Journal of Contemporary Medicine

YEAR:2022 VOLUME:12 ISSUE:3

JOURNAL OF CONTEMPORARY MEDICINE

e-ISSN 2667-7180

Formerly Çağdaş Tıp Dergisi

YEAR 2022 VOLUME 12 ISSUE 3

The Owner and Publishing Manager on behalf of the Journal of Contemporary Medicine

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JOURNAL OF CONTEMPORARY MEDICINE

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Solca M. Acute pain management: Unmet needs and new advances in pain management. Eur J Anaesthesiol 2002; 19(Suppl 25): 3-10.

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Online article not yet published in an issue

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Book

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Chapter in a book

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Journal article on the Internet

Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]; 102. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 Jul 2002]. Available from: www.cancer-pain.org

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The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

Acknowledgements

The source of financial grants and the contribution of colleagues or institutions should be acknowledged.

Tables

Tables should be complementary, but not duplicate information contained in the text. Tables should be numbered consecutively in Arabic numbers, with a descriptive, self-explanatory title above the table. All abbreviations should be explained in a footnote. Footnotes should be designated by symbols in the following order: *,†, ‡, §, ¶.

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Drugs should be referred to by their generic names, rather than brand names.

Editorial Correspondence

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JOURNAL OF
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DOI:10.16899/jcm.1034446
J Contemp Med 2022;12(3):410-414

Orijinal Araştırma / Original Article

Does the Disinfectant Efficacy of the 2% Gluteraldehide Solution Change with the Aging of the Solution?

%2 Gluteraldehit Solusyonunun Dezenfektan Etkinliği Solusyonun Yaşlanması ile Değişir Mi?

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Abstract

Purpose: In our study, it was aimed to determine whether the disinfectant efficacy of 2% glutaraldehyde solution changes with the aging of the solution.

Material and Method: In our study, metal obtained from k-wire, plastic obtained from serum sets, and glass balls were used to imitate metal, plastic, and glass materials found in surgical instruments. Each study day, 20 pieces of metal, plastic, and glass materials were contaminated with *Klebsiella Pneumoniae, Staphylococcus Aerius, Pseudomonas Aeruginosa*, and *Escherichia Coli* and Maya. The materials were divided into groups of 10. The first group was thrown into the glutaraldehyde solution taken from the aging activated 2% glutaraldehyde solution pool into plastic pet glasses, each piece in separate pet glasses, and kept in the solution for 15 minutes. Afterward, the materials were taken from the cups using different sterile forceps for each piece. The other group was washed with physiological saline solution for 1 minute. After the procedures, it was sent to the microbiology laboratory without waiting and cultured on EMB agar and blood agar.

Results: No growth was detected on the 1st, 14th, and 28th days in all metal, plastic, and glass materials disinfected with 2% alkaline glutaraldehyde solution. In the control groups, growth rates were 53.3%, 50%, and 63.3%, respectively.

Conclusions: If the guidelines and manufacturer's recommendations are followed in the preparation and use of 2% alkaline glutaraldehyde solution, it provides an effective disinfection without being affected by the aging of the solution.

Keywords: İnfection, sterilization, disinfection, gluteraldehyde, arthroscopic instrument

Öz

Background: Çalışmamızda %2 gluteraldehit solusyonunun dezenfektan etkinliğinin solusyonun yaşlanması ile değişime uğrayıp uğramadığının tespiti amaçlanmıştır.

Gereç ve Yöntem: Çalışmamızda cerrahi aletlerde bulunan metal, plastik ve cam malzemeleri taklit etmek adına 2 cm uzunluğunda k telinden elde edilen metal, serum setlerinden elde edilen plastik ve cam bilyeler kullanıldı. Her birinden 20'şer adeti solusyonun 1.,14. ve 28. gününde *Klepsiella Pneumoniae*, *Staphilococcus Aerius*, *Pseudomonas Aeruginosa*, *Escherichia Coli* ve Maya ile kontamine edildi. 10'ar tanesi %2 gluteraldehit solusyon havuzundan plastik pet bardaklara alınan gluteraldehit solusyonu içine her bir parça ayrı pet bardaklarda olacak şekilde atıldı ve 15 dakika süre ile solusyon içerisinde bekletildi. Sonrasında malzemeler bardaklardan her bir parça için ayrı steril forseps kullanılarak alındı. Diğer 10'ar adeti 1 dakika boyunca serum fizyolojik solüsyon ile yıkandı. İşlemler sonrasında bekletilmeden mikrobiyoloji laboratuarına gönderilerek EMB agar ve kanlı agarda kültürlendi.

Results: %2 alkalen gluteral solüsyonu ile dezenfekte edilen metal, plastik ve cam malzemelerde 1., 14. ve 28. günde üreme tespit edilemedi. Kontrol gruplarında ise sırası ile %53,3, %50 ve %63,3 oranlarında kontaminasyonda kullanılan mikroorganizmalardan bir ve ya birkaçında üreme tespit edildi.

Sonuç: %2 alkalen gluteral solüsyonu hazırlanması ve kullanılmasında kılavuz ve üretici önerilerine dikkat edilmesi halinde solüsyonun yaşlanmasından etkilenmeden aktif olduğu süre boyunca etkin bir dezenfeksiyon sağlar.

Anahtar Kelimeler: Enfeksiyon, sterilizasyon, dezenfeksiyon, gluteraldehit, artroskopik alet

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Received *(Geliş Tarihi)*: 08.12.2021 **Accepted *(Kabul Tarihi)*:** 22.04.2022

INTRODUCTION

2% glutaraldehyde solution is a disinfectant class chemical. While it does not show any sporicidal activity in acid character, its activated form with alkali gains sporicidal activity.[1] Since alkaline pH decreases its activity over time by providing polymerization of the glutaraldehyde molecule, 2% glutaraldehyde solution activated with alkali (pH 7.5 - 8.5 increased) is effective for 14-28 days. Here, it is extremely important and necessary to have a color change when the activator is added to the solution so that the activated and unactivated solutions can be easily separated from each other. In addition, chemical test strips are required to check for the decreasing glutaraldehyde concentration at 14-28 days. Although the glutaraldehyde solution maintains its activity in the presence of organic matter, strips are also required here, as organic substances mixed in the solutions in which the instruments are immersed can reduce the glutaraldehyde concentration.

2% activated alkaline glutaraldehyde is widely used for disinfection of heat-sensitive equipment, especially flexible fibreoptic endoscopes. It is effective against a wide variety of pathogens and is not corrosive.[2,3] Although this frequently used disinfectant is effective, there are studies in the literature indicating that infection develops after arthroscopic procedures using arthroscopic instruments disinfected with 2% glutaraldehyde.[4,5] In addition, evidence has been presented in the last decade that reprocessing endoscopic instruments is generally not effective. In studies, microbial growth was detected between 16% and 71% in samples taken from flexible endoscopes disinfected with high-level disinfectants.[6-8]

Alkaline pH decreases its effectiveness over time by providing the polymerization of the glutaraldehyde molecule. In our study, it was aimed to determine whether the microbiological disinfectant effectiveness of 2% glutaraldehyde solution, which enters the aging process after the activator is added, will change over time.

MATERIAL AND METHOD

The study was designed as a prospective, experimental study after obtaining approval from the local ethics committee with registration number 20-KAEK-156. In our hospital, glutaraldehyde solution is used in arthroscopic instrument disinfection. This solution contains 2% glutaraldehyde, anticorrosive materials, auxiliary materials, and de-ionized water. After the solution is prepared in containers large enough to fit the surgical instruments comfortably, its effectiveness is evaluated daily with test strips and used for 28 days. The solutions that are found to have ceased efficacy with test strips and/or whose color change is detected in the solution are discontinued from use.

In the study, the microbiological disinfectant efficacy of 2% glutaraldehyde solution, which is made alkaline after adding the activator on the 1st, 14th, and 28th days was evaluated. To imitate metal, plastic, and glass materials found in surgical instruments, 2 cm metal obtained from k-wire, 2 cm plastic obtained from serum sets, and glass balls were used. Each study day, 20 pieces of metal, plastic, and glass materials were contaminated with *Klebsiella Pneumoniae (K. pneumoniae), Staphylococcus Aerius (S. aureus), Pseudomonas Aeruginosa (P. aeruginosa),* and *Escherichia Coli (E. coli)*, and Yeast which there are grown on Blood agar and EMB agar. After the materials to be contaminated were placed in the petri dish and the petri lid was closed, they were shaken until they were contaminated, and the contamination process was ensured. After contamination, 10 pieces of metal, plastic, and glass materials were thrown into the glutaraldehyde solution taken from the glutaraldehyde solution pool in separate containers, and kept in the solution for 15 minutes. The materials were then taken from the containers using separate sterile forceps for each. The other 10 pieces of metal, plastic, and glassware were washed with saline solution for 1 minute. The materials were immediately sent to the microbiology laboratory after the procedure. The samples taken for evaluation were planted in 5% sheep blood agar (RDS, Turkey), Eosin Methylene Blue agar (RDS, Turkey), and chocolate agar (RDS, Turkey). It was incubated in the oven at 35-37°C for 24-48 hours. Strains were identified by catalase test and tube coagulase test in gram positive bacteria, oxidase test and biochemical tests in gram negative bacteria, and gram staining in yeasts. In addition, it was confirmed that the 2% glutaraldehyde solution pool was active with the test strip on each study day. In addition, patients who underwent arthroscopic surgery during this period were followed for postoperative infection for 6 months. Parts treated with 2% glutaraldehyde solution constituted the working group, while parts washed with SF made up the control group.

RESULTS

In our study where we analyzed whether the disinfection efficiency of 2% Glutaraldehyde changes with the aging of the solution;

1. No growth was detected in any material in the study group on day 1 of the solution. In the control group, reproduction was detected in 16 (53.3%).
2. There was no growth in the study group on the 14th day of the solution as on the 1st day. Reproduction was detected in 15 (50%) of the control group.
3. While there was no growth in the study group on the 28th day of the solution as in the 1st and 14th days, 19 (63.3%) growth was detected in the control group.

Microorganisms grown in the control group on days 1, 14 and 28 included one or more of the microorganisms used in contamination.

During this period, no infection was observed in any of the 45 arthroscopic surgical interventions (17 shoulders, 22

knees, 5 ankles, and 1 elbow) performed with arthroscopic materials disinfected using 2% glutaraldehyde solution during the 6-month follow-up.

DISCUSSION

Arthroscopic surgery has become a frequently performed orthopedic surgical procedure due to the increasing frequency and the widening of the range of indications. With this increase, it may not be economically feasible to have sufficient surgical equipment to perform more than one arthroscopic procedure on the same day. Arthroscopes that enter sterile body areas should ideally be sterilized before use. Steam autoclaving is recommended for this job. [9] Repeated steam autoclaving can shorten the lifetime of arthroscopes and laryngoscopes by causing the adhesives between the main lenses to deteriorate and the light intensity to decrease.[9,10] Gas sterilization with ethylene oxide is effective and safe, but has the disadvantage that it is not available in every institution; It is also a very time-consuming process as it requires four to twelve hours for sterilization and aeration. In studies comparing ethylene oxide sterilization and high-level disinfection of glutaraldehyde, no difference was found between infection rates.[11]

2% alkaline glutaraldehyde has a wide spectrum of action against bacteria and their spores, fungi, and virus. [12] Although sterilization is preferred for arthroscopic instruments, when the sterilization of arthroscopes and laparoscopes is examined; While studies are stating that 2% alkaline glutaraldehyde is an acceptable decontamination method.[5,13,14] studies are stating that a sufficient decrease in the number of coloni forming units(CFU) could not be detected after high-level disinfection with glutaraldehyde in the opposite direction. [15,16] Over the past 10 years, evidence has been presented that reprocessing for endoscopes is generally not effective. Studies have documented microbial growth rates between 16% and 71% in samples taken from flexible endoscopes disinfected with high-level disinfectants[6-8] Reprocessing failures can have serious consequences for patients. Post-endoscopic infections can be common (> 3%) even if patients take prophylactic antimicrobials.[6,17] In our study, the absence of culture growth in plastic, metal, and glass materials decontaminated with 2% glutaraldehyde on the 1st, 14th, and 28th days and the absence of infection after arthroscopic surgeries supports the studies stating that 2% glutaraldehyde is effective in decontamination, but it differs from studies in the opposite direction.

This difference in the literature, between studies;

1. Human factors that contribute to non-compliance with the guidelines, standards, and manufacturer's instructions for use,
2. Clinical use of visibly damaged endoscopes,
3. From the use of products that may interfere with rework (simethicone, lubricants, and tissue glue)
4. After manual cleaning, the presence of residual dirt,
5. Rinsing water quality problems,
6. Moisture retained in completely reprocessed endoscopes,
7. Differences between rigid and flexible endoscopes
8. It has been stated that it is caused by the differences in the anatomical region and the environment in which the medical procedure is performed.[18-21]

While baths containing 2% activated alkali glutaraldehyde has a minimum shelf life of 14 days, new glutaraldehyde formulations produced in the last 30 years have overcome the problem of rapid activity loss and excellent microbicidal activity has been achieved for 28-30 days. [22,23] With the aging of the alkaline glutaraldehyde solution, its concentration and pH decrease, and the protein concentration increases.[24,25] It has been stated that more dilution occurs in automatic glutaraldehyde baths compared to manual baths.[24,25] Accordingly, studies are stating that its effect on microbiological activity will be adversely affected.[14,26,27] In addition, it has been stated that the number of devices subjected to a chemical under re-use conditions may cause a loss of efficiency. [24,25] In the literature, it has been stated that 1% to 1.5% glutaraldehyde shows a minimum effective concentration when used as a high-level disinfectant.[28,29] Our study data show that the reuse of 2% glutaraldehyde is effective for 28 days. In this event; The fact that we are doing the disinfection process in operating room conditions and with operating room personnel, using a manual glutaraldehyde bath, disinfection cycle, and the amount of disinfected equipment may affect.

Postoperative infection can be devastating for patients after clean joint surgery.[30] A retrospective study involving 12,505 arthroscopic procedures found an infection rate of 0.04% (five infections) when arthroscopes were immersed in 2% glutaraldehyde for 15-20 minutes. In four patients, infection developed after the combination of open surgery after arthroscopy.[5] In another arthroscopy study, infection developed in three patients following 151 arthroscopies over a period of 2 months. After the improvement of environmental conditions, it was stated that there was no infection in 222 arthroscopies[4] In those studies, the source of infection was expressed as skin flora and contamination from the environmental environment. In our study, although the number of patients who were operated on with decontaminated arthroscopic instruments was low, the absence of a patient who developed an infection clinically supports the fact that effective disinfection was obtained by keeping the arthroscopic surgical instruments in 2% glutaraldehyde solution for 15 minutes. Although

high infection rates.[6-8] are indicated in samples taken after disinfection for re-use for endoscopes and bronchoscopes, low infection rates after arthroscopic surgeries; may be due to multifactorial reasons such as the use of short, smooth-surfaced, jointless rigit arthroscopes, the procedures being performed in operating room conditions, compliance with the rules in disinfectant preparation and follow-up, and more attention to the disinfection process, the use of positive pressure washing solutions to expand the working area in the joint, and working in sterile anatomical areas.

CONCLUSIONS

Arthroscopes, laparoscopes, etc. surgical equipment that penetrates sterile tissue, such as, should be sterilized before each use; If this is not possible, at least a high level of disinfection is required. 2% alkaline glutaraldehyde solution; It shows an effective disinfectant activity for 28 days if it is observed in the preparation and disinfection process following the guidelines and the manufacturer's recommendations, paying attention to the maintenance of the surgical equipment and cleaning before and after the operation, taking care of environmental factors such as temperature and humidity, and evaluating the daily activity of the solution with test strips.

While evaluating the disinfectant activity with the aging of 2% alkaline glutaraldehyde solution, the fact that dilution amount, pH changes, and protein concentration values that may affect the disinfectant efficacy with aging were not examined constitute the negative aspects of our study.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study after obtaining approval from the local ethics committee with registration number 20-KAEK-156.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.894397
J Contemp Med 2022;12(3):415-418

Original Article / Orijinal Araştırma

Relationship Between Retinopathy and Mean Platelet Volume

Retinopati Şiddeti ile Ortalama Trombosit Hacmi Arasındaki İlişki

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Abstract

Objective: Platelet activation is thought to play a role in the angiogenesis process involved in the pathophysiology of retinopathy of prematurity (ROP). We planned this study to investigate whether the mean platelet volume (MPV), used to assess platelet activation, could be used as a biomarker in the diagnosis and treatment of ROP.

Material and Method: In our study, we evaluated infants who underwent ROP examination among infants born at 32 weeks or less and/or 1500 grams or less as well as infants who had more than these values but experienced a bad neonatal period. These patients were divided into two groups as those with and without ROP, and in those with ROP group, as requiring treatment and not requiring treatment. We recorded the patients' identity, maternal characteristics, antenatal/natal/postnatal features, and complications during follow-up, ROP control times, and complete blood count parameters (platelet count, MPV, platelet count/MPV). Primarily, we evaluated the differences of platelet parameters, especially the MPV values, between treatment requiring ROP and non-treatment requiring ROP groups and secondarily, we evaluated the correlation between scanned parameters and ROP development.

Results: Of the 144 patients included in the study, 49 patients (34%) had ROP and 25 patients (16.6%) had ROP requiring treatment. There were statistically significant differences between patients who were diagnosed with ROP and who were not, in terms of gestational age, birth weight, respiratory distress syndrome, surfactant use, duration of oxygen use, intraventricular hemorrhage, patent ductus arteriosus, neonatal sepsis, number of blood transfusions, necrotizing enterocolitis, bronchopulmonary dysplasia and time to catch up birth weight. However, there was no significant difference in terms of MPV, platelet count and platelet/MPV ratio. The gestational week, invasive ventilation day and duration of oxygen use, BPD and time to catch up birth weight were found to be statistically high in treatment-requiring rather than non-treatment-requiring ROP groups. There was no significant difference in MPV, platelet count, platelet/MPV ratio among these groups. A statistically significant difference was found in the most advanced stage ROP and plus existence in the treatment requiring ROP group.

Conclusion: As a result of our study, we could not find enough data to say that MPV is a marker that can be used in the diagnosis of ROP and in measuring the severity of retinopathy. We suggest that more studies should be done on this subject.

Keywords: Prematurity, retinopathy of prematurity, mean platelet volume

Öz

Amaç: Prematüre retinopatisi (Retinopathy of prematurity-ROP) patofizyolojisinde yer alan angiogenezis sürecinde platelet aktivasyonunun rolü olduğu düşünülmektedir. Platelet aktivasyonunu değerlendirmek için kullanılan ortalama platelet hacmi (Mean platelet volüm-MPV)'nin ROP tanı ve tedavisinde de kullanılabilecek bir belirteç olup olamayacağını araştırmak amacıyla bu çalışmayı planladık.

Gereç ve Yöntem: Biz çalışmamızda 32 hafta ve altında ve/veya 1500 gram ve altında doğan bebeklerin yanı sıra hafta ve ağırlığı bu değerlerden fazla olup kötü bir yenidoğan süreci geçiren bebeklerden, ROP muayenesi yapılan hastaları değerlendirmeye aldık. Bu hastaları ROP gelişen ve gelişmeyen; ROP gelişen hastaları da tedavi gerektiren ve gerektirmeyen şeklinde iki gruba ayırdık. Hastaların kimlik bilgileri, maternal özellikleri, antenatal/natal/postnatal özellikleri, takipleri sırasında gelişen komplikasyonlar, ROP kontrol zamanları ve doğdukları gün bakılan tam kan parametrelerini (platelet sayısı, MPV, platelet sayısı/MPV) kaydettik. Primer olarak ROP tedavisi gerektiren ve gerektirmeyen hastaların trombosit parametreleri, özellikle MPV değerleri arasındaki farklılığı sekonder olarak taranmış olan parametreler ile ROP gelişimi arasındaki korelasyonu değerlendirdik.

Bulgular: Çalışmaya dahil edilen 144 hastadan 49 (%34)'unda ROP, 25 (%16.6)'in de tedavi gerektiren ROP saptandı. ROP tespit edilen hastaların gebelik yaşı, doğum ağırlığı, RDS görülme sıklığı, sürfaktan kullanımı, oksijen kullanım süresi, intraventriküler kanama, PDA, neonatal sepsis, eritrosit transfüzyon sayısı, NEK, BPD ve doğum ağırlığını yakalama zamanı ROP tespit edilmeyenlere oranla yüksek tespit edildi. Ancak MPV, platelet sayısı ve platelet/MPV oranı açısından anlamlı fark bulunmadı. Tedavi gerektiren ve gerektirmeyen ROP grupları arasında ise gebelik yaşı, invaziv ventilasyon günü ve toplam oksijen kullanım süresi, BPD ve doğum ağırlığını yakalama zamanı tedavi gerektirmeyen gruba oranla yüksek bulundu ve bu sonuçlar istatistiksel olarak anlamlıydı. Bu gruplar arasında MPV, platelet sayısı, platelet/MPV oranı açısından anlamlı fark bulunmadı. Tedavi gerektiren ROP grubunda en ileri evre ve plus varlığı açısından istatistiksel olarak anlamlı yükseklik tespit edildi.

Sonuç: Çalışmamızın sonucunda MPV'nin ROP tanısında ve retinopati şiddetini ölçmede kullanılabilecek bir belirteç olduğunu söylemek için yeterli veri bulamadık ve bu konu ile ilgili daha fazla çalışmalar yapılması gerektiğini önermekteyiz.

Anahtar Kelimeler: Prematürite, premature retinopatisi, ortalama trombosit hacmi

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Received *(Geliş Tarihi)*: 10.03.2021 **Accepted *(Kabul Tarihi)*:** 17.04.2022

INTRODUCTION

Retinopathy of prematurity (ROP), first reported by Terry in 1942, is a physiopathological condition that occurs due to abnormal proliferation of retinal vessels in preterm babies but its pathogenesis is not fully known.[1] Despite the increased possibilities of effective screening and early treatment, the fact that babies born earlier and with lower birth weight become viable causes an increase in the frequency of severe ROP cases located in the posterior pole.[2]

Although many etiological factors have been considered in the development of ROP, the most well-known risk factors are low birth weight and gestational week.[3]

Recent studies have shown that platelets play a role in the etiology of vascular diseases in the process of angiogenesis. It is known that there are changes in thrombocyte functions especially in obstructive vascular diseases. Therefore, it suggests that platelet activation may have a possible role in the pathogenesis of ROP.[4]

Mean platelet volume (MPV) is an important marker that can be used in the evaluation of platelet activity. It is known that large platelets are more metabolically and enzymatically active than small ones. For this reason, we planned this study to show the possible relationship between ROP requiring treatment and MPV and whether MPV can be used as a marker in the diagnosis and treatment of ROP.[5]

MATERIAL AND METHOD

This thesis study was initiated after receiving the Ethics Committee Approval with the decision of the Ethics Committee of Medicine and Non-Medical Device Researches Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine, dated 04/14/2017 and numbered 2017/866.

For the study, 144 cases that were followed up and evaluated for ROP in Necmettin Erbakan University Meram Medical Faculty Neonatal Intensive Care Unit between January 2016 and May 2017 were retrospectively analyzed. These patients were compared in terms of their demographic characteristics (**Table 1**), as well as platelet count, MPV, and platelet/MPV ratios in complete blood counts were taken when they were diagnosed with ROP. The cases in requiring and not requiring treatment groups were compared in terms of platelet count, MPV, platelet/MPV ratios as well as the highest stage, highest zone, presence of plus and first ROP detection time.

In this study, SAS University Edition 9.4 program was used for statistical analysis. In the analysis of parameters conforming to normal distribution, Independent sample t test was used to compare two groups and the results were reported as mean and standard deviation. Continuous variables not conforming to normal distribution were evaluated with the Mann-Whitney U test and the results were reported as median (Q1-Q3). Chi-square and Fisher tests were used to examine the relationship between categorical variables. The results were evaluated at the significance level of $p < 0.05$.

Tablo 1. Patient's demographic characteristics

	ROP diagnosed group (n=49)	non-ROP group (n=95)	p value
Maternal age (mean±SD)	29.12±6.25	28.51±5.67	0.55
Gestational age (weeks) (mean±SD)	28±2	31±2	<0.0001
Gender (n) (%)			
Girl	24 (49%)	48 (50.5%)	0.86
Boy	25 (51%)	47 (49.5%)	
Birth weight (grams) (mean±SD)	1055.3±292.1	1436.9±322.1	<0.0001
Birth way (n) (%)			
NSVY	9 (18.4%)	7 (7.4%)	0.055
C/S	40 (81.6%)	88 (92.6%)	
Grouping by birth weight (n) (%)			
SGA	5 (10.2%)	14 (14.7%)	0.43
AGA	44 (89.8%)	79 (83.2%)	
LGA	0 (0%)	2 (2.1%)	
Multiple pregnancies (n) (%)			
Single	38 (77.6%)	75 (78.9%)	0.88
Twin	10 (20.4%)	17 (17.9%)	
Triplets	1 (2%)	3 (3.2%)	
In vitro fertilization (n) (%)			
Yes	6 (12.2%)	13 (13.7%)	0.81
No	43 (87.8%)	82 (86.3%)	
Maternal steroid use (n) (%)			
No	13 (26.5%)	24 (25.3%)	0.32
Single dose	17 (34.7%)	23 (24.2%)	
Two doses	19 (38.8%)	48 (50.5%)	
Chorioamnionitis (n) (%)			
Yes	8 (16.3%)	12 (12.6%)	0.54
No	41 (83.8%)	83 (87.4%)	
Preeclampsia/Eclampsia (n) (%)			
Yes	13 (26.5%)	38 (40%)	0.14
No	36 (73.5%)	57 (60%)	
Maternal Diabetes (n) (%)			
Yes	3 (6.1%)	7 (7.4%)	0.78
No	46 (93.9%)	88 (92.6%)	

RESULTS

As a result of the evaluation of the patients, ROP was detected in 49 patients and ROP was not detected in 95 patients. 49 patients with ROP were divided into two groups as requiring and not requiring treatment. While the number of patients requiring treatment was 24, the number of patient's not requiring treatment was 25.

When MPV, platelet counts and platelet/MPV ratios of the groups with and without ROP were examined, no statistically significant difference was found between the groups for all three parameters (**Table 2**). Mean MPV values were 9.81±1.76 f/L in the group with ROP, and 9.55±1.57 f/L in the group without ROP (p=0.38). Mean platelet values were 220.9±118.7 10^3/μL in the group with ROP and 229.1±80.9 10^3/μL in the group without ROP (p=0.63). Mean Platelet/MPV ratios were 23.2±13.6 in the group with ROP, and 24.7±9.8 in the group without ROP (p=0.46). Mean Platelet/MPV ratios were 23.2±13.6 in the group with ROP, and 24.7±9.8 in the group without ROP (p=0.46).

Table 2: MPV, platelet values and platelet/MPV ratios of the groups with and without ROP

	ROP detected group (n=49)	ROP not detected group (n=95)	p value
MPV (f/L) (mean±SD)	9.81±1.76	9.55±1.57	0.38
Platelet (10^3/μL) (mean±SD)	220.9±118.7	229.1±80.9	0.63
Platelet/MPV ratio (mean±SD)	23.2±13.6	24.7±9.8	0.46

When the patients in the group with ROP were divided into subgroups requiring treatment and not requiring treatment, and when MPV, platelet numbers and platelet/MPV ratios of the groups were examined, no statistically significant difference was found between the groups for all three parameters (**Table 3**). Mean MPV values were 9.54±1.73 f/L in the ROP requiring treatment group and 10.06±1.79 f/L in the ROP not requiring treatment group (p=0.301). Mean platelet values were 208.6±117.8 10^3/μL in the ROP requiring treatment group and 232.8±120.7 10^3/μL in ROP not requiring treatment group (p=0.48). The platelet/MPV ratios were 22.78±14.9 in the ROP requiring treatment group and 23.74±12.5 in the ROP not requiring treatment group (p=0.81).

Table 3: MPV, platelet values and platelet/MPV ratios of the groups requiring and not requiring treatment.

	ROP group requiring treatment (n=24)	ROP group not requiring treatment (n=25)	p value
MPV (f/L) (mean±SD)	9.54±1.73	10.06±1.79	0.301
Platelet (103/μL) (mean±SD)	208.6±117.8	232.8±120.7	0.48
Platelet/MPV ratio (mean±SD)	22.78±14.9	23.74±12.5	0.81

Tablo 4. Evaluation of statistically significant clinical findings of ROP groups requiring and not requiring treatment.

	Treatment requiring ROP group (n=24)	Treatment not requiring ROP group (n=25)	p value
Invasive ventilation time (days) (median)	17 (4-30)	2 (0-7)	0.018
Total oxygen use (days) (median)	58.5 (38-83)	30 (13-56)	0.01
BPD (n) (%)			
Yes	16(66.7%)	8(32%)	0.015
No	8(33.3%)	17(68%)	
Day to catch up birth weight (day) (mean±SD)	15.45±6.93	11.8±4.33	0.031

DISCUSSION

Parallel to the developments in neonatal care in our country, the increase in the survival chances of premature babies with a much smaller gestational age (GA) and birth weight (BW) causes ROP, which can cause vision problems and blindness, to be a more frequent problem. In a multi-center study conducted by the Turkish Neonatal Society in 2014, the incidence of ROP in preterm babies with very low birth weight was found to be 42%, and the incidence of advanced stage ROP was 8.2%.[5] In our study, we found the incidence of ROP as 34% and ROP requiring treatment as 16.6% in our premature babies.

ROP is an abnormal vascularization process triggered by prematurity and its associated negative processes.[6] In our study, we aimed to show the effect of platelet function parameters, which is one of these factors, on the development of ROP.

Platelets have been shown to play a role in the etiology of vascular diseases. Various studies have reported that MPV values are higher, especially in occlusive vascular diseases, compared to the normal population.[7,8]

The relationship between MPV and many diseases has been examined in the literature. Platelets with a large MPV value are more reactive than platelets with a small MPV, produce more thromboxane A2, express more glycoprotein Ib and glycoprotein IIb/IIIa. They aggregate more easily.[9]

The relationship between MPV and ROP has also been recently considered. In the study of Çekmez et al, MPV was measured in the cord blood of 272 patients with a gestational week of <34 and a birth weight of <1500 g, and this parameter was repeated in the first three days of their lives and there was no significant difference in MPV values in both groups with and without ROP.[10] In another study, laser-treated ROP patients constituted the case group, while those who did not develop ROP and those with stage 1 ROP were included in the control group, and the most recent platelet and MPV values of the patients were recorded.[11] MPV values in the ROP requiring laser treatment group were statistically significantly higher than in the control group, but no significant difference was found in terms of platelet and MPV/platelet ratio. In addition, it was seen that as the MPV value increased, there was a 1.94 fold increase in ROP risk. It was concluded that MPV, used as the most common measure of platelet size, is a potential marker of platelet reactivity. In our study, we evaluated MPV, platelet counts and platelet/MPV ratios in complete blood count on the first day of life in groups with and without ROP, but we could not find a statistically significant difference between the groups. We also compared these parameters between the ROP requiring treatment and ROP not requiring treatment groups and likewise, we could not find a statistically significant difference between these groups. Although we attribute the inadequacy of our study to show the relationship between MPV and retinopathy to the low number of our patients, we believe that evaluating these parameters together with the results not only in the blood tests taken on the first day of life but also in the intermittent blood counts will help us more in understanding the relation of MPV with the presence and severity of retinopathy.

There are studies in the literature investigating the parameters associated with retinopathy between ROP requiring treatment and ROP not requiring treatment groups.[12] In our study, we found that gestational week, invasive ventilation and total oxygen use time, BPD and day to catch up birth weight were higher in the ROP requiring treatment group compared to the group that did not require treatment, and these results were statistically significant. We compared the most advanced stage, the most advanced zone, the presence of plus and the first age (in days) which was ROP detected parameters

between the groups, and we found a statistically significant increase in the most advanced stage and presence of the plus in the ROP requiring treatment group. These results obtained in our study supported that the presence of stage and plus are important parameters in the treatment decision.

CONCLUSION

In conclusion, there are limited studies in the literature investigating the relationship between MPV and ROP. As a result of our study, we cannot say that MPV is a marker that can be used in the diagnosis of ROP and in measuring its severity. We think more numerous and more comprehensive studies are needed to understand the relationship between MPV, which is used to show the activity of platelets, which is known to have a role in the etiology of vascular diseases, and the presence or severity of retinopathy. In addition, we think that screening premature babies in neonatal units for retinopathy and early referral of risky babies to a limited number of treatment centers will be of great importance in preventing blindness due to prematurity.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Medicine and Non-Medical Device Researches Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine, dated 04/14/2017 and numbered 2017/866.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1050045
J Contemp Med 2022;12(3):419-423

Original Article / Orijinal Araştırma

Evaluation of the Reasons for Emergency Department Application in Patients with Peritoneal Dialysis

Periton Diyalizli Hastalarda Acil Servis Başvurusu Nedenlerinin Değerlendirilmesi

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Abstract

Aim: Severe acute problems, which are related to different systems, could be reasons for applying to the emergency department in patients with peritoneal dialysis. In this study, the aim was to evaluate the reasons and treatment of applications to the emergency department in these patients after office hours.

Material and Method: This study included followed up CAPD patients, who applied to the Emergency Department between January 2017 and May 2020 at our University. Demographical, biochemical, and clinical data, such as, renal, peritoneal, and weekly Kt/V, normalized protein catabolic rate (nPCR), peritoneal UF, and GFR were recorded from the outpatient's department data. In addition, reasons for application to emergency services and hospitalization were evaluated.

Results: 38 peritoneal dialysis patients applied 88 times to the emergency department and were hospitalized between 2017 and 2020. Patients, who applied after office hours were included in the study. Around 130 patients were regularly followed-up in our CAPD outpatient clinic during this period. While the most important peritoneal reasons for admission were exit site infection and catheter dysfunction, extra peritoneal complications were various. Patients were hospitalized in the Cardiology and General Surgery departments with a high rate of acute cardiovascular events and acute abdominal pathologies.

Conclusion: Although the first approach to these patients in the emergency department is usually performed by a consulted nephrologist, effective and priority treatment could only be given by an emergency doctor, who has knowledge about the special problems of dialysis patients.

Keywords: Peritoneal dialysis, emergency, hemodyalisis

Öz

Amaç: Periton diyalizi olan hastalarda farklı sistemlere bağlı ciddi akut problemler acil servise başvuru nedeni olabilir. Bu çalışmada bu hastalarda mesai saatleri dışında acil servise başvuru nedenleri ve tedavilerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmaya Üniversitemizde Ocak 2017-Mayıs 2020 tarihleri arasında Acil Servise başvuran takipteki SAPD hastaları dahil edildi. Renal, peritoneal ve haftalık Kt/V, normalize protein katabolik hızı (nPCR), peritoneal UF ve GFR gibi demografik, biyokimyasal ve klinik veriler poliklinik verilerinden kaydedildi. Ayrıca acil servise başvuru ve hastaneye yatış nedenleri değerlendirildi.

Bulgular: 2017-2020 yılları arasında 88 kez acil servise başvuran 38 periton diyalizi hastası hastaneye yatırıldı. Çalışmaya mesai saatleri dışında başvuran hastalar dahil edildi. Bu süre içinde SAPD polikliniğimizde yaklaşık 130 hasta düzenli olarak takip edildi. En önemli peritoneal yatış nedenleri çıkış yeri enfeksiyonu ve kateter disfonksiyonu iken, ekstra peritoneal komplikasyonlar çeşitliydi. Hastalar yüksek oranda akut kardiyovasküler olay ve akut karın patolojileri ile Kardiyoloji ve Genel Cerrahi bölümlerine yatırıldı.

Sonuç: Bu hastalara acil serviste ilk yaklaşım genellikle konsülte edilen bir nefrolog tarafından yapılsa da etkili ve öncelikli tedavi ancak diyaliz hastalarının özel sorunları hakkında bilgi sahibi bir acil servis doktoru tarafından verilebilir.

Anahtar Kelimeler: Periton diyalizi, acil servis, hemodiyaliz

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Received *(Geliş Tarihi)*: 28.12.2021 **Accepted *(Kabul Tarihi)*:** 07.01.2022

INTRODUCTION

Peritoneal dialysis (PD) has been used to treat acute kidney failure (ARF) in humans since 1923. It is one of the effective treatment strategies, which has been used in both acute and chronic renal disease, using the persons own peritoneal membrane without the need of expensive machinery and equipment. Acute complications of PD are common and management could be easier if recognized early.[1-3] Mechanical complications, peritonitis, pleural effusion, volume changes, and electrolyte imbalance are common complications in patients, who were admitted to the emergency department. In addition, it was reported that cardiac complications and problems associated with acute abdomen are also common in this patient group.[3] The mechanical complications may be related to insufficient drainage and leakage. Leakage at the exit site of the catheter may require surgical consultation. Arising from catheter or exit-site leakage may also require surgical evaluation. Peritonitis is the most common infectious problem. It is the most common reason for hospitalization in the continuous ambulatory peritoneal dialysis (CAPD) group, who were admitted to the emergency department.[4,5] Exit-site infection is one of the infectious complications, which usually occurs with exudative drainage with erythema, and irritation.[6]

Patients are also admitted to emergency departments because of "surgical" peritonitis due to other intra-abdominal pathologies but most of them are initially treated as PD-associated peritonitis. However, clinicians should be alerted to the possibility of peritoneal emergency with a lack of response to the standard approaches and when there is presence of enteric organisms particularly E. coli. Diagnosis can be difficult in these patients and early surgical referral and appropriate surgical approach (laparotomy rather than simple catheter removal) should be performed immediately to reduce morbidity and mortality.[7,8] Hernias are common problems among other abdominal complications, which were reported in 10 to 25% of CAPD patients. When a hernia is incarcerated, patients can present with pain and vomiting, which is a result of intestinal obstruction.[9] As known, cardiovascular problems are the most common cause of death in the dialysis population. The need of emergency cardiac care, which is provided by emergency physicians, will be increased as the dialysis population ages. Coronary artery disease, angina, and arrhythmias, especially are among the reasons for applying to the emergency department of these peritoneal dialysis patients. In addition, many acute problems, which are related to different systems, could be reasons for applying to the emergency department by peritoneal dialysis patients.[10,11]

In this study, we aimed to evaluate the application reasons, treatment, and complications of peritoneal dialysis patients in the emergency department after office hours.

MATERIAL AND METHOD

After obtaining ethics committee approval from the Medical School (no: 2020/618), consent was obtained from all participants. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study included CAPD follow up patients, who applied to the Emergency Department between January 2017 and May 2020. Hemoglobin (Hb), leukocyte, blood urea nitrogen, creatinine (Cr), uric acid, calcium (Ca), phosphorus (P), alkaline phosphatase, albumin, C-reactive protein (CRP) levels, and medication history were obtained from the patient records. In our study, all patients were on a standard PD treatment schedule (4 or 5 times a day, 2000- or 2500-mL volume change). Demographic and clinical data, such as 4-hour peritoneal equalization test (D/P Cr), renal, peritoneal, and weekly Kt /V, normalized protein catabolic rate (nPCR), and peritoneal UF and GFR were recorded from the outpatient's department data. In addition, reasons of application to emergency services and hospitalization were evaluated.

Statistical Analysis

The SPSS 15.0 package (Statistical Packages for Social Sciences; SPSS Inc. Chicago, Illinois, USA) was used to analyze the data. The data that could be measured and provided parametric conditions were given as arithmetic mean±standard deviation (x±ss). the data that could be measured but did not provide parametric conditions were defined as median (25% -75%). Suitability of normal distribution was evaluated with the "Kolmogorov-Smirnov" test. One-way Anova (Tukey test) was used to evaluate the difference between groups. Kruskal- Wallis was performed for nonparametric data. Pearson correlation was used for correlation. A p value, which was < 0.05 was considered significant.

RESULTS

The demographical and clinical data of the patients is summarized in **Table 1**. The mean age of the patients was 56.6±14.5 and the duration of dialysis was 43±29.0 months. 38 peritoneal dialysis patients applied 88 times to the emergency department and were hospitalized between 2017 and 2020. Only the patients who applied after office hours were included. It was observed that patients, who received peritoneal dialysis treatment, sometimes came to the hospital after office hours due to their living in villages and therefore applied to emergency services. Around 130 patients were regularly followed-up in our CAPD outpatient clinic during this period. The patients most frequently applied to the emergency department with complaints of abdominal pain, nausea-vomiting, and fever.

Table 1. Clinical and demographical features of the patients

Parameters	Patients (n=38)
Age (year)	56.6±14.5
Gender male (%)	22 (57)
Cause of chronic renal failure	
Diabetes mellitus	16
Hypertension	10
Polycystic kidney disease	3
Pyelonephritis	2
Glomerulonephritis	2
Amiloidosis	1
Unknown	4
Duration of CAPD (month)	43± 29.0
Body mass index (kg/m²)	25.3±3.41
WBC (mm³)	8030±3092
Hemoglobin (g/dl)	10.9±1.8
Albumin (g/dl)	3.85±0.5
Residual urine volume (ml/day)	930± 510
Kt/V	2.21±0.84
D/P Creatinine	0.70 ±0.08

CAPD: Continuous Ambulatory Peritoneal Dialysis, WBC: White Blood Cell, Kt/V: Urea Clearance Normalized To Total Body Water, D/P Creatinine:Urine Creatinine To Serum Creatinine

The most common causes of primary renal failure of the patients were diabetes mellitus and hypertension. The PD-related complications of the patients are summarized in **Table 2**. The most important reasons for admission were peritoneal, exit site infection, and catheter dysfunction followed by extra peritoneal complications, which were rarer. The most common factors of patients hospitalized for peritonitis are summarized in **Table 3**. The most common cause was S. epidermidis, a gram-positive bacterium. Patients hospitalized in several departments for peritoneal or extra peritoneal reasons are summarized in **Table 4**.

Table 2. Reasons for admission to the Nephrology clinic from Emergency department

Reasons	N
Peritonitis	26
Exit site infection	5
Hypervolemia	4
Kateter Dysfunction	5
Uremic Symptoms	2
Leakage	2
EPS	1
Hydrotorax	1

EPS :ekstrapritoneal symptoms

Mainly, the patients were hospitalized in the Cardiology and General Surgery departments with a high rate of acute cardiovascular events and acute abdominal pathologies. In addition, intracranial pathologies were also frequently seen. During the follow-up of these patients, one died in the Neurosurgery intensive care unit (ICU), 4 patients died in the Internal medicine ICU, 4 died in the Cardiology department and 2 died in the Nephrology department.

Table 3. Causative organisms grown in peritoneal fluid culture.

Microorganism	n (%)
Gram-positive	
S. epidermidis	6 (23%)
MSSA	4 (15%)
MRSA	3 (11%)
CNS	1 (3%)
Enterococcus	1 (3%)
Gram-Negative	
E. coli	3 (11%)
Pseudomonas	1 (3%)
Culture-negative	7 (26%)

MRSA: Methicillin resistance in Staphylococcus aureus, MSSA: Methicillin-susceptible S. aureus CNSA:Coagulase-negative Staphylococcus

Table 4. Reasons for hospitalization into the other clinics from Emergency Department

Admission Numbers	Hospitalization	Diagnosis
2	Obstetric and gynecology	Ovarian cyst rupture
		Ectopic Pregnancy
3	Neurosurgery	Subarachnoid hemorrhage
		Intracranial hemorrhage
		Cerebral travma
2	Orthopedic surgery	Diabetic Foot
		Hip/femur fracture
8	General Surgery	İleus (3)
		Acute incarcerated inguinal hernia
		Volvulus
		Acute cholecystitis
		Intraabdominal abscess
		Acute pancreatitis
2	Gastroenterology / Hepatology	Upper gastrointestinal bleeding
2	Endocrinology	Diabetic ketoacidosis
		Hypoglycemia
1	Dermatology	Anaphylaxis
1	Ear, Nose and Throat Disorders	Pharyngeal Abscess
12	Cardiology	Myocardial infarction/ Angina pectoris (6)
		Cardiac Failure (3)
		Arrhythmia
		Pericarditis
		Warfarin Overdose
4	Infections Diseases	Peritonitis (3)
		Covid 19 infection
1	Intensive Care (Internal Medicine)	Sepsis
2	Neurology	Cerebrovascular disease
2	Intensive Care (Neurosurgery)	Loss of consciousness

DISCUSSION

The number of patients, who underwent hemodialysis and peritoneal dialysis, has increased worldwide. Cardiovascular disease and infections are among the leading causes of death in this patient group. In addition, bleeding, cardiac tamponade, electrolyte imbalance, pericardial tamponade, and acute abdomen are other important causes of mortality.[12]

In our study, the most common causes of emergency department applications were cardiac and acute abdomen related problems and the most common causes of deaths were relevant to these complications. This is similar to the cases of admission to the emergency department in our country. The high incidence of hypertension and diabetes in the dialysis population may be responsible for the increased risk for myocardial infarction. In addition to atherosclerosis, anemia and heart failure related to low cardiac output could reduce the myocardial oxygen supply. Left ventricular hypertrophy, volume overload, and hypertension caused increased left ventricular wall stress and increased myocardial oxygen request.[12,13] Arrhythmia prevention, relief from pain and anxiety, and treatment of heart failure should be performed for dialysis patients with myocardial infarction or unstable angina in the emergency department. Diagnosis of unstable angina and infarction in dialysis patients could be difficult to understand, so hospitalization may be required in both cases. The cause of death in patients with myocardial infarction was mostly cardiac arrhythmias. Serum especially with electrolyte imbalances was common causes of arrhythmias in these patients. Arrhythmia due to hypotension and acute volume changes can often happen in patients with atherosclerotic heart disease during dialysis break. Arrhythmias are also common in severe anemia, left ventricular hypertrophy, and digitalis usage.[14] Acute heart failure in dialysis patients is often caused by increased salt in the diet or excessive loading of intravenous fluids.[15,16] Basic treatment principles consist of supportive oxygen, preload reduction, and ultrafiltration. It is necessary to identify the cause of acute decompensation and reverse it. For reducing cardiac preload, furosemide has efficiency as diuresis.[12] Pericarditis occurs at any time especially in 40% of cases within 3 months of starting dialysis and has been seen in 2% to 19% of long-term dialysis treatments and could cause fatal complications. Fatal complications develop at any time in long-term dialysis patients, but 40% of cases occur within 3 months of starting dialysis.[17-20]

Although humoral and cellular immunity may be altered in dialysis patients, it was clear that the main reason for the increased incidence of infection was exposure to pathogens in the blood and peritoneal access sites. Clinicians should consider peritonitis a possibility when blurred dialysate occurs. Symptoms such as fever and abdominal pain, nausea, vomiting and diarrhea generally are seen together. Empirical treatment should be initiated in these patients immediately after taking the necessary samples.[5,21] However, patients with renal failure could have more than one medical problem at the same time because their immune system is suppressed. Even a simple PD catheter replacement could cause surgical peritonitis, which cannot be treated. Delays in diagnosis and treatment for surgical peritonitis inevitably lead to increased morbidity and mortality. Early diagnosis and referral to a surgeon with sufficient experience would reduce the mortality in these patients. Clear peritoneal fluid with pain that is out of proportion to the abdominal examination findings should be considered as a possible incarcerated hernia.[22] Acute pleural effusion is a rare complication and usually occurs in early treatment periods. In one study, the most common PD complication was over hydration. If the patient is gaining weight, central venous pressure is rising, or the recovered waste is not at least 90% of the infused dialysate, the treatment should be changed to ultrafiltration with higher dextrose (2.5% or 4.25%) solutions. Acute hydrothorax is a rare complication of PD and has been reported in only 1.6% of 3,195 CAPD patients in a series. The majority (88%) was right-sided effusions and was associated with dyspnea.[3,23]

In our study, we evaluated PD patients, who applied to the emergency department, with several different symptoms and were hospitalized in various clinical departments. Although complications were predominantly related to peritoneal dialysis, cardiovascular problems and acute abdominal surgery were also prominent. However, it should be kept in mind that these patients could present with other acute problems independent of the underlying renal failure and the diagnosis could be harder than with renal failure itself. Since patient complaints include a wide variety of clinics from simple dyspepsia to acute abdomen, the emergency department physician has a great responsibility.

CONCLUSION

We think that several problems of patients with renal failure could be delayed by referral to a nephrologist. Furthermore, emergency doctors should be prepared to recognize and treat life-threatening problems during this period. Even though cardiovascular problems, infection, and electrolyte abnormalities are more common, recognizing other pathologies, which require acute surgical intervention, may help reduce mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: After obtaining ethics committee approval from the Medical School (no: 2020/618), consent was obtained from all participants.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1033147
J Contemp Med 2022;12(3):424-430

Original Article / Orijinal Araştırma

The Attitudes of Undergraduate Nursing Students to Childhood Vaccines

Hemşirelik Lisans Öğrencilerinin Çocukluk Çağı Aşılarına Yönelik Tutumu

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Abstract

Aim: This study aims to determine the attitudes of undergraduate nursing students studying at a public university toward childhood vaccines and investigate whether students' attitudes change according to sociodemographic characteristics, vaccination history, and perceived level of knowledge.

Material and Method: This descriptive study was conducted with 83 students studying in the Department of Nursing at a public university in Konya between May 2020 and September 2021. The data were collected using the Information Form and the Public Attitude toward Vaccination-Health Belief Model Scale. The data were analyzed through descriptive statistics and the Mann Whitney U and Kruskal Wallis non-parametric tests.

Results: When the childhood vaccination attitude scores of the students were examined according to their sociodemographic characteristics, it was seen that there was a statistically significant difference between gender and the perceived barriers attitude score; between the economic status of the family and the perceived severity and perceived barriers attitude scores; the location of the high school graduated and the perceived severity, perceived susceptibility, perceived benefit and health motivation attitude scores. When the distribution of students' childhood vaccination attitude scores across their childhood vaccination history and perceived level of knowledge about vaccines was examined, it was observed that there was a statistically significant difference between having sufficient knowledge about childhood vaccines and the perceived barriers attitude score.

Conclusion: Our study revealed that gender, economic status, the location of the high school graduates, and the perceived level of knowledge about childhood vaccines affect vaccination attitudes.

Keywords: Vaccine, children, attitude, vaccination refusal, nursing

Öz

Amaç: Bir kamu üniversitesinde eğitim gören hemşirelik lisans öğrencilerinin çocukluk çağı aşılarıyla ilgili tutumunu belirlemek ve öğrencilerin tutumunun sosyodemografik özellikler, aşı öyküsü ve algılanan bilgi durumuna göre farklılık gösterip göstermediğini incelemektir.

Gereç ve Yöntem: Tanımlayıcı türde olan araştırmamız Mayıs 2020-Eylül 2021 tarihleri arasında Konya'da bir Kamu Üniversitesinde Hemşirelik bölümünde eğitim gören gönüllü 83 öğrenci ile yapılmıştır. Veriler bilgi formu ve Aşıyla ilgili toplum tutumu-sağlık inanç modeli ölçeği ile toplanmıştır. İstatistiksel analizlerde tanımlayıcı istatistikler; Nonparametrik testlerden Mann Whitney U ve Kruskal Wallis testi kullanılmıştır.

Bulgular: Öğrencilerin çocukluk çağı aşı tutum puanları sosyodemografik özelliklere göre incelendiğinde cinsiyet ile algılanan engel tutum puanı alt boyutunda; ailenin ekonomik durumu ile algılanan duyarlılık ve algılanan engel tutum puanı alt boyutları arasında; mezun olunan lisenin yeri ile algılanan duyarlılık, algılanan ciddiyet, algılanan yarar ve algılanan sağlık sorumluluğu tutum puanları arasında istatistiksel olarak anlamlı bir farklılık olduğu belirlenmiştir ($p<0.05$). Öğrencilerin çocukluk çağı aşı tutum puanları ile çocukluk çağı aşı öyküsü ve algılanan bilgi durumu özelliklerine göre dağılımı incelendiğinde çocukluk çağı aşıları hakkında yeteri kadar bilgi sahibi olma durumu ile algılanan engel tutum puanı alt boyutu arasında istatistiksel olarak anlamlı bir farklılık olduğu belirlenmiştir ($p<0.05$).

Sonuç: Araştırmamızda cinsiyet, ekonomik durum, mezun olunan lisenin yeri, çocukluk çağı aşıları hakkında bilgi durumunun aşı tutumları üzerinde etkili olduğu sonucuna ulaşılmıştır.

Anahtar Kelimeler: Aşı, çocuk, tutum, aşı reddi, hemşirelik

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Received *(Geliş Tarihi)*: 06.12.2021 **Accepted *(Kabul Tarihi)*:** 04.01.2022

INTRODUCTION

Immunization is an important preventive health service that ensures the reduction of infant mortality and the eradication of many infectious diseases.[1] The World Health Organization (WHO) considers immunization as an important intervention in public health to prevent diseases and deaths that result from diseases and which could be eliminated through vaccination.[2] Thanks to immunization, babies, children, and society are protected against diseases; relapse of diseases and the sequelae caused by diseases are prevented; death rates are reduced; epidemics and pandemics are prevented, and health expenditures can be prevented be incurred by diseases are minimized.[3]

Although vaccination services at the community level are implemented in practice, the attitudes known as not accepting or delaying vaccination are defined as vaccine rejection.[4] The parties that show an anti-vaccine attitude are families, health workers, and society. While the number of anti-vaccination families in our country was 183 in 2011, it increased to 23,000 in 2018.[5] In retrospect, some populations have been skeptical of vaccination since the introduction of the vaccine; They showed the vaccine as the cause of some pathological problems and also suggested that the side effects of the diseases developed due to the substances in the vaccine.[6] It is an event that took place in England, which still has echoes today and forms the basis of the claims of anti-vaccine opponents about the relationship between vaccine and autism.[7] In this case, Wakefield et al.[8] published an article in a journal and suggested that there is a relationship between MMR (measles, rubella, mumps) vaccine and autism. Most families have not had their children vaccinated for MMR due to the fear of their child having autism, so MMR vaccination rates in England and Wales have remained low for many years, with vaccination rates even lower than 80%.[8] Afterward, a major epidemic occurred in the 2000s.[9] Studies conducted in the USA have associated decreases in vaccination rates with vaccine-preventable outbreaks.[10] Another issue regarding vaccine opposition is the view that thiomersalin in the vaccine will cause autism.[11] Thiomersal, an organic compound, has been used in multiple-dose vaccines since the 1930s and helps prevent pathogen contamination. The American Academy of Pediatrics and the Public Health Service wanted to gain a protective perspective by recommending that mercury content be kept away from all vaccines, but it led to the formation of anti-mercury groups.[12] Thereupon, America, England, and Denmark conducted three large epidemiological studies and as a result, it was revealed that there is no relationship between mercury and autism.[13] However, mercury-containing vaccines have led to an increase in anti-vaccination, and the US has not implemented mercury-containing vaccines since 2001 in order not to decrease vaccination rates.[14]

According to the current studies, the reasons for being an anti-vaccine are negative attitudes about vaccines in social media, lack of knowledge about vaccines, mistrust of vaccine benefit, fears about side effects of the vaccine, age of children, the belief that sick children will have a low tolerance to the vaccine, the belief that vaccines can cause different diseases, social characteristics, and cultural structure.[15,16] It has been revealed that worldwide vaccination rates have decreased by approximately 85%, and in Turkey, the vaccination rate decreased from 98% in 2017 to 96% in 2018.[17] The decrease in vaccination rates in the world and our country leads to an increase in vaccine-preventable diseases. For example, the incidence of measles in our country increased from 0.01 in 2016 to 0.09 in 2017.[18]

Anti-vaccine attitudes risk public health, and health workers have important duties to change these attitudes.[19] The duties of nurses in this process from the planning of the immunization services to the evaluation of the results are learning the benefits, indications, and contraindications of the vaccine and informing individuals about these; learning about the cold chain practices for the protection of the vaccine, complying with the general principles and taking the necessary precautions against any reaction.[20] The key roles of nurses in safe immunization are researcher, planner, educator, and practitioner. In this process, health workers can change attitude and behavior in every individual they are in contact with, and therefore in society.[21]

Studies have revealed that the level of knowledge about vaccines, the number of children, the sources of information about vaccines, educational status, socioeconomic status, and the cost of vaccines influence vaccination attitude.[22,23] There are limited studies on whether the person's age, the number of siblings, whether their vaccinations are complete, the education level of the mother and father, and the place where they live for a long time affect the vaccination attitude. This study aims to fill this gap in the literature. The data obtained about the vaccination attitude of nursing students is believed to be useful in terms of drawing attention to the subject and presenting information that can be used in nursing education.

The study aims to determine the attitudes of undergraduate nursing students studying at a public university about childhood vaccines and to investigate whether students' attitudes differ across their sociodemographic characteristics, vaccination history, and perceived knowledge.

Research Questions

1. What is the childhood vaccination attitude level of undergraduate nursing students?
2. Do students' childhood vaccination attitude scores differ according to their sociodemographic characteristics?
3. Do the childhood vaccination attitude scores of the students differ according to their vaccination history and level of knowledge?

MATERIAIL AND METHOD

Research type

This is a descriptive- correlation study.

Research population and the sample

The study's target population is 168 senior nursing students studying at Selcuk University, Faculty of Nursing. Given the effect size of 0.35, 95% statistical power, and 0.05 significance level, the minimum sample size was determined as 83 (24). International students were excluded from the study due to language and cultural differences.

Data collection tools and procedure

The questionnaires were prepared electronically, and a research link was created (http://www.surveey.com/SurveyStart.aspx?lang=1&surv=70b99bc0ddc54bc396dfafcb01a67e6d). Then, the online survey link was shared with the senior students through their social media accounts (WhatsApp and Instagram). The Information Form and the Public Attitude toward Vaccination-Health Belief Model Scale were used to collect data.

Information Form

The researchers' information form based on the literature consists of 11 questions and two parts.[16,22,23,25-28] The first part includes questions regarding sociodemographic characteristics [age, gender, education level of parents, place of residence for the longest period, economic situation, location of the high school (city center/town), and the number of siblings]. The second part includes questions about childhood vaccination history and perceived level of knowledge (whether they have enough information about childhood vaccines and whether they were completed).

The Public Attitude toward Vaccination-Health Belief Model Scale

The scale was developed by three researchers[25] to measure public attitudes towards vaccination. It measures individuals' attitudes towards childhood vaccines. The scale consists of five factors: perceived severity (4 questions), perceived susceptibility (4 questions), perceived benefit (5 questions), perceived barriers (8 questions), and health motivation (5 questions). The responses revealing the vaccination attitudes of individuals are rated on a five-point Likert scale from "5-strongly agree" to "1- strongly disagree". The content validity of the scale was examined. Based on expert opinion, it was found to be between 0.769-1.00. In addition, exploratory and explanatory factor analyses were performed and it was reported that the validity was high. Five factors explain 68.9% of the total variance. Internal consistency and invariance over time were also examined to test reliability. Cronbach's alpha was found to be 0.86 for the whole scale and between 0.85 and 0.90 for the factors. High scores indicate a positive attitude towards vaccines in all factors except for the perceived barriers factor. On the other hand, low perceived barriers' low scores indicate positive attitudes towards vaccination.[25]

Data Analysis

In statistical analyses, descriptive statistics were shown with numbers and percentage distributions. The Kolmogorov-Smirnov/Shapiro test was used to understand whether the data showed normal distribution. The Mann Whitney U and Kruskal Wallis tests, which are non-parametric, were used because the data were not suitable for normal distribution. Statistical significance was set at $p<0.05$.

Ethical Issue

Ethics Committee was obtained from Selçuk University, Faculty of Medicine, Non-Interventional Research Ethics Committee (Date: 17.06.2020, Decision No: 2020/253), and institutional permission was obtained from the Dean of the Faculty of Nursing. Informed consent was obtained from the nursing students who agreed to participate in the study. The study followed the principles of the Declaration of Helsinki.

RESULTS

Table 1. Sociodemographic characteristics, vaccination history, and perceived level of knowledge of the participants

Variables		Number	%
Gender	Female	68	81.92
	Male	15	18.08
Mother's Education Level	Primary School	64	77.1
	High School	13	15.66
	University	6	7.22
Father's Education Level	Primary School	50	60.24
	High School	17	20.48
	University	16	19.27
Place of residence for the longest period	Village	12	14.45
	District	18	21.68
	City	53	63.85
Economic Situation	Good	11	13.25
	Moderate	67	80.72
	Poor	5	6.02
The number of siblings	0	11	3.61
	1-2	18	21.68
	3 and ↑	26	31.32
Location of the high school	Metropolitan	21	25.3
	City center	52	62.65
	Town	10	12.04
Childhood vaccination history	Fully vaccinated.	72	86.74
	Unvaccinated	3	3.61
	I Don't Know	8	9.63
Perceived level of knowledge about childhood vaccines	Yes	45	54.21
	No	15	18.07
	Undecided	23	27.71

The mean age of the students was 22.27±1.025. 81.92% of the students are women, 77.1% of the mothers and 60.24% of the fathers of the students are primary school graduates, 63.85% of the participants live in the city, 80.72% perceive their economic situation as moderate, 31.32% have three or

more siblings and 62.65% graduated from a high school in the city. When the students' childhood vaccination history and knowledge status were examined, it was revealed that 86.74% were fully vaccinated. 18.27% of the students stated that they had insufficient knowledge about vaccines and 27.71% reported that they were undecided about their knowledge of vaccines.

When the distribution of childhood vaccination attitude scores of the students across sociodemographic characteristics was examined, it was observed that there was a statistically significant difference between gender and the perceived barriers attitude scores ($p<0.05$). It was revealed that the perceived barriers attitude scores of the male students were higher than those of the female students. Furthermore, a statistically significant difference was found between the economic status of families and the factors of perceived severity and perceived barriers attitude scores ($p<0.05$). It was determined that the students caused this difference with good economic status and their perceived severity scores, and the students with a bad economic status and their perceived barriers attitude scores. It was also found that there was a statistically significant difference between the locations of the high schools the students graduated from and their perceived severity, perceived susceptibility, perceived benefit, and health motivation ($p<0.05$). This difference seems to stem from the students who graduated from a high school in the city. It was determined that there was no significant difference between the mother's education level, father's education level, place of residence for the longest period, and the number of siblings, and the factors the Public Attitude toward Vaccination-Health Belief Model Scale ($p>0.05$) (**Table 2**).

Table 2. Distribution of the students' childhood vaccination attitude scores across sociodemographic characteristics

Variables		Perceived Severity Median (Min-Max)	Perceived Susceptibility Median (Min-Max)	Perceived Benefit Median (Min-Max)	Perceived Barriers Median (Min-Max)	Health Motivation Median (Min-Max)
Gender	Female	18 (15-20)	16.50 (12-20)	22 (17-25)	14.50 (8-27)	23 (17-25)
	Male	18 (12-20)	18 (4-20)	21 (16-25)	22 (12-40)	22 (17-25)
	Test p	MU: 98.500 p:0.889	MU:522.000 p:0.824	MU:444.500 p:0.428	MU:857.500 *p:0.000	MU:432.000 p:0.349
Mother's education level	Primary school	18 (12-20)	17 (12-20)	22 (16-25)	15 (8-40)	23 (17-25)
	High school	17 (16-20)	18 (14-20)	22 (18-25)	16 (9-22)	21 (18-25)
	University	18 (16-20)	15.5 (4-20)	22.5 (19-25)	15 (11-24)	23 (19-25)
	Test p	KW:0.45 p:0.623	KW:1.296 p:0.523	KW:0.798 p:0.671	KW:0.133 p:0.936	KW:1.618 p:0.445
Father's education level	Primary School	18 (12-20)	16 (12-20)	22 (16-25)	16 (8-40)	23 (17-25)
	High School	17 (15-20)	16 (12-20)	22 (18-25)	15 (8-27)	23 (18-25)
	University	19.5 (16-20)	18.5 (4-20)	23.5 (19-25)	12 (8-24)	24 (18-25)
	Test p	KW:2.935 p:0.232	KW:2.718 p:0.257	KW:1.729 p:0.421	KW:5.568 p:0.062	KW:0.709 p:0.701
Place of residence for the longest period	Village	17.5 (12-20)	16 (13-20)	21.5 (16-25)	16 (8-40)	22 (17-25)
	District	17 (16-20)	16.5 (13-20)	22 (19-25)	14.5 (8-22)	21.5 (19-25)
	City	18 (14-20)	18 (4-20)	23 (17-25)	15 (8-40)	23 (17-25)
	Test p	KW:1.272 p:0.529	KW:0.608 p:0.738	KW:0.467 p:0.792	KW:1.773 p:0.412	KW:0.85 p:0.958
Economic situation	Good (a)	20 (16-20)	18 (14-20)	25 (19-25)	15 (9-40)	24 (20-25)
	Moderate (b)	18 (12-20)	17 (4-20)	22 (16-25)	15 (8-29)	23 (17-25)
	Poor (c)	16 (15-20)	16 (13-20)	20 (18-23)	20 (17-30)	21 (20-24)
	Test p	KW:6.247 *p:0.044 a>b, c	KW:1.664 p:0.435	KW:5.120 p:0.077	KW:7.030 *p:0.030 c>a, b	KW:2.931 p:0.231
The number of siblings	0	19 (16-20)	17.5 (16-20)	22.5 (17-25)	11.5 (8-16)	25 (20-25)
	1-2	17 (14-20)	17 (14-20)	16 (4-20)	21 (17-25)	22 (17-25)
	3 and ↑	18 (12-20)	18 (13-20)	22.5 (16-25)	15 (8-40)	23.5 (17-25)
	Test p	KW:3.958 p:0.138	KW:3.644 p:0.162	KW:2.496 p:0.287	KW:3.570 p:0.168	KW:5.796 p:0.055
Location of the high school	Metropolitan (a)	18.5 (14-20)	18.5 (4-20)	23 (17-25)	14.5 (8-40)	23 (18-25)
	City center (b)	17 (12-20)	16 (14-20)	21 (16-25)	16 (8-40)	22 (17-25)
	Town (c)	16 (16-20)	15 (13-20)	20 (20-25)	17 (8-20)	20 (18-25)
	Test p	KW:7.219 *p:0.027 a>b, c	KW:9.261 *p:0.010 a>b, c	KW:6.118 *p:0.047 a>b, c	KW:2.030 p:0.362	KW:6.325 *p:0.042 a>b, c

KW: Kruskal Wallis; MU: Mann Whitney U, *p<0.05

When the distribution of the childhood vaccination attitude scores of the students across their childhood vaccination history and perceived level of knowledge was examined, it was seen that there was a statistically significant difference between having sufficient knowledge about childhood vaccines and the perceived barriers attitude score ($p<0.05$). It was found that this difference stemmed from the students who did not think that they had enough knowledge about vaccines. No significant difference was found between perceived severity, perceived susceptibility, perceived benefit, and health motivation attitude scores and having sufficient knowledge about childhood vaccines and completeness of childhood vaccines ($p>0.05$) (**Table 3**).

DISCUSSION

When the vaccination attitude scores, sociodemographic characteristics, childhood vaccination history, and the perceived knowledge levels of the undergraduate nursing students were evaluated, it was determined that there were significant differences between vaccination attitude scores and gender, economic status, the locations of the high schools the students graduated from and having knowledge about childhood vaccines.

When the vaccination attitude scores of the students were evaluated according to gender, it was determined that the male students obtained higher scores than the female students in the perceived barriers factor, and the male students had a more negative attitude towards vaccination. In their study with healthcare professionals, Barbara et al. (2020) found that men were vaccinated more than women.[29] As opposed to our research, the study conducted by Topaloğlu et al. (2013) revealed no significant relationship between the status of parents vaccinating their children and gender.[30] In the study conducted by Başar et al. (2019), no significant relationship was found between the level of knowledge about the Human papillomavirus (HPV) vaccine and gender.[31] It is seen that our research finding is different from the studies in the literature.

In parallel to the studies in the literature, our study revealed a significant difference between the factors of perceived severity and perceived barriers and the economic status and the vaccination attitude score. It has been determined that the students with good economic status had a positive attitude towards vaccination, while the students with poor economic status had a more negative attitude. In their study, Bülbül et al. (2013) found that the rate of having the vaccines provided by the state free of charge is higher than having the paid vaccines.[32] Özer et al. (2016) reported that the factors that affect the acceptance of the chickenpox vaccine are the cost of the vaccine and whether the vaccine is administered by a specialist.[26] Polat et al. (2017) found that families with social security had their children regularly vaccinated.[33] Brown et al. (2018) revealed that the vaccine acceptance rate was higher in families with good economic status, while this rate decreased as the economic situation worsened.[34] Studies in the literature support our research findings. Individuals with good economic status seem to adopt positive attitudes and behaviors concerning vaccination.

In our study, the perceived barriers score of the students who believed that they do not know about childhood vaccines was found to be higher, and it was determined that these students had more negative attitudes towards vaccines than other students. A systematic review reported that education about vaccination is important in immunization.[35] Another study also stated that as parents are more informed about vaccination, they get their children vaccinated more.[36] Thus, it is seen that having sufficient knowledge about vaccines is important in developing a positive attitude towards vaccines. Our study further revealed that the vaccination attitude of the students who completed their high school education in the city is positive. This finding may be attributed to the education and the correct information received in the schools located in cities. Our findings suggest that the importance of immunization can be understood and more positive attitudes about vaccines can be adopted if society's awareness is raised by imparting accurate information about childhood vaccines.

Table 3. Distribution of students' childhood vaccination attitude scores across their vaccination history and perceived level of knowledge

Variables		Perceived Severity Median (Min-Max)	Perceived Susceptibility Median (Min-Max)	Perceived Benefit Median (Min-Max)	Perceived Barriers Median (Min-Max)	Health Motivation Median (Min-Max)
Childhood vaccination history	Fully vaccinated.	18 (12-20)	17 (4-20)	22 (16-25)	15 (8-40)	23 (17-25)
	Unvaccinated	18 (17-20)	15 (15-16)	24 (20-25)	16 (15-20)	24 (21-25)
	I don't know	16.5 (14-20)	16 (12-20)	21 (17-25)	17 (9-40)	21 (19-25)
	Test p	KW:1.403 p:0.496	KW:2.858 p:0.240	KW:0.456 p:0.796	KW:2.029 p:0.363	KW:1.435 p:0.488
Perceived level of knowledge about childhood vaccines	Yes (a)	18 (16-20)	18 (12-20)	22 (17-25)	14 (8-40)	24 (18-25)
	No (b)	17 (12-20)	16 (4-20)	20 (16-25)	20 (11-40)	22 (17-25)
	Undecided (c)	17 (15-20)	16 (13-20)	22 (18-25)	16 (9-27)	22 (18-25)
	Test p	KW:2.902 p:0.234	KW:1.864 p:0.394	KW:3.917 p:0.141	KW:14.507 *p:0.001 b>a, c	KW:4.769 p:0.92

KW: Kruskal Wallis; MU: Mann Whitney U, *p<0.05

A study conducted in Brazil revealed that the 25-year-old group had the lowest vaccine acceptance rate, while the 60 and over age group had the highest vaccine acceptance rate.[34] Nalbantoğlu et al. (2010) reported that hepatitis B vaccination rates decreased as age decreased.[22] Since the age groups were very similar in our study, vaccine attitude scores were not evaluated according to age.

Our study revealed no statistical difference between the number of siblings, the education level of the parents, the place of residence for the longest period, whether the childhood vaccines were complete or not, and the vaccination attitude scores. The literature reports that there is a difference between the number of siblings, parental education level, place of residence for the longest period, whether childhood vaccines are complete or not, and vaccination attitude scores.[30,31,33,37,38] These differences across studies may be attributed to the easy access to health services and the conscious behavior of people thanks to the developments in socio-cultural environments.

Limitations

The research is limited to a public university and the senior students studying at that university. All the senior nursing students in the university (n:168) were invited to the study; however, the study was completed with 83 students. Due to time constraints, the opportunities available, the interruption of education because of the COVID-19 pandemic, and difficulties in communicating with the target population face-to-face, the study had to be completed with this sample.

CONCLUSION

Our study revealed that gender, economic status, the locations of the high schools the students graduated from, and their perceived level of knowledge about childhood vaccines affect vaccination attitudes. It was also revealed that the nursing students think they do not have enough information about childhood vaccines. Nursing students, who have important duties in immunization, can be provided with adequate and accurate information about childhood vaccines. In this way, they can develop positive attitudes towards vaccination, and important steps can be taken in immunization by ensuring that society also has a positive attitude toward vaccines.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics Committee was obtained from Selçuk University, Faculty of Medicine, Non-Interventional Research Ethics Committee (Date: 17.06.2020, Decision No: 2020/253), and institutional permission were obtained from the Dean of the Faculty of Nursing.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Note: Only the summary of this study was presented at the 5th International 23rd National Public Health Congress (13-18 December 2021).

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1034411
J Contemp Med 2022;12(3):431-436

Original Article / Orijinal Araştırma

Evaluation of Medical Malpractice in Urology Cases Resulting in Death

Ölümle Sonuçlanmış Üroloji Vakalarında Tıbbi Uygulama Hatalarının Değerlendirilmesi

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Abstract

Aim: This study aimed to present 96 cases evaluated by the 1st Specialization Committee of The Council of Forensic Medicine, which included medical malpractice claims about urologists resulting in death between 2010 and 2015 and to increase the awareness of urologists about medical malpractice claims.

Material and Method: The reports prepared by the 1st Specialization Committee of The Council of Forensic Medicine between 2010–2015 were reviewed retrospectively. All of the cases treated in Urology clinics, alleged medical malpractice, and resulted in death, participated in the study.

Results: In this study, 96 cases were included. It was reported that there was medical malpractice in 16 (16.7%) cases. Seventy–six of the patients (79.2%) were female; the most common age range was ≥ 60 years (n:46 47.9%); the mean age was 54,90±19,59 years. Seventy–three (76%) cases were followed up under elective conditions. Complications developed in 20 (20.8%) of the cases during their treatment course. Surgical treatment was applied in 68 (70.8%) patients. Twenty (20.8%) cases were diagnosed with urinary system stone disease and 16 (16.7%) cases with benign prostatic hyperplasia. The committee attributed malpractice to the doctors most frequently due to lack of treatment (n:6, 37.5%).

Conclusion: We think that a comprehensive review of the cases with medical malpractice claims will contribute to a better understanding of these cases, the improvement of the medical service provided, and public health.

Keywords: Medical malprtactice, urology, forensic medicine

Öz

Amaç: Çalışmamızda Üroloji hekimleri hakkında 2010-2015 yılları arasında ölümle sonuçlanan tıbbi kötü uygulama iddiası içeren ve Adli Tıp Kurumu (ATK) 1. İhtisas Kurulunca değerlendirilen 96 olgunun sunulması ve tıbbi kötü uygulama iddiaları ile ilgili üroloji hekimlerinin farkındalığının arttırılması amaçlanmıştır.

Gereç ve Yöntem: Adli Tıp Kurumu 1. İhtisas Kurulunca 2010-2015 yılları arasında düzenlenen raporlar retrospektif olarak incelenmiş ve Üroloji kliniklerinde tedavi gören, tıbbi uygulama hatası iddiası bulunan ve ölümle sonuçlanan olguların tamamı çalışmaya dahil edilmiştir.

Bulgular: Çalışmaya 96 olgu dahil edilmiştir. Olguların 16'sında (%16,7) tıbbi kötü uygulama olduğu, 80'inde (%83,3) olmadığı yönünde rapor düzenlenmiştir. Olguların 76'sının (%79,2) kadın, en sık yaş aralığının 60 yaş ve üzeri (n:46 %47,9); ortalama yaşın 54,90±19,59 olduğu tespit edilmiştir. Yetmiş üç (%76) olgu elektif şartlarda takip edilmiştir. Olguların 20'sinde (%20,8) bir komplikasyon gelişmiştir. Olguların 68'inde (%70,8) cerrahi tedavi uygulanmıştır. Yirmi (%20,8) olgu üriner sistem taş hastalığı ve 16 (%16,7) olgu benign prostat hiperplazisi tanısı almıştır. Kurul tarafından en sık tedavi eksikliği (n:6, %37,5) nedeniyle doktora kusur atfedilmiştir.

Sonuç: Tıbbi uygulama hatası iddiası bulunan olguların kapsamlı incelemesinin bu olguların daha iyi anlaşılmasına, sunulan tıbbi hizmetin ve toplum sağlığının iyileşmesine katkıda bulunacağını düşünmekteyiz.

Anahtar Kelimeler: Tıbbi uygulama hatası, üroloji, adli tıp

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Received *(Geliş Tarihi)*: 10.12.2021 **Accepted *(Kabul Tarihi)*:** 10.01.2022

INTRODUCTION

There is a dramatic increase in medical malpractice claims in our country and worldwide.[1-3] The expansion of medical malpractice litigations directly affects physicians and the health care they provide. Physicians are turning to defensive (recessive) medicine practices. Defensive medicine may manifest itself in unnecessary tests and imaging techniques, and consultations at every possible stage. Physicians refuse difficult cases that require complex procedures and patients with comorbidities.[3-6] This makes it difficult for the patient to access health services and increases public health expenditures.[2] The Urology departments ranked 12th in China, 10th in Spain, and 8th in the United States in medical malpractice claim frequency.[7-9] Urology ranked 8th among the surgical departments sued in Turkey.[10] Medicolegal risks also affect future physicians. Studies have shown that medical students decide on low-risk specialties due to medical malpractice lawsuits.[1,11,12] Urology departments and urologists make no exception to this situation. The urology department is considered a high-risk specialty from the point of medical malpractice.[13,14] Kaplan showed that 91 doctors on the list of top doctors in the USA faced an average of 2.36 medical malpractice claims during their careers. He also found that 122 physicians who applied for recertification to the American Urologists Association had an average of 1.9 medical malpractice claims throughout their careers.[15] Another study indicated that urologists are exposed to an average of two medical malpractice claims during their career, more than half of urologists did not accept cases that they considered complex and limiting their field of practice, a quarter considered changing their profession, almost half considered quitting medical practice.[5]

This study aimed to present 96 cases evaluated by the 1st Specialization Committee of The Council of Forensic Medicine, which included medical malpractice claims about urologists resulting in death between 2010 and 2015 and to increase the awareness of urology physicians about medical malpractice claims.

MATERIAL AND METHOD

Sampling

The 1st Specialization Committee of The Council of Forensic Medicine is the board that carries out independent and impartial expert evaluations in cases of medical malpractice claims resulting in death sent from the prosecutor's office and courts throughout the country, under the administrative authority of the Ministry of Justice. In our study, the cases reported by the 1st Specialization Committee of The Council of Forensic Medicine due to the alleged medical malpractice between 2010 and 2015 were evaluated retrospectively. All the claims in which urologists were accused of medical malpractice were included in the study.

Diagnostic Methods

The cases are sent to the 1st Specialization Committee of The Council of Forensic Medicine by the judicial authorities to evaluate the medical malpractice. The rapporteur examines all medical documents, medical imaging materials, statements of witnesses, defendants, and plaintiffs and requests from the judicial authority if any are missing. After the deficiencies are completed, the rapporteur prepares a detailed report and presents it to the Committee. Each case is evaluated separately by the chairman and the members of the Committee, and a decision is made. Finally, a detailed report is prepared and sent to the judicial authorities.

Data Collection and Proccessing

Age, gender, the reason for coming to the hospital, academic title of the physician, being a primary or consultant physician, presence of complications, surgical treatments, the health institution, the diagnosis made in the hospital, whether there was medical malpractice, and the reason for medical malpractice parameters were evaluated. Since our study was designed retrospectively, no informed consent form was created. Ethical approval was obtained from the Scientific Academic Committee of the Council of Forensic Medicine, dated 15.12.2015, and numbered 971. Our study respected the ethical standards in the Helsinki Declaration of 1964, as revised in 2013.

Statistical Analysis

Statistical Package For Social Science SPSS, version 21.0 (IBM SPSS Statistics for Window, Version 21.0, Armonk, NY: IBM Corp.) statistics program was used for data analysis of the study. Descriptive statistics are presented with frequency, percentage, mean, standard deviation (SD), minimum (min), and maximum (max) values.

RESULTS

In our study, 96 cases were included. 76 (79.2%) cases were female, and 20 (20.8%) were male. The mean age of the cases was 54.90±19.59 (min: 1 month, max: 84). Almost half of the cases (47.9%) were 60 years or older (**Table 1**). In our study, there were medical malpractice allegations about 114 urology physicians (82 specialists, 14 residents, nine associate professors, six professors, three assistant professors) (**Table 2**). In 73 (76.0%) cases, the accused physician was the primary responsible physician, while in 23 (24%), it was the consultant physician (**Table 2**). Medical intervention was performed under elective conditions in 73 (76%) cases and emergency conditions in the remaining 23 (24%) patients (**Table 2**).

Complications developed in 20 (20.8%) of the cases. Sixty-eight (70.8%) cases underwent surgical treatment, while 28 cases (29.2%) only received medical treatment. When the most common diagnoses in health institutions are examined, 20 (20.8%) cases were diagnosed with urinary system stone disease, and 16 (16.7%) cases were diagnosed with benign prostatic hyperplasia (**Table 1**).

Table 1. Distribution of age groups, primary disease and reasons for complaint

Age groups	n	%
0–17 years	6	6.3
18–39 years	12	12.5
40–59 years	32	33.3
≥ 60 years	46	47.9
Diagnosis		
Urinary system stone disease	20	20.8
Benign prostatic hyperplasia	16	16.7
Trauma	15	15.6
Urinary system malignancy	13	13.6
Urethral stricture	4	4.2
Urinary system infection	3	3.1
Pyelonephritis	2	2.1
Chronic kidney failure	2	2.1
Retroperitoneal fibrosis	2	2.1
Others	19	19.7
Reason of complaint		
Lack of attention (negligence, indifference, rude manners, etc.)	22	22.9
False treatment	19	19.8
Delay in the initiation of therapy	11	11.5
Insufficient treatment	9	9.4
Failure to diagnose on time	8	8.2
Incorrect surgical practice	5	5.2
Misdiagnosis	5	5.2
Not hospitalization	4	4.2
Early discharge	4	4.2
Deficiency of diagnostic test	4	4.2
Lack of referring	2	2.1
Lack of informed consent	2	2.1
Lack of monitoring/follow up	1	1.0
Total	96	100

Table 2. Distribution of physician title, primary responsible-consultant, and medical intervention

Urology physicians title	n	%
Residents	14	12.3
Specialists	82	71.9
Asssistant professor	3	2.6
Associate professor	9	7.9
Professor	6	5.3
Total	114	100
Urology physicians		
Primary responsible physician	73	76
Consultant physician	23	24
Medical intervention		
Elective condition	73	76
Emergency condition	23	24
Total	96	100

In this study, 22 (22.9%) of the plaintiffs filed a lawsuit due to lack of care, 19 (19.8%) improper treatment, and 11 (11.5%) treatment delay (**Table 1**). Reports were prepared by the committee that there was medical malpractice in 16 (16.7%) cases and that there was no medical malpractice in 80 (83.3%) cases. In 16 cases with malpractice, a total of 16 physicians were attributed faults. It was determined that 14 (87.4%) of the doctors who were attributed faults were specialists, one (6.3%) was an associate professor, and one (6.3%) was an assistant professor. In the 16 cases with medical malpractice, the most common cause of the error was lack of treatment (n=6, 37.5%) (**Table 3**).

Table 3. Distribution of the type of error in physicians with medical malpractice

Classification of Medical Errors	n	%
Lack of treatment	6	37.5
Lack of the necessary laboratory test and radiological examination	5	31.3
Lack of referring	1	6.3
Lack of monitoring/follow up	1	6.3
Missed or misdiagnosis	1	6.3
Lack of consultation	1	6.3
Insufficient informed consent	1	6.3
Total	16	100

DISCUSSION

Age

In a study conducted in the USA that included 259 medical malpractice claims, 68.5% of the cases were 35-70 years old.[16] The mean age of the cases was 56.5 (min:44, max:71) in the study performed on the malpractice alleged cases with penile prosthesis.[17] In a study examining cases of testicular torsion claiming medical malpractice, mean patient age was reported as 15.4±10.4.[18] In this study, the mean age of the cases was 54.90±19.59 (min: 1 month, max: 84). Almost half of the our cases (47.9%) were 60 years or older.

Sex

It was reported in a study that 83.5% of the plaintiffs were women.[13] In another study, it was shown that 16 (64%) of 25 cases were female, and nine (36%) were male (2). In a study conducted in California examining urological catheter-related medical malpractice claims, it was found that 52% of the complainants were male.[19] In this study, the majority (79.2%) of the cases were female compatible with literature.

Physician

Studies investigating medical malpractice claims in Turkey have reported that 82.9% of general surgeons and 90.9% of obstetricians were specialists (20,21). In this study, it was found that 71.9% of the accused urologists were specialists (**Table 2**). We think that this situation was due to the higher number of specialists in general.

Consultation

Physicians specialized in a single branch may ask the opinion of doctors of other specialties in complex patients or patients with complications. Although the physician following the patient is responsible for the patient's treatment, the consultant also has accountabilities. The consultant has to

inform the responsible physician clearly and understandably, in writing, about their opinions about the patient, their diagnosis, and the most appropriate treatment method to be followed.[22,23] Only 24% of the accused physicians in this study were consultants (**Table 2**).

Emergent-Elective Cases

In Belgium, only 24% of surgical-related medical malpractice claims are emergency cases.[24] Kahan et al., examined 259 malpractice cases and observed that the alleged medical malpractice occurred in the hospital setting in 181 instances, the office in 73 cases, and the emergency room in five cases.[16] In a study of 53 cases diagnosed with testicular torsion and alleged medical malpractice, 26 (51%) of the cases presented to the emergency department.[18] In a study conducted in Turkey, 54.3% of general surgeons and 79.8% of obstetricians accused of medical malpractice examined the patient under emergency conditions.[20,21] In this study, only 24% of the cases were treated under emergency conditions (**Table 2**). This may be related to the lower number of emergency patients in the urology department than other surgical branches.

Presence of Complications

Duty et al., examined 25 cases of alleged medical malpractice due to endourological procedures. They reported that 16 (64%) cases experienced complications leading to further operations, and six (24%) died due to sepsis.[2] Kahan et al., reported that postoperative complications developed in 39% of urological cases.[16] In a study using the "PubMed" and "Educus" databases, 6.2% of the claims were due to complications.[4] In the study of Gaither et al., two of the 53 cases had medical malpractice claims due to postoperative complications.[18] In the analysis of 469 cases with indemnity payment in the USA, it was stated that complications developed after surgery in 101 patients, and the most common cause of malpractice claims was the development of postoperative complications in these cases.[25] In this study, complications developed in 20 (20.8%) cases.

Surgical Treatment

In the study of Duty et al., 23 (92%) of 25 cases had a history of surgical procedures.[2] In the study of Kahan et al., surgical operations were performed in 135 (52.1%) of 259 cases.[16] In a study conducted in England, 260 (52.7%) of 493 cases were closed with indemnity payments complained about surgical intervention.[26] In this study, surgical treatment was applied to more than half of the cases (n:68, 70.8%), corresponding with the literature.

Diagnosis

A diagnostic error was found in 75 of 469 cases where medical malpractice was claimed due to missed or delayed diagnosis in New York. Of these 75 diagnostic errors, 58 were made in urological diagnoses, and 17 were made in non-urological diagnoses. Of the 58 missed urological diagnoses, there were 34 malignancy, seven testicular torsions, two urinary system stone disease, two bladder perforations, and one each had kidney injury, urethral stricture, foreign body, undescended testis, renal abscess, and gangrenous testis.[14] In a survey study, 28% of 683 physicians were accused of medical malpractice in urological oncology, 12% in endourology, and 10% in female urology.[5] In the study of Duty et al., 22 of the 25 cases had urinary stone diseases, and the remaining three (12%) had ureteral obstructions.[2] In the study of Kahan et al., 30 (22.2%) of 259 cases underwent endoscopic procedures, 20 (14.8%) orchiectomy, 16 (11.8%) penile prosthesis, 12 (8.9%) nephrectomy, nine (6.7%) prostatectomy, seven (5.2%) circumcision, and four (2.9%) bladder sling surgery.[16] In the study of Osman et al., with 493 cases, the most common cause of plaints of operations were TURP (Transurethral resection of the prostate) in 30 patients, nephrectomy in 26 cases, ureteroscopy in 23 cases, ureteral stents in 22 cases, vasectomy in 19 cases, and urethral catheterization in 15 cases.[26] The most common diagnoses in this study were; 20 (20.8%) cases with urinary system stone disease, 16 (16.7%) cases with benign prostatic hyperplasia, and 13 (13.5%) cases with urinary system malignancies.

Reason of Complaint

In a study of 522 cases with ureteral injuries were examined; there were 474 (90.8%) intraoperative neglect, 110 (21.1%) postoperative neglect, 68 (13.0%) inadequate preparation claims.[13] Duty et al., reported that 17 of 25 patients for whom indemnity was paid were due to improper surgical technique, four due to failure to organize follow-up, two for delay in treatment, one for failure to diagnose, and one for improper patient contact.[2] In the study of Stimson et al., it was reported that 40% of the complaints were about care and treatment, 24% lack of communication, 22% accessibility, 10% patient and family concerns, 5% billing.[27] In the study of Awad et al., in urethral catheter-related cases, 14 (48%) cases complained of traumatic insertion, eight (28%) removal, three (10%) mechanical failure, three (10%) lack of consent, one (3%) non-sterile insertion.[19] In the study conducted by Sunaryo et al. on cases with penile prostheses, the surgical technique was inadequate in 20 (48.8) cases, seven (17.1%) cases had diagnosis and treatment errors, five (12.2%) cases had surgical complications, three (7.3%) cases had errors in prosthesis removal, two (4.9%) cases had device failure, two (%4.9) cases lack informed consent, one (2.4%) case had inflated foley catheter removal, and one (2.4%) case had contraindicated prescription of the device.[17] In a study conducted among obstetricians, the most common claims were lack of care (47.5%), treatment delay (13.1%), diagnostic error (12.5%), and improper treatment (11.4%) (20). In this study, there were claims of lack of care in 22 (22.9%) cases, improper treatment in 19 (19.8%), and treatment delay in 11 (11.5%) cases (**Table 1**).

Malpractice Rate

In a study conducted with urologists, only 3.5% of the cases closed in favor of the complainants, 13.2% of the accused physicians, 46.9% rejected or dropped without a trial, 36.3% closed via mediation in pretrial phases.[5] It has been reported that 66% of urethral catheter-related medical malpractice

cases were ended with a verdict favoring the defendant, 28% favoring the plaintiff, and mediation was reached in 7% of them.[19] In a study on penile prosthesis cases, a verdict favoring defendants was achieved in 23 (57.5%) cases and the plaintiffs in 17 (42.5%) cases.[17] In a study of medical malpractice claims directed to urologists between 1985 and 2007 conducted in Chicago, only 29.41% of 5577 cases resulted in indemnity payments.[3] A study conducted with cases of medical malpractice claims related to endourological operations determined that 23% (n:137) of 585 allegations closed with indemnity payments. The same study determined that indemnity payments were made in 10 (40%) of 25 cases associated with endourological operations.[2] In this study, only 16.7% of the cases were reported as medical malpractice by the committee. This shows that 83.3% of malpractice claims in urology are filed without a just claim. Medical malpractice allegation lawsuits are very lengthy trials. Malpractice laws are needed to prevent unjust claims due to their adverse effects on the physician.

Reason of Malpractice

Badger et al. found that 75 out of 469 cases (16%) of missed diagnoses claims were closed with indemnity payments.[14] In their study of 5,557 cases, Benson et al. found improper performance in 36%, diagnostic error in 15%, and lack of supervision or monitorization in 5.6% of the cases.[3] In the United States between 2003 and 2012, indemnities for urological medical malpractice were frequently paid due to misdiagnoses, improper performances, failure in the follow-up, and failure of the complication management.[4] In the study of Osman and Collins, which included urological cases that ended with indemnity, the most common non-operative claim was the failure of cancer diagnosis/treatment (n: 69), the most common intraoperative complaint was perforation/organ injury (n: 38), the most common postoperative claim was forgotten ureteral stent (n:23).[26] In the study of Perrotti et al. in 469 cases, it was reported that compensation was paid due to postoperative events in 101 cases, surgical negligence or perforation in 96 cases, misdiagnosis in 60 cases, medication errors in 21 cases, and forgotten foreign body in 20 cases.[25] This study determined that malpractice was decided most frequently by the committee due to lack of treatment (n:6, 37.5%) and lack of the necessary laboratory test and radiological examination (n:5, 31%) (**Table 3**).

Limitations: In this study, we only could evaluate the claims of medical malpractice that resulted in death. Therefore, all types of medical malpractice could not be represented. In addition, The Council of Forensic Medicine, where the study was conducted, is only an expertise institution and is not the final decision-maker. Judges may request another expert appraisal. The fact that the final decision and the amount of indemnity payment could not be reached is another significant limitation of this study. However, our study focused on why physicians were accused of medical malpractice rather than why malpractice judgment was made.

CONCLUSION

No-fault was attributed to 83.3% of the accused urologists in our study. Most medical malpractice claims, which are increasing day by day, are concluded in favor of physicians. Physicians are often accused of unjust claims. We showed that the relatives of the patients most frequently claimed lack of attention (22.9%). In addition, we determined that the most common fault was attributed to the physician by the committee due to lack of treatment and workup. We think that a comprehensive examination of the cases with medical malpractice claims will contribute to a better understanding of these cases, reduce possible future claims, and thus improve the health service offered and public health.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the Scientific Academic Committee of the Council of Forensic Medicine, dated 15.12.2015, and numbered 971.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Note: This study was presented as an oral presentation at the 2nd International 18th National Congress of Forensic Science

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1039032
J Contemp Med 2022;12(3):437-443

Original Article / Orijinal Araştırma

Treatment of Peripheral Nerve Injury with Tension Stitch Method: an Experimental Study

Gergi Dikişi Yöntemi ile Periferik Sinir Yaralanmalarının Tedavisi: Deneysel Bir Çalışma

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Abstract

Objective: The aim of our study is to examine the tension stitch method we use to prevent unwanted tissue deficiency between the cut nerve endings in rats that will be kept waiting for secondary neurorrhaphy.

Material and Method: 30 male Wistar Albino rats were randomly divided into three groups. The right sciatic nerve was released proximally from the sciatic nerve 1/3 bifurcation area in the first and second groups and anastomosed with the tibial nerve in the third group. After 4 weeks, the region was reopened, unhealthy nerve endings were cut under the microscope, and secondary neurorrhaphy was performed end-to-end.

Results: In the third experimental group, it was observed that there was no change in the position of the tension stitches placed on the distal and proximal ends of the sciatic nerve, and the nerve endings adhered to the area where they were positioned by suture. At the eighth week, it was observed that the rats that could not use their right lower extremities in the preoperative and early postoperative periods used their extremities more actively. At the twelfth week, it was observed that the rats in all groups had complete recovery of trophic disturbances and the animals started to walk better visually.

Conclusion: In our study, the electrophysiological and histopathological data obtained at the eighth week and obtained at the twelfth week were significantly better in the tension-stitched group compared to the other groups, indicating that the best early and late nerve healing was in this group.

Keywords: Neurorrhaphy, tension stitch, nerve healing, end-to-end

Öz

Amaç: Çalışmamızın amacı sekonder nörorafi için bekletilecek ratlarda kesilen sinir uçları arasındaki istenmeyen doku eksikliğini önlemek için kullandığımız gergi dikiş yöntemini incelemektir.

Gereç ve Yöntem: 30 adet erkek Wistar Albino rat randomize olarak üç gruba ayrıldı. Sağ siyatik sinir, birinci ve ikinci grupta siyatik sinirin 1/3 bifurkasyon alanından proksimalde serbest bırakılırken, üçüncü grupta tibial sinir ile anastomoz yapıldı. Dört hafta sonra bölge yeniden açıldı, mikroskop altında sağlıksız sinir uçları kesildi ve uçtan uca sekonder nörorafi yapıldı.

Bulgular: Üçüncü deney grubunda siyatik sinirin distal ve proksimal uçlarına konulan gergi dikişlerinin pozisyonunda herhangi bir değişiklik olmadığı, sinir uçlarının sütür ile yerleştirildiği bölgeye yapıştığı gözlendi. Sekizinci haftada ameliyat öncesi ve ameliyat sonrası erken dönemde sağ alt ekstremitesini kullanamayan ratların ekstremitelerini daha aktif kullandıkları görüldü. On ikinci haftada tüm gruplardaki ratlarda trofik bozuklukların tamamen düzeldiği ve hayvanların görsel olarak daha iyi yürümeye başladıkları görüldü.

Sonuç: Çalışmamızda sekizinci ve on ikinci haftada elde edilen elektrofizyolojik ve histopatolojik veriler gergi dikişli grupta diğer gruplara göre anlamlı olarak daha iyiydi, bu da en iyi erken ve geç sinir iyileşmesinin bu grupta olduğunu göstermektedir.

Anahtar Kelimeler: Nörorafi, gergi dikişi, sinir iyileşmesi, uçtan uca

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Received *(Geliş Tarihi)*: 07.01.2022 **Accepted *(Kabul Tarihi)*:** 05.05.2022

INTRODUCTION

Traumatic injury, congenital anomalies and tumor destruction are among the situations that can cause peripheral nerve injury with serious consequences on quality of life. Since 1964, it has been clearly demonstrated that the outcome of epineural anastomosis under magnification is better than operative corrections,[1,2] which made microsurgical end-to-end (ETE) neurorrhaphy the gold standard for nerve repair;[3] however, in cases of extensive or long-standing injuries, ETE nerve repair is nigh impossible. Other repair methods, such as nerve grafting, nerve transfer and direct neurotization, have been used as alternative procedures.[4,5]

The mainstay of end-to-end nerve coaptation is to repair an injured nerve by borrowing axons from an intact donor nerve without damaging its function. Although it has been reported for a long time that end-to-end neurorrhaphy attracts axonal sprouts without damaging the donor nerve function,[6-11] its functional results remain unclear. Despite an increasing number of studies, quantitative research assessing this topic is limited and evidence is scarce concerning the early and late impacts on donor nerves.[12] As the potential role of end-to-end nerve coaptation remains controversial, various authors have discussed the theoretical foundations for applying the method in the clinical setting.[13-15]

The gold standard treatment for peripheral nerve repair is autologous nerve grafting with the aid of a surgical microscope. Although this technique procures positive outcomes, there are some disadvantageous factors associated with the procedure, including limitation of the caliber, length and area of the donor nerves, and the likelihood of secondary morbidity.[16-18] In this sense, the tubularization technique has been shown to be an appropriate and alternative method in clinical practice, which is a method performed by fixing and directing a tubular segment (of biological or synthetic origin) between the stumps of the injured nerve.[19,20]

The aim of our study was to examine the tension stitch method which we use to prevent unwanted tissue deficiency between the cut nerve endings, by utilizing a rat model with delayed application of secondary neurorrhaphy.

MATERIAL AND METHOD

Thirty male young adult Wistar Albino rats weighing 223-300 g were randomly divided into three experimental groups. The animals were allowed ad libitum access to standard rodent chow and tap water. The living conditions were: temperature was kept at 22±2 °C, humidity was 50±10 %, and the day-night cycle was automated with lights on from 06:00 to 18:00. There were no cases of wound infection during the experiment. In this research, the data before 2020 was used and the research was concluded before 2020. This study was prepared in accordance with the 2013 Brazil revision of the Helsinki Declaration and guidelines for Good Clinical Practice. Ethics committee approval was not obtained because there was no ethical committee approval obligation at the time of the study (1998).

The rats were randomized into three groups (1, 2 and 3). Anesthesia was applied with 5 µg/kg medetomidine hydrochloride (Domitor, Orion Oyj, Espoo, Finland) and 750 µg/kg ketamine hydrochloride (Ketalar, Pfizer Oy, Helsinki, Finland) before operations. In groups 1 and 2, the right sciatic nerve was cut at the 1/3 bifurcation site and released (**Figure 1**). In group 3, the right sciatic nerve was cut in the same fashion and each end was turned and fixed with consecutive 10-0 sutures (Nylon, S&T AG, Neuhausen, Switzerland) onto surrounding muscles to prevent re-innervation (**Figure 2**).

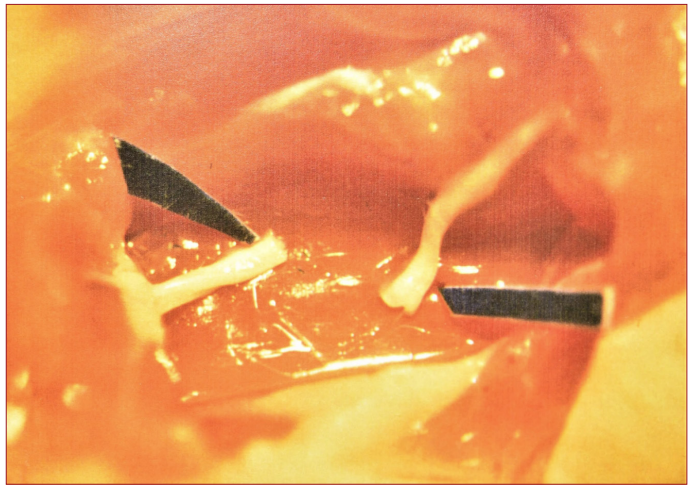

Figure 1. Cutting and releasing the sciatic nerve in the first and second groups

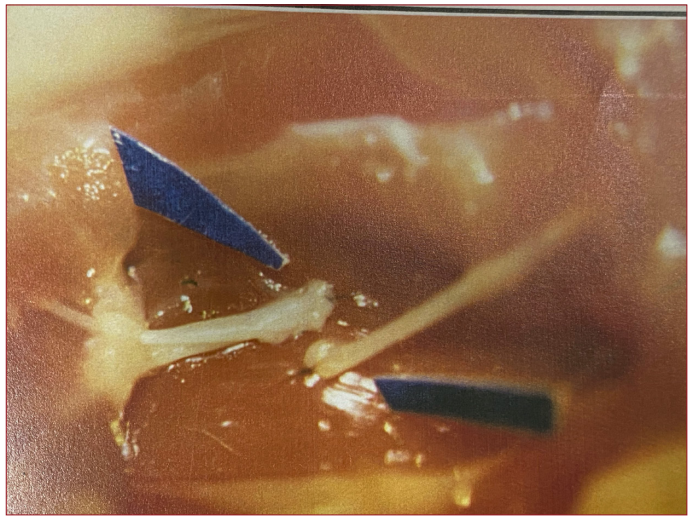

Figure 2. In the third group, the sciatic nerve is cut and sutured to the surrounding muscle fascia.

In all animals, the muscle layer and skin were closed with respect to anatomical layers with 5-0 absorbable sutures (Bondek Plus, Deknatel, TFX Medical Ltd., High Wycombe, UK). In all animals, the muscle layer and skin were closed with respect to anatomical layers with 5-0 absorbable sutures (Bondek Plus, Deknatel, TFX Medical Ltd., High Wycombe, UK) after each procedure. After 4 weeks, the region was reopened, unhealthy nerve endings were cut under the microscope, and secondary neurorrhaphy was performed end-to-end.

In group 1, secondary neurorrhaphy was applied under the present tension without grafting. In group 2, a Wild M3Z microscope (Wild Leitz Ltd., Heerbrugg, Switzerland) was used for secondary neurorrhaphy without grafting which was performed with grafting. In group 3, primary neurorrhaphy was applied although both nerve edges appeared to be healthy, they were renewed minimally. At the eighth and twelfth weeks after initial intervention, the right sciatic nerves of the rats were evaluated electrophysiologically and histopathologically in groups of five.

Perioperatively, animals were injected subcutaneously with 5 ml sodium chloride 9 mg/ml (Fresenius Kabi AB, Uppsala, Sverige) to maintain fluid balance. The animals were given a subcutaneous injection of 5 mg / kg carprofen (Rimadyl, Vericode Ltd., Dundee, UK) as an analgesic drug for three postoperative days.

Finally, animals were sacrificed by an overdose of ketamine hydrochloride (Dopalen®) and Xylazine Hydrochloride (Antisedan®) at postoperative week 12, and tissues were obtained, including the soleus (SO) and extensor digitorum longus (EDL) muscles.

Histological and Electrophysiological Examination

The SO and EDL muscle samples were reduced to cylindrical pieces after resection and the Optimal Critical Temperature Tissue-Tek® gel (OCT, Sakura Finetek, Torrance, USA) was used for the subsequent snap-freezing via immersion in liquid nitrogen. All frozen samples were stored at -80 °C until analysis. Histological sections were obtained at -20 °C in a Leica cryostat - Model CM 1850 and stained with Hematoxylin and Eosin (HE) and Masson's trichrome for morphometric analysis. Bioscience 10550 Kymograph, stimulator, Polygraph, Pentium 75 computer, and electrodes were used for electrophysiological examination.

Morphometric Analysis

Cross sectional area and minimum diameter: Images were taken with an Olympus BX 50, a photomicroscope connected to a computer, and three different areas of each sample were photographed with a 20X objective. For morphometric analysis, 220 muscle fibers of each animal were manually measured via the Image Pro-Plus® 6.2 program (Media Cybernetics, Bethesda, MD, USA); in addition, area and minimum diameter were measured.

Connective tissue density: Using Masson's trichrome staining, a photograph of the transverse cross-sectional area of the entire muscle was taken using a 2X lens to measure total area, and then a 20X lens was used to obtain an image for the ProPlus® 6.2 software, in order for it to recognize Aniline Blue. After the measurements, the percentage of connective tissue in the muscle was calculated.

This study was produced from Dr. Ali Sakinsel's Specialization Thesis in Plastic and Reconstructive Surgery numbered 70646, which was presented and approved at Istanbul Şişli Hamidiye Etfal Training and Research Hospital / Department of Plastic and Reconstructive Surgery in 1998 (thesis title: Evaluation of neurorrhaphy results with and without tension suture in secondary nerve repairs)

Statistical Analysis

For statistical analysis of muscle weight, muscle fiber morphometry, connective tissue morphometry and functional index, groups were compared with analysis of variance (ANOVA), and if this analysis detected a significant difference, the Tukey test was used for pairwise comparisons. A P-value of ≤0.05 was considered to demonstrate statistical significance.

RESULTS

During the four-week period from the dissection of the right sciatic nerves of the rats to the nerve repairs, the right leg and feet of the rats were examined. Four rats in the first group, five in the second group and five in the third group had ulcers on their right feet. There were various degrees of trophic disturbances in the lower extremities of all rats, and it was observed that they could not use their right lower extremities adequately while walking (**Figure 3**). Surgical wounds in the incision sites healed without complications within 10 to 15 days in all animals. Fibrosis, lymphocytic infiltration, and regeneration are graded up to 3 points. Besides myelination is percent according to the first-order state.

Figure 3. Trophic disturbance in the right extremities of rats.

In the first and second groups, where the free nerve endings were retracted in the distal and proximal directions, it was found that these released nerve endings had adhered to the surrounding muscles and fascia. The distal part of the nerve was thinner and more fibrotic than the proximal part. The nerve endings were further separated from each other compared to the initial state, with around 5–6 mm of distance. In the examination of both groups, while neuroma was found in one rat in the first group, the surrounding muscle tissues were healthy.

In the third experimental group, it was observed that there was no change in the position of the tension stitches placed on the

distal and proximal ends of the sciatic nerve, and the nerve endings adhered to the area where they were positioned by suture. In this group, the distal nerve section was thinner and more fibrotic than proximal. In this group, the distance between nerve endings remained within acceptable levels, with around 1-2 mm of gap. Neuroma was observed in one rat in this group.

Findings in Eighth and Twelfth Weeks After Repair

In the eighth week, in the first group, it was found that the ulcers which had developed in four animals had healed in three of them. In the second group, all of the ulcers (five animals) had healed. In the third group, leg ulcers present in five animals had healed in four, while the remaining rat suffered from a loss of about 1/3 of the distal tip of the right foot. It was observed that the rats, which could not use their right lower extremities in the preoperative and early postoperative periods, were able to use their extremities more actively in the eighth week. By the twelfth week, it was observed that all rats had complete recovery of trophic disturbances and their gait had considerably improved. Average histopathological evaluation results of the groups at the eighth and twelfth weeks are shown in **Table 1**.

Table 1. Average histopathological evaluation results of the groups at the eighth and twelfth weeks.

Groups	Fibrosis	Myelination	Lymphocytic Infiltration	Regeneration
Group 1	3+ \3+	50%\56%	3+ \3+	1+ \1+
Group 2	2+ \3+	67%\74%	2+ \2+	2+ \2+
Group 3	1+ \1+	85%\95%	1+ \1+	3+ \3+

Electrophysiological Results

Electrophysiological analyses were performed at the eighth and twelfth postoperative weeks. The first group has a higher score than the third groups and the second group has a higher score than the third groups for OELD and OGLD($p<.001$ and $p<.001$) also the third group has higher than the second and the second group higher than the first group amplitude($P<0.001$). In the first group, lymphocytic response prominence, edema and the presence of sparse Schwann cells were noted, and there was intense fibrosis in the sections. Distal myelination and regeneration were limited, and the myelinated fibers were found to be irregular (**Figure 4a**). In the second group, it was observed that fibrosis and lymphocytic infiltration were moderate, but edema was prominent especially in the graft. Myelination and regeneration were moderate, and the irregularity of myelinated fibers was noted (**Figure 4b**). In the third group, fibrosis and lymphocytic infiltration were relatively less prominent compared to the other groups, and myelination and regeneration were better. Schwann cells increased compared to other groups, and plasma cells had appeared. Additionally, there was a good level of vascularization (**Figure 4c**). Average electrophysiological evaluation results of the groups are shown in **Table 2**.

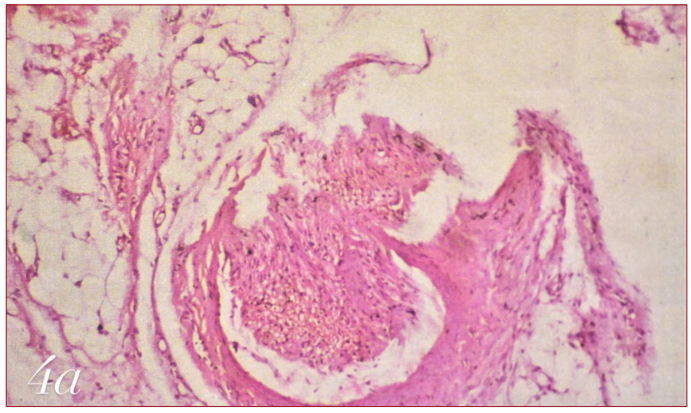

Figure 4a. The appearance of weak myelination and excessive fibrosis in the sample taken from the distal of the sciatic nerve at the eighth week of the first group. (H.E X 125).

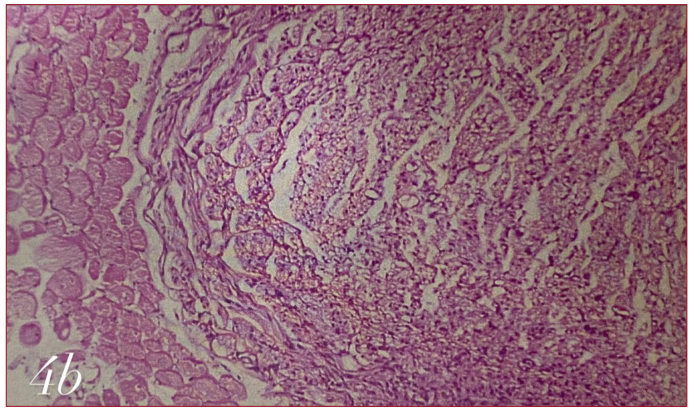

Figure 4b. Moderate myelination and fibrosis appearance in the sample taken from the distal of the sciatic nerve at the eighth week of the second group. (H.E X 125)

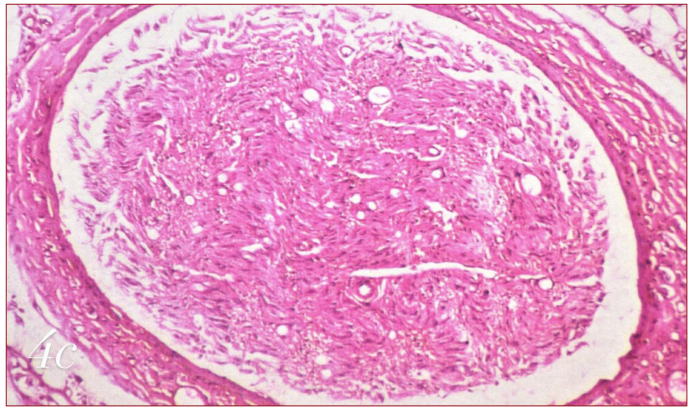

Figure 4c. Good degree of myelination and less fibrosis in the sample taken from the distal of the sciatic nerve at the eighth week of the third group. (H.E X 125)

Table 2. Average electrophysiological evaluation results of the groups.

Groups	Early Latent Period (ms)	Late Latent Period (ms)	Amplitude (mV)
Group 1	4.4\3.6	8.2\8	33.7\41.7
Group 2	4\3.4	8 \ 7.4	36.5\42.5
Group 3	2.6 \2.2	2.6\5.2	44.8\54.1

DISCUSSION

The aim of our study was to determine whether tissue deficiency occurring between the injury (nerve cut) and application of secondary neurorrhaphy can be prevented by the tension stitch method in rats, and to assess the histological and electrophysiological results of this approach in order to determine whether it can provide better results in terms of nerve healing and functions compared to alternative applications in nerve tissue deficiency.

As a result of experimental and clinical studies, the superiority of primary nerve repair over secondary repair is considered indisputable.[21,22] However, in cases where primary repair cannot be applied, secondary nerve repair is required. The problem encountered in secondary repairs is the fact that it is exceedingly difficult to prevent deterioration in the nerve tissue. According to Dellon et al. the reason for this problem is associated with the excision of the damaged nerve section and the shortening caused by elastic and fibrotic retraction.[23]

The main purpose in secondary repair is to obtain acceptable axonal regeneration extending to the target organ by eliminating the deficiency in the nerve tissue.[22,24,25] Especially in high energy nerve traumas, nerve damage might continue for several weeks at cellular level. Consequently, before final nerve repair, waiting until the demarcation line becomes apparent is crucial. For this purpose, some treatment methods have been developed. Various methods, such as bone shortening, transferring the nerve into a new bed, tense repair or adding new tissue into the gap, have been proposed.[22,26] The use of surgical microscopy and the appropriate selection of sutures and tools in has increased success in grafting techniques.[25,27] However, bone shortening is not used in neurosurgery except for amputations. Additionally, releasing the nerve from large areas and transferring it into a new bed is still a controversial method because of its limited use and the possibility of encountering supply problems in the nerve tissue.[23,28]

It is therefore important to apply measures that can favor the injured nerve during the time that will surpass until secondary nerve repair. Finding ways to prevent the shortening of tissue (due to elastic retraction) and the loss of nerve shifting ability (due to fibrosis) are crucial steps in treatment.[23,27] In our study, we used the tension stitch technique to prevent the cut nerve endings from retracting back from their position and to prevent the nerve tissue deterioration. We found that there was no tension during the repair in rats whose nerve length shortening was prevented by elastic retraction using the tension stitch technique (group 3). In the repair of free nerve endings of rats in the first and second groups, the length of the nerve endings that retreated with elastic retraction was shortened. The shear and stretching properties of the nerve endings were also reduced due to fibrosis developing in the surrounding and nerve tissue. Trehan et al. reported in their article that elastic retraction and fibrosis led to deficiency in nerve tissue and caused tension in secondary repairs.[24]

In our study, we divided the rats to be repaired four weeks after their sciatic nerves were cut into three groups according to the repair methods and the current tension. In the first and second groups, we saw that the presence of around 5-6 mm deficiency caused serious tension. We repaired the first group under present tension, and the second group with graft in order to remove the tension. In the third group, where tension stitch was applied, we observed around 1-2 mm deficiency – which did not create tension.

In the first group of rats in our study, the histopathological studies performed at the eighth week showed that distal myelination was low (50%), regeneration was poor, and fibrosis was intense. In the twelfth week, it was found that the present findings did not change much and the distal myelination reached 56%. Additionally, suture granulomas, which we attributed to foreign body reaction and tension, were added to the picture. In the comparative analysis of histopathological data with the other groups, it was seen that all data showing nerve healing (except for fibrosis) were significantly worse compared to other groups at the twelfth week.

In their systematic examination, Trehan et al. stated that, in injuries with nerve repair under severe tension, excessive fibrosis will occur in the suture line and axonal passage to the distal part will be prevented.[24] Our histopathological findings in the first group were consistent with Trehan et al.'s findings. In electrophysiological studies performed in the eighth and twelfth weeks, we found that the first group had lower amplitude and longer latent periods compared to the third group. As stated by Buena et al. and other researchers, the increase in amplitude and shortening of the latent period is a parameter that reflects nerve fiber thickness and the state of excitable myelinated neural elements.[25,29,30] Electrophysiological findings in the first group were worse compared to the third group in terms of both myelination and nerve regeneration. The histopathological data of the second group, which was repaired without tension (using a graft), also indicated worse results compared to the third group–in which the tension stitch method had been applied. We attributed this to the excessive amount of fibrosis and the inability of regenerated axons to pass completely from the two neurorrhaphy lines to the distal nerve section.

Murphy et al. reported that the most common problem in nerve grafting is the application of repair in two regions of the nerve tissue and the necessity of crossing the regenerated axons from two lines (instead of one) which will facilitate fibrosis and might block axonal regeneration.[31] The second group in our study had worse results compared to the third group, and, in the light of the available histopathological data, we attributed this result to the excessive amount of fibrosis and the presence of two neurorrhaphy lines. When the electrophysiological data of this group in the eighth and twelfth weeks were compared with the third group, it was found that amplitude was significantly lower and the latent periods were significantly longer, indicating worse function

in the second group. Increase in amplitude and shortening of the latent period are parameters that are accepted to reflect nerve fiber thickness and the state of excitable myelinated neural elements.[29,30] These findings show that the recovery of nervous tissue in the third group of rats, which were repaired without tension and had a single suture line, was better than the other groups. It is important to reiterate that, at the end of the fourth week, there was a nerve tissue deficiency of approximately 5–6 mm in the first and second groups of rats; whereas this deficiency was around 1–2 mm in the third group. It was observed that the trophic disturbances in rats until the fourth week improved over time after the repair in all subjects. At the eighth and twelfth weeks, the electrophysiological and histopathological data of the rats were compared. Histopathological data revealed that the third group had better myelination, better regeneration, less lymphocytic infiltration and less fibrosis than the other groups. Electrophysiological data of the group showed that it had higher amplitude and shorter latent periods.

As the reason for these findings, we determined that the tense repair in the first group increased connective tissue proliferation and caused excessive fibrosis; therefore, resulting in blockage of axonal passage to the distal nerve section. In the second group, the presence of fibrosis and double neurorrhaphy lines, although this group was repaired without tension, lead to worse nerve healing than the third group. Of note, late occurrence of fibrosis in the second group (compared to the first group) did not prevent axonal transition from the proximal to the distal nerve section in the eighth week, and the second group provided a greater degree of improvement compared to the first group. In the literature, there are many studies that show stem cell based therapies may enhance nerve healing by decreasing fibrosis and by secreting nerve stimulating growth factors.[32,33] These new modalities have some ethical considerations in humans and are highly expensive.

Histopathological and electrophysiological data of the third group of rats were significantly better than other groups, indicating that the best nerve healing was achieved in group 3. The deficiency between the ends after the nerve cuts is the most common and difficult problem to solve in secondary neurorrhaphy. However, we have seen that the tension stitch method is able to reduce this deficiency and can positively affect nerve healing by preventing tension during repair.

CONCLUSION

The electrophysiological and histopathological data obtained in the eighth and twelfth weeks of our study were significantly better in the tension-stitched group compared to the other groups, indicating that nerve healing can be increased with this approach when performing secondary neurorrhaphy.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was not obtained because there was no ethical committee approval obligation at the time of the study.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1054683
J Contemp Med 2022;12(3):444-448

Original Article / Orijinal Araştırma

Evaluation of Preliminary Results Of Laparoscopic and Open Surgery in Gastrectomy For Gastric Cancer: Single-Center Experience

Mide Kanseri İçin Yapılan Gastrektomide Laparoskopik ve Açık Cerrahinin Erken Sonuçlarının Değerlendirilmesi: Tek Merkez Deneyimi

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Abstract

Aim: This study aims to compare the early results of laparoscopic and open surgery of gastric cancer, which is the sixth most common cancer in all age groups and both genders.

Material and Method: Patients who were diagnosed with locally advanced gastric cancer and operated on between May 2018 and October 2021 were retrospectively screened. The data of patients who underwent laparoscopic and open surgery were collected and short-term results were compared.

Results: The results of 140 patients included in the study were analyzed. In laparoscopic surgery, the length of stay in the intensive care unit was shorter and the number of lymph nodes removed was found to be higher. Length of hospital stay and postoperative complications were similar. The operation time was longer in laparoscopic surgeries.

Conclusion: Considering the results of this study, in which we compared our short-term results, we can predict that laparoscopic gastric resection can be safely performed by experienced surgeons in appropriate centers. As surgical experience increases, we believe that laparoscopy, which is the gold standard in surgeries such as gallbladder, appendectomy, and prostatectomy, may become the gold standard in gastric cancer surgery in the future.

Keywords: Gastric cancer, laparoscopic surgery, preliminary results

Öz

Amaç: Bu çalışmamızın amacı tüm yaş gruplarında ve her iki cinsiyette en sık görülen altıncı kanser olan mide kanserinin, laparoskopik ve açık cerrahi erken sonuçlarının karşılaştırılmasıdır.

Gereç ve Yöntem: Mayıs 2018-Ekim 2021 tarihleri arasında lokal ileri mide kanseri tanısı alan ve ameliyat edilen hastalar geriye dönük olarak tarandı. Laparoskopik ve açık cerrahi uygulanan hastaların verileri toplandı ve kısa dönem sonuçları karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen 140 hastanın sonuçları incelendi. Laparoskopik cerrahide yoğun bakımda kalma süresi daha az ve çıkarılan lenf nodu sayıları daha fazla olarak bulundu. Hastanede yatış süresi ve postoperatif komplikasyonlar benzerdi. Operasyon süresi laparoskopik cerrahilerde daha uzundu.

Sonuç: Kısa dönem sonuçlarımızı karşılaştırdığımız bu çalışmanın sonuçlarına bakıldığında, laparoskopik gastrik rezeksiyonun deneyimli cerrahlar tarafından uygun merkezlerde güvenle yapılabileceğini öngörebiliriz. Cerrahi deneyim arttıkça safra kesesi, apendektomi, prostatektomi gibi ameliyatlarda altın standart olan laproskopinin ilerleyen dönemlerde gastrik kanser cerrahisinde de altın standart olabileceği kanaatindeyiz.

Anahtar Sözcükler: Mide kanseri, laparoskopik cerrahi, erken dönem sonuç

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Received *(Geliş Tarihi)*: 07.01.2022 **Accepted *(Kabul Tarihi)*:** 05.05.2022

INTRODUCTION

The sixth most common cancer in the world, gastric cancer affects people of all ages and genders. It is also the fourth leading cause of death from cancer.[1] Despite recent medical advances, the risk of developing gastric cancer rises as one gets older, as life expectancy rises in most countries.[2,3] Total and distal gastrectomy with D2 lymph node dissection is the recommended surgical procedure for patients with resectable (curable) gastric cancer (GC).[4] Until Kitano et al.[5] conducted a laparoscopic gastrectomy (LG) for early-stage gastric cancer(EGC) in 1994, conventional open gastrectomy (OG) was the usual surgical treatment for gastric cancer. Widespread use of laparoscopic gastric surgery (LGS) over the past decade has been shown to improve better short-term outcomes and quality of life compared to standard techniques.[6] It has gained acceptance as a viable alternative to EGC management, particularly in Japan and Korea.[6,7]

According to studies evaluating the early and long-term results of the LG technique applied in EGC, it has been shown that minimally invasive gastrectomy procedures have faster postoperative recovery, shorter hospital stay, fewer postoperative complications, less intraoperative blood loss, and similar oncological results compared to OG.[8-11]

The application of laparoscopic procedures in advanced gastric cancers (AGC) is more difficult due to the wide lymph node dissection area. This problem has been resolved with the increase in the experience of laparoscopic surgeons.[9,10,13,14]

There was no significant difference in disease-free survival and overall survival rates in recent prospective randomized clinical studies.[9,14-16] However, laparoscopic surgeries have disadvantages such as a long learning curve, higher costs, and longer operations compared to open surgeries.[17]

The purpose of this study was to add to the literature by comparing the short-term postoperative clinical findings after LG and AG procedures conducted at our center.

MATERIAL AND METHOD

After obtaining the approval of the ethics committee of Hitit University non-interventional studies (date: 09/11/2021, no: 2021-81), patients who were diagnosed with locally advanced gastric cancer and operated on between May 2018 and October 2021 were retrospectively screened. The study comprised a total of 147 individuals with locally advanced gastric cancer. All patients were diagnosed with gastric cancer histopathologically by preoperative endoscopic biopsy. Oral and intravenous contrast-enhanced thoracic and abdominal computed tomography was performed on all patients to determine the extent of the disease. Diagnostic examination with endoscopic ultrasound and PET-CT was performed in selected patients. The study was carried out by the Declaration of Helsinki Principles. An informed consent form was approved by all individuals included in the study.

Patients aged 18-75 years were analyzed according to demographic findings and preoperative clinical findings. These findings included gender, age, American Association of Anesthesiologists (ASA) score, pathological tumor size-lymph node metastasis-metastasis (pTNM) stage, tumor location, and histological differentiation. Exclusion criteria were endoscopic mucosal resection, endoscopic submucosal dissection, previous gastric surgery, presence of other malignant disease, complications such as bleeding, perforation, and obstruction caused by gastric cancer, and patients with metastasis according to preoperative imaging and intraoperative findings.

Gender, age, concomitant diseases, ASA scores, whether or not he received adjuvant therapy for gastric cancer, surgical techniques (laparoscopic/open surgery, total/distal gastrectomy), anastomosis type (intracorporeal, extracorporeal), operation time, intraoperative and postoperative complications, length of stay duration, tumor localization, and histological type, number of lymph nodes removed, pathology stage of the tumor were obtained from computer records and patient files.

Tumor localization was evaluated as upper, middle, and lower parts according to the Japanese gastric carcinoma classification (JCGC)(18). Intraoperative complications were classified as bleeding, vascular injury, and organ injuries. The Clavien-Dindo Classification (CDC) system was used to grade postoperative problems. Grades 1-2 were used to classify minor issues, and grades 3a-3b were used to classify serious complications (19).

Statistical Analysis

SPSS for Windows 22.0(IBM SPSS program, USA) program was used for statistical analysis. Age was given as mean±standard deviation and amount and percentage(%) from descriptive analyses. To see if the distribution between groups was normally distributed, the Kolmogorov-Smirnov test was utilized. The mean standard deviation (SD) or median (minimum-maximum) values were used to depict the continuous data. The Student t-test was used to compare parametric measurements, whereas the Mann-Whitney U test was used to examine non-parametric analyses. For categorical variables, the Chi-square test was utilized. Significant values were those with a P-value of 0.05 or less.

RESULTS

Between May 2018 and October 2021, 140 participants underwent gastric cancer surgery for the study. The patients' average age was 68.85±10.96 (min-max 36-95). Of the patients, 107 (76.4%) were male and 33 (23.6) were female. Of the operated patients, 115 were operated openly and 25 were operated laparoscopically (**Table 1**). Even as open total gastrectomy was performed in 70 patients (50%) and laparoscopic total gastrectomy was performed in 14 patients

(10%), open subtotal gastrectomy was performed in 45 patients (32.1%) and laparoscopic subtotal gastrectomy was performed in 11 patients (7.9%).

Table 1. Descriptive Analisis

	Total (n:140)	Open Surgery (n:115)	Laparoscopic Surgery (n:25)	p value
Age, year	68.85±10.96	69.1±10.9	67.6±10.9	0.558†
Sex (%)				
Female	33(23.6)	27	6	0.569†
Male	107(76.4)	88	19	
Hospital Stay, day, (min-max)	17.34(6-69)	16(6-69)	14(9-37)	0.205‡
Critical Care Stay, day, (min-max)	1.84(0-10)	1(0-10)	1(0-3)	<0.001‡
LN counts, SD	21.85(1-56)	20.67±10.7	27.2±5.7	0.004*
Metastatic Lenf node, (min-max)	6.28(0-44)	3(0-44)	2(0-19)	0.945‡
Operation Time, minute, SD (min-max)	191±69.1(79-400)	174.6±56.5	226.1±72.7	<0.001*
Blood Transfusion	1(0-6)	1(0-6)	1(0-2)	0.057‡

SD: Standard deviation; n: patient counts; LN: Lymph node; Met: Metastatic LN. *Student T-test, †Chi-Square test, ‡ Mann-Whitney U test, Statistically significant data bolded

There was no difference between open and laparoscopic surgical patients in terms of age, gender, length of stay, number of metastatic lymph nodes harvested, or transfusion replacement. The number of days spent in the intensive care unit was shown to be lower in the laparoscopic patient group. Furthermore, the number of lymph nodes removed in the laparoscopic surgery group was higher. In open surgery, the operation time was statistically shorter.

Afterward, patients who underwent Total Gastrectomy were compared openly and laparoscopically, and patients who underwent subtotal gastrectomy were compared by separating open and laparoscopic sickles. When all groups were examined, no difference was found in terms of age and gender (p: 0.585, p: 0.685, respectively). Also, there was no difference in terms of hospitalization day, blood transfusion, or metastatic LN counts (p:0.082, p:0.130, p:0.162, respectively).

In terms of hospitalization days in the intensive care unit, there was a statistical difference between the groups (p: 0.003). The reason for this disparity was the fact that total gastrectomy patients who underwent laparoscopic surgery spent less time in the intensive care unit (p: 0.006). In terms of hospitalization in the intensive care unit, there was no statistically significant difference between patients who had laparoscopic surgery and those who had a subtotal gastrectomy (p: 0.368).

When evaluated in terms of the number of lymph nodes removed, a difference was found between the groups (p:0.006). There was no difference in the number of lymph nodes in open or laparoscopic total gastrectomy. When the duration of the operation was examined, there was no difference between whether the operation was subtotal or total gastrectomy, but laparoscopic surgeries were completed in a statistically longer time (p<0.001)(**Table 2**).

In terms of complications, there was no statistical difference between laparoscopic and open surgery, nor between the subgroups (**Table 3**).

Table 2. Subgroup Analisis

	Open Surgery (n:115)		Laparoscopic Surgery(n:25)		p-value
	Total Gastrectomy	Subtotal Gastrectomy	Lap. Total Gastrectomy	Lap. Subtotal Gastrectomy	
Type of Surgery(%)	70(50)	45(32.1)	14(10)	11(7.9)	
Hospital Stay, day,(min-max)	15(7-49)	16(6-69)	16(11-37)	13(9-19)	0.082*
Critical Care Stay, day,(min-max)	1(1-10)	1(0-10)	1(0-1)	1(1-3)	0.003*
Lymph node, SD	22(1-56)	19(2-40)	27(17-39)	28(18-36)	0.006*
Metastatic Lenf node,(min-max)	4(0-44)	1(0-23)	1.5(0-16)	4(0-19)	0.162*
Operation Time, minute, SD(min-max)	169.5(80-390)	160(79-240)	297(180-400)	235(145-360)	<0.001*
Blood Transfusion	1(0-4)	1(0-6)	1(0-2)	1(1-2)	0.130*

*Kruskal-Wallis Test

Table 3. Clavien-Dindo Classification

Dindo-Clavien	Total Gastrectomy	Subtotal Gastrectomy	Lap. Total Gastrectomy	Lap. Subtotal Gastrectomy	Total
Grade I	31	6	13	2	52
Grade II	29	8	30	9	76
Grade IIIa	9	0	1	0	10
Grade IIIb	1	0	1	0	2
TOTAL	70	14	45	11	140

*Chi-Square test, p:0.542

DISCUSSION

This study shows that LG's postoperative stay in intensive care and lymphatic dissection performed by surgical oncological principles are more advantageous than OG. However, while the postoperative stay in the intensive care unit was shorter than in open surgeries, there was no significant difference in terms of length of stay, intraoperative and postoperative complications. The operative time was found to be longer in LG.

Laparoscopic procedures have been widely used by surgeons in recent years after increasing surgical experience and advances in technology. Especially compared to traditional procedures, widespread use of laparoscopic gastric surgery (LGS) has been demonstrated to improve short-term outcomes and quality of life.[6]

Because of the increased risk of locoregional recurrence induced by poor lymphadenectomy, the oncological safety of laparoscopic surgery in stomach cancer was questioned.[20] Many studies have found a link between the number of lymph nodes resected and long-term oncological outcomes in LG.[16,17] In the CLASS-1 randomized clinical study conducted by Hyung-Ho Kim et al.[17] they showed that when LG and OG were compared, equivalent surgical and pathological oncological efficacy was observed, the number of lymph nodes dissected, overall and cancer-specific survival was similar, and laparoscopic procedures were oncologically safe.

According to studies evaluating the early results of the LG technique applied in EGC, lower complication rate, faster recovery, and less postoperative pain were observed compared to OG.[8-11] In the CLASS2 multicenter randomized study conducted by Liu F. et al.[21] they attributed more severe complications in the LG group than the OG group to the surgeons' inexperience in laparoscopy. In the study of Zeng F. et al.[22] it was shown that patients lost less blood during the operation, developed fewer complications, required less analgesia, had an earlier oral intake, and had a shorter hospital stay compared to OG in LG. While there was no significant difference between LG and OG in terms of complications in our study, the day of hospitalization in the intensive care unit was significantly shorter in LG. The duration of surgery was significantly longer in LG than in OG.[12,21,22] Consistently, the operative time was found to be longer in LG. As experience increases in surgeries performed with laparoscopy, the duration of the operation can be shortened. By reducing the difference, laparoscopy can be made the gold standard treatment as in gallbladder and appendectomy surgeries.[23] Thus, better results can be obtained by using technological advantages instead of traditional surgical methods.

The limitations of the study are that it is primarily retrospective, the number of cases is relatively low, it is single-centered, and the long-term results are not comparable. Another limitation is related to the study; The fact that the length of stay of the patients in the intensive care unit is associated with comorbid diseases and this has not been examined by us. In this study, in which we aim to present our early results, we want to show that advanced laparoscopy operations can be performed by experienced surgeons outside of central hospitals and we want to share our prospective long-term results. Although the complication rates were the same, we could not compare the incisional hernia rates in open surgeries. However, in the studies, it is clear that incisional hernia rates are more common in open surgeries than in laparoscopic surgeries.[24]

CONCLUSION

As a result of our study, we aimed to present our early results after laparoscopic gastric cancer surgeries. As a result, we showed that LG has better early postoperative results compared to OG and that lymph node dissection can be performed by experienced surgeons with good results in small centers according to oncological principles. We believe that larger randomized controlled trials should be conducted for laparoscopic gastric cancer surgery to be the gold standard treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: After obtaining the approval of the ethics committee of Hitit University non-interventional studies (date: 09/11/2021, no: 2021-81)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1065721
J Contemp Med 2022;12(3):449-454

Original Article / Orijinal Araştırma

The Effects of Metformin on Hyperandrogenism and Menstrual Functions in Insulin Resistant Adolescents with PCOS

Adolesan Polikistik Over Sendromlu Hastalarda Metformin Tedavisinin Hiperandrojenizm ve Menstrual Fonksiyonlar Üzerine Etkisi

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Abstract

Aim: To investigate the effects of metformin therapy on hyperandrogenism and menstrual functions in adolescent patients with polycystic ovary syndrome (PCOS) and insulin resistance (IR).

Material and Method: This study was conducted with 50 adolescents with PCOS. Hormonal and ultrasonographic assessments were done at the early follicular phase. On the day of 19-21 of the cycle, progesterone levels were measured and patients were questioned for menstrual periods. Body-mass-indexes (BMI), waist-hip ratios, and Ferriman-Gallwey scores were calculated for all patients. IR is diagnosed according to HOMA index and insulin-resistant patients were instructed to use 1500 mg/day metformin for 3 months. After treatment, measurements were repeated by the same researcher.

Results: Mean age and BMI values were similar between groups. Although the values of BMI and waist/hip ratio decreased after treatment, the decrement didn't reach the values of the IR- group. Free testosterone levels were significantly higher in IR+ subjects compared to controls and decreased considerably after metformin. Sex hormone-binding globulin levels were increased with treatment and as a result, free androgen indexes were decreased. 17 OH progesterone levels were significantly higher in the IR+ group and regressed to similar levels with IR negatives with metformin. While mean levels of fasting insulin were 19.21 IU/ml in the IR+ group, it regressed to 13.14 IU/ml after treatment. Also fasting glucose/insulin ratios were increased as expected. Finally, a significant improvement in the treatment group was observed at menstrual irregularity.

Conclusion: Consequently, this study supports the conclusion that metformin reduces hyperandrogenism, regulates menstruation and improves ovulatory functions.

Keywords: Adolescent, polycystic ovary syndrome, insulin resistance, metformin

Öz

Amaç: Çalışmamızda insülin direnci olan adolesan polikistik over sendromlu hastalarda metformin tedavisinin hiperandrojenizm ve menstrual fonksiyonlar üzerine etkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışmamıza, polikistik over sendromlu 50 adolesan hasta dahil edildi. Erken foliküler fazda hormonal ve ultrasonografik değerlendirmeler yapıldı. Tüm hastaların vücut kitle indeksleri (VKİ), bel-kalça oranları ve Ferriman-Gallwey skorları hesaplandı. Hastalar menstrual fonksiyonlar açısından sorgulanıp ovulasyon tespiti için siklusun 19-21. günlerinde progesteron düzeyleri ölçüldü. HOMA indeksi kullanılarak insülin resistansı (IR) tanısı konulan hastalara 3 ay süreyle 1500 mg/gün metformin kullanması önerildi. Tedavi bitimi tüm ölçümler aynı araştırmacı tarafından tekrarlandı.

Bulgular: Gruplar arasında ortalama yaş ve VKİ açısından anlamlı fark yoktu. İnsülin rezistansı olan grubun bel çevresi kontrol grubuna göre fazla olup, tedavi sonrası kontrollerle benzer seviyelere inemediği gözlendi. Serbest testosteron seviyeleri, IR+ hastalarda IR negatiflere kıyasla anlamlı oranda daha yüksekti ve tedaviden sonra önemli ölçüde azaldı. SHBG düzeylerinin metformin tedavisi ile arttığı, dolayısıyla serbest androjen indeksinin azaldığı izlendi. 17 OH progesteron seviyeleri IR+ grupta anlamlı olarak daha yüksekti ve metformin tedavisi ile IR negatiflerle benzer seviyelere indi. IR+ grubunda ortalama açlık insülin düzeyi 19,21 IU/ml iken tedavi sonrası 13,14 IU/ml'ye gerildi. Beklenildiği gibi açlık glukoz/insülin oranı da metformin tedavisi sonrası artış gösterdi. Son olarak tedavi grubunda menstrual düzensizlikte istatistiksel olarak anlamlı oranda düzelme gözlendi.

Sonuç: Bu çalışma, metforminin hiperandrojenizmi azalttığı, menstruasyonu düzenlediği ve ovulatuar fonksiyonları iyileştirdiği sonucunu desteklemektedir.

Anahtar kelimeler: Adolesan, polikistik over sendromu, insülin direnci, metformin

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Received *(Geliş Tarihi)*: 31.01.2022 **Accepted *(Kabul Tarihi)*:** 17.04.2022

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex common gyneco-endocrine pathology of reproductive age.[1,2] It is an entity with many clinical signs of hyperandrogenism such as acne, hirsutism, and menstrual irregularities secondary to anovulation. The diagnosis of the adolescent age group is controversial, temporary functional hyperandrogenism and peripubertal menstrual disorders make the diagnosis difficult.[3] Hyperpulsatile gonadotropin release, hyperactive ovarian and adrenal androgen production are similar events in puberty and adolescents with PCOS. Besides this, the pathophysiological process is often associated with insulin resistance in adolescents with PCOS. Compensatory hyperinsulinemia can be the cause or result of hyperandrogenism.

Since the relationship between hyperandrogenemia secondary to stimulated androgen production from theca cells decreased sex hormone binding globin (SHBG) and IGFBG-1, and exaggerated insulin secretion was discovered; insulin-sensitizing agents have been used for the treatment of both hyperinsulinemia and hyperandrogenemia.[4] Metformin has been studied extensively in many phenotypes of PCOS in these agents. Although the adolescent group is a sensitive population, studies must be designed with increased scrutiny; metformin has been used in adolescents with type 2 diabetes and found in a safe area on the risk-benefit ratio.[5] But it is still not well documented in insulin-resistant adolescents and also its effects not have been presented on hyperandrogenism signs and symptoms in adolescents with PCOS. This study, it is aimed to evaluate the effects of metformin treatment on clinical and biochemical hyperandrogenism and menstrual functions in insulin-resistant adolescent patients with PCOS.

MATERIAL AND METHOD

This study was conducted with 25 patients between the age of 12 and 18 who were diagnosed with PCOS accompanying insulin resistance in the Gynecology and Obstetrics Department of a tertiary center between January 2012 and April 2013. 25 PCOS patients of the same age without insulin resistance were included as control group. PCOS was diagnosed as the presence of two of the following three findings: hyperandrogenism, ovulatory dysfunction, and polycystic ovaries, after exclusion of the other endocrine disorders like congenital adrenal hyperplasia and hypothyroidism. At the first visit, all patients' heights, weights, waist and hip circumferences were measured and physical examination for hirsutism was done by only one observer. Body mass indexes (BMI), waist-hip ratios, and Ferriman-Gallwey scores were calculated for all patients.

Transabdominal ultrasounds were applied between the 2nd and 5th days of the menstrual cycle. Increased ovarian volume (>10 cm^3) and presence of 2-9 mm follicles more than 12 in number on each ovary of patients were considered as polycystic ovaries. Blood samples were collected early in the morning after 8-10 hours of fasting on the 2-4th day of the cycle. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), prolactin (PRL), free testosterone (FT), total testosterone (TT), dehydroepiandrosterone sulfate (DHEA-S), 17 hydroxyprogesterone (17 OH progesterone), insulin, glucose, HDL cholesterol, LDL cholesterol, VLDL cholesterol, total cholesterol, and triglyceride measurements were recorded. For fasting blood glucose and fasting insulin, HOMA and QUICKI indexes were calculated. Scores higher than 2.1 for HOMA and lower than 0.357 for QUICKI were considered as insulin resistance.[6,7] Patients were questioned for menstrual periods and patterns. On the day of 19 – 21 of the cycle progesterone levels were measured for evaluation of ovulation and scores higher than 3 ng/ml were considered as ovulation.[8,9]

Insulin resistant 25 patients were instructed to use 2x850 mg/day metformin for 3 months (Glucophage®, Merck, Germany). After treatment ended all measurements were repeated by the same researcher. Menstrual periods and patterns after treatment were recalled from patients. The study was approved by the Local Ethics Committee of the Fatih University with the approval number of 2013/100.1. All patients and their legal representatives provided written informed consent to participate.

Statistical Analysis

The data of both groups were statistically analyzed with SPSS 17.0 (Statistical Package for Social Sciences) program. While evaluating the study data, besides descriptive statistical methods, the student t-test was used for comparing the parameters with normal distribution between groups in comparison of quantitative data. Pearson's correlation test was used to examine the relationships between parameters. If $P < 0.05$, at the 95% confidence interval, the result was considered statistically significant.

Clinical Assessment and Hormone Assay

Height and weight were measured to calculate the BMI with weight(kg) / [height(m)]^2 formula. Hirsutism was evaluated according to the Ferriman-Gallwey score system. According to this system, each patient was evaluated in 9 anatomical regions by the same researcher and a score between 0 (no terminal hair growth) and 4 (maximum hair growth) was given for each region. A score below 8 was considered normal, while a score above 8 was considered pathological.[10] Waist and hip circumference was measured by tape measure, to the nearest 0.5 cm for waist circumference, the narrowest diameter between crista iliaca and the costa were used as reference. The hip circumference was measured at the level of maximal anteroposterior excursion at the level of thighs.[11]

Transabdominal ultrasounds were applied with a full bladder using a 3.5 MHz convex probe (General Electric Logiq 7, USA) by the same researcher on the day of 2-5 of the menstrual cycle.[12,13] Plasma levels of FSH, LH, estradiol, progesterone, TSH,

free T4, free T3, prolactin, total testosterone, free testosterone, DHEA-S, 17 OH progesterone, insulin were measured using radioimmunoassay (Roche Diagnostics, Cobas Integra, France). Fasting glucose, HDL, LDL, VLDL, cholesterol, and triglyceride measurements were performed using calorimetric studies (Roche Diagnostics, Cobas Integra, France). QUICKI indexes calculated as 1/[log(Insulin)+log(Glucose)] and the HOMA-IR was determined from [Insulin X Glucose (mmol/L) X 0.055/22.5] formula.[14,15] The free androgen index (FAI) was the equation of (testosterone/SHBG) x 100).[16]

RESULTS

Mean age and BMI values were similar between IR+ and IR- groups. Both BMI and mean waist circumference values were higher in the insulin-resistant group compared to the control group, while differences at mean waist circumference were significant (77.84 vs 71.68, p<0.05). Although the values of BMI and waist/hip ratio decreased after the treatment, the decrement didn't reach the values of the control group (67.20 vs 64.92, p>0.05 and 77.84 vs 76.36, p>0.05)(**Table 1**).

FSH, LH, E2, DHEA-S, and total testosterone levels were similar between IR+ and IR- groups and didn't affected significantly after the treatment. 17 OH progesterone levels were significantly higher in the IR+ group compared to the control group and regressed to similar levels with IR negatives after metformin. Free testosterone levels were significantly higher in IR+ subjects compared to control subjects (2.67 vs 1.98, P<0,05) and decreased considerably after the treatment (p>0.05). Although didn't reach statistical significance; SHBG levels increased with metformin treatment and as a result, the free androgenic indexes decreased (38.82 vs 42.45 and 0.92 vs 0.80, p>0.05)(**Table 2**). HDL, LDL, total cholesterol, and triglyceride values were similar between the insulin-resistant and non-resistant groups and didn't significantly differ in IR patients after the treatment (**Table 3**).

Table 1. Comparison of demographic characteristics and anthropometric measurements between groups

	IR (+) Group		IR (-) Group	P		
	Before Treatment (a)	After Treatment (b)	Control (c)	a-c	b-c	a-b
Age	16.28±1.30	16.28±1.30	16.00±1.71	0.764	0.764	1.00
Weight(kg)	67.20±8.11	64.92±7.00	63.16±7.71	0.061	0.264	0.322
Height(m)	1.64±0.04	1.64±0.04	1.63±0.06	0.407	0.407	1.00
BMI(kg/m^2)	24.86±2.70	24.02±2.35	23.77±2.55	0.128	0.509	0.299
Waist(cm)	77.84±8.89	76.36±6.63	71.68±5.60	0.011	0.013	0.793
Hip(cm)	105.0±9.27	103.28±7.41	100.68±4.77	0.132	0.231	0.634
Waist/Hip	0.75±0.09	0.74±0.05	0.71±0.04	0.057	0.070	0.793

Body-mass-indexes; BMI.

Table 2. Comparison of hormonal parameters between groups

	IR (+) Group		IR (-) Group	P		
	Before treatment (a)	After treatment (b)	Control (c)	a-c	b-c	a-b
FSH (mIU/mL)	4.62±2.07	4.25±1.33	5.41±2.01	0.130	0.023	0.698
LH (mIU/mL)	7,00±4.06	6.36±3.62	6.11±3.00	0.516	0.771	0.594
LH/FSH	1.82±1.21	1.56±0.75	1.20±0.54	0.071	0.086	0.594
E2	50.82±53.89	43.39±31.70	50.81±43.40	0.554	0.712	0.669
DHEA-S (µg/dL)	228.56±107.38	233.72±112.54	210.56±100.79	0.567	0.388	0.884
17 OH Progesteron (ng/mL)	2.00±0.94	1.43±0.72	1.40±.726	0.024	0.869	0.026
Total Testosteron (ng/mL)	0.33±0.14	0.31±0.14	0.30±0.21	0.248	0.372	0.698
Free Testosteron (ng/mL)	2.67±1.19	2.24±0.89	1.98±0.69	0.012	0.225	0.181
SHBG (nmol/L)	38.82±11.53	42.45±12.50	41.20±17.27	0.854	0.547	0.327
FAI (U/mL)	0.92±0.50	0.80±0.39	0.86±0.81	0.133	0.308	0.560

FSH; Follicle-stimulating hormone LH; luteinizing hormone, E2; estradiol, DHEA-S; dehydroepiandrosterone sulfate, 17 OH progesterone; 17 hydroxyprogesterone, SHBG; sex hormone-binding globin, FAI; free-androgen index.

Table 3. Comparison of lipid values between groups

	IR (+) Group		IR (-) Group	P		
	Before treatment(a)	After treatment(b)	Control (c)	a-c	b-c	a-c
Total Cholesterol (mg/dL)	183.68±25.61	174.60±32.19	169.16±28.18	0.087	0.621	0.207
HDL (mg/dL)	48.28±8.52	49.0±7.52	51.04±8.54	0.190	0.268	0.676
LDL (mg/dL)	102.23±21.03	98.92±22.98	94.44±19.24	0.240	0.479	0.669
VLDL	20.64±8.85	18.66±6.02	16.71±5.71	0.052	0.190	0.342
Trigliseride (mg/dL)	103.18±44.27	93.32±30.12	83.56±28.54	0.052	0.190	0.342

HDL; High-density lipoprotein, LDL; Low-density lipoprotein, VLDL; Very low-density lipoprotein.

While fasting insulin levels were 19.21 IU/ml in the group with insulin resistance, they regressed to 13.14 IU/ml (p<0,05) after treatment. Also, the fasting glucose/ insulin ratio was increased from 5.36 to 8.35 after metformin (p<0,05) (**Table 4**). When treatment efficiency regarding menstrual function, ovulation, and hirsutism scores were compared between groups, significant improvement in the treatment group was observed at menstrual irregularity (22 vs 12, p<0.05). The ovulatory cycle rate increased slightly but it was not statistically significant (52% vs 32%, p>0.05). Hirsutism scores measured by the modified Ferriman-Gallwey scoring system were similar between the two groups when compared before and after the treatment (**Table 5**).

DISCUSSION

PCOS is still a controversial status in terms of etiopathogenesis, diagnosis, and treatment. It is a disease that should be evaluated in a wide range with its fairly broad spectrum. The primary clinical symptoms may occur in the late phase or immediately after puberty. It is difficult to diagnose of PCOS in the adolescent age group, but reaching a definitive diagnosis at an early age is very important for the attentive lifelong medical follow-up due to the long-term risks of the disease.

Increased obesity and impaired body fat distribution, which are characteristic of adult women with PCOS, could not be shown in adolescent PCOS patients in studies. While Rosenfield et al. found the obesity prevalence similar in adolescents with adult PCOS,[17] Van Hoff et al. showed that BMI is lower in adolescents.[18] In this study, both insulin resistant and IR- groups BMI were under 25 kg/m^2. When the BMI values were compared, there was no statistically significant difference between the IR- group and the study group (p>0.05). Although a specific diet program was not applied to the patients included in the study, an average weight loss of 2.1 kg was observed in the group using metformin, but no significant difference was observed when compared with the pre-treatment and control groups.

Studies have shown that 30% to 50% of women with PCOS have an increased waist/hip ratio, and this android type obesity is predisposed to glucose intolerance, lipid abnormalities, and hyperandrogenism.[19] In the study, it was observed that the waist circumference measurements of the group with insulin resistance were more than the control group, and although it decreased after the treatment, it didn't decrease to similar levels with the controls.

One of the controversial issues in the diagnosis and treatment of PCOS is the clinical signs of hyperandrogenism. Because of ethnic differences, epilation methods used before clinical evaluation, and subjective detection, diagnosis of hirsutism is difficult.[20] Researchers have focused on this subject and developed standardized scoring methods to use in clinical practice Although the number of studies on polycystic ovary syndrome in the adolescent age group is more limited compared to the adult age group, the percentage of hirsutism was reported to be 67% in an adolescent PCOS study by Orsino A. et al.[21] In this study, the frequency of hirsutism was found to vary between 88-92% in the measurements made according to the Ferriman-Gallwey scoring. In the literature, it was argued that metformin treatment was an effective way to treat hirsutism by increasing insulin sensitivity,[22] but it was found no significant change for hirsutism between the group before and after treatment. Acne, another finding of hyperandrogenism, is frequently observed in the adolescent age group, but it is accepted as a multifactorial, transient phenomenon.[23] Therefore, in the patient population of this study, the presence of acne at presentation was not evaluated within the diagnosis of hyperandrogenism.

Table 4. Comparison of fasting glucose, insulin and glucose/insulin ratio between groups

	IR (+) Group		IR (-) Group	P		
	Before treatment (a)	After treatment(b)	Control (c)	a-c	b-c	a-b
Fasting Glucose(mg/dL)	89.73±6.78	89.20±6.86	84.52±6.03	0.008	0.007	0.884
Fasting Insulin(mIU/mL)	19.21±9.68	13.14±6.30	8.46±3.07	< 0.001	0.004	0.003
Glucose /Insulin	5.36±0.05	8.35±1.12	11.75±0.72	<0.001	0.002	0.004

Table 5. Comparison of the effect of metformin treatment on insulin resistance, menstrual function, ovulation and hirsutism

		IR (+) Group		IR (-) Group	P		
		Before treatment (a)	After treatment (b)	Control (c)	a-c	b-c	a-b
IR (HOMA)	+	25 (100%)	17 (68%)	25 (100%)	<0.001	0.005	0.004
	-	0 (0%)	8 (32%)	0 (0%)			
IR (QUICKI)	+	25 (100%)	5 (20%)	25 (100%)	<0.001	0.039	0.050
	-	0 (0%)	20 (80%)	0 (0%)			
Ovulation	+	13(52%)	16 (64%)	15 (60%)	0.375	0.773	0.762
	-	12 (48%)	9 (36%)	10 (40%)			
Hirsutism	+	22 (88%)	23 (92%)	23 (92%)	1.000	1.000	1.000
	-	3 (12%)	2 (8%)	2 (8%)			
Menstruel irregulation	+	22 (88%)	12 (48%)	17 (68%)	0.091	0.156	0.003
	-	3 (12%)	13 (52%)	8 (32%)			

HOMA; Homeostasis model assessment, QUICKI; The quantitative insulin-sensitivity check index.

In the insulin-resistant group with the changes mentioned above, 17 OH Progesterone levels were significantly decreased to similar levels with the control group after treatment. While free testosterone levels were significantly higher in the resistant group than in the control group before treatment, this rate decreased after the treatment, but could not reach the control group. SHBG levels were increased with metformin treatment, thus free androgen indexes were decreased in the IR+ group ($p>0.05$). Finally, the average LH / FSH ratio decreased from 1.82 to 1.59 in the IR+ group, while it was 1.20 in controls. When these data were compared before and after treatment and the control group, no significant change was found. But in our opinion, it is an important finding as in the literature, the increased LH level is present only in 40-60% of adolescents with hyperandrogenism, thus the LH / FSH ratio has no significant value in the diagnosis of PCOS in adolescents.[24] The obtained data show that LH / FSH ratio may have predictive value for insulin resistance and IR+ PCOS patient's follow-up.

The most studied insulin-sensitizing agent in the treatment of insulin resistance in patients with PCOS is metformin. Metformin, an oral antidiabetic from the biguanides group, is the most commonly used and oldest oral antidiabetic in the world.[25] Positive effects on impaired glucose mechanisms were found in patients with PCOS treated with metformin. Minimum 12-weeks therapy of metformin is were suggested in the studies for improved insulin sensitivity.[26] In another study, 18 patients with PCOS aged between 15 and 18 were given metformin treatment for 6 months, and significant improvements in insulin resistance were reported.[27] In this study, a statistically significant decrease was found in insulin resistance in the IR+ group after 3 months of metformin treatment. Fasting insulin levels decreased from 19.21 to 13.14, both HOMA and QUICKI indexes were changed, such that 8 patients were recognized as non-resistant due to HOMA, this number was 20 when measurements were done with QUICKI.

When the effectiveness of the treatment was compared in terms of menstrual function and ovulation rates between the groups; there was a significant improvement in the treatment group (52% vs 64%, respectively), and even better results were obtained than the control group (60%) in ovulation rates according to progesterone levels between days 19-21. For menstrual irregularity which was subjectively questioned, significant improvement in the treatment group was observed at menstrual irregularity (12% vs 52%, $p<0.05$). These results led metformin to be associated with an improvement in ovulatory functions.

The main limitation of this study is the small sample size and non-randomization. With a large size of the sample, the study power would increase, and also more significant differences would be achieved if the groups were determined by randomization and the late results of the control group were included. On the other hand this study is considered to be the first prospective study to investigate the efficacy and safety of metformin in the adolescent population. Although side effects have not been documented there was no patient reported any repercussion.

CONCLUSION

In conclusion, this study revealed that 3 months of metformin treatment in adolescents with PCOS accompanied by insulin resistance reduced fasting plasma glucose and insulin levels resulting in decreased insulin resistance. As a secondary outcome, free androgen indexes statistically significantly decreased in accordance with decreased free testosterone levels and increased sex hormone-binding globulin levels. Although it was not possible to evaluate the alteration in clinical hirsutism status due to a short interval of treatment for about 12 weeks, it is possible to declare that metformin has favorable effects on hyperandrogenism.

Additionally, the treatment was found to statistically significantly reduce menstrual irregularity accompanied by increased ovulation rates which have been demonstrated by luteal phase progesterone levels. Hence, this study supports the conclusion that metformin improves menstrual and ovulatory functions, and by putting forward efficiency and safety of the treatment it encourages the development of fully powered trials in adolescent population.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Local Ethics Committee of the Fatih University with the approval number of 2013/100.1.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1064396
J Contemp Med 2022;12(3):455-459

Original Article / Orijinal Araştırma

Evaluation of the Status of Infectious Diseases in Military Personnel Who Visit Clinics Due to Tick Bite

Kene Isırması ile Gelen Askeri Personelde İnfeksiyöz Hastalık Olma Durumunun Değerlendirilmesi

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Abstract

Introduction: Tick bite has been a big risk for the military personnel who have to perform their profession, both in operations and training, in rural areas with a high risk of tick bites. The considerable increase in the number of those visiting the emergency departments of military hospitals and the increase in the pauses in the military exercises or operations due to tick bites have caught the attention of military physicians, and so they have started to look for better ways to prevent such problems by making military equipment more resistant. This study aims to evaluate and present the findings obtained from medical diagnosis and follow-up of military personnel admitted to the relevant units due to tick bites.

Material and Method: In this study, which was planned as a single-center observational study, all volunteer military patients who applied to the Emergency Service of Military Medical Faculty Hospital with the complaint of tick bite between December 2012 and December 2013 were included. . The Hospital, where the study was conducted, is a third-level hospital that accepts patients by referral from neighboring provinces and is the largest military hospital in Turkey.

Results: 101 of 89421 patients had a complaint of tick bite. 79 of these patients consisted of military personnel. Of the 79 patients, 76 were found to be male (96%) and 3 were female (4%). The average age was 24 years. The ticks attach to the body of 12 (15%) of 79 patients were removed by the medical personnel. The bites were observed to be in the head and neck (8.8%), torso (17.7%), upper extremity (24%), lower extremity (45.5%) and genital area (3.8%). There was no statistically significant relationship between the change in vital symptoms of patients and the presence of ticks in their physical examination, as well as between the change in vital findings and the location of bite site (p>0,05). In addition, there was no statistically significant relationship between the change in leukocyte, AST, ALT, LDH, PTZ and other biochemical parameters and the presence of ticks in the examination, as well as a change in biochemical parameters and the bite site (p>0.05). Patients were followed for 10 days. None of the 79 patients progressed the disease; no patients died, and all of them recovered and were discharged from the hospital.

Conclusion: The clinical and laboratory findings related to tick bite may not be always observed on the visiting military personnel, and different diseases such as Crimean-Congo hemorrhagic fever, hantavirus infections, leptospirosis and borreliosis diseases could be observed; therefore, the interrupt of military operation is not thought to be necessary due to tick bite related causes Only all tick bites in endemic areas and patients in the risk group with complaints can be followed up and if necessary, it can be ensured that they do not participate in military operations and trainings.

Keywords: Soldier, military operation, tick, tick bite, emergency service

Öz

Giriş: Kene ısırması riskli yüksek olan kırsal bölgelerde gerek operasyonlar, gerekse eğitimler şeklinde mesleğini icra etmek zorunda olan askeri personel bu hastalıklar açısından riskli grupların başında gelmektedir. Kene ısırması nedeniyle askeri hastanelerin acil servislerine başvuru sayısında ciddi bir artış olması ve askeri tatbikat ya da operasyonda kene ısırmaları nedeniyle yavaşlama-durmalar bu hastalığa askeri hekimlerin ilgisini arttırmış, bu tür kayıpların önlenmesi için askeri teçhizatın dirençli hale getirilmesi de dahil ciddi arayışlar içerisine girilmesine yol açmıştır. Bu çalışmanın amacı; kene ısırması nedeniyle başvuran askeri personelin tıbbi tanı ve takibinin değerlendirilerek sunulmasıdır.

Gereç ve Yöntem: Tek merkezli gözlemsel çalışma olarak planlanan bu çalışmaya Aralık 2012-Aralık 2013 tarihleri arasında kene ısırması şikayetiyle müracaat eden gönüllü tüm asker hastalar dahil edildi. Çalışmanın yapıldığı Hastane, çevre illerden sevk ile hasta kabul eden 3. basamak bir hastanedir ve Türkiye'nin en büyük askeri hastanesidir.

Bulgular: Toplam 89421 hastadan 101 tanesinde kene ısırması şikayeti vardı. Bu hastaların 79 tanesi askeri personelden oluşuyordu. 79 hastanın 76'sı erkek (%96) ve 3'ü kadındı (%4). Hastaların ortalama yaşı 24 idi. 79 hastadan 12(%15) hastadaki kene sağlık personeli tarafından çıkarıldı. Isırmalar vücut bölgeleri sırasıyla baş-boyun (%8,8), gövde (%17,7), üst ekstremite (%24), alt ekstremite (%45,5) ve genital (%3,8) görüldü. Hastaların vital bulgularında değişiklik ile muayenesinde kene bulunması arasında ve vital bulgularında değişiklik ile ısırılma bölgesi arasında istatistiksel olarak anlamlı ilişki saptanmadı ((p>0,05). Ayrıca lökosit, AST, ALT, LDH, PTZ ve diğer biyokimyasal parametrelerde değişiklik ile muayenesinde kene bulunması arasında ve biyokimyasal parametrelerde değişiklik ile ısırılma bölgesi arasında istatistiksel olarak anlamlı ilişki saptanmadı (p>0,05). 79 hastanın hiçbirinde hastalık gelişmedi, ölen hasta olmadı ve tamamı iyileşerek taburcu edildi.

Sonuç: Kene ısırması ile gelen askeri personelde her zaman klinik ve laboratuar bulgu olmayabileceği, Kırım Kongo Kanamalı Ateşi, hantavirüs enfeksiyonları, leptospirosis, borelliozis ve riketsiyoz gibi farklı hastalıkların olabileceği, bu sebepten askeri operasyonlara ara verilmesine gerek olmadığı düşünülmektedir. Yalnız endemik bölgelerdeki tüm kene ısırıkları ve şikayeti olan risk grubundaki hastaların takibi yapılabilir ve gerekirse askeri harekat ve eğitimlere katılmamaları sağlanabilir.

Anahtar Kelimeler: Asker, askeri operasyon, kene, kene ısırması, acil servis

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Received *(Geliş Tarihi)*: 28.01.2022 **Accepted *(Kabul Tarihi)*:** 03.05.2022

INTRODUCTION

Ticks transmit many infectious diseases. These diseases may cause serious symptoms such as bleeding as well as some other initial symptoms such as fever. They can even be fatal by affecting many other organs, showing a severe course.[1-3] These diseases may include Crimean-Congo Hemorrhagic Fever, Hantavirus infections, leptospirosis, borreliosis and rickettsiosis.[4,5] Of the 878 known tick species, 30 carry the agents causing the disease. In nature, the cycle is in the form of tick-vertebrate-tick. It can be found in cattle, sheep, hedgehogs, rabbits, horses, donkeys, goats and pigs.[6] The only hosts in which the disease has been identified are humans, and they do not cause disease in animals.[6-8] Ticks usually live in thickets, grasses, lawns, forests, animal shelters.[9] When ticks bite, they do not hurt because they secrete narcotizing liquid, and meanwhile, they infect viruses and bacteria in the digestive system.[6] The diseases can be observed in various parts of the world, especially in Europe and Africa, and some of them may even be endemic.

As can be understood from the geographical location of Turkey, being close to Europe and Asia, it is one of the countries where tick-borne diseases are common. Another factor affecting the epidemiology of the disease, other than geographical location, is the professions of those infected with this disease.[3] Military personnel who have to perform their profession in rural areas, where they are more likely to be exposed to tick bites, are among the groups at the highest risk for this disease.[2,3] The fact that the disease can lead to loss during the military training performed except the times of conflict, the considerable increase in the emergency visits to military hospitals due to tick bite, the pause and slow down in the military exercises or operations due to tick bite have attracted the attention of military physicians, and they have started to look for solutions such making military equipment more resistant to prevent serious losses. Some of these are long-acting drugs such as Permethrin, which is rarely absorbed from the skin and can stay for a long time, insect repellents called 'Repellent' (Dietiktoluamide) are absorbed into people's clothing in the form of spray or liquid and are safe drugs as their toxicity is low.[10,11]

Favourable climatic conditions throughout Europe and Turkey, the abundance of ticks, the trade of wild animals and their interaction with domestic animals, tourist and refugee movements have been the basis for the disease and its spread. The risk of developing potentially fatal diseases in soldiers exposed to tick bites causes great concern in military medicine. Turkey is among the most populous armies in the world with over 450 thousand soldiers. Hospital, which is a third-level hospital that accepts patients by referral from neighboring provinces, is Turkey's largest military hospital. This study aims to examine the medical diagnosis and follow-up of patients admitted to the Emergency Department of Hospital due to tick bites and present the relevant findings.

MATERIALS AND METHOD

This study was designed as a single-center observational study. Relevant permission was received from the Ethics committee of Hospital on 05.12.2012 and numbered 2012/11. Of the 89421 patients who applied to Hospital Emergency Department between December 2012 and December 2013, 101 had a complaint of tick bites. Of these patients, 79 were military personnel who voluntarily agreed to participate in the study. Other patients who were not volunteers and were not military personnel were excluded from the study.. In the study, sociodemographic data form and tick bite follow-up form prepared specifically for this study were used. In this form, the patients' socio-demographic data, along with how the bite occurred (the place where you were bitten, bitten body part, species of biting ticks) initial vital symptoms and physical examination findings, initial laboratory measurement values (hemogram, biochemical parameters, bleeding parameters), and whether drug treatment was needed, if needed, the reasons for this and the interventions applied; and physical examination and laboratory findings during the follow-up period. As a standard all of the cases were reinvited to the Emergency Department for follow-up evaluation after 10 days and the related parameters were filled through follow-up measurements and evaluations in the relevant form.

Statistical Analysis

Jamovi version 1.6.18 program was used in the statistical analysis of the data, The data were expressed in the form of mean, standard deviation and percentage. The Kolmogorov-Smirnov test was used to check the distribution of the data. The continuous variables with a nonparametric distribution were compared with the Wilcoxon test, and the continuous variables with parametric distribution were compared with the Paired T-test. The McNemar test was used to examine the relationship between the two variables. The discrete variables (gender, presence of tick, bite site) were compared with the Chi-Square test. $P<0.05$ value was considered statistically significant.

RESULTS:

Of the 79 patients, 76 were male (96%) and 3 of them were female (4%). The average age of the patients was 24 (19-48) (**Table 1**). Medical personnel at the hospital removed the ticks in 12 (15%) patients. When all admission and control laboratory tests of the patients were compared, no statistically significant relationship was found between them. ($p>0.05$) (**Table 1**). Bites were observed in the following body parts; genital 3 (3.8%) head-neck 7(8.8%), torso 14 (17.7%), upper extremity 19 (24%), lower extremity 36 (45.5%), respectively (**Table 2**). There was no statistically significant relationship between the bite area and the increase in vital symptoms; between the rise in vital symptoms and the presence of the tick in the initial

examination (**Table 2**). Of the patients, 4 (5%) had fever at the initial stage and 5 (6%) had leukocytosis. There was no statistically significant relationship between the laboratory tests of patients at the arrival and control stage when they were compared with the McNemar test (p>0.05) (**Table 3**). In addition, there was no statistically significant relationship between an increase in biochemical parameters and the presence of ticks in the examination, as well as an increase in biochemical parameters and bite site (p>0.05). None of the 79 patients developed the disease; no patients died, and all of them recovered and were discharge from the hospital.

Table 1. Demographic and Clinical Characteristics of All Patients

	Average	Min-Max
Age	24.0	(19-48)
Gender (Female/Male)	3/79	
Initial fever measured	36.6	(36.3-38.7)
Pulsation on arrival	72	(61-88)
Arterial Pulse on arrival	110/70	(90/60-130/80)
Control fever	36.7	(36,5-36,8)
Control pulse	70	(64-86)
Control arterial pulse	110/70	(90/60-130/80)

Table 2. The Statistical evaluation of patients who visit the clinic with ticks on examination

	Tick on examination Yes	No	Total	p value
Bite site, lower extremity	8	28	36	
Bite site, upper extremity	3	16	19	
Bite site, torso	1	13	14	
Bite site, genital	0	3	3	
Bite site, head and neck	0	7	7	
Bite site	**12**	**67**	**79**	**0.422**
Vital symptoms on follow-up (higher)	0	4	4	
Vital symptoms on follow-up (remain normal)	12	63	75	
Vital symptoms on follow-up	**12**	**67**	**79**	**0.385**
Control laboratory value (higher)	1	4	5	
Control laboratory value (remain normal)	1	16	17	
Control laboratory value	**2**	**20**	**22**	**0.334**
Control laboratory value (higher)	3	25	28	
Control laboratory value (remain normal)	9	42	51	
Control laboratory value	**12**	**67**	**79**	**0.412**

Table 3. Control Laboratory Values of All Patients on Arrival

	N	Mean	SD	Median	p value
Initial Wbc	79	7.89	1.71	7.60	
Control Wbc	79	7.68	1.35	7.60	0.354
Initial LDH	79	349	82.1	336	
Control LDH	79	340	67.4	338	0.622
Initial CK	79	174	364	106	
Control CK	79	160	211	102	0.226
Initial AST	79	24.3	9.19	23.0	
Control AST	79	23.4	7.82	23.0	0.117
Initial ALT	79	22.7	6.43	23.0	
Control ALT	79	23.1	6.15	23.0	0.221
Initial Plt	79	274	53.2	274	
Control Plt	79	272	53.3	271	0.824
Initial PT	79	14.3	1.53	14.0	
Control PT	79	14.6	1.22	15.0	0.123
Initial Sed	79	10.1	3.81	10.0	
Control Sed	79	10.0	3.69	10.0	0.933

Wbc: White blood cell, LDH: Lactate dehydrogenase, CK: Creatine phosphokinase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, Plt: Platelet, PT: Prothrombin time, Sed: Sedimentation.

DISCUSSION

In this study, medical status and follow-up data of 79 military personnel admitted to the emergency department due to tick bites were presented. As much as we know, this study is the follow-up study conducted with the most extensive sample examining the tick bites in military personnel. In a study conducted in 2008/2009 and 2012-2014, during a total of 36 months of training, the tick bites and emerging diseases of 1156 fresh military personnel were examined through their medical records. In this study, 66 cases of tick bites were found during 317,059 hours of field training. In only one of these cases, the bite resulted in an infection that required treatment. It was found that the risk of tick bites is associated only with the season. Similarly, our study found no relationship between the risk of tick bite and other variables and did not result in an infection requiring treatment.[12] In a study conducted by LG Goldfarb et al., one out of every five people who go to the hospital due to a tick bite reported developing a tick-borne infection and reported a 0.215' probability of developing the disease.[13] In a study conducted on tick-borne disease in Turkey, 90% of cases are farmers,[1,14,15] the second most affected group is health workers.[3] In a large-scale study conducted between 2002 and 2010, 4453 patients were infected with a tick-borne infection and 218 of them died.[16]

In a study conducted on a civilian population in the same region as this study in Turkey, it was found that 9 out of 70 patients (12.9%) died in a hospital due to an infection that developed after a tick bite.[17] It is noteworthy that 94 percent of the patients who developed an infection in this study were farmers. In addition, the average age of the patients in this study is 49. This may be related to the type of ticks that live on agricultural land, as well as to the predisposition of elderly patients to the disease.

Similar to the results obtained with this study, it is observed that in many studies, no predictive relationship could be established between the prognosis and blood parameters after a tick bite, since the infection development rates are very low. However, in a study conducted by D. Öztürk Engin et al., it is stated that leukocytosis was measured in the initial parameters of a patient who died.[18] In a study on tick bites in 6 patients out of 8 cases and fever was experienced in all of them; leukopenia was measured in 8 patients and thrombocytopenia was measured in 7 patients.[18] Aspartate aminotransferase (AST) (mean 107 U/L) and alanine aminotransferase (ALT) (mean 117 U/L) were found to be high in all cases. Lactate dehydrogenase (LDH) (mean 636 U/L) was high in 6 of them, and creatine phosphokinase (CK) (mean 266 U/L) was found to be high in 4 of them.[18] In another study, the increase in AST, the decrease in platelet count and the increase in Activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT) and International Normalized Ratio (INR) values were found to be statistically significant.[17]

In many studies, the mean ALT level was 137 U / L in the surviving patients, but there were no significant differences.[15,17] The CK values of the lost patients were measured as 588 and 1307, respectively, but there was no statistically significant difference between them and the surviving patients.[17] In our study, although leukocytosis was observed in 5 (6%) patients initially, the clinical findings of these patients did not worsen and these values returned to normal after follow-up. AST (mean 24 U/L) was found to be high in 4, LDH was high in 4 (mean 349 U/L), and CK was high in 15 (mean 173 U/L). ALT (mean 22 U/L), PLT (mean 274 x10.e3/microL) and other tests were found to be normal in all patients (**Table 3**).

In our study, no clinical infection development was observed in any case. Although one of the reasons for this could be that serological examination has not been performed and possible asymptomatic transmission cannot be measured, the low seroprevalence of the tick-borne virus could also be considered as a factor. Only 3 (1.16%) of 516 blood donors were positive in a serological study informing about the circulation of the causative agent of tick-borne infection in asymptomatic individuals in Spain.[19] Interestingly, it was found that one-fifth of these individuals are engaged in animal husbandry.[19] In addition, in the study investigating the tick exposure of military personnel in the field of military training in Germany between January and December 2009, 566 personnel were exposed, and the overall seroconversion rate was found to be 1.7%.[20]

The results obtained with this study support studies that have revealed that tick-borne infections observed in military personnel are less risky than in people engaged in animal husbandry and farming. However, these results do not support the former studies suggesting that military personnel take extra precautions such as using factory-treated, long-lasting permethrin-impregnated clothing for tick bites in field operations or even pausing military operations due to tick bites.[11]

However, it should be remembered that there may not always be clinical and laboratory signs in military personnel visiting clinics due to a tick bite.[21] For this reason, it is recommended to have tracking algorithms and follow-up protocols for patients coming to military hospital emergency departments due to a tick bite.

CONCLUSION

The clinical and laboratory findings related to tick bite may not be always observed on the visiting military personnel, and different diseases such as Crimean-Congo hemorrhagic fever, hantavirus infections, leptospirosis and borreliosis diseases could be observed; therefore, the interrupt of military operation is not thought to be necessary due to tick bite related causes. Only all tick bites in endemic areas and patients in the risk group with complaints can be followed up and if necessary, it can be ensured that they do not participate in military operations and trainings.

Limitations

The Hospital, where the study was conducted, is a third-level hospital that accepts patients by referral from neighboring provinces and is the largest military hospital in Turkey. Despite this, the lack of significant difference between the variables may be due to the small number of participants. Since there are not many recent studies on military personnel, it has been compared with a limited number of studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: Relevant permission was received from the Ethics committee of Hospital on 05.12.2012 and numbered 2012/11.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1001344
J Contemp Med 2022;12(3):460-464

Original Article / Orijinal Araştırma

Analysis of 12-Lead Electrocardiograms Shared on Twitter

Twitter'da Paylaşılan 12 Derivasyonlu Elektrokardiyogramların Analizi

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Abstract

Aim: A large number of electrocardiograms (ECG) are shared on Twitter every day. Some of them aim to provide information to the readers, and some of them aim to provide training with a mini quiz. This study aimed to discuss the evaluability of ECG images shared on Twitter.

Material and Method: The study sample consisted of 12-lead ECG images shared on Twitter. ECG images shared on 01/08/2020 - 31/01/2021 were manually scanned.

Results: A total of 286 tweets matching the criteria were included in the study on the specified dates. The majority of them (n=231. 80.5%) asked the reader about the ECG. The average number of the tweets' interactions was 70.42±112.17, and the interaction was mainly in the form of "likes" (50.49±80.64). 83.5% of ECGs had a rhythm strip. Total interaction numbers and other parameters were compared. ECGs from which small squares could be selected collected more interactions (p=0.015). ECGs explained the case or whose diagnosis was clearly stated collected more interactions (p <0.001). Also, it was observed that ECGs without a rhythm strip contained more interaction (p <0.001).

Conclusions: We concluded that 12-derivation ECGs shared on Twitter are highly evaluable. There was also a moderate correlation between the number of followers and the number of interactions (r=0.493. p=0.001). For this reason, it is important for accounts with a high number of followers to following that are experts in their field to prevent information pollution.

Keywords: Electrocardiography, social media, Twitter messaging

Öz

Amaç: Twitter'da her gün çok sayıda elektrokardiyogram (EKG) paylaşılmaktadır. Bazıları okuyuculara bilgi vermeyi, bazıları ise mini bir quiz ile eğitim vermeyi amaçlıyor. Bu çalışma Twitter'da paylaşılan EKG görüntülerinin değerlendirilebilirliğini tartışmayı amaçlamıştır.

Gereç ve Yöntem: Çalışma örneklemi Twitter'da paylaşılan 12 derivasyonlu EKG görüntülerinden oluşturuldu. 01/08/2020 - 31/01/2021 tarihinde paylaşılan EKG görüntüleri manuel olarak taranmıştır.

Bulgular: Belirlenen tarihlerde kriterlere uyan toplam 286 tweet çalışmaya dahil edildi. Çoğunluğu (n=231, %80,5) okuyucuya EKG'yi sordu. Tweetlerin ortalama etkileşim sayısı 70,42±112,17 idi ve etkileşim ağırlıklı olarak "beğeni" (50,49±80,64) şeklindeydi. EKG'lerin %83,5'inde ritim şeridi vardı. Toplam etkileşim sayıları ve diğer parametreler karşılaştırıldı. Küçük karelerin seçilebildiği EKG'ler daha fazla etkileşim topladı (p=0,015). Vakayı açıklayan veya tanısı açıkça belirtilen EKG'ler daha fazla etkileşim topladı (p <0,001) . Ayrıca ritim şeridi olmayan EKG'lerin daha fazla etkileşim içerdiği gözlendi (p<0,001).

Sonuç: Twitter'da paylaşılan 12 derivasyonlu EKG'lerin yüksek derecede değerlendirilebilir olduğu sonucuna vardık. Takipçi sayısı ile etkileşim sayısı arasında da orta düzeyde bir ilişki vardı (r=0,493, p=0,001). Bu nedenle takipçi sayısı yüksek, alanında uzman hesapların bilgi kirliliğini önlemesi önemlidir.

Anahtar Kelimeler: Elektrokardiyografi, sosyal medya, Twitter mesajlaşma

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Received *(Geliş Tarihi)*: 27.09.2021 **Accepted *(Kabul Tarihi)*:** 05.01.2022

INTRODUCTION

Social media has an extensive place in shopping, official announcements, scientific sharing, and educational activities in addition to personal sharing. With the Coronavirus 2019 disease (COVID-19) pandemic, social media has become more prominent in education and training activities.

Twitter is a popular microblogging site with an enormous user base and free access.[1] In addition to their video, photo, and access link, users share texts of 280 characters called "tweets." Due to the limited number of characters allowed, users use abbreviations, phrases, or hashtags to convey a message. Hashtags define keywords and make certain information easy to organize and search. Followers of the person or organization that created the tweet can view, retweet, or add to likes it. Thanks to retweeting, it becomes possible for the followers of the follower to see the message, and the interest increases. This offers the advantage of quickly spreading information to large numbers of people. Users' shares are constantly updated with a timeline.[2] It has been shown that social media is an effective way of informing and educating about health.[3,4]

Electrocardiography (ECG) is the process of detecting and recording the heart's electrical activity through electrodes placed on the skin.[5] ECG training and its effectiveness on social media have been researched before, but its efficiency has not been explained well.[6] On the other hand, in a study comparing two groups who received ECG education through electronic learning (e-learning) and face-to-face training, it was shown that the ECG skills of both groups increased after the training, but there was no difference between them.[7]

A large number of ECGs are shared on Twitter every day. Some of them aim to provide information to the readers, and some of them aim to provide training with a mini quiz. It is also known that the quality of medical images shared with social media applications may deteriorate.[8] This study aimed to discuss the evaluability of ECG images shared on Twitter.

MATERIAL AND METHOD

Study Design and Sampling

The study sample consisted of 12-lead ECG images shared on Twitter. The minimum sample size required for research in proportional data for which the sample size is not known precisely was determined by performing power analysis. Accordingly, a minimum of 255 samples was required (effect size 0.5, error level 0.05, and 0.95 confidence interval). ECG images shared on 01/08/2020 - 31/01/2021 were manually scanned. The following categories were searched using the words #ECGChallenge, #ECG, #EKG, #Electrocardiography, #electrocardiogram, #ECG lovers, EKG, ECG, ECG Challenge, Electrocardiography, Electrocardiogram, and ECG lovers; the most popular tweets, the latest tweets, contacts, and photos. Detected 12-lead ECG images were included in the study. Links containing an ECG assessment were not included in the study. Retweets containing twits included in the study were excluded.

Standard ECG tracing consists of 12 leads. Electrodes are placed on all four limbs and in specific areas on the chest wall, allowing them to evaluate potential electrical changes in the heart from different locations. Bipolar leads called DI, DII, DIII, and other unipolar leads follow; aVR, aVL, and aVF limb leads, precordial leads V1-V6. The usual paper speed is 25 mm/sec, and when it is shot at this speed, the duration of a small square in the ECG is 0.04 seconds, and the duration of a large frame consisting of 5 small squares is 0.20 seconds. Heart rate in an ECG with a 25 mm/sec paper speed It is calculated using 1500/small square number between two consecutive R waves or 300/a large number of frames between two consecutive R waves.[9]

Data Collection

The date of the tweeted images, the total number of interactions (comment, like, retweet), and the number of followers of the tweeted user were recorded. The photos in the tweets were evaluated on a desktop computer monitor. The evaluation was done by an emergency medicine specialist and a cardiologist in a single-blind fashion. Both evaluators were asked whether the ECGs were suitable for evaluation. During the assessment, the 12 leads should be indicated on the ECG strips, the clear visibility of the squares on the paper (large and small squares separately), the presence of the rhythm strip, the status of aVR (positive/negative), the ECG paper speed, the predictability of the heart rate, the prediction of the rhythm, and the selectability of the isoelectronic line was examined. Afterward, it was checked whether the tweet was a question or a direct explanation, whether the tweet owner provided sufficient proof, and whether it stated a precise diagnosis. A rubric was used for ECG evaluation. Pearson correlation test was used to show agreement between raters, and there was a very high correlation between raters ($p < 0.05$, $r = 0.94$).

Ethical statement

All information collected from this study was from open accessed Twitter accounts. This study contains publicly available data.

Statistical Analysis

The compliance of the data to normal distribution was examined with the Kolmogorov Smirnov test. The student's t-test was used to compare normally distributed characteristics in two independent groups. A one-way analysis of variance (ANOVA) test was used to compare more than two independent groups. The Mann-Whitney U test was used to compare the features that were not normally distributed in two independent groups, and the Kruskal Wallis test was used to compare more than two independent groups. Pearson Correlation test was used to determine rater reliability, which shows consistency between raters. Relationships between numerical variables were tested with the Pearson correlation coefficient. Simple linear regression analysis was performed between interaction number and follower values. As descriptive statistics, mean±standard deviation and median (min-max) values for numerical variables; Number and%

values are given for categorical variables. SPSS Windows version 23.0 package program was used for statistical analysis, and p <0.05 was considered statistically significant.

RESULTS

A total of 286 tweets matching the criteria were included in the study on the specified dates. The majority of them (n=231, 80.5%) asked the reader about the ECG. Tweets were created from 45 accounts, and the median number of followers of the accounts was 15125. The average number of the tweets' interactions was 70.42±112.17, and the interaction was mainly in the form of "likes" (50.49±80.64). 83.5% of ECGs had a rhythm strip, 99% had clear derivation names, 21.2% indicated paper speed, 81.9% had negative aVR, 99% had prominent large squares, small squares were also apparent in 80.8%, the heart rate could be assessed in 94.8%, the isoelectric line could be selected in 95.5%. An explanation was made about the case in 91.6%, and the diagnosis was clearly stated in 88.9% (**Table 1**).

Table 1. Descriptive data of 12-lead electrocardiographs shared on Twitter

Parameters	Value
Number of tweets (n,%)	
Total	286 (100)
Question	231 (80.5)
Explanation	55 (19.2)
Undetermined	1 (0.3)
Accounts that post tweets (n)	45
Possible personal account	182 (63.9)
Possible corporate account	103 (36.1)
Number of followers of the accounts [median (q1-q3)]	15125 (13450-28342)
Interaction count of tweets (mean ± sd)	70.42±112.17
Comment	5.13±8.98
Retweet	14.82±25.17
Like	50.49±80.64
Is there a rhythm strip? (n,%)	
Yes	240 (83.5)
No	47 (16.5)
Are the derivations clearly evident? (n,%)	
Yes	284 (99)
No	3 (1)
Is the paper speed shown? (n,%)	
Yes	61 (21.2)
No	226 (78.8)
Status of aVR (n,%)	
negative	235 (81.9)
positive	23 (8)
uncertain/not evaluated	29 (10.1)
Are large squares prominent? (n,%)	
Yes	284 (99)
No	3 (1)
Are small squares prominent? (n,%)	
Yes	232 (80.8)
No	55 (19.2)
Can the heart rate be calculated? (n,%)	
Yes	272 (94.8)
No	15 (5.2)
Can the isoelectric line be evaluated? (n,%)	
Yes	274 (95.5)
No	13 (4.5)
Is there any explanation about the case? (n,%)	
Yes	263 (91.6)
No	24 (8.4)
Is the diagnosis clearly stated? (n,%)	
Yes	255 (88.9)
No	32 (11.1)

Total interaction numbers and other parameters were compared. ECGs from which small squares could be selected collected more interactions (p=0.015). ECGs explained the case or whose diagnosis was clearly stated collected more interactions (p <0.001). Also, it was observed that ECGs without a rhythm strip contained more interaction (p <0.001) (**Table 2**).

Table 2. Comparison of interaction numbers and descriptive data

Parameters		Total number of interactions		
		Mean±sd (M)	min-max	p
Is there a rhythm strip?	Yes	55.39±87.36 (23)	0-712	<0.001
	No	146.85±176.98 (108)	2-987	
Are derivations clearly evident?	Yes	70.68±112.65 (26)	0-987	0.880
	No	46.00±52.85 (30)	3-105	
Are large squares prominent?	Yes	69.78±112.01 (26)	0-987	0.396
	No	130.67±135.34 (105)	10-277	
Are small squares prominent?	Yes	78.23±121.36 (28)	0-987	0.015
	No	37.62±48.16 (19)	2-277	
Can the heart rate be calculated?	Yes	72.68±114.53 (27)	0-987	0.064
	No	29.67±35.93 (16)	3-122	
Is the paper speed shown?	Yes	53.72±70.59 (28)	3-402	0.727
	No	74.85±120.57 (25)	0-987	
Can the isoelectric line be evaluated?	Yes	70.91±113.20 (26)	0-987	0.441
	No	60.15±990.95 (23)	3-277	
Status of aVR	Negative	72.14±120.52 (25)	0-987	0.425
	Pozitive	61.57±68.16 (28)	3-245	
	Uncertain	63.59±58.38 (36)	3-206	
Tweet feature	Question	71.46±107.23 (24)	0-712	0.089
	Explanation	67.02±132.98 (42)	3-987	
Is there any explanation about the case?	Yes	74.92±114.95 (28)	2-987	<0.001
	No	21.29±56.73 (2)	0-277	
Is the diagnosis clearly stated?	Yes	76.89±116.19 (28)	2-987	<0.001
	No	19.03±49.25 (3,5)	0-277	

There was a moderate positive correlation between interaction and number of followers (r=0.493; p=0.001). A 1 unit increase in the number of followers resulted in a 1.01 unit increase in the number of interactions (**Figure 1**). According to the univariate linear regression analysis, 24.3% of the interaction change was explained by the number of followers (**Table 3**).

Table 3. Relationship between interaction and number of followers

	Unstandardized Coefficient[a]		P
	B	Std. Error	
Constant	1.12	0.51	0.001
Number of followers	1.01	0.01	0.001

[a]Dependent variable: interaction; Independent variable: number of followers, * Significant at 0.05 level

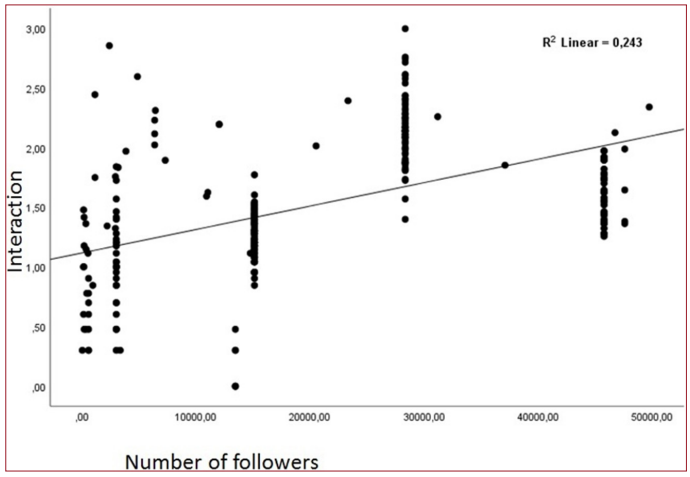

Figure 1. Distribution chart between interaction and number of followers

DISCUSSION

The most important part of this study was to investigate ECGs' evaluability shared on Twitter, the largest social media platform, due to the uptrend of internet-mediated education rather than face-to-face education due to the current COVID-19 pandemic as well as the technology age we are in. In our study, small squares were evident in more than 4/5 of the tweets, and case information was available. It was determined that ECG tweets with these features received significantly high interaction. At the same time, it was observed that the tweets that also reported the diagnosis indicated by the ECG received significantly more interaction.

Cardiovascular diseases are currently the most common cause of death worldwide.[10] An ECG reflects the heart's electrical activity, providing a tremendous amount of information about heart function, which is essential for accurate diagnosis of various diseases. ECG is still the most widely used method for examining the heart's electrical activity due to its easy and fast application, reproducibility, noninvasiveness, and cost-effectiveness.[11] Luigi Galvani first determined the electrical activity of the heart in 1791.[12] Since ECG was introduced by Einthoven in 1902, it has been an essential diagnostic modality for heart diseases.[13,14] In addition to cardiac pathologies, 12-lead ECG is one diagnostic tool that provides crucial information in examining the effect of non-cardiac causes on the heart.

Although the basic ECG interpretation skill is critical for physicians, unfortunately, most universities' education on this subject does not seem sufficient, and the knowledge gap continues.[15] The need for alternative ways to improve ECG training is obvious. Web-based education is a branch of e-learning that is increasingly used due to the advantages of the internet, such as accessibility, geographic independence, flexibility, advanced visualization, and interaction opportunity.[15,16] Medical posts by healthcare professionals are frequently encountered on social media channels such as Twitter.[17] However, there is not enough data about the evaluability of shared ECGs. These shares generally aim to transfer education, knowledge, and experience. Our study observed that approximately 81% of the tweets about ECG had the quality of teaching the reader through questions, while the posts on ECG were appreciated. These results show us that ECG, which is vital in patient evaluation, attracts healthcare professionals' attention and has teaching and learning anxiety in this area.

In our study, it was observed that the interaction was significantly high in tweets with case information sharing in addition to the ECG image. However, it is seen that the evaluability of the posts lacks at some points. It was determined that the information about the paper speed, which is essential to know in the basic ECG evaluation, was included in only 21% of the tweets. However, this may be due to the paper speed is ignored because it is generally accepted speed unless otherwise stated. It is not yet fully understood the optimal methods to improve ECG interpretation skills and maintain information persistence.[18,19] ECG teaching via Twitter, which has high interaction possibilities, should be considered an excellent alternative option. For this reason, it is crucial to provide the necessary information and to have good image quality, both in order not to be misinterpreted and to prevent underestimation.

In our study, there was a moderate correlation between the number of followers and the number of interactions. In almost all of the shared ECGs, derivations could be evaluated, paper speed was not specified in about 1/5 of them, and small squares could not be assessed. The posts that did not have a rhythm strip, small squares could be noticed, and explanations made about ECG received significantly more interaction. The fact that followers retweet, add to likes, or reply to a post can encourage the tweet's creator to post new, excessive, jarring, or funny information without being sure of the accuracy of the information being shared. The tweets sent by healthcare professionals may violate patient privacy and cause unethical behavior. Healthcare professionals may engage in risky behaviors such as not taking the possible negative effects of tweets seriously.[20,21] Therefore, linking comments to original evidence, high-quality statements, slide presentations, and lectures can add value to the tweets posted and provide a way for followers to explore the topic further, grasp the topic's nuances, and develop their perspectives.[22]

Limitations

We also believe that hundreds of 12-lead ECGs escaped from this manual scan. While publishing data belonging to a patient in any scientific journal, we get a "signed patient consent form," but it seems that we do not have such a concern in these posts made on social media. This is an important issue that concerns patient confidentiality. Also we cannot detect the healthcare professional status account.

Another limitation of our study was that the effect of twits on improving ECG knowledge was excluded from the study's scope. Studies on ECG learning via social media are needed. There is also a need for researches on how and by whom such ECG sharing should be made.

CONCLUSION

We concluded that 12-derivation ECGs shared on Twitter are highly evaluable. Although the posts are not subject to editorial and reviewer evaluation, social media's role in ECG education before and after graduation is increasing gradually due to its availability at all times. In our study, the posts where small squares could be noticed and case information was presented received significantly more interaction. There was also a moderate correlation between the number of followers and the number of interactions.

ETHICAL DECLARATIONS

Ethics Committee Approval: All information collected from this study was from open accessed Twitter accounts. This study contains publicly available data.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1066691
J Contemp Med 2022;12(3):465-470

Original Article / Orijinal Araştırma

Evaluation of Computed Tomography and PCR Results of Patients Admitted to Pandemic Hospital in Terms of COVID-19

Pandemi Hastanesine Başvuran Hastaların Bilgisayarlı Tomografi ve PCR Sonuçlarının COVID-19 Açısından Değerlendirilmesi

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Abstract

Aim: COVID-19 is an infectious disease that primarily affects the respiratory system and spreads rapidly. In addition to reverse transcription-polymerase chain reaction (RT-PCR), which is the primary diagnostic method in the COVID-19 pandemic, Computed Tomography (CT) method is also used. The aim of this study is to evaluate the appearance and distribution of abnormal parenchymal findings with thorax CT in patients diagnosed with COVID-19 by RT-PCR method and to evaluate the relationship between the severity of lung infection and the clinical course of the disease in these patients.

Materials and Methods: Patients (n:613) with a preliminary diagnosis of COVID-19 who applied to Selçuk University Training and Research Hospital were evaluated retrospectively between December 2020 and February 2021. Nasopharyngeal samples were studied for COVID-19 with RT-PCR by Selçuk University Medical Faculty Microbiology Laboratory. Thoracic CT images of 361 patients with positive COVID-19 PCR tests were examined for the presence of COVID-19 pneumonia. The clinical course of patients with COVID-19 pneumonia was evaluated.

Results: RT-PCR results was positive in 361 (58.9%) of 613 patients. While 243 (67.3%) of the PCR positive patients had signs of pneumonia, 118 (32.7%) of them had normal lung parenchyma. There was consolidation in 22% of the patients, and ground glass with consolidation in 20%. Thirty four patients (14%) had crazy-paving pattern and 19 (7.8%) patients had reverse halo appearance. A significant relationship was found between the severity of lung infection involvement and the clinical course of the disease.

Conclusion: A comprehensive understanding of diagnostic imaging features is essential for effective patient management and treatment.

Keywords: COVID-19, Computed Tomography, PCR

Öz

Amaç: COVID-19, öncelikle solunum sistemini etkileyen ve hızla yayılan bulaşıcı bir hastalıktır. COVID-19 pandemisinde primer tanı yöntemi olan ters transkripsiyon-polimeraz zincir reaksiyonu (RT-PCR) yanısıra bilgisayarlı tomografi (BT) yöntemi de kullanılmaktadır. Bu çalışmanın amacı, RT-PCR yöntemi ile COVID-19 tanısı konulan hastaların toraks BT ile anormal parankimal bulguların görünüm ve dağılımını ve akciğer enfeksiyonun şiddeti ile hastalığın klinik seyri arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Aralık 2020 ile Şubat 2021 tarihleri arasında Selçuk Üniversitesi Eğitim ve Araştırma Hastanesi'ne COVID-19 ön tanısı ile başvuran hastalar (n:613) retrospektif olarak değerlendirildi. Nazofaringeal sürüntü örnekleri Selçuk Üniversitesi Tıp Fakültesi Mikrobiyoloji Laboratuvarında RT-PCR ile COVID-19 açısından çalışıldı. COVID-19 PCR testi pozitif olan 361 hastanın toraks BT görüntüleri COVID-19 pnömonisi açısından incelendi. COVID-19 pnomonisi olan hastaların klinik seyirleri değerlendirildi.

Bulgular: RT-PCR testi 613 hastanın 361'inde (%58.9) pozitifti. RT-PCR testi pozitif olan hastaların 243'ünde (%67.3) pnömoni bulguları varken, 118'inde (%32.7) akciğer parankimi normaldi. Covid-19 hastalarının akciğer bulgularının büyük bir kısmını (%90) buzlu cam görüntüsü oluşturuyordu. Hastaların %22'sinde konsolidasyon, %20 'sinde buzlu cam ile konsolidasyon birlikteliği vardı. Hastaların 34'ünde (%14) çılgın döşeme paterni ve 19'unda (%7.8) ters halo görünümü vardı. Akciğer enfeksiyonu tutulumunun şiddeti ile hastalığın klinik seyri arasında anlamlı ilişki bulundu.

Sonuç: Etkin hasta yönetimi ve tedavisi için tanısal görüntüleme özelliklerinin kapsamlı bir şekilde anlaşılması şarttır.

Anahtar Kelimeler: COVID-19, Bilgisayarlı tomografi, PCR

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Received *(Geliş Tarihi)*: 01.02.2022 **Accepted *(Kabul Tarihi)*:** 18.04.2022

INTRODUCTION

A new type of coronavirus, called severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2), was isolated from lower respiratory tract samples by the International Virus Taxonomy Committee.[1] The disease was named the new coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) on February 11, 2020.[2] Since COVID-19 spread rapidly all over the world, it was declared as a pandemic by WHO.[3] Clinical findings in people infected with COVID-19 range from an asymptomatic course to severe pneumonia requiring mechanical ventilation. The most common symptoms of COVID-19 disease have been defined as fever, dry cough, shortness of breath, muscle pain, loss of taste and smell, diarrhea, and vomiting.[4,5]

Rapid diagnosis is needed because the symptoms of COVID-19 are not specific to the disease and the disease can rapidly progress to severe pneumonia and even cause death.[6] Because of the high contagiousness of COVID-19, it is important to detect the disease early and isolate the infected person from the healthy population. For the definitive diagnosis of COVID-19, the SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) test must be positive from the nasopharyngeal and throat swab samples. RT-PCR test is considered the gold standard in the diagnosis of COVID-19. RT-PCR sensitivity has been reported between 30% and 60% in the first test due to difficulties in sampling, processing, and kit performance.[7] In cases where RT-PCR is false negative, imaging methods have gained importance for the diagnosis of rate. Chest radiography has played an important role in the clinical follow-up of COVID-19 patients, especially intensive care patients. During the pandemic process, Computed Tomography (CT) has been accepted as the most valid imaging method because its sensitivity in showing COVID-19 pneumonia is 98%.[8]

In suspicious cases, CT imaging has gained great importance in terms of making a diagnosis before the RT-PCR test and reducing the risk of transmission by early isolation of the infected person.[9] Currently, thoracic CT has been accepted as one of the main tools for screening, primary diagnosis and evaluation of disease severity.[10] The aim of this study is to evaluate the appearance and distribution of abnormal parenchymal findings from thorax CT images of patients diagnosed with COVID-19 by RT-PCR and to evaluate the relationship between the severity of lung infection and the clinical course of the disease in these patients.

MATERIAL AND METHOD

It is a retrospective study evaluating patients who applied to Selçuk University Training and Research Hospital between December 2020 and February 2021 due to COVID-19. Samples taken from patients with suspected COVID-19 were evaluated by Selçuk University Medical Faculty, Medical Microbiology Laboratory and patients who were found to be RT-PCR positive were included in the study. Pulmonary parenchymal findings of patients with positive RT-PCR test were evaluated in terms of COVID-19 in thorax CT taken at Selçuk Unviersity Training and Research Hospital.

Nasopharyngeal swab samples taken with dacron swaps from patients with suspected COVID-19 were sent to Selçuk University Medical Faculty Hospital Medical Microbiology Laboratory with transfer tubes containing 2 ml VNAT (Viral Nucleic Acid Buffer). After the samples were vortexed, the RT-PCR step took place. BioSpeedy® Direct RT-qPCR SARS-CoV-2 (Bioeksen R&D Technologies Ltd., Istanbul, Turkey) kit was used for RT-PCR. After PCR, RT-qPCR was performed on LightCycler96 (Roche, Switzerland) instrument in accordance with the manufacturer's instructions. Samples that formed a logarithmic curve at the end of the study were accepted as positive (cq<38).

Parenchymal involvement of patients with COVID-19 lung involvement was evaluated as right, left and both lungs from thorax CT images. A severity score was calculated by adapting the scoring made by HYF Yong et al. The involvement score of 0% was scored as zero, the involvement score of less than 5%, the score as 1, the 5-25% involvement score as 2, the 25-50% involvement score as 3, the 50-75% involvement score as 4, and the more than 75% involvement score as 5. The sum of the scores will provide a semi-quantitative assessment for general lung involvement. (Maximum CT score for both lungs was 25). Scoring determined for lung involvement was divided into groups as lung infection severity. The total lung involvement score in the right and left lungs is grouped as 0-5 (Mild), 6-10 (Mild-Moderate), 11-15 (Moderate), 16-20 (Moderate-Severe) and 21-25 (Severe) lung infection.

In addition, patients with lung infections were grouped as outpatients, those who were treated in the hospital ward and intensive care unit, and those who were dead. COVID-19 lung involvement was evaluated in terms of the most common ground glass pattern (GGO), cobblestone view (interlobular and intralobular septal thickening with GGO), consolidation (homogeneous opacification). In addition, secondary findings such as linear opacity (linear, curvilinear opacity or subpleural reticulation), pleural and pericardial effusion, nodule, reverse halo, and lymph node with a short axis greater than 1 cm were also evaluated. The presence of pulmonary lesions were grouped as peripheral (outer 1/3 of the lung parenchyma) and central (inner 2/3 of the lung parenchyma) and diffuse (peripheral and central). Involvement of pulmonary lesions was noted as single lobe, unilateral multilobe and bilateral multilob.

Our study was approved by the Ethics Committee of the Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee of Selçuk University in 24.02.2021, with the decision of the ethics committee numbered 2021/96.

Statistical Analysis

All statistical analyzes were carried out with the help of IBM SPSS 21.0 package program. Before statistical analysis, the normal distribution compliance of the semi-quantitative scoring used to determine the degree of lung involvement was checked with the Shapiro Wilk normality test. Scoring findings

were given as mean ± standard deviation, and findings related to other radiological parameters used in the study were given as frequency (n) and percentage (%). Comparison of the involvement scores of the patients in the lower and upper lobes of the lungs was compared using an independent sample t-test. In statistical tests, the significance level was taken as 5%. Data are described as number, percentages (95% confidence intervals). Confidence intervals were calculated by Clopper-Pearson method. p-value was calculated using Chi-square proportion test.

RESULTS

613 patients who applied to Selçuk University Training and Research Hospital were evaluated retrospectively. While 361 (58.9%) of the RT-PCR 613 patients were positive, 252 (41.1%) patients were negative. The lung parenchyma was normal in 118 (32.7%) while there were abnormal findings in the lung parenchyma in 243 of the PCR positive patients (67.3%). While 57 (22.6%) of 252 patients with negative RT-PCR test had abnormal findings in the lung parenchyma, 195 (77.4%) had normal lung parenchyma (**Table 1**). Thoracic CT sensitivity 67.3% (95% CI 62-72%), specificity 77.4% (95% CI 71-82%), positive predictive value 81% (95% CI 77-84), and negative predictive value 62% (95% CI 58-66%) were detected.

Table 1. Evaluation of lung involvement with RT-PCR in patients admitted to the hospital (n = 613)

	Lung involvement positive N(%)	Lung involvement negative N(%)	Total
RT-PCR (+)	243 (67.3)	118 (32.7)	361
RT-PCR (-)	57 (22.6)	195 (77.4)	252

Abnormal findings were found in the lung parenchyma in 243 (67.3%) of 361 patients with positive RT -PCR test. The distribution of lung parenchymal findings of RT-PCR positive COVID-19 patients (n = 243) with lung involvement is shown in **Table 2**. Right and left lung involvement rates were very similar and there was no significant difference ($p < 0.05$). Although the bilateral lower lobe involvement percentage was higher, there was no significant difference between the upper and lower lobe involvement rates ($p < 0.05$).

Abnormal parenchymal findings observed in 243 of RT-PCR positive COVID-19 patients were evaluated as primary and secondary findings and summarized in **Table 3**. The majority of the lung findings of COVID-19 patients were ground glass (GGO). Pericardial effusion was not detected in any patient.

Table 2. Distribution of lung parenchymal findings of RT-PCR positive COVID-19 patients (n = 243) with lung involvement

	N (%)
Right lung	234 (96.3)
Left lung	229 (94.2)
Bilateral lung	221 (90.9)
Single lobe	23 (9.4)
Single sided multilob	217 (89.3)
Bilateral multilob	184 (75.7)
Peripheral	234 (96.3)
Central	136 (56)
Peripheral and central	134 (55.1)
Right lung upper lobe	174 (71.6)
Right lung middle lobe	191 (78.6)
Right lung lower lobe	225 (92.6)
Left lung upper lobe	207 (85.2)
Left lung lower lobe	214 (88.1)
Upper lobe involvement	223 (91.8)
Lower lon involvement	233 (95.9)

Table 3. Characteristics and distribution of parenchymal findings of Covid-19 patients with lung involvement (n:243)

COVID-19 primary findings	N (%)
Ground glass (GGO)	233 (95.9)
Consolidation	54 (22.2)
Ground glass + consolidation	49 (20.2)
Crazy paving	34 (14)
Secondary findings	
Linear opacity	61 (25.1)
Reverse halo	19 (7.8)
Nodule	32 (13.2)
Pleural effusion	9 (3.7)
Mediastinal lymph node	25 (10.3)
Pericardial effusion	0

The distribution of lung parenchymal involvement according to lobes and scores is shown in **Tables 4** and **5**. In lung parenchymal involvement scoring, 3 and above (≥ 25-50%) involvement rate was evaluated as high score; Scores below 3 are considered as low scores. While high score was higher in upper lobes, low score was observed more in lower lobes. The difference between them is statistically significant ($p < .001$). The mean lung involvement score was higher in the left lung compared to the right lung. The mean score in the right lung was highest in the lower lobe; It was mostly detected in the upper lobe of the left lung.

Table 4: Distribution of lung parenchymal involvement by lobes and scores

	Score 0 (%)	Score 1 (%)	Score 2 (%)	Score 3 (%)	Score 4 (%)	Score 5 (%)	Mean±SD
Right lung upper lobe	28.3	46.9	14.8	5.7	3.2	0.8	1.11±1.04
Right lung middle lobe	21.3	49	18.5	4.5	4.5	1.2	1.25±1.06
Right lung lower lobe	7.4	41.9	27.5	9.8	4.1	9	1.37±1.05
Left lung upper lobe	14.8	53.4	19.3	6.1	4.9	1.2	1.88±1.34
Left lung lower lobe	11.9	46.9	20.9	9.4	2.4	8.2	1.68±1.34

Table 5. Lung parenchymal involvement scoring and statistical comparison (n:243)

	Score <3 (Low Score) N (%)	Score ≥3 (High Score) N (%)	P value
Right lung upper lobe	24 (9.9)	219 (90.1)	<.001
Right lung middle lobe	25 (10.3)	218 (89.7)	<.001
Right lung lower lobe	56 (23)	187 (77)	<.001
Left lung upper lobe	30 (12.4)	213 (87.6)	<.001
Left lung lower lobe	49 (20.2)	194 (79.8)	<.001

Scoring determined for lung involvement was divided into groups as lung infection severity. The total lung involvement score in the right and left lung was grouped as 0-5 Mild, 6-10 Mild-Moderate, 11-15 Moderate, 16-20 Medium-Severe and 21-25 Severe lung infection. In addition, patients with lung infections were grouped as outpatients, those treated in the hospital ward and intensive care unit, and those who were dead. A significant relationship was found between the severity of lung infection involvement and the clinical course of the disease. While 58.3% of the patients with mild lung infection were treated on an outpatient basis; 80.9% of the patients with mild-moderate lung infections were treated in the service at the hospital. While none of the patients with moderate and severe lung infections were on an outpatient basis, 36% were found to be dead, 9% were treated in the intensive care unit and the rest in the service. There was a significant relationship between the course of the disease and age, and as the age increased, the treatment and ex rates in the intensive care unit increased. While the average age of the outpatients was 47; The average age of those treated in the intensive care unit and the patients who died was 69 years old. There was no significant relationship between the severity of lung infection and age.

DISCUSSION

COVID-19 is an infectious disease that primarily affects the respiratory system, starting in China and causing a pandemic by spreading all over the world. Early diagnosis methods play an important role in controlling the disease.[11] RT-PCR and thorax CT imaging has been accepted as the most important diagnostic methods. Although RT-PCR is the gold standard, radiological imaging methods have gained importance because of its false negative results. Thorax CT has become the prominent diagnostic method in COVID-19 due to its high sensitivity in showing abnormal changes in the lung parenchyma in the early period.[12,13]

In the study conducted by T.Ai et al.[14] on 1014 patients, the sensitivity of thorax CT in demonstrating COVID-19 infection was found to be 97% and specificity 25% by reference to RT-PCR. In our study, thorax CT sensitivity was found lower and specificity was higher. More than 80% of patients with negative RT-PCR tests had typical CT signs. On the one hand, because of the overlap of CT imaging features between COVID-19 and other viral pneumonia, false positive cases of COVID-19 can be identified by chest CT.

T.Ai et al.[14] in 90% of 888 patients, Chung et al.[12] in 76% of 21 patients, a review study of 919 patients,[15] 87.5% of bilateral lung involvement was demonstrated. Bilateral lung involvement was 61.2% in our study, and bilateral lung involvement was less than other studies. In addition, no significant difference was reported between the rates of right and left lung involvement in the studies performed, and similarly, no significant difference was found between the two lung involvement rates in our study.[16,17]

Song et al.[18] reported single lobe involvement 8% and five lobe involvement 39%; Liu et al.[19] reported a single lobe involvement rate as 8% and five lobe involvement rate as 43%, Chung et al.[12] reported a five-lobe involvement rate as 38%. In our study, the single lobe involvement rate was 9.4% and the five lobe involvement rate was 35%, which is similar to other studies. Peripheral location rate was reported by Han et al.[20] 90% of 108 patients, Song et al.[18] reported 84%, and 76% in a review study[15] of 919 patients. Since the blood and lymph flow is more intense in the peripheral area, the inflammatory response to the virus is most common in these areas. Lesions in thoracic CT imaging are often thought to be secondary to this hypothesis with peripheral localization.[20] In our study, central and peripheral-central (mixed) involvement was similar, and no difference was observed.

Han et al. detected ground glass in 80% of 108 patients, ground glass and consolidation in 41%, and crazy paving stone pattern in 40%.[20] W. Zhao et al.[22] found the ground glass frequency 86.1% and consolidation frequency 43.6%; Wu et al.[21] reported the ground glass ratio as 53.2% and the consolidation rate and ground glass ratio together as 46.2%. T.Ai et al.[14] detected ground glass in 46% and consolidation in 50% of 888 patients. Similar to other studies, the rate of ground glass was found to be higher in our study. Consolidation and consolidation-ground glass association was less determined.

Table 6. Comparison of the severity and clinical course of lung parenchymal involvement

Score	Lung Involvement Severity	N (%)	Outpatient Treatment N (%)	Treatment in the Ward N (%)	Intensive care N (%)	Ex N (%)	P
							<.001
0-5	Mild	110 (45)	63 (58.3)	42 (8.9)	2 (1.9)	1 (0.9)	
6-10	Mild-Moderate	89 (36.6)	12 (13.5)	72 (80.9)	1 (1.1)	4 (4.5)	
11-15	Moderate	22 (9)	2 (9.1)	17 (77.3)	1 (4.5)	2 (9.1)	
16-20	Medium-Severe	13 (5.3)	0 (0)	9 (69.2)	0 (0)	4 (30.8)	
21-25	Severe	9 (3.7)	0 (0)	3 (33.3)	2 (22.2)	4 (44.4)	

Jin et al.[23] found secondary findings such as bronchial wall thickening, pleural effusions, lymphadenopathy, and ground glass-surrounded pulmonary nodules in approximately 7% of patients. In our study, 25 (10%) patients had mediastinal lymph nodes, 19 (7.8%) patients had reverse halo, 32 (13%) patients had nodules, and 9 (3.7%) patients had pleural effusion. Secondary findings were detected low. In some studies,[15,24] differences in ground glass and consolidative opacity ratios were found to be statistically significant between age groups ($p < 0.001$). In our study, no significant relationship was found between age and the pattern of ground glass, consolidation, ground glass-consolidation, and crazy paving lung involvement. While Song et al. Commonly reported secondary findings in elderly patients, no significant relationship was found between these findings and age in our study.[18]

There are not many studies evaluating pulmonary parenchymal involvement by scoring in the literature. In this study, a semi-quantitative scoring method was used to assess the amount of lung opacification of 5 lobes and the COVID-19 burden. In our study, the mean lung involvement score was higher in the left lung than in the right lung. R. Yang et al.[25] did not find a significant difference between left and right lung scores. In our study, while 3 or more (≥ 25-50%) involvement rate was evaluated as a high score in the scoring of lung parenchymal involvement; scores below 3 are considered as low scores. R. Yang et al. used a different scoring method than our study. However, they found lower lobe scores higher than middle-upper lobe scores in both patients with low and high scores. In our study, while the high score was higher in the upper lobes, the low score was observed more in the lower lobes. The difference between them was statistically significant ($p < .001$).

Among the secondary findings, only a relationship was observed between pleural effusion and moderate to moderate-severe lung infection, but no significant relationship was observed between other secondary findings and the severity of lung infection. While R.Yang et al.[25] detected pleural effusion in seven cases and lymphadenopathy in two cases in the severe group, they did not detect pleural effusion and lymphadenopathy in the mild group.

Ground glass pattern was the most common in patients with low and high scores. Patients with pure consolidation with ground glass and consolidation were mostly high scored patients. The crazy paving pattern was more common in high scoring patients than in low scoring patients. Li K et al.[26] compared the chest CT findings of patients with severe and mild COVID-19 pneumonia and reported that the consolidation rate was 88% in patients with severe disease and 53.4% in patients with milder symptoms. Similarly, in our study, more consolidation was observed in patients with high scores than in patients with low scores.

There was no relationship between the ground glass pattern and the course of the disease. Patients with consolidation (15%) compared to patients without (4%) consolidation with ground glass (11%), those with a crazy-paving pattern (21%) compared to those without (4%), compared to those without (4%) It was thought that the ex rate increased. There was no significant relationship between pulmonary involvement patterns and those treated in the intensive care unit, suggesting that patients with consolidation, consolidation and ground glass, crazy-paving pattern had a worse prognosis than those without.

CONCLUSION

While there are abnormal findings in the lung at the time of diagnosis in the majority of RT-PCR positive patients; there were also patients who were negative for RT-PCR but showed typical findings for covid pneumonia in the lung. In the cases of COVID-19, a largely ground-glass pattern with peripheral localization was observed on CT. While ground glass pattern was observed in patients with low and high scores, consolidation on ground glass, pure consolidation, and crazy cobblestone view were observed more in patients with high scores. While the high score was higher in the upper lobes, the lower score was higher in the lower lobes. Among the secondary findings, a relationship was observed between pleural effusion and the severity of infection. A significant relationship was found between the severity of lung infection involvement and the clinical course of the disease. While none of the patients with moderate and severe lung infections were on an outpatient basis, one third of them died and the rest were treated in the intensive care unit and the ward. A significant relationship was found between the course of the disease and age, and as age increased, treatment and ex rates in the intensive care unit increased.

A comprehensive understanding of diagnostic imaging features is essential for effective patient management and treatment. In the patient population suspected of COVID-19, typical imaging findings of COVID-19 should be interpreted with caution. In addition, this study provides a simple semi-quantitative method to assess the severity of COVID-19 on initial chest CT images. Thus, the course of the disease can contribute to patient management.

This study had some limitations. While evaluating the thorax CT sensitivity and specificity, the interpretation was made according to the first RT-PCR and thorax CT images.

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved by the Ethics Committee of the Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee of Selçuk University in 24.02.2021, with the decision of the ethics committee numbered 2021/96.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1076070
J Contemp Med 2022;12(3):471-475

Original Article / Orijinal Araştırma

Herpes Zoster in Children with Underlying Comorbidities: Evaluation of the 10-Year Retrospective Single Center Experience

Altta yatan Komorbiditeleri Olan Çocuklarda Herpes Zoster: 10 Yıllık Retrospektif Tek Merkez Deneyiminin Değerlendirilmesi

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Abstract

Aim: It was aimed to evaluate the complications and prognosis of pediatric patients diagnosed with Herpes zoster (HZ) with an underlying comorbidity.

Material and Method: Between 01.01.2011-01.01.2021 in our clinic; patients aged 0-18 years, with underlying comorbidities and diagnosed with HZ, who were followed up and treated, were evaluated retrospectively. A total of 45 patients were included in the study. Sociodemographic characteristics, clinical findings, treatments applied during hospitalization, complications developed during follow-up and prognosis were obtained from hospital file archive records.

Results: The mean age was 9.25±4.79 years, and 53.4% of patients were male. The most common symptom was rash, followed by pain and itching. Most commonly, 23 (51.1%) patients had thoracic dermatome involvement. Dissemination did not develop in any of the patients. 11.1% of the patients had chickenpox, 6.6% had Varicella vaccine, and 44.4% had no history of Varicella Zoster Virus transmission. Acute leukemia and having had a bone marrow transplant were the most common co-existing conditions. Median time between onset of symptoms and diagnosis was 3 (min-max=1-10) days. Median length of hospitalization was 7 (min-max=3-21) days, and the mean total treatment time was 9.33±3.58 days. It was determined that only four patients developed secondary skin infection, 44 patients were cured, and 1 patient died due to the primary disease.

Conclusion: While HZ is rare in healthy children, it can progress with serious complications in those with an underlying disease. To consider HZ in differential diagnosis of vesicles in immunocompromised patients, to start treatment with early diagnosis; It is of great importance in terms of complications and prognosis that may develop.

Keywords: Herpes zoster, child, underlying disease, immunocompromise, prognosis

Öz

Amaç: Altta yatan ek hastalığı olan Herpes zoster (HZ) tanısı almış çocuk hastaların komplikasyonlarının ve prognozlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Kliniğimizde 01.01.2011-01.01.2021 tarihleri arasında 0-18 yaş arası altta yatan ek hastalığı bulunan ve HZ tanısı konularak takip ve tedavi edilmiş hastalar retrospektif olarak değerlendirildi. Çalışmaya toplamda 45 hasta dahil edildi. Sosyodemografik özellikleri, klinik bulguları, hastane yatışları süresince uygulanan tedaviler ve takipte gelişen komplikasyonları ve prognozları dosya kayıtlarından elde edildi.

Bulgular: Ortalama yaş 9,25±4,79 yıl olup hastaların %53.4'ü erkek idi. En yaygın semptom döküntü iken bunu ağrı ve kaşıntı izlemekteydi. En sık olarak 23 (%51.1) hasta ile torakal dermatom tutulumu mevcuttu. Dört (%8.8) hastada birden fazla dermatom tutulumu vardı. Hastaların hiçbirinde disseminasyon gelişmedi. Hastaların %11,1'i suçiçeği geçirmiş, %6,6'sı suçiçeği aşısı olmuş, %44,4'ünün Varisella Zoster Virus enfeksiyonu geçirme öyküsü bilinmiyordu. Akut lösemi ve kemik iliği nakli olmuş olma en sık altta yatan ek durumlardandı. Semptomların başlama ve tanı koyma arasındaki ortanca süre 3 (min-max=1-10) gündü. Hastaların tümüne asiklovir tedavisi başlandı. Yatış ortanca süresi 7 (min-max=3-21) gün, toplam tedavi süresi ortalama 9,33±3,58 gündü. Sadece dört hastada sekonder cilt enfeksiyonu geliştiği, 44 hastanın şifa ile iyileştiği ve 1 hastanın primer hastalığı nedeniyle exitus olduğu saptandı.

Sonuç: HZ sağlıklı çocuklarda nadir iken alta yatan hastalığı olanlarda ciddi komplikasyonlarla seyredebilir. İmmünkompromize hastalarda veziküllerin ayırıcı tanısında HZ'yi düşünmek, erken tanı konularak tedavi başlamak; gelişebilecek komplikasyonlar ve prognoz açısından büyük öneme sahiptir.

Anahtar Kelimeler: Herpes zoster, çocuk, altta yatan hastalık, immünkompromize, prognoz

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Received *(Geliş Tarihi)*: 21.02.2022 **Accepted *(Kabul Tarihi)*:** 15.03.2022

INTRODUCTION

Herpes zoster (HZ), also known as shingles, is a viral infectious disease that occurs as a result of the reactivation of the latent Varicella Zoster Virus (VZV) in the sensory ganglia. It is characterized by a painful, vesicular rash, usually unilateral, limited to the dermatome.[1,2] Shingles is a disease seen in old age. It is extremely rare in healthy children. The incidence of HZ infection is 2.6/1000 per year in children with previous chickenpox.[3] Lesions are usually in thoracic and cervical dermatomes and the most common symptoms are pain and itching.[3]

Especially with T cell deficiency, HZ may progress more frequently and severely in cases of immunodeficiency such as Human Immunodeficiency Virus infection, malignancies such as leukemia or lymphoma, transplant recipients, primary immunodeficiency, and use of immunosuppressive drugs.[1,4-6] It can lead to serious complications such as postherpetic neuralgia, visceral dissemination, HZ ophthalmicus, HZ oticus, acute retinal necrosis, neurological (aseptic meningitis, encephalitis, myelitis, Guillain Barre Syndrome), secondary bacterial infection, and even death, especially in immunocompromised patients.[1,4,7-9] Early diagnosis and treatment in immunocompromised individuals determine the prognosis.

The aim of this study was to evaluate the demographic clinical features of pediatric patients diagnosed with HZ with an underlying disease, and to determine the complications and prognosis of the disease in these patients.

MATERIAL AND METHOD

Patients under the age of 18 with an underlying disease diagnosed with HZ, who were followed up in the Çukurova University Medical Faculty, in Department of Pediatric Infection Disease Clinic between 01.01.2011 and 01.01.2021, were included in the study. The files of the patients were reviewed retrospectively. The age, gender, complaint and duration of admission, underlying diseases, immunosuppressive drugs used, physical examination findings, laboratory findings, Varicella or vaccination status, duration of hospitalization, treatment and duration, complications and prognosis were recorded in the follow-up sheets. The diagnosis of HZ was made by physical and clinical examinations. Ethical approval of the study was obtained from the local ethics committee (No: 108, 12/02/2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical analysis

SPSS version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) was used for statistical analysis. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean, deviation, and minimum-maximum.

RESULTS

In a 10-year period, 50 patients were diagnosed with HZ. Five healthy patients were excluded from the study. 45 patients with underlying disease were included in the study. 24 patients (53.4%) were male and 21 (46.6%) were female. The mean age was 9.25±4.79 years. Nine (20%) patients were immigrants. 11.1% of the patients had chickenpox, 6.6% had Varicella vaccine, 37.8% was Varicella IGG positive, and the history of VZV was unknown in 44.4%. The demographic characteristics of the patients are shown in **Table 1**.

Table 1. Demographic Characteristics of Patients with Herpes Zoster

		Mean±SD
Age (year)		9.25±4.79
Hospitalization period (day)		7.89±4.17
Treatment period (day)		9.33±3.58
		n (%)
Gender	Male	24 (53.4)
	Female	21 (46.6)
Ethnicity	Turkish Republic citizen	36 (80)
	Syria	9 (20)
Encountering with Varicella	Chickenpox	5 (11.1)
	Chickenpox vaccinated	3 (6.6)
	Varicella IGG positivity	17 (37.8)
	Unknown	20 (44.4)
Dermatome involvement	Thoracic	23 (51.1)
	Cervical	6 (13.3)
	Trigeminal	5 (11.1)
	Lumbar	5 (11.1)
	Sacral	2 (4.4)
	Lumbar + Sacral	2 (4.4)
	Thoracic + Cervical	1 (2.2)
	Cervical+ Trigeminal	1 (2.2)

The most common involvement was thoracic dermatome in 23 (51.1%) patients. Six (13.3%) patients had cervical, five (11.1%) trigeminal, five (11.1%) lumbar, and two (4.4%) patients had sacral involvement. Four (8.8%) patients had more than one dermatome involvement. Two (4.4%) patients had lumbar and sacral involvement, one (2.2%) patient had thoracic and cervical involvement, and one (2.2%) patient had cervical and trigeminal involvement. None of the patients had facial nerve and generalized involvement. No involvement was detected in the eye examination of the patient with trigeminal involvement.

The most common symptom was pain and itching after the rash. 21 (46.6%) patients had only rash, 12 (26.6%) had pain, four (8.8%) had itching, four (8.8%) had pain and itching, three patients (6.6%) had fever, and one (2.2%) patient had pain and fever. Median time between onset of symptoms and diagnosis was 3 (min-max=1-10) days.

The most common underlying diseases were acute leukemia and bone marrow transplantation (**Table 2**). 26 of the patients were receiving active chemotherapy, three patients were

using high-dose steroids, and six patients were using other immunosuppressive drugs. Two patients were receiving monthly IVIG therapy. 10 patients were not receiving any treatment.

Table 2. Underlying Diseases of the Patients

	n (%)
Acute leukemia	17 (37.7)
Bone marrow transplant	9 (20)
Lymphoma	3 (6.6)
Medulloblastoma	3 (6.6)
Solid organ transplant	2 (4.4)
Hemophagocytosis	2 (4.4)
Immunodeficiency	2 (4.4)
Chronic myeloid leukemia	1 (2.2)
Angiosarcoma	1 (2.2)
Histiocytosis	1 (2.2)
Malignant mesenchymal tumor	1 (2.2)
Uveitis *	1 (2.2)
Metabolic disease	1 (2.2)
Nephrotic syndrome	1 (2.2)

*Biological agent use

Acyclovir treatment was started in all patients. Intravenous acyclovir treatment at a dose of 10 mg/kg/dose three times a day or oral acyclovir 80 mg/kg four times a day was administered. The median hospital stay was seven (min-max=3-21) days, and the mean total treatment time was 9.33±3.58 days.

Secondary skin infection developed in only four (8.8%) patients. It was determined that 44 patients recovered with healing and one patient died due to the primary disease.

DISCUSSION

The Centers for Disease Control and Prevention (CDC) estimates that about 30% of people in the United States will have HZ in their lifetime.[10] HZ can occur at any time after people have had chickenpox infection or have been vaccinated. It is rare in healthy children, however the occurrence of HZ does not always mean that there is an underlying immunodeficiency or malignancy.[11] Early diagnosis and treatment in HZ infection are of great importance in terms of preventing complications and prognosis.

The most common symptoms of the disease are pain and pruritus associated with a unilateral vesicular rash, typically involving a single dermatome. These symptoms interfere with quality of life and may impair functionality.[2] Studies have reported that the most common symptoms in healthy children are pain, followed by itching and fever.[12,13] In a study, it was reported that fever, pain, and general symptoms were less common in immunocompromised patients compared to healthy children, and itching was more common.[14]

In our study, the most common symptoms were pain, followed by itching and fever, and 4.4% of the patients did not have any complaints and were discovered by chance. HZ should be considered in the differential diagnosis of vesicle in immunocompromised patients and patients with underlying disease, and it should also be considered that it may be asymptomatic. Even if there are no symptoms, especially in immunosuppressive patients, the importance of performing a detailed physical examination has emerged once again.

The most common dermatome involvement is seen in the thoracic region. Different results in terms of localization of the lesion have been reported between immunocompromised and immunocompetent patients. It has been reported in studies that thoracic and trigeminal dermatomes are the most frequently involved, respectively, and lumbar-sacral dermatome is more common in immunocompromised patients.[7,15] Kuchar et al.[14] reported that thoracic and cranial-cervical dermatome involvement was the most common, but there was no difference in terms of localization between immunocompromised and healthy patients. It has been reported that dissemination is more common in immunocompromised patients.[14,15] All of the patients in our study were immunosuppressive patients with an underlying disease, and we found thoracic, cervical, trigeminal, and dermatome involvement, respectively (51.1%, 13.3%, 11.1%). We did not have any patients with disseminated involvement, but four (8.8%) patients had involvement in two different dermatomes. More than one dermatome has not been reported in studies conducted in healthy children in the literature.[12,13] These results support the conclusion that more than one dermatome involvement and the risk of dissemination are higher in immunocompromised patients. Consistent with the literature in terms of gender, it was found to be higher in males.[7,8,12,15] However, there are also studies reporting that it is more dominant in females.[16] In general, the incidence is lower in children aged 0-5 years compared to adolescents.[17] In the literature, they found the incidence to be high between the ages of 7-14 years.[4,8,18,19] The median age in our patient group was 10.08 years. The age of onset of shingles is similar between immunocompromised and immunocompetent patients.[4,15]

The most common complication of HZ is post-herpetic neuralgia. Other complications include bacterial superinfection of the eye, neurological system, and skin. Immunocompromised patients are at risk of more frequent episodes of HZ and/or serious complications associated with VZV. Serious complications include cutaneous spread and visceral involvement.[2] Grote et al.[7] reported that the most common skin infections were ophthalmic zoster and meningoencephalitis as complications, and that no complications other than disseminated HZ were statistically significantly more common in immunocompromised children. Takayama et al.[15] reported complications of dissemination, meningitis, and facial nerve palsy, and they found no difference between the two groups. Kuchar et al.[14] also found no difference between the two groups in terms

of complications. Kanamori et al.[8] observed that the most common complication was secondary skin infection, and facial paralysis, uveitis/keratitis, and acute retinal necrosis were more serious complications, and they reported complications to be more frequent in immunocompromised patients. In our study, secondary skin infection was seen in only four patients. With these results, it should be emphasized that the disease is not always a mild course in healthy children, and it can be seen with serious complications such as in patients with an underlying disease. It has been reported that the incidence of HZ is high in immunocompromised patients, complications are more common, and the hospitalization period is long.[6,20-22] However, Grote et al.[7] reported that 41% of the 244 HZ patients who were hospitalized and followed up had an underlying disease (32% immunosuppressed and the majority of them were hemato-oncological diseases) and the average hospitalization period was 7 (min-max=5-10) days. All of our patients were hospitalized and 37.7% had leukemia. The average length of hospital stay was 7 (min-max=3-21) days. The duration of hospitalization and treatment differed from patient to patient.

In order to heal HZ lesions faster, to prevent the development of new lesions, to reduce the risk of transmission, and to reduce the severity and duration of pain associated with acute neuritis, it is recommended to start treatment in the first 72 hours after the onset of symptoms.[23,24] In immunocompromised patients, treatment should be initiated even if they apply to the hospital later. Recognition of symptoms and initiation of early treatment are of great importance, especially in cancer patients, in children with cancer since HZ can cause serious complications such as herpetic neuralgia, dissemination, acute or progressive outer retinal necrosis and even death.[4]

Acyclovir has been shown to be effective in the treatment of HZ in healthy and immunocompromised patients. We started acyclovir intravenously in all of our patients because they had an underlying disease independent of the duration of the symptoms. Therefore, we did not see any serious complications. Although the duration of treatment is 7 days on average, it can be continued until two days after the new lesion has stopped.[2,25] In our study, the mean duration of acyclovir treatment was found to be 7 days. However, we had a patient who received treatment for 21 days depending on his clinical condition. We think that it would be an appropriate approach to decide the duration of treatment, especially in immunocompromised patients, according to the clinical situation and to evaluate it on a patient basis.

The most important risk factor for the development of HZ has been reported to be intrauterine or chickenpox in the first years of life.[26] The main reasons for the development of HZ in pediatric patients are, the immature immune system and low cellular response, and primary infection in the first year of life.[26] Although it has been suggested that Varicella vaccine may increase the risk of HZ in immunocompromised patients, several studies have reported that Varicella vaccine reduces the incidence of HZ.[27,28] However, the effectiveness of vaccination in preventing complications is unknown. In our study, 44.4% of the patients did not have any information or evidence of previous vaccination or chickenpox. Only five patients had a history of chickenpox, and three patients had a history of vaccination. In 17 of the patients, Varicella IGG was positive, and we could not reach sufficient information whether these antibodies were from vaccinated or not. In our study, HZ was evaluated only in patients with underlying disease. Therefore, the data are limited. Healthy children were excluded from the study due to the very small number of children. More multicenter studies are needed to compare the two groups in terms of frequency and prognostic complications.

CONCLUSION

HZ can be seen in healthy or immunocompromised pediatric patients. It may be more frequent and at risk for complications in immunosuppressive patients with underlying disease. Considering HZ in the differential diagnosis of vesicle, especially in patients with underlying disease and immunocompromised, is of great importance in terms of early diagnosis, initiation of treatment, complications, and prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained from Çukurova University Non-Interventional Clinical Research Ethics Committee (Date: 12/02/2021, Number of Meeting/ Decision No:108/4).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.931808
J Contemp Med 2022;12(3):476-477

Case Report / Olgu sunumu

A Case of Maturity Onset Diabetes of the Young: Just Keep of Mind

MODY Tip Diyabet Olgu Sunumu: Sadece Akılda Tutun

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Abstract

Maturity onset diabetes of the young (MODY) is a monogenic, autosomal dominant form of diabetes characterised by mutations in genes resulting in dysfunction of pancreatic β-cells and subsequent insulin production. HNF1A-MODY is nonketotic diabetes with onset during childhood, adolescence, or early adulthood, progressive character of hyperglycemia with a high risk for chronic microvascular diabetes complications.[1] We present a child with HNF1A-MODY due to a likely pathogenic mutation HNF1-A gene (c,787C > T(p.R263C) (c.Arg263ys)) diagnosed incidentally.

Keywords: MODY, hyperglycemia, diabetes

Öz

MODY tip diyabet , pankreas β hücrelerinin işlev bozukluğu ve ardından insülin üretimi ile sonuçlanan , monojenik, otozomal dominant bir diyabet formudur. MODY, kronik mikrovasküler diyabet komplikasyonları açısından yüksek riskli, hipergliseminin ilerleyici karakterde olduğu , çocukluk, ergenlik veya erken yetişkinlik döneminde başlayan, ketotik olmayan diyabet tipidir.[1] Bu yazıda rastlantısal tanı alan HNF1-A genine (c, 787C> T (p.R263C) (c.Arg263ys)) gen mutasyonuna bağlı HNF1A-MODY'li bir hasta sunuldu.

Anahtar kelimeler: MODY, hiperglisemi, diyabet

INTRODUCTION

Diabetes mellitus is commonly known to be divided into type 1 and type 2, both with etiologies involving complex interplay between multiple genetic and environmental factors. In addition and less well-known, there is a third category of diabetes with specific etiologies including diabetes secondary to a drug, transplant, injury, or other genetic or non-genetic illness; and syndromic and non-syndromic forms caused by a mutation in a single gene. MODY is one of the most well-known forms of monogenic diabetes.[2] Genetic variants of 13 known genes cause MODY through pancreatic beta cell dysfunction that leads to elevated blood glucose. MODY is estimated to make up at least 1% of all cases of diabetes. The three most common forms of MODY are caused by mutations in HNF4A, GCK, and HNF1A, and they make up the majority of all MODY cases.[3,4]

CASE REPORT

A 13 year old male syrian refugee patient referred from ophtalmology department because of hyperglycemia. He was hospitalized with the diagnosis of iridocyclitis. His blood glucose level was 1066 mg/dl in the absence of ketoacidosis. There was no ketonuria or glycosuria. He had not any complaint or symptoms. Initial glycosylated haemoglobin (HbA1c) was 20.7%. His body weight was 52 kg (0.16 sds), with a height of 162 cm (0.72 sds).He was at Tanner stage III. The rest of the physical examination were normal. Treatment was started in the form of multiple-dose insulin with basal insulin (glargine) and bolus insulin (aspart), resulting in acceptable blood glucose levels. The celiac disease markers were negative, and the thyroid profile was normal. Microalbuminuria proved negative. The other study findings at the start of diabetes, with cardiological, ophthalmological

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Received *(Geliş Tarihi)*: 03.05.2021 **Accepted *(Kabul Tarihi)*:** 05.01.2022

and neurological evaluations were normal. The family history revealed type 2 diabetes mellitus in the father and grandmother. GAD autoantibodies and AI2 autoantibodies were negative.After negative antibodies were confirmed, and together with the described family history, absence of ketoacidosis unusually with extreme hyperglicemia a MODY study was made, which revealed a heterozygote mutation on HNF1-A gene (c,787C > T(p.R263C) (c.Arg263ys)).

With the confirmed diagnosis of MODY-3,we planned to change treatment with sulfonylureas.We tried to reach the patient, but could not succeed because of lack of contact information. The current status of the patient is unknown.

DISCUSSION

Maturity onset diabetes of the young comprises a distinct group of monogenic and autosomal dominant inherited forms of diabetes mellitus due to β-cell dysfunction with onset at a young age.

MODY is caused by mutations resulting in pancreatic β-cell dysfunction in the production or excretion of insulin.

As MODY shares clinical features with the more common forms of diabetes mellitus, the true prevalence is probably underestimated but but is estimated to be responsible for at least 1% of cases of diabetes mellitus.[3,4]

At present, mutations in 13 genes linked to different types of MODY have been identified. In general, GCK-MODY and HNF1A-MODY each represent 20-70% of all cases.

Mutations in the GCK gene cause a mild, asymptomatic and non-progressive fasting hyperglycaemia from birth usually requiring no treatment. In contrast, mutations in the genes encoding the transcription factors HNF1A cause a progressive insulin secretory defect and hyperglycaemia that can lead to vascular complications.[5]

The diabetes in HNF1A-MODY typically presents in adolescence or early adulthood before the age of 25 years These patients are born with normal glycaemia, tend to be slim and have normal insulin sensitivity.[6,7]

Microvascular and macrovascular complications are observed in HNF1A-MODY and are related to poor glycaemic control.[8]

Patients with HNF1A MODY have some interesting extra-pancreatic features reflecting that the HNF1A gene is expressed in tissues outside the pancreas.

These patients have glycosuria because of a low renal threshold for glucose, thought to be due to reduced expression of the sodiumglucose cotransporter 2 (SGLT-2) and reduced glucose reabsorption in the proximal tubule.[9]

In addition, these patients have a higher than normal high density lipoprotein (HDL) cholesterol concentration.This observation may be predicted to decrease cardiovascular risk, but despite the high HDL cholesterol, incidence of coronary heart disease is greater in HNF1A-MODY than in patients with Type 1 diabetes but less than those with Type 2 diabetes.[10]

Patients with HNF1A mutations show marked sensitivity to the oral sulphonylurea. Despite the efficacy of sulfonylurea derivative treatment insulin therapy may be required in some patients as β-cell dysfunction progresses.[5]

Since MODY-3 is an unusual form of diabetes in paediatric patients, we consider the publication of this case. We underline the importance of clinical suspicion in establishing a proper diagnosis. As progression of diabetes is generally slow in MODY patients, early diagnosis and start of appropriate treatment might reduce the risk of diabetic complications.

ETHICAL CONSIDERATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Status of Peer-review: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.1031231
J Contemp Med 2022;12(3):478-479

Letter to the editor/ Editöre Mektup

Tetanus Risk in Migrants: a Case of Tetanus with Recovery in a Migrant Patient

Göçmenlerde Tetanoz Riski: Göçmen Bir Hastada İyileşen Tetanoz Vakası

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Dear Editor,

A comprehensive immunization program is in place in our country against tetanus, a preventable but potentially fatal disease. In this way, no deaths due to neonatal tetanus have been reported since 2014.[1] However, it has drawn our attention that tetanus cases continue to be reported in older children and adults and that the common factor in these cases is migrant patients.[2] In addition, the case of tetanus, which we diagnosed in a migrant patient in our clinic, directed us to examine this issue. A 25-year-old migrant male patient presented to our emergency department with a contraction in his jaw. The patient had fallen off the bike ten days ago and was presented to another hospital because of a cut in his ear. There, it was learned that the incision was sutured, but the patient was not vaccinated against tetanus. The patient did not have a tetanus vaccine and could not remember having childhood vaccinations in his country. On physical examination, the patient had a Glasgow coma scale score of 15, and signs of trismus and risus sardonicus were observed. There was a clean, 2-centimeter sutured wound on his left ear. The patient was started on 750IU human-derived tetanus immunoglobulin, tetanus vaccine, and metronidazole 500 milligrams 4x1 intravenous treatments, and was admitted to the intensive care unit. On the second day, the patient had increased spasms in the jaw and stiffness in the abdominal muscles, and he was intubated. The patient was discharged with healing after 29 days of hospital follow-up.

As in the world, the migrant population has health problems in our country, and the Ministry of Health is working on vaccinations, especially for children. Despite this, there is evidence in the literature that vaccination and immunization are still insufficient. In a recent study of 2827 migrant children, it was shown that although 74% of children aged 0–4 was born in Turkey, 20.3% of them were never vaccinated.[3] In addition, the World Health Organization has reported that 3.6% of pregnant women were not vaccinated against tetanus, and 37.1% of children aged 0–59 months were not vaccinated with a combined tetanus, diphtheria, and acellular pertussis vaccine in a pilot study.[4] In similar studies around the world, it has been shown that the number of migrants who do not have protective antibodies against tetanus is still high and that the antibody titers of those with protective antibodies decrease with age.[5] Low economic status, language problems, and educational problems limit migrants' access to health services. It is undeniable that these problems can also complicate immunization against tetanus. Turkey is one of the countries with the highest number of migrants in the world, and there are currently over 3.5 million migrants in the country.[3,4] Considering these factors, it is an acceptable hypothesis that the need for immunization against tetanus in migrant individuals is still high. As we saw in a patient in our clinic, the continued reporting of tetanus cases in migrants in our country is an important example of this. In conclusion, we would like to remind and emphasize the importance of questioning tetanus immunization, especially in migrant patients presenting with trauma.

Keywords: Tetanus, migrant, immunization

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Received *(Geliş Tarihi)*: 01.12.2021 **Accepted *(Kabul Tarihi)*:** 25.12.2021

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Note: This case presented as a poster presentation to the 7th Eurasia and 17th Turkey Emergency Medicine Congress, dated 25-28 November 2021, with the title 'A case of tetanus with recovery in a migrant patient: a rare case report'.

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JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.973832
J Contemp Med 2022;12(3):480

Letter to the editor/ Editöre Mektup

Re: Does Monocyte Distribution Width (MDW) Have Prognostic Value in Acute Pancreatitis?

Yanıt: Monosit Dağılım Genişliği (MDW) Akut Pankreatitte Prognostik Değere Sahip mi?

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Dear Editor,

We have read the article titled "Does Monocyte Distribution Width (MDW) Have Prognostic Value in Acute Pancreatitis?" published by Senlikci et al. with great interest.[1] We thank the authors for this informative and successful manuscript. We also would like to mention a few important points about the interpretation of the statistical tests performed in the study.

In statistical analysis, first, patients were grouped as mild acute pancreatitis and moderate or severe acute pancreatitis, and nonparametric comparison tests were used to determine the relationship between MDW and severity of acute pancreatitis. MDW was significantly higher in the patients with mild acute pancreatitis than the patients with moderate or severe acute pancreatitis. A further analysis was performed based on the ROC curve to determine the MDW's ability to differentiate cases of mild pancreatitis from moderate and severe pancreatitis. AUC value < 0.5 was evaluated as indistinguishable from random, while those close to 1 were considered close to the perfect predictor.[2,3] It has been reported that the AUC value should be > 0.8 for a model to predict mortality well.[2,3] In the discriminatory power analysis, authors determined the AUC value of MDW as 0.618, which was considered to be unacceptable. Although MDW was significantly higher in the patients with mild acute pancreatitis than the patients with moderate or severe acute pancreatitis, MDW's ability to differentiate cases of mild pancreatitis from moderate and severe pancreatitis is close to random. Thus, we think that according to results of Senlikci el al.'s study, MDW haven't prognostic value in acute pancreatitis.

Keywords: Acute pancreatitis, monocyte distribution width, prognosis

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Received *(Geliş Tarihi)*: 22.07.2021 **Accepted *(Kabul Tarihi)*:** 16.02.2022