conclusion: The coexistence of headache with depression and anxiety disorders leads to negative effects on both physical and psychological quality of life of children and adolescents with headache.

Keywords: Primary headache, child, adolescent, anxiety disorder, quality of life

Introduction

The prevalence of headache in childhood and adolescence increases with age and reaches adult values towards the end of adolescence (1). Tension-type headache (TTH) and migraine are the most common types of headache in children and adolescents (2,3). Headache is a common disease leading to serious effects on the quality of life in childhood and adolescence. Moreover, headache has been reported to be common among school-age children and to be one of the most common reasons for referral to the emergency departments in this age group (4). In such patients, the uncertainty of the prognosis of the pain and regular use of medication at a young age cause future anxiety. In turn, increased anxiety and mood disorders such as depression cause children to refrain from social activities and reduce their school performance (3,4).

In this study, we aimed to investigate the effect of coexistence of primary headache with depression, anxiety, and anxiety disorder on patients' quality of life and the variability of this effect according to the types of primary headache in children and adolescents that were followed up with a diagnosis of primary headache in our hospital.

Methods

The retrospective study included patients aged 8-18 years who presented to our Neurology clinic between January 1, 2017 and November 1, 2019 with the complaint of headache and were diagnosed as having primary headache according to the International Classification

Yazışma Adresi/Address for Correspondence: Rabia Gokcen Gozubatik-Celik, University of Health Sciences Turkey, Bakırkoy Prof. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey
E-mail: gokcen3@hotmail.com ORCID: orcid.org/0000-0002-8186-8703
Received: 06.08.2020 **Accepted:** 22.02.2021

of Headache 3rd edition (5). Multiple measures including the Screen for Child Anxiety-Related Disorders (SCARED), the Children's Depression Inventory (CDI), the Pediatric Quality of Life Inventory (PedsQL), and Visual Analogue Scale (VAS) were administered to each participant on a voluntary basis for the establishment of the diagnosis. A control group of 31 healthy children and adolescents of similar age groups and sociodemographic characteristics was also included in the study on a voluntary basis. All the tests and scales were administered to both groups by the same physician. Patients diagnosed with primary headache and migraine were assigned into Group I, patients diagnosed with TTH were assigned into Group II, and the control subjects were assigned into Group III. All the participants were continuing their school education. Children that could not fill out the questionnaire form due to the presence of severe mental retardation or a serious psychiatric disease such as severe depression, those with secondary causes of headache, illiterate children, and children whose legal guardian did not provide a consent form were excluded from the study. Headache characteristics (severity, number of attacks per month, comorbidities) and sociodemographic characteristics (age, gender, income level of the family, number of siblings, and educational level) were recorded in the form prepared by the researchers.

Measures

The SCARED: SCARED is a 41-item inventory consisting of five subscales: separation anxiety, social phobia, generalized anxiety, panic/somatic, and school phobia. Each item is scored on a scale from 0 to 2: "0" not true or hardly ever true, "1" sometimes true, and "2" true or often true. SCARED measures the symptoms experienced in the last three months (6).

The CDI: CDI is a self-report measure assessing self-reported symptoms of depression in children and adolescents aged 7-17 years. The inventory consists of 27 multiple-choice questions with three options each. CDI measures the frequency and severity of depressive symptoms in the last two weeks. Higher scores indicate greater depressive symptoms. The reliability and validity of the Turkish version of CDI were performed by Oy (7), who determined the pathological cutoff point as 19.

The PedsQL: PedsQL is a 23-item generic health status instrument used for assessing five domains of health (physical functioning, emotional functioning, psychosocial functioning, social functioning, and school functioning) in children and adolescents aged 2-18 years. Each item is reverse-scored and converted to a 0-100 scale: "100" Never, "75" Almost Never, "50" Sometimes, "25" Often, "0" Almost Always (8,9).

Visual Analogue Scale: VAS is used for assessing the severity of pain on a 0-10 scale.

The study was approved by our local ethics committee (Date: January 7, 2020; No: 400). For the control subjects aged under 18 years, an informed consent was obtained from their legal guardians.

Statistical Analysis

Data were analyzed using SPSS for Windows version 17.0 (Chicago, IL, USA). Normal distribution of data was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were expressed as mean ± standard deviation (SD) and median (minimum-maximum) and categorical variables were expressed as frequencies (n). Categorical variables were compared using chi-square test and Fisher's Exact test. Independent continuous variables were compared using the Mann-Whitney U test. Three or more continuous variables were compared using One-way ANOVA test for data with normal distribution and using Kruskal-Wallis test for data with non-normal distribution. Correlations between continuous variables with normal distribution were analyzed using the pearson correlation coefficient. A p-value of <0.05 was considered significant.

Results

The study included 61 patients (37 girls and 24 boys) and 31 healthy controls (18 girls and 13 boys). The mean age was 12.5±3.3 years in the patients and was 10.0±4.5 years in the control subjects ($p>0.05$). In the patients, mean age was 11.8±1.3 years in girls and 13.2±0.9 years in boys. In the control subjects, the mean age was 11.0±2.4 years in girls and 13.2±2.6 in boys. No significant difference was found between patients and control subjects with regard to gender distribution ($p>0.05$).

Patients were divided into two groups: Group I, migraine (n=29) and Group II, TTH (n=32). Group I included 19 and Group II included 18 girls ($p=0.204$ and $p=0.473$, respectively). In group I, the mean age was 10.3±2.5 years in girls and 12.1±1.4 years in boys. In group II, mean age was 9.8±3.1 years in girls and 13.7±2.5 years in boys ($p=0.172$ and $p=0.286$, respectively). Mean disease duration was 2.9±1.6 (median, 2.0) years in Group I and 3.0±1.3 (median 2.0) years in Group II ($p=0.285$) (Table 1).

The most common triggering factors for headache were stress (68.8%; 42/61) and sleep disturbance (49.1%; 30/61), followed by menstrual period, physical activity, and trauma (Figure 1).

No patient had a history of cigarette smoking or alcohol/substance abuse. Moreover, 87% of the patients were living with their family members (parents and siblings), 7% of them were single child of the family, 71% of them had only one sibling, and 82% of the mothers were housewives. No significant difference was found

between the patients and control subjects with regard to sociodemographic characteristics (p=0.593).

The mean SCARED score was 32.0±3.1 in Group I, 16.0±2.5 in Group II, and 8.0±1.3 in Group III and these scores were significantly higher in patient groups than in the control group (p=0.001). Additionally, the SCARED scores in Group I were significantly higher than those in Group II and III (p<0.001) (Table 2).

The mean CDI score was 22.0±2.7 in Group I and 26.0±4.3 in Group II and no significant difference was found (p=0.439). In contrast, the mean CDI score in the control group was 10.0±4.0 and it was significantly lower than those of patient groups (p=0.002) (Table 2).

Mean PedsQL score was 59.31±13.5, 62.08±21.2, and 86.83±31.7 in Group I, II, and III, respectively. The mean PedsQL scores in the patient groups were significantly lower than that of the control group (p<0.001). Similarly, the mean scores for the physical, emotional, school, and psychosocial subscales were also significantly lower in the patient groups than in the control group (p<0.001). However, although the mean PedsQL score was lower in Group I than in Group II, no significant difference was established (p=0.791) (Table 3).

The PedsQL scores were further analyzed by dividing the patients in terms of the number of attacks per month regardless of the types of headaches. Accordingly, the mean PedsQL score was 76.12±10.2 in 18 patients with 1-3 attacks/month, 66.00±9.0 in 7 patients with 7 attacks/month, and 58.42±8.3 in 22 patients with ≥8 attacks/month. The PedsQL scores of patients with ≥8 attacks/month were significantly lower than those of other patients and control subjects (p<0.001). However, no significant difference was found between patients with 1-3 and 4-7 attacks/month with regard to PedsQL scores (p>0.05). It was also revealed that as the number of attacks per month increased, the PedsQL scores decreased, though insignificantly.

The mean VAS score was significantly higher in Group I compared to Group II (9.0±1.0 vs. 6.0±1.0) (p=0.003). (Table 3,4). On the other hand, a negative correlation was found between the PedsQL and VAS scores (p<0.001, r=-0.68235) and a positive correlation was found between the SCARED and VAS scores (p<0.001; r=0.54821).

Table 1. Demographic and headache characteristics

	Migraine (n=29)	Tension-type headache (n=32)	p
Gender (Female/Male) (n) (%)	19 (65.5%) 10 (34.5%)	18 (56.2%) 14 (43.8%)	0.242
Mean age (years) ± SD	12.0±2.3	13.0±4.3	0.196
Mean disease duration (years) ± SD	2.9±1.6	3.0±1.3	0.285

SD: Standard deviation

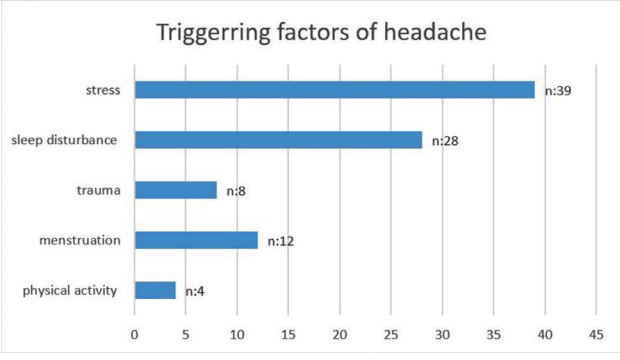

Figure 1. Triggering factors for headache

Discussion

The findings indicated that children and adolescents with headache had significantly higher anxiety and depression scores and lower quality of life scores compared

Table 2. Depression, anxiety, and pain scores

Measures	Migraine (n=29)	Tension-type headache (n=32)	Control (n=31)	p*
CDI	22.0±2.7	26.0±4.3	10.0±4.0	0.002
SCARED	32.0±3.1	16.0±2.5	8.0±1.3	0.001
VAS (during attack)	9.0±1.0	6.0±1.0	-	0.003

*Between patient groups and control group; SCARED: The Screen for Child Anxiety-Related Disorders, CDI: The Children's Depression Inventory, VAS: Visual Analogue Scale

Table 3. Quality of life scores

PedsQL subscales	Migraine (n=29)	Tension-type headache (n=32)	Control (n=31)
Physical	55.80±9.5	59.13±16.4	89.10±12.6
Emotional	61.32±10.9	63.53±11.2	85.23±31.2
Social	60.93±11.6	65.17±8.1	86.13±10.6
School	59.72±14.4	62.02±12.3	81.36±27.1
Psychosocial	60.6±15.7	64.11±14.2	84.44±17.5
Total score	59.31±13.5	62.08±21.2	86.83±31.7

PedsQL: The Pediatric Quality of Life Inventory

Table 4. VAS scores in patient groups

	Migraine (n=29)	Tension-type headache (n=32)	
Maximum VAS score (during attack)	6±1.0	9±1.0	p=0.003 r=72946
Mean VAS score (during attack)	5.5±2.0	8±1.9	p<0.001 r=80152

VAS: Visual Analogue Scale, p<0.05

to control subjects. Additionally, the quality of life scores were significantly lower in migraine patients compared to TTH patients and control subjects. It was revealed that as the number of attacks per month and the severity of headache increased, the quality of life scores decreased.

Literature indicates that migraine patients are accompanied by more psychopathological symptoms than healthy individuals (10-13). In a previous prospective study, Fearon and Hotopf (14) reported that childhood headache is a risk factor for psychiatric diseases in adolescence. In a study conducted in Turkey, Senturk et al. (11) reported that the anxiety scores were significantly higher and the quality of life scores were significantly lower in children with migraine (n=30) and TTH (n=31) compared to the control subjects. In the same study, unlike in our study, no significant difference was found between the two patient groups with regard to anxiety and quality of life scores (11). Akca et al. (13) reported that the continuous anxiety levels were higher in children with migraine and also noted that the children with migraine who had higher anxiety levels had a more severe pain and more frequent attacks. Another study investigated the prevalence of pediatric headache and reported that the scores of each subscale of the quality of life scale were negatively affected by the presence of headache (15). Strine et al. (16) evaluated children with frequent or severe headache and reported that these children had a higher prevalence of emotional and behavioral disorders, inattention-hyperactivity, and peer problems. However, the authors did not investigate the relationship between these conditions and headache types (16). Studies conducted with children and adolescents show that children with headache have a higher prevalence of mental disorders and that this phenomenon could be associated with the anxiety caused by the untimely onset of the pain, the difficulty it creates, withdrawal from social activities due to pain, and falling behind at school and games. In addition to the stress and anxiety caused by pain, the problems and mood disorders mentioned above are likely to affect patients' quality of life. Moreover, all the studies conducted on this subject, in a similar way to our study, suggest that this issue should be taken into consideration in children and adolescents with headache (17-21).

Studies investigating headache types and patients' anxiety levels and quality of life have reported controversial findings. Some studies found no significant difference between migraine and TTH patients, while the others found higher anxiety levels and lower quality of life scores in migraine patients compared to TTH patients. Nevertheless, we consider that in such patients, the severity of the headache and the frequency of attacks are more important issues to be addressed. In a study conducted in Turkey, Yilmaz and Alemdar (4) evaluated 100 children and adolescents who presented to the pediatric emergency department with the complaint of headache and reported that school stress was the most common triggering factor for migraine. Another study reported that general anxiety disorders, obsessive-compulsive disorder, panic disorder, and depression were the most common risk factors for the chronification of headache, particularly migraine (22). In a 2018 review, Ozge et al. (23) evaluated the disease burden and comorbidities in chronic migraine patients and suggested that he hypothalamic-pituitary-adrenal axis disorders, hormonal changes, serotonergic dysfunction, and psychogenic factors may play a role in the coexistence of migraine and anxiety disorder. In our study, the severity of pain and anxiety levels was higher in migraine patients compared to TTH patients. These findings implicate that in migraine patients, the increased severity of pain leads to increased anxiety levels. On the other hand, a positive correlation was found between anxiety levels and VAS scores and the anxiety levels were significantly higher in children who experienced 8 or more attacks in a month, which is a warning number of attacks in terms of chronicity.

Study Limitation

Our study was limited since it had a small patient population and had a cross-sectional design. In cross-sectional studies, the assessment of anxiety levels leads to difficulties that vary according to the time of assessment and the mood of the person at the time of assessment. To minimize this limitation, we used scales whose validity and reliability had been approved in Turkish population.

Conclusion

The coexistence of headache with depression and anxiety disorders leads to negative effects on both physical and psychological quality of life of children and adolescents with headache. Both the studies in the literature and our study indicated that prompt diagnosis of accompanying mood disorders in children and adolescents with headache is highly important to allow for effective treatment in the early stage and prevention of chronicity in the late stage.

Authorship Contributions

Concept: R.G.G.C., M.O., Design: R.G.G.C., M.O., Data Collection or Processing: R.G.G.C., M.O., Analysis or Interpretation: R.G.G.C., M.O., Literature Search: R.G.G.C., M.O., Writing: R.G.G.C., M.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2021.6713
Med Bull Haseki 2021;59:172-177

Comparison of Treatment Results and Satisfaction Levels of Endoscopic Thoracic Sympathectomy Techniques Performed in Primary Focal Hyperhidrosis

Servet Ozdemir

University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Clinic of Thoracic Surgery, Istanbul, Turkey

Abstract

Aim: This study aims to investigate whether the cauterization or clipping techniques performed in endoscopic thoracic sympathectomy surgery (ETS) in a tertiary center differ in terms of postoperative results and satisfaction level and to compare the results according to the surgical methods performed.

Methods: In the study, the data of 94 cases treated with ETS due to primary focal hyperhidrosis in a thoracic surgery clinic between 2015 and 2018, were retrospectively analyzed. Patients consisted of two different surgical groups. The cauterization method was performed on 56 (59.6%) of the patients whereas the clipping was performed on 38 (40.4%) of them. The patients were compared in terms of recurrence, reflex sweating, and satisfaction, as well as demographic characteristics.

Results: As a result of the Univariate Logistic Regression Analysis, it was found that the increase in age among all cases increased the risk of dissatisfaction with the treatment [odds ratio (OR): 1.11, 95% confidence interval (CI): 1.03-1.20, p=0.005] whereas the cauterization method (OR: 0.26, 95% CI: 0.09-0.77, p=0.015), absence of recurrence (OR: 0.03, 95% CI: 0.01-0.12, p<0.001), and absence of reflex sweating (OR: 0.09, 95% CI: 0.01-0.68, p=0.020) increased the satisfaction in all patients.

Conclusion: The increase in age, the clipping method, the presence of recurrence, and the presence of reflexive sweating are the risks of decreasing the level of patient satisfaction.

Keywords: Primary local hyperhidrosis, endoscopic thoracic sympathectomy, sympathectomy, endoscopic sympathetic clips

Introduction

Hyperhidrosis is defined as a pathological dimension of sweating more than physiologically needed to control body temperature (1). Hyperhidrosis, which is seen in approximately 3% of the general population, is frequently detected in people between the ages of 25 and 64, and it creates a psychological and social burden as it affects the daily activities of people negatively (2). Although there is no standard algorithm in the treatment of hyperhidrosis, it can be examined into two main groups as conservative medical methods (topical treatments, systemic treatments, Iontophoresis and botulinum toxin injection) and interventional treatment methods (local surgical procedures, stereotactic percutaneous thermal ablation, and sympathectomy) (3,4).

In the treatment of hyperhidrosis, it has been stated that ETS is the best surgical method although the superiority of the methods (cauterization or clip) used to interrupt the sympathetic chain is controversial, and the success of the performed surgical method may vary depending on the age of the patient, the severity of the disease, the type of the disease, and the area where the surgical procedure was performed (T2, T3, T4) (1,5). It has been also mentioned that there is a significant increase in the quality of life of patients with hyperhidrosis after the surgical procedure and that those people have a high degree of satisfaction

Address for Correspondence/Yazışma Adresi: Servet Ozdemir, University of Health Sciences Turkey, Bakırkoy Dr. Sadi Konuk Education and Research Hospital, Clinic of Thoracic Surgery, Istanbul, Turkey
Phone: +90 212 414 71 71 E-mail: servetozdemir74@hotmail.com ORCID: orcid.org/0000-0002-8458-0772
Received/Geliş Tarihi: 20.11.2020 **Accepted/Kabul Tarihi:** 19.01.2021

with the treatment. The surgical method is, therefore, the most appropriate option as the primary-care in those cases (6). In a study in which the efficacy of cauterization and clipping methods were compared in the treatment, both two methods were found quite effective in the treatment of primary focal hyperhidrosis, although the recurrence rate of the disease was higher in the cauterization group (7).

We aimed to investigate whether the cauterization or clipping techniques performed in endoscopic thoracic sympathectomy surgery (ETS) in a tertiary center differ in terms of postoperative results and satisfaction level and to compare the results according to the surgical methods performed.

Methods

The data of one hundred fifteen cases treated with ETS in the thoracic surgery clinic due to the primary focal hyperhidrosis (palmar and/or Axillary) were retrospectively analyzed between January 1, 2015, and December 31, 2018, in the study. Ethical consent for the study was obtained from the ethics committee of the hospital before the study (protocol number: 2020/479). Cases operated at least two years ago were evaluated in the study. The contact information of the patients and their relatives was obtained from the medical records, and patients were gone through the phone in order to learn their satisfaction level with the treatment. Since 21 patients could not be contacted in the study, the data of the remaining 94 cases were examined. Patients consisted of two different surgical groups. The cauterization method was performed on 56 (59.6%) of the patients whereas the clipping was performed on 38 (40.4%) of them. The patients were compared in terms of recurrence, reflex sweating, and satisfaction, as well as demographic characteristics. The cases who were contacted via phone were informed about the study, the consent was obtained from the patients that they volunteered to participate in the study, and their treatment satisfaction was questioned. In these interviews, each patient was asked to evaluate how satisfied they were with the hyperhidrosis treatment in a standard way, as not satisfied (1), partially satisfied (2), moderately satisfied (3), satisfied (4), and very satisfied (5). The reason why this method was preferred in the research was the absence of a valid and reliable measurement tool that measures treatment satisfaction to question via the phone in the country. Then, the responses of patients who underwent surgery with a diagnosis of hyperhidrosis in the past were recorded on the case form. Besides, demographic and clinical characteristics of the patients such as age, education level, length of stay, and the type of surgical procedures were registered in the case form.

The inclusion criteria for the study were the diagnosis of primary focal hyperhidrosis in patients who did not benefit from any medical treatments performed before the ETS and the patient's voluntary participation in the study. Patients who were not contacting by phone after surgery (n=21) were excluded.

Surgery Procedure

Based on the examination of medical records, it was observed that all of the patients were intubated with a double-lumen endotracheal tube under general anesthesia, and bilateral ETS surgery was performed in the same session. Besides, the patients were operated on in a semi-sitting position and by providing single-lung ventilation. Approximately 1-1.5 cm single-port incision was made in the fourth intercostal space in the mid-axillary line. Moreover, zero-degree, 5 mm optical, and endoscopic instruments were placed in the thorax. With the determination of thoracic sympathetic chain in cases, "T3-T4" sympathetic ganglion and chain intervention (clip or hook electrocautery) were performed as standard in 2 levels in all patients. Subsequently, the nerve of Kuntz was also cauterized in all patients. It was determined that care was taken not to damage the stellate ganglion and intercostal vessels located near the surgical site and after the hemorrhage and air leak control, one Nelaton catheter was inserted into the thorax from the same incision site. To ensure lung expansion, the lungs were ventilated so that the other end of the catheter was in a container with serum physiological. Then, when it was observed that the air outlet from the tip of the catheter had completely ceased, the catheter was withdrawn and the incision was closed without placing the thorax tube. The procedure was performed for the other side in the same session.

Statistical Analysis

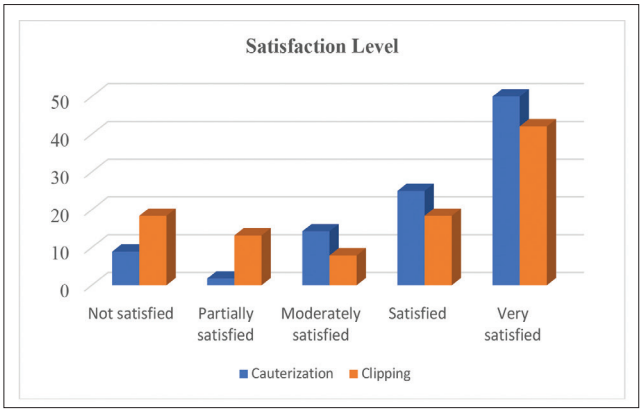
The clinical and demographic characteristics of the cases diagnosed with primary focal hyperhidrosis were evaluated by descriptive statistical analyzes such as number, percentage, mean, and standard deviation. Numerical data such as age and length of stay among the cases with the cauterization and the clipping were obtained using independent groups t-test whereas proportional data such as gender, recurrence, and treatment satisfaction level were evaluated by chi-square analyzes (Fischer's exact chi-square analysis was used if the proportional data was below 5%). Numerical data such as age and length of stay between cases with and without recurrence were examined using the Mann-Whitney U test whereas proportional data such as gender and type of surgical procedure was evaluated by chi-square analysis (Fischer's exact chi-square analysis was used if the proportional data was below 5%). Satisfaction with the treatment was

divided into two groups: insufficient (dissatisfied, partially satisfied) and sufficient (moderate, good, and very good satisfied). Therefore, univariate logistic regression analysis was used to examine the probability of dissatisfaction with the treatment at a sufficient level and the variables that may have an impact on the probability of recurrence. The significance level for all analyzes was set as $p<0.05$. IBM SPSS 22.0 program was used to evaluate the analyzes.

Results

The mean age of the cases evaluated in the study was 22.82±6.88 years [minimum (min): 12.00-maximum (max): 44.00], and 44 (46.2%) of the patients were male. In the evaluation made after the operation, it was found that the disease recurred in 14 (14.9%) of all cases and reflex sweating was found in 62 (66.0%) of the cases. The mean length of stay was 2.26±1.01 days (min: 1-max: 5). It was evaluated that complication developed in 3 (3.2%) cases (ptosis in 1 patient, ongoing inadequate expansion in 2 patients). It was detected that 2 patients with inadequate expansion were treated with tube thoracostomy. In the interview about satisfaction with treatment after the operation, 12 (12.8%) of the cases were reported as 1 (not satisfied) whereas 6 (6.4%) of them reported the satisfaction level as 2 (partially satisfied), 11 (11.7%) of them reported as 3 (moderately satisfied), 21 (22.3%) of them reported 4 (satisfied), and 44 (46.8%) of them reported as 5 (very satisfied).

According to the independent groups t-test, the mean of age (t=-1.35, p=0.182), the mean of length of stay (t=-0.48, p=0.633), and the mean of follow-up years (t=0.11, p=0.108) were found to be statistically similar. In comparison between surgical methods according to chi-square analysis, gender (X^2=0.26, p=0.609), recurrence (X^2=0.63, p=0.429), reflex sweating (X^2=0.00, p=0.977), and complication (X^2=0.07, p=0.999) rates were not found to be statistically significantly different. Based on the Fischer's exact chi-square analysis, it was found that satisfaction rates were not also statistically significantly different (X^2=7.28, p=0.114) between surgical procedures performed (Table 1). Besides, the pairwise comparison of the groups was examined using the Bonferroni correction and it was found that there was no statistically significant difference (p>0.05) between the groups (Graphic 1).



Graphic 1. Comparison of the satisfaction levels of the patients according to the surgical method

Table 1. Comparison of demographic and clinical characteristics of the cases according to surgical methods

		Cauterization	Clipping	X^2/t	p
Age (Year) (Mean ± SD)		22.04±6.10	23.97±7.84	-1.35	0.182
Gender (n/%)	Male	25 (44.6)	19 (50.0)	0.26	0.609
	Female	31 (55.4)	19 (50.0)		
Length of follow-up (year) (Mean ± SD)		2.98±0.96	3.29±0.80	0.011	0.108
Length of Stay (day) (Mean ± SD)		2.21±0.91	2.32±1.14	-0.48	0.633
Recurrence (n/%)	No	49 (87.5%)	31 (81.6)	0.63	0.429
	Yes	7 (12.5)	7 (18.4)		
Reflex sweating (n/%)	No	19 (33.9)	13 (34.2)	0.00	0.977
	Yes	37 (66.1)	25 (65.8)		
Complication (n/%)	No	54 (96.4)	37 (97.4)	0.07	0.999
	Yes	2 (3.6)	1 (2.6)		
Satisfaction (n/%)	Not satisfied (1)	5 (8.9)	7 (18.4)	7.28	0.114[a]
	Partially satisfied (2)	1 (1.8)	5 (13.2)		
	Moderately satisfied (3)	8 (14.3)	3 (7.9)		
	Satisfied (4)	14 (25.0)	7 (18.4)		
	Very satisfied (5)	28 (50.0)	16 (42.1)		

SD: Standard deviation, X^2: Chi-square analysis, t: Independent groups t-test, [a]: Fischer's exact, chi-square analysis

The insufficient level of satisfaction with treatment (n=18; 18.1%) was coded as negative in regression analysis, whereas the sufficient level of satisfaction with treatment (n=78; 81.9%) was coded as positive in the study. According to the results of univariate logistic regression analysis, increment in age [odds ratio (OR): 1.11, confidence interval (CI):1.03-1.20; p=0.005] was found to increase the probability of dissatisfaction with treatment. Besides, the cauterization method (OR: 0.26, CI: 0.09-0.77; p=0.015), the absence of recurrence (OR: 0.03, CI: 0.01-0.12; p<0.001), and the absence of reflex sweating (OR: 0.09, CI: 0.01-0.68; p=0.020) was found to reduce the probability of dissatisfaction with the treatment (Table 2).

Of the 14 cases with post-treatment recurrence of hyperhidrosis, 5 (35.7%) were male, 7 (50%) were cauterized, 13 (92.9%) had reflex sweating whereas the mean age of these cases was 24.93 years (median: 23.50, min: 15.00-max: 43.00) and the mean of the length of stay was 2.57 days (median: 2.50, min: 1.00-max: 4.00). Besides, of the 80 cases without recurrence, 39 (48.8%) were male, 49 (61.3%) were cauterized, 49 (61.3%) had reflex sweating, and 3 (3.8%) had complications, whereas the mean age of these cases was 22.45 (median: 20.00) and the mean length of stay was 2.20 (median=2.00). Based on the chi-square analysis and Mann-Whitney U tests, it was found that the other variables were not statistically different between the cases with and without recurrence, except for the reflex sweating rate (X^2=5.30, p=0.030).

Table 2. Univariable logistic regression analysis result associated with treatment dissatisfaction

	OR	95% CI	p
Age	1.11	1.03-1.20	0.005
Gender (Male)	0.67	0.24-1.92	0.456
Surgical method (cauterization)	0.26	0.09-0.77	0.015
Recurrence (No)	0.03	0.01-0.12	<0.001
Reflex sweating (No)	0.09	0.01-0.68	0.020
Length of stay	0.83	0.47-1.42	0.497

OR: Odds ratio, CI: Confidence interval

Table 3. Univariable logistic regression analysis results associated with recurrence risk

	OR	95% CI	p
Age	1.05	0.97-1.13	0.218
Gender (Male)	0.58	0.18-1.90	0.371
Surgical method (cauterization)	0.63	0.20-1.98	0.431
Length of stay	1.43	0.82-2.47	0.205

OR: Odds ratio, CI: Confidence interval

Recurrence (n=14) was coded as negative in regression analysis, and non-recurrence (n=80) was coded as positive in the study. Additively, multiple analysis was not preferred due to the limited distribution of the number of subjects in terms of the variables. Regarding the results of univariate logistic regression analysis, age, gender, surgical method, and length of stay were not statistically effective factors (p>0.05) on the probability of increasing recurrence in hyperhidrosis cases (Table 3).

Discussion

Satisfaction rates of patients in the study were found to be similar among the cases diagnosed with primary focal hyperhidrosis, in which cauterization or clipping method was performed in the past. Moreover, the recurrence rates were identified as statistically similar between the two groups. As a result of the logistic regression analysis, it was determined that the increment in age among all cases increased the probability of dissatisfaction with the treatment whereas the method of cauterization, the absence of recurrence, and the absence of reflex sweating were found to reduce the probability of dissatisfaction with the treatment.

In the literature, different ETS methods (cauterization, clipping) performed in cases diagnosed with primary focal hyperhidrosis have been found to differ in terms of treatment success and patient satisfaction (1,5). Findikcioglu et al. (7) stated that the clipping method is more successful than other methods in increasing the quality of life of patients. In a meta-analysis study, it was stated that although the clipping method is more successful than cauterization in terms of patient satisfaction and recurrence rate, this method may have a higher risk for complications (8). In the current study, it was observed that the satisfaction rates were higher in cases with cauterization in terms of the overall picture, the difference was, however, not significant and the recurrence rates did not differ between the two groups, supporting the view that the two surgical methods are not different from each other in terms of those features. Similarly, in a meta-analysis study conducted by Du et al. (9), it was detected that the cauterization and the clipping method gave similar results in terms of patient satisfaction in primary focal hyperhidrosis case.

Result

Of the interview about the treatment satisfaction with people with a diagnosis of primary focal hyperhidrosis evaluated in the study, it was seen that the rate of people who were dissatisfied with ETS treatment was 6.4%. Thus, other individuals were found to be partially or significantly satisfied with the treatment. In a study in which

hyperhidrosis patients undergoing surgical treatment were followed up, it was evaluated that 84% of the cases had an increase in the quality of life, also, 97% of the cases were satisfied with the surgical procedure (10). For this reason, it can be said that the satisfaction level reported by the cases in this study was consistent with the literature. Primary focal hyperhidrosis negatively affects the daily activities of people and can cause psychological and social problems (2,11). Therefore, the data obtained from this study support the view that ETS used in the treatment of hyperhidrosis is one of the most reliable treatment methods that help to solve the social and psychological problems caused by the disease in addition to the physical symptoms (1).

According to logistic regression analysis, it has been reported that being older than 21 years of age has negatively affected the treatment results in patients who underwent ETS due to primary focal hyperhidrosis (12). Leiderman et al. (13) stated that the effect of age on patient satisfaction and quality of life in cases of hyperhidrosis treated surgically was not sufficiently examined, therefore, in their study, sweating symptoms decreased more with increased age and better results were obtained, especially in elderly individuals. Karaçam et al. (14) found that the risk and severity of compensatory hyperhidrosis increased with both age and prolongation of symptom duration. The ages of the cases evaluated in this study ranged from 12 to 44 years, and the study found that the risk for dissatisfaction with treatment increased with age. Hence, the result of this study shows that satisfaction with treatment may be affected by age characteristics. Moreover, new studies with larger samples and a wider age range can contribute to the literature by showing the effect of age characteristics of hyperhidrosis cases on treatment results.

ETS is primarily a treatment method for cases that do not respond to medical treatment and offers patients a new opportunity to recover (3). Therefore, one of the factors that significantly reduces the risk of dissatisfaction with the treatment in this study can be considered as an expected condition that the disease does not recur. In other words, failure to satisfy the treatment expectations of patients who expect recovery after the surgical procedure will be one of the factors that significantly reduce treatment satisfaction.

The recurrence rate in the study was stated as 14.9% in hyperhidrosis cases, whereas lower recurrence rates were reported in the literature. Besides, the global recurrence rate was 8.8% in cases who underwent surgery, whereas it was reported that sweating in 86.4% of the patients could continue at a compensatory degree (15). However, in a study carried out by Doğru et al. (16), recurrence rates of hyperhidrosis cases surgically treated in Turkey were detected to be 16.4% and it can be said that this rate is similar to the findings obtained from the current study. The retrospective analysis of the data and the fact that the severity of ongoing sweating symptoms was not examined in detail may affect the recurrence rate in the current study. Besides, the change in follow-up periods of 2-5 years may also be an effective factor in the recurrence rate.

In the study, although the satisfaction rates were similar between the cases who underwent cauterization and the clipping method, it was found that the cauterization method reduced the risk of dissatisfaction with the treatment in the logistic regression analysis. However, it was found that surgical methods did not increase the risk in terms of recurrence. In other words, in this study, it was found that the clipping method was a factor that reduces the satisfaction of the treatment, but the surgical methods were ineffective in increasing the risk of recurrence. It has been known that regression models in studies give more reliable results than analyzes comparing proportional data (16). Therefore, considering the results obtained from this study, it can be said that a higher satisfaction level is more likely in cases evaluated at the end of two years and treated with cauterization. Du et al. (9) and Divisi et al. (8) have reported that cauterization and clipping methods did not make a difference in terms of treatment satisfaction and that the clipping method was more disadvantageous in terms of some risks (e.g., infection). Besides, the limited number of participants in the study restricted the use of multiple regression analyzes, thus, the effect of confounding variables on the results obtained could not be analyzed. Therefore, the results of new studies that control the severity of the disease and the effects of other variables and that include multiple regression models to determine the superiority of different surgical methods used in ETS may contribute to the literature.

Reflex sweating has been one of the complications that occur due to the surgical procedure in cases of hyperhidrosis (17). In the current study, it was found that 66% of the operated cases had reflex sweating and the risk for dissatisfaction with the treatment was significantly reduced in cases without this complication. Reflex sweating has been one of the undesirable surgical complications after the operation, especially for surgeons performing ETS. In a study, it has been found that 37.5% of the hyperhidrosis cases undergoing surgical procedures had reflex sweating (18). After ETS, it has been reported that reflex sweating developed in 46 of 247 cases and the treatment of this complication could last for two years (19). It should be, therefore, kept in mind that reflex

sweating that develops after ETS is one of the important factors that reduce the treatment satisfaction of patients.

Study Limitations

The low number of cases is one of the important limitations of the study. Besides, the fact that multiple regression analysis cannot be used due to the limited distribution of the number of subjects according to the variables is another limitation of the study. Moreover, retrospective studies offer more limited results than prospective studies. The last limitation of the study is that patient satisfaction levels were determined by the interview method rather than a measurement tool. Despite these limitations, the presented study may contribute to the literature in evaluating the surgical methods applied in terms of patient satisfaction.

Conclusion

As a result of the study, it can be said that recurrence, reflex sweating, and satisfaction rates are similar among the cases treated with cauterization or clipping, in addition to this, increase in age, the use of clipping method, recurrence, and the presence of reflex sweating in cases of primary focal hyperhidrosis are effective factors in reducing patient satisfaction. Besides, new studies examining the effect of the clipping method on patient satisfaction may contribute to the literature.

Financial Disclosure: The author declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2021.6860
Med Bull Haseki 2021;59:178-183

The Role of Whole-blood Parameters in Predicting the Severity of Acute Rheumatic Carditis in Children

Yeter Duzenli Kar, Ufuk Utku Gullu*

Afyonkarahisar Health Sciences University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Hematology and Oncology, Afyonkarahisar, Turkey

Erzurum Regional Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Hematology and Oncology, Erzurum, Turkey

**Erzurum Regional Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Cardiology, Erzurum, Turkey*

Abstract

Aim: Acute rheumatic fever (ARF) is the most common cause of acquired heart disease especially in developing countries. This study is intended to evaluate the relationship between severity of cardiac involvement and hematological parameters in children diagnosed with carditis at the first episode of ARF.

Methods: In this study, 45 children with carditis at the first episode of ARF and 30 healthy children of the same age and gender, between September 2015 and February 2019, were retrospectively reviewed. The data of the patients were recorded from the hospital automation system. Patients with acute rheumatic carditis (ARC) were grouped into two as mild (n=30) and moderate-severe ARC (n=15). Hemoglobin, red blood cell distribution width (RDW), leukocyte, neutrophil, monocyte, lymphocyte, platelet counts, neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte (PLR), monocyte-to-lymphocyte ratio (MLR) were compared between control and all carditis patients, mild and moderate-severe carditis.

Results: In ARC patients, hemoglobin and RDW values were statistically significantly lower ($p<0.0001$, $p=0.0001$, respectively) and leukocyte, neutrophil, platelet, NLR, PLR, MLR were statistically significantly higher ($p<0.0001$, $p<0.0001$, $p=0.0001$, $p<0.0001$, $p=0.0022$, $p=0.0032$, respectively) than in control. A statistically significant difference was determined between hemoglobin, RDW in mild and moderate-severe carditis ($p<0.05$).

Conclusions: In our study, it was found that RDW increased significantly in moderate-severe carditis compared to mild ARC and could be used as an indicator of severe carditis in ARF.

Keywords: Child, red blood cell distribution width, rheumatic fever, rheumatic heart disease

Introduction

Acute rheumatic fever (ARF) is a systemic, inflammatory disease which occurs with the group a beta-hemolytic streptococcus emerges 1-5 weeks after upper respiratory tract infection and it can affect the joints, brain, heart, blood vessels, skin and subcutaneous connective tissue (1). It is seen especially in developing countries and it is the most common cause of acquired heart disease in children and young adults in many parts of the world (1,2). Around 500,000 new cases of ARF are seen annually worldwide, and about 15 million people are known to have chronic rheumatic heart disease (2). Carditis is detected in 50-80% of ARF patients and most commonly affects the mitral and aortic valves (1-3). Carditis is the most common and major symptom after arthritis that can lead to acute heart failure and chronic valve disease and increase mortality. Although the endocardium is frequently affected, myocardium and pericardium may also rarely be affected (2,4). Severe carditis occurs at the rate of 20% approximately and may cause congestive heart failure (2).

Blood cell interactions play an important role in inflammation, immune response, oncogenesis and

Yazışma Adresi/Address for Correspondence: Yeter Duzenli Kar, Afyonkarahisar Health Sciences University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Hematology and Oncology, Afyonkarahisar, Turkey
Phone: +90 555 316 26 50 E-mail: yeterduzenli@yahoo.com ORCID: orcid.org/0000-0003-2917-7750
Received: 30.12.2020 **Accepted:** 06.02.2021

hemostasis. It is known that neutrophils are indicative of nonspecific inflammation, lymphocytes are involved in immune response regulation and platelets play an important role in inflammation by secreting various chemokines and cytokines (5). The relationship between acute rheumatic carditis (ARC) and systemic inflammation was previously studied in several studies, but there are a limited number of studies on children (5-7).

The relationship between inflammation markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), red blood cell distribution width (RDW), platelet count, easily calculated from whole blood count parameters, and the severity of many inflammatory diseases such as cancer, systemic lupus erythematosus, psoriasis, atopic dermatitis, Kawasaki, ARF was investigated (5-10).

The aim of the study was to examine the relationship between whole blood parameters in children with cardiac involvement at the time of ARF diagnosis (hemoglobin, RDW, mean corpuscular volume (MCV), leukocyte, neutrophil, monocyte, lymphocyte and platelet counts) and hematological indices derived from these whole blood parameters NLR, PLR, MLR with carditis severity.

Methods

Study Design

This study was approved by the local ethics committee (07.10.2019, 2019/12-121) (number: 37732058/514-10). and written informed consent was obtained from the parents or guardians of both the patients and the controls. Between September 2015 and February 2019, 45 children diagnosed with ARC at the first episode of ARF at our hospital Pediatric Cardiology Clinic and 30 healthy children of the same age and gender were included in the study. There were no pre-existing rheumatic illnesses. Patients with a history of nonsteroid anti-inflammatory drug, corticosteroid use within 4 days before applying to hospital, patients with impaired renal and kidney function, patients with thalassemia carriage and hemolytic anemia, those with iron, folate and B12 deficiency anemia, patients with signs of infection, patients with reproduction in blood and urine cultures, and patients with a history of antibiotic use in the past week were excluded from the study. Healthy control group was selected from healthy volunteers who were referred to our hospital for cardiac murmur, who underwent electrocardiogram and echocardiography, and had no history or symptoms of acute or chronic disease. Physical examination of all patients and healthy control group was performed by the same pediatric cardiologist.

ARF was diagnosed using modified Jones criteria and by the differential diagnosis of all other causes (11).

Echocardiographic Assessment

Echocardiographic examinations of all patients were performed by an experienced pediatric cardiologist before initiating anti-inflammatory treatment. The Vivid 5 Pro Ultrasound System (GE MedicalSystems, NE) was used for two-dimensional, M-modeandcolour-flow Doppler imaging. For the echocardiographic diagnosis of pathological valve insufficiency, the criteria previously defined and then updated by the World Heart Federation in 2012 were used. For mitral valve insufficiency, the following should be present: insufficiency jet should be seen at least two different sections, jet length should be at least 2 cm, and during systole peak flow rate should be at least 3 m/s. For aortic valve insufficiency were as follows: insufficiency jet should be seen in at least two different sections, jet length should be at least 1 cm, and peak flow velocity along the diastole should be >3 m/s (12). Mitral and aortic regurgitation were classified as mild, moderate, or severe according to published standards (13). For the echocardiographic diagnosis of mild-moderate-severe carditis, the criteria previously defined were used (14).

Mild Carditis

(Valvular regurgitation is relatively mild in the absence of pre-existing disease; in first episodes of ARF)

Mild mitral or aortic regurgitation clinically and/or on echo, with no evidence of cardiac chamber enlargement on chest X-ray, electrocardiography, or echo and no clinical evidence of heart failure.

Moderate Carditis

Any valve lesion of moderate severity clinically (e.g., mild or moderate cardiomegaly), or echocardiographic demonstration of enlargement in any of the heart chambers or any moderate severity valve lesion on echo: (When there is both mitral and aortic regurgitation, one must be moderate by echo criteria for the carditis to be classified of moderate severity), mitral regurgitation is considered moderate if there is a broad high-intensity proximal jet filling half the left atrium or a lesser volume high-intensity jet producing prominent blunting of pulmonary venous inflow. Aortic regurgitation is considered moderate if the diameter of the regurgitant jet is 15%-30% of the diameter of the left ventricular outflow tract with flow reversal in the upper descending aorta.

Severe Carditis

Any impending or previous cardiac surgery for rheumatic heart disease, or any severe valve lesion (significant cardiomegaly, and/or heart failure), or any severe valve lesion on echo: Doppler flow patterns and abnormal regurgitant color in pulmonary veins are a prerequisite for severe mitral regurgitation. Reversing

in lower descending aorta is required for severe aortic regurgitation.

Blood Samples

Patient data were retrospectively reviewed. The full blood count analysis was done by Sysmex XN-10 analyzer in the laboratory of our institution. Hemoglobin, MCV, RDW, leukocyte count, neutrophil count, monocyte count, lymphocyte count, platelet count, NLR, PLR, MLR, erythrocyte sedimentation rate, C-reactive protein levels (CRP), anti-streptolysin-O (ASO) levels at the time of diagnosis were retrieved from the patient charts. The NLR was calculated as a simple ratio between absolute neutrophil and absolute lymphocyte counts, the PLR was calculated as a simple ratio between platelet and absolute lymphocyte counts, the MLR was calculated as a simple ratio between absolute monocytel and absolute lymphocyte counts.

Statistical Analysis

Statistical Packageforthe Social Sciences 15.0 version statistical packet program was used for statistical analysis of the data. Descriptive statistics were expressed as number and percentage for categorical variables, and as mean and standard deviation for numerical variables. In the analyses comparing the groups, Mann-Whitney U test was used for continuous variables in comparison of two groups and chi-square test and Fisher's Exact test were used for categorical variables. Results were evaluated at 95% confidence interval and significance was evaluated at $p<0.05$ level.

Results

Group a total of 45 ARC patients and 30 healthy children were included in the study. The mean age of the patient group ARC was 11.87±2.47 (range=7.5-17.1) years and the female/male ratio was 27/18. The mean age of the control group was 11.53±2.75 (range=7-17) years and the female/male ratio was 15/15. In ARC patients, hemoglobin, RDW values were statistically significantly lower ($p<0.0001$, $p=0.0001$, respectively) and leukocyte, neutrophil, platelet counts and NLR, PLR, MLR ratio were significantly higher than healthy control group ($p<0.0001$, $p<0.0001$, $p=0.0001$, $p<0.0001$, $p=0.0022$, $p=0.0032$, respectively) (Table 1). The hemoglobin, MCV, RDW, leukocyte, neutrophil, monocyte, lymphocyte, and platelet counts and the NLR, PLR, MLR, erythrocyte sedimentation rate, CRP and ASO levels values of the patient and control groups were shown in Table 1.

The Distribution of Heart Valve Involvement in Patients Diagnosed with ARC and the Relationship Between Hematological Parameters and Severity of Cardiac Involvement

Two of our patients diagnosed with ARC had aortic regurgitation, 19 patients had mitral insufficiency and 24 of them aortic regurgitation and mitral insufficiency.

Of 45 patients with ARC, 30 had mild, 10 had moderate, and five had severe ARC. The mean age of 30 patients with mild ARC was 12.02±2.49 years, and the female/male ratio was 15/15; the mean age of 15 patients with moderate-severe ARC was 11.58±2.48

Table 1. Demographic and laboratory characteristics of the acute rheumatic carditis patient and control groups

Characteristics	Control group	Acute rheumatic carditis	p
Age (year) (mean ± SD)	11.53±2.75	11.87±2.47	0.5805 [a]
Sex (Female/Male) (n (%))	15/15 (50%/50%)	27/18 (60%/40%)	0.3927 [b]
Hb (g/dL) (mean ± SD)	14.29±0.91	12.38±1.57	<0.0001 [a]
MCV (fL) (mean ± SD)	82.08±4.43	80.45±5.36	0.3223 [a]
RDW (%) (mean ± SD)	13.15±0.70	12.05±1.44	0.0001 [a]
Leukocyte (/mm^3) (mean ± SD)	6637.67±1439.83	11555.51±2847.88	<0.0001 [a]
Neutrophil (/mm^3) (mean ± SD)	3300.67±1183.27	7942.40±2698.86	<0.0001 [a]
Lymphocyte (/mm^3) (mean ± SD)	2436.33±595.32	2534.00±886.29	0.8967 [a]
Platelet (/mm^3) (mean ± SD)	317566.67±75275.90	435812.22±136986.25	0.0001 [a]
NLR (mean ± SD)	1.45±0.70	4.01±4.25	<0.0001 [a]
PLR (mean ± SD)	137.93±46.10	207.07±194.14	0.0022 [a]
MLR (mean ± SD)	0.24±0.10	0.42±0.51	0.0032 [a]
ASO (U/mL) (mean ± SD)	-	1057.24±541.81	-
ESR (mm/hour) (mean ± SD)	-	41.22±18.05	-
CRP (mg/L) (mean ± SD)	-	7.39±6.23	-

[a]: Mann-Whitney U test [b]: chi-square test
Hb: Hemoglobin, MCV: Mean corpuscular volume, RDW: Red blood cell distribution, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, ASO: Anti-streptolysin-O, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein levels

years and the female/male ratio was 12/3. A significant difference was found in hemoglobin, MCV, RDW between mild and moderate-severe ARC ($p<0.05$). The duration of hospitalization was significantly longer in moderate-severe ARC patients than in mild ARC patients ($p<0.01$). Erythrocyte sedimentation rate, CRP and ASO levels values were higher in moderate-severe ARC patients compared to mild ARC patients (Table 2).

Discussion

In our study, two-thirds of the patients diagnosed with ARC at the first episode of ARF were mild carditis cases. We found that severe ARC cases were less frequent in accordance with the literature (2,14). Today, we think that there are fewer cases of severe ARC because of better living conditions, easier access to health care services, early diagnosis of the disease, adequate and timely initiation of penicillin treatment and prophylaxis, better patient follow-up and the application of improved diagnostic methods such as echocardiography in almost all centers.

Although the pathogenesis of the disease is not fully elucidated, the most accepted theory is cross-reactivity. Accordingly, depending on the similarity of some streptococcal antigens to tissue antigens, it can be explained that immunological reactions resulting from activation of the humoral and cellular immune system cause inflammatory response (3). In the acute phase of ARF, disruption of connective tissue and edema occur due to infiltration of myocardium and valve by T-lymphocytes, B-lymphocytes, macrophages and mast cells. In the healing process of ARC, various degrees of fibrosis and valve damage are seen in the heart (7). Although any layer of the heart may be affected in cardiac involvement, endocardial and myocardial involvement is the most common. As a serious complication of the disease, congestive heart failure, which is indicative of myocarditis, may develop and the disease may be fatal. Valve lesions occur due to endocardial involvement. Mitral and aortic valves are affected most commonly (2,3). In our study, congestive heart failure secondary to myocarditis was not detected in our patients. In accordance with the literature, mitral and aortic valves were the most commonly affected valves.

In recent years, there are many studies investigating neutrophil, lymphocyte and platelet count, NLR, mean platelet volume values and cardiovascular disease severity. In a study in adults, Akboga et al. (15) found that RDW value was higher in patients with chronic rheumatic mitral valve stenosis as an indicator of persistent chronic inflammation than in the healthy control group. In the same study, no statistically significant difference was found in NLR in patients with chronic rheumatic mitral valve stenosis compared to the healthy control group, but they found a positive correlation between RDW and NLR/CRP. They suggested that RDW is an independent predictor risk factor for chronic rheumatic mitral valve stenosis. Ozturk et al. (16) reported that NLR elevation could be used as an independent predictor of spontaneous echocardiographic

Table 2. Evaluation of demographic and hematological parameters of mild and moderate-severe acute rheumatic carditis groups

Characteristics	Mild acute rheumatic carditis	Moderate-severe acute rheumatic carditis	p
Age (year) (mean ± SD)	12.02±2.49	11.58±2.48	>0.9999[a]
Sex (Female/Male) (n%)	15/15 (50%/50%)	12/3 (80%/20%)	0.0632[b]
Hb (g/dL) (mean ± SD)	12.90±1.30	11.34±1.59	0.0403[a]
MCV (fL) (mean ± SD)	82.00±4.23	77.35±6.13	0.0179[a]
RDW (%) (mean ± SD)	11.53±1.04	13.10±1.58	0.0010[a]
Leukocyte (/mm^3) (mean ± SD)	11501±2421	11663±3650	>0.9999[a]
Neutrophil (/mm^3) (mean ± SD)	7766±2257	8294±3483	>0.9999[a]
Lymphocyte (/mm^3) (mean ± SD)	2612±961	2377±717	0.7283[a]
Platelet (/mm^3) (mean ± SD)	428555±136654	450326±141261	>0.9999[a]
NLR (mean ± SD)	4.13±5.05	3.78±1.96	>0.9999[a]
PLR (mean ± SD)	210.49±233.46	200.22±73.98	0.7611[a]
MLR (mean ± SD)	0.44±0.62	0.37±0.18	>0.9999[a]
ASO (U/mL) (mean ± SD)	1033.43±573.51	1104.87±487.48	0.5001
ESR (mm/hour) (mean ± SD)	38.13±14.90	47.40±22.43	0.2521[a]
CRP (mg/L) (mean ± SD)	7.23±7.19	7.72±3.85	0.1854[a]

[a]: Mann-Whitney U test [b]: chi-square test
Hb: Hemoglobin, MCV: Mean corpuscular volume, RDW: Red blood cell distribution, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, ASO: Anti-streptolysin-O, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein levels

contrast in patients with rheumatic mitral stenosis. Polat et al. (17) reported that as the severity of rheumatic mitral valve stenosis increases, NLR increases as well, and when the NLR cut off value is taken as 2.56, it has the power to predict severe rheumatic mitral valve stenosis with 75% sensitivity and 74% specificity. They reported that NLR is useful in predicting both the presence and severity of rheumatic mitral valve stenosis. Ozdemir et al. (18), in accordance with our study, stated that hemoglobin value was significantly lower but leukocyte and platelet value were significantly higher in ARC patients compared to the control group; Küçük et al. (19), however, reported that leucocyte and platelet count in ARC patients was statistically significantly higher than in the control group. They also hypothesized that high levels of RDW after ARC treatment may be used as an indicator of heart valve stenosis in the later years. Similar to the results of our study, Asık et al. (20) reported that neutrophil, leukocyte, NLR were significantly increased in patients with ARF compared to healthy children, and these parameters could be used in the diagnosis of ARF. Karpuz et al. (21) reported that RDW in children with ARF was significantly higher than healthy controls. They suggested that in the chronic phase of ARF, RDW showed a positive correlation with CRP and erythrocyte sedimentation rate, which are chronic inflammation markers, and that RDW could be used as a diagnostic marker in the diagnosis of the disease. In our study, similar to the study by Çelik et al. (7) on child cases consisting of those with ARC and healthy control group, we found that hemoglobin and RDW values were lower and leukocyte, neutrophil, platelet count and NLR were higher in ARC. In addition, in our study, hemoglobin and MCV values were significantly lower in moderate-severe ARC patients compared to mild ARC patients and RDW values were significantly higher in moderate-severe carditis patients. We can infer that hemoglobin levels of patients reduce when carditis severity increases because the patients are susceptible to inflammation anemia due to increased carditis severity. Unlike the literature, we think that the reason why we did not find any relationship between ARC patients and NLR in our study was because we included ARC patients at the first episode, so patients were accompanied by one or more of the modified Jones Criteria and other major or minor criteria for the diagnosis of ARF in addition to carditis. In addition, we think that it is because there are adult studies in the literature and therefore the relationship between the degree of mitral stenosis and hematological indices parameters has been examined.

Study Limitations

The limitations of our study were the low number of patients and the presentation of a single-center experience.

The fact that it is a retrospective study, it can't evaluate post-treatment measurements and the absence of long-term follow-up are the limitations of our study. However, our study is important because it is one of the rare studies on the subject in children with ARC.

Conclusion

There are a limited number of studies examining the relationship between the degree of cardiac involvement and hematological parameters in patients diagnosed with ARC at the first episode of ARF in children. In our study, it was shown that RDW increased significantly in moderate-severe ARC patients compared to mild ARC patients and RDW could be used as an indicator of severe carditis in ARF. However, since the severity of inflammation may change due to the presence of different major and minor criteria for the diagnosis of ARF in ARC patients, it was detected that leukocyte, neutrophil, platelet, monocyte, NLR, PLR, MLR levels were not guiding in predicting the degree of carditis in ARC.

Authorship Contributions

Concept: Y.D.K., U.U.G., Design: Y.D.K., Data Collection or Processing: Y.D.K., U.U.G., Analysis or Interpretation: Y.D.K., U.U.G., Literature Search: Y.D.K., U.U.G., Writing: Y.D.K.

Conflict of Interest: The authors declared no conflicts of interest concerning the authorship and publication of this article.

Financial Disclosure: The authors received no financial support for the research and/or authorship of this article

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