ISSN: 1305-9319 | e-ISSN: 1305-9327 | Number: 1 | Volume: 20 | Year: 2024

MEDICAL JOURNAL OF BAKIRKÖY

www.bakirkoytip.org

ISSN: 1305-9319 | e-ISSN: 1305-9327 | Number: 1 | Volume: 20 | Year: 2024

MEDICAL JOURNAL OF BAKIRKÖY

Medical Journal of Bakırköy of is an official scientific Journal of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (BMJ)

It is published quarterly as 4 issues every year (March, June, September, December).

Please refer to the journal's webpage **(https://bakirkoymedj.org/)** for "Ethical Policy" and "Instructions to Authors".

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the ICMJE, WAME, CSE, COPE, EASE, and NISO. The journal conforms with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice). The Medical Journal of Bakırköy is indexed in **Web of Science; Emerging Sources Citation Index (ESCI), TUBITAK ULAKBIM TR Index, Scopus, EBSCO – Academic Search Complete, J-Gate, Embase, CINAHL Complete, ScopeMed, WorldCat, Infobase, Ulrich's Database, Ideal Online, Türkiye Atıf Dizini, Türk Medline** and **CNKI**.

The journal is published online.

Owner: University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital

Responsible Manager: Musa Çırak

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
GSM: +90 530 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Printing Date: March 2024
ISSN: 1305-9319 **E-ISSN:** 1305-9327
International scientific journal published quarterly.

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Editorial

Dear Colleagues;

Medical Journal of Bakirkoy (BMJ), which is the periodic scientific publication of University of Health Sciences Türkiye, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital, has been published uninterruptedly for 20 years. When we look back, we can see that our Journal has achieved this success with your hard work and valuable contributions. First of all, we congratulate and thank everyone who contributed to this success. We would also like to express our gratitude to all previous editors and editorial boards who contributed to the development of this journal.

Our journal is currently indexed within the scope of ESCI, as well as many important national and international indexes. Our primary goal is to move this journal to higher indexes (SCI and SCIE). The efforts and work started in the past for this purpose will continue to increase and intensify in the future. In order to achieve this goal, we are trying to fulfill our responsibilities as the editorial board, with your support.

We would like to share with you the excitement and happiness of publishing the first issue of our Journal in 2024. In this issue, as in the past, we tried to present you with a journal that is very interesting and full of studies that you can follow with interest. We hope you enjoy this new issue. We also believe that you will choose us for your high quality new research and studies in our future issues, as in the past.

We would like to thank all authors and scientists for your high interest and contributions to our journal.

Musa ÇIRAK, MD., PhD.
Editor-in Chief

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:1-6
DOI: 10.4274/BMJ.galenos.2023.2023.7-1

Research

Single Center Data of Kahramanmaraş Earthquake: Bakırköy Dr. Sadi Konuk Training and Research Hospital, Nephrology Department Experience

Kahramanmaraş Depreminin Tek Merkez Verileri: Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi Nefroloji Bölümü Deneyimi

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ABSTRACT

Objective: The Kahramanmaraş earthquake resulted in great destruction and death. We presented the characteristics of patients with crush syndrome (CS) and acute kidney injury (AKI) brought to our hospital from this region.

Methods: Data of all earthquake victims admitted to our hospital between February 7th, 2023 and February 15th, 2023 were reviewed in this retrospective study. Data of 51 victims over 17 years who were rescued from the rubble were reviewed and the demographic, laboratory, and clinical findings of these patients were investigated. They were evaluated for mortality, AKI, renal replacement therapy (RRT) requirement, and complications, including fasciotomy, amputation, intensive care unit (ICU) hospitalization requirement, microbial growth, antibiotic requirement, and duration of antibiotic treatment days.

Results: Twenty patients (39.22%) required ICU hospitalization, 21 patients (41.18%) had AKI, but 10 of the total patients (19.61%) required RRT, 1 patient (1.9%) died. There was a positive correlation between the time of the patients under the dent and the maximum creatine kinase (CK) level, severity of renal failure, number of hemodialysis sessions, number of albumin and erythrocyte replacements, and length of stay in the ICU. A positive correlation was found between CK and creatinine level, as well as between creatinine level and number of complications.

Conclusion: Patients with CS should be closely followed in terms of their renal survival, and early treatment should be started. Follow-up of these patients requires a multidisciplinary approach with the contribution of surgeons and nephrologists.

Keywords: Rhabdomyolysis, crush syndrome, acute kidney injury

ÖZ

Amaç: Kahramanmaraş depremi büyük bir yıkım ve ölümle sonuçlanmıştır. Bu bölgeden hastanemize getirilen crush sendromu (CS) ve akut böbrek hasarı (ABH) olan hastaların özelliklerini sunmayı amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışmada, hastanemize 7 Şubat 2023 ile 15 Şubat 2023 tarihleri arasında başvuran tüm depremzedelerin verileri incelendi. Enkazdan kurtarılan 17 yaş üstü 51 depremzedenin verileri tarandı. Bu hastaların demografik, laboratuvar ve klinik bulguları incelendi. Hastalar; mortalite, ABH, renal replasman tedavisi (RRT) gereksinimi, fasyotomi, amputasyon, yoğun bakım ünitesi (YBÜ) gereksinimi, mikrobiyal üreme, antibiyotik gereksinimi, antibiyotik verilen gün sayısı gibi komplikasyonlar açısından değerlendirildi.

Bulgular: Yirmi hastada (%39,22) yoğun bakım ihtiyacı, 21 hastada (%41,18) ABH gelişti, ancak 10 hastada (%19,61) RRT gerekti, 1 hasta (%1,9) öldü. Göçük altında geçen süre ile maksimum kreatinin kinaz (CK) düzeyi, girilen hemodiyaliz seans sayısı, albümin ve eritrosit replasman sayısı ve YBÜ yatış günü arasında pozitif korelasyon saptandı. CK ile kreatinin düzeyi arasında ve kreatinin düzeyi ile de komplikasyonların sayısı arasında pozitif korelasyon bulundu.

Sonuç: CS'li hastalar renal sağkalım açısından çok yakından takip edilmeli ve erken tedaviye başlanmalıdır. Aksi takdirde ciddi komplikasyonlar meydana gelebilir.

Anahtar Kelimeler: Rabdomiyoliz, crush sendromu, akut böbrek hasarı

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Cite as: Ergün Sezer G, Dirim AB, Güleç E, Yılmaz M. Single Center Data of Kahramanmaraş Earthquake: Bakırköy Dr. Sadi Konuk Training and Research Hospital, Nephrology Department Experience. Med J Bakirkoy 2024;20:1-6

Received: 10.07.2023
Accepted: 13.09.2023

INTRODUCTION

Crush syndrome (CS) is a systemic consequence of rhabdomyolysis caused by prolonged pressure on muscle tissue. Rhabdomyolysis varies from transient hyperkalemia, hypocalcemia, and elevated creatinine phosphokinase (CK) levels to cardiac arrhythmia, hypovolemic shock, and acute kidney injury (AKI) (1,2). The most important cause of CS is earthquakes; it is also the second most common cause of death after the direct effect of trauma in earthquakes (3).

There are various causes of AKI in CS. The direct nephrotoxic effects of heme products, such as myoglobin and urate crystals, cause tubular obstruction, and hypotension and hypoperfusion contribute to acute tubular necrosis (4). Crush-associated AKI manifests as rhabdomyolysis and myoglobinemia, hyperkalemia, hyperphosphatemia, and myoglobinuria. AKI patients who survive and do not become chronically dependent on dialysis have a good prognosis. Even under optimal conditions, the risk of dialysis is approximately 10% (5). The severity of AKI depends on the extent of muscle injury, degree of volume depletion, presence or absence of underlying comorbid conditions, and development of complications such as sepsis (6).

In our country, the 1999 Marmara earthquake, the 2011 Van earthquake, and finally the 2023 Kahramanmaraş earthquake caused thousands of deaths and injuries and showed that Türkiye is an earthquake country (7,8). In the earthquake that occurred in Kahramanmaraş on February 6th, 2023, many surrounding cities were also affected. The hospitals in the region were also damaged, and health services were insufficient. Therefore, earthquake victims were referred to our hospital from the area, but the patients who came to us were in relatively mild clinics. In this study, we investigated the severity of renal failure, the number of hemodialysis sessions, the number of albumin and erythrocyte replacements, and the length of intensive care unit (ICU) stay of patients who were removed from the rubble and admitted to our hospital during the Kahramanmaraş earthquake.

METHODS

Patients and Follow-up

Data of all earthquake victims admitted to our hospital between February 7th, 2023 and February 15th, 2023 were reviewed in this retrospective study (case series). Data of 51 victims over 17 years who were rescued from the rubble were reviewed and the demographic, laboratory, and clinical findings of these patients were investigated.

All procedures performed in studies involving human participants were conducted under the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2023-08-06, date: 17.04.2023).

Primary and Secondary Outcomes

The primary outcomes were AKI, renal replacement therapy (RRT) requirement, and complications, including fasciotomy, amputation, ICU admission, and length of stay in ICU. The secondary outcome was mortality. In addition, microbial growth, antibiotic requirement, and duration of antibiotic treatment days were evaluated. These data were obtained from the system retrospectively.

Statistical Analysis

SPSS version 25.0 program was used for data analysis. The conformity of the variables to the normal distribution was examined using histogram graphics and the Kolmogorov-Smirnov test. Mean, standard deviation, median, and minimum-maximum (min-max) values were used when presenting descriptive analyses. The Pearson chi-square test was used for comparison between two variables. The Mann-Whitney U test was used to evaluate non-normally distributed (non-parametric) variables between groups. Spearman's correlation test was used in the analysis of the measurement data with each other. Cases with a p-value 0.05 were considered statistically significant.

RESULTS

The mean age of the patients was 45±19 years, 50.98% of patients were male, mean hours under dent was 22.8±28 hours. Twelve of the victims were transferred from Adıyaman (23.53%), 26 from Hatay (50.98%), 8 from Kahramanmaraş (15.69%), and 5 from Malatya (9.8%). Seventeen of the patients had comorbidities including diabetes mellitus, hypertension, hypothyroidism, hyperthyroidism, and chronic heart diseases (33.33%) (Table 1).

At admission, mean serum albumin was 3.58±0.74 g/dL, hemoglobin (Hb) 12.68±3.03 g/dL, CK 15109.8±30313.12 U/L, and creatinine 1.63±1.54 mg/dL. In the follow-up of the patients, the mean of min Hb was 9.83±2.78 g/dL, albumin 2.86±0.8 g/dL, estimated glomerular filtration rate (eGFR) 74.59±46.34 mL/min/1.73 m^2; max creatinine was 2.08±2.39 mg/dL, CK 23412.8±43712 U/L (Table 2).

Twenty patients (39.22%) required ICU care, and the mean length of stay in the ICU was 3.45±8.53 days. Nine patients (17.4%) underwent fasciotomy and 6 patients (11.77%) underwent amputation. Twenty-one patients (41.18%) had

Table 1. Demographic of the patients at admission

		n	%
Gender	Female	25	49.02
	Male	26	50.98
Province in which the patients was under the rubble	Adıyaman	12	23.53
	Hatay	26	50.98
	Kahramanmaraş	8	15.69
	Malatya	5	9.80
Comorbidity		17	33.33

Data were expressed as n (%) for nominal parameters

Table 2. Laboratory data of the patients

	Mean ± SD	Median (min-max)
First Hb (g/dL)	12.68±3.03	12.4 (5.7-20)
First cre (mg/dL)	1.63±1.54	0.9 (0.33-6.12)
First eGFR (mL/min/1.73 m^2)	77±43.89	81 (8-138)
First CRP (mg/L)	78±72.21	66 (1-264)
First albumin (g/dL)	3.58±0.74	3.8 (1.9-4.8)
First CK (u/L)	15109.8±30313.12	1493 (31-115,754)
Min Hb (g/dL)	9.83±2.78	9.8 (4.9-16.4)
Min albumin (g/dL)	2.86±0.8	2.9 (1.5-4.6)
Max cre (mg/dL)	2.08±2.39	0.9 (0.33-10.7)
Min eGFR (mL/min/1.73 m^2)	74.59±46.34	89 (2-152)
Max CK (u/L)	23412.8±43712.2	2319 (53-236,092)

Data were expressed as median (interquartile range) for quantitative variables.
Hb: Hemoglobin, cre: Creatinine, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, CK: Creatinine kinase, SD: Standard deviation, min-max: Minimum-maximum

AKI, but 10 of the total patients (19.61%) required RRT. Four patients (7.8%) were given hyperbaric oxygen therapy and 12 patients (23.53%) had bacterial growth (Table 3). Only 1 patient died (1.9%).

The rate of ICU requirement in patients with renal dysfunction was higher than that in patients without renal dysfunction ($p<0.001$). The risk of developing AKI was found to be low in the group with normal CK ($p<0.001$) (Table 4).

In patients with AKI, the length of stay in the ICU, first C-reactive protein, max creatinine level, max CK level, eritrocyte replacement number, albumin replacement number, and duration of antibiotic treatment days were higher than those without AKI ($p<0.001$, $p=0.031$, $p<0.001$, $p<0.001$, $p=0.004$, $p=0.002$, $p=0.008$, respectively). In the patients with AKI, the first eGFR, min Hb value, min albumin, and min eGFR were lower than those without AKI ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively) (Table 5).

Table 3. Complications after the earthquake

	n	%
Need for ICU care	20	39.22
Fasciotomy	9	17.64
Amputation	6	11.77
AKI	21	41.18
Hemodialysis requirement	10	19.61
HBO number	4	7.84
Bacterial growth	12	23.53

Data were expressed as n (%) for nominal parameters.
ICU: Intensive care unit, AKI: Acute kidney injury, HBO: Hyperbaric oxygen

Table 4. Comparison of patients with and without renal failure

		Renal failure				p-value
		Yes (n=21)		No (n=30)		
		n	%	n	%	
Gender	Female	11	52.38	14	46.67	0.688
	Male	10	47.62	16	53.33	
ICU requirement	Yes	16	76.19	4	13.33	**<0.001**
CK group	Normal	3	14.29	7	23.33	**<0.001**
	170-1000 (U/L)	0	0.00	4	13.33	
	1000-10,000 (U/L)	2	9.52	16	53.33	
	10,000-50,000 (U/L)	6	28.57	3	10.00	
	50,000-100,000 (U/L)	6	28.57	0	0.00	
	>100,000 (U/L)	4	19.05	0	0.00	
Fasciotomy	Yes	6	28.57	3	10.00	0.087
Amputation	Yes	2	9.52	4	13.33	0.678
RRT requirement	Yes	10	47.62	0	0.00	**<0.001**
HBO therapy	Yes	2	9.52	2	6.67	0.709
Microbial growth	Yes	7	33.33	5	16.67	0.167
Comorbidity	Yes	10	47.62	7	23.33	0.070
Mortality	Yes	0	0.00	1	3.33	0.398

Data were expressed as n (%) for nominal parameters.
ICU: Intensive care unit, CK: Creatinine kinase, RRT: Renal replacement therapy, HBO: Hyperbaric oxygen

Table 5. Comparison of patients with and without renal failure as laboratory data

	Renal failure		p-value
	Yes	No	
	Median (min-max)	Median (min-max)	
Duration under the rubble (hour)	21 (4-56)	10.5 (0.5-168)	0.086
Length of stay in ICU	2 (0-42)	0 (0-10)	**<0.001**
First Hb (g/dL)	12 (6.9-20)	12.55 (5.7-16.4)	0.931
First eGFR (mL/min/1.73 m^2)	28 (8-81)	114.5 (55-138)	**<0.001**
First CRP (mg/L)	84 (3-239)	40 (1-264)	**0.031**
First albumin (g/dL)	3.6 (1.9-4.4)	3.8 (2.1-4.8)	0.139
First CK (u/L)	2829 (31-115,754)	1371 (66-38,480)	0.069
Min Hb (g/dL)	8.2 (4.9-11.6)	11.2 (5.7-16.4)	**<0.001**
Min albumin (g/dL)	2.5 (1.5-3.3)	3.2 (1.8-4.6)	**<0.001**
Max cre (mg/dL)	3.64 (0.46-10.7)	0.7 (0.33-1.17)	**<0.001**
Min eGFR (mL/min/1.73 m^2)	16 (2-124)	111 (42-152)	**<0.001**
Max CK (u/L)	23231 (53-236,092)	1491.5 (66-38,480)	**<0.001**
Erythrocyte replacement number	1 (0-7)	0 (0-6)	**0.004**
Albumin replacement number	0 (0-6)	0 (0-3)	**0.002**
Number of extremities underwent fasciotomy	0 (0-3)	0 (0-1)	0.083
Number of extremities underwent amputation	0 (0-1)	0 (0-2)	0.632
HBO number	0 (0-12)	0 (0-16)	0.774
Antibiotic treatment days	15 (0-53)	2 (0-41)	**0.008**

ICU: Intensive care unit, Hb: Hemoglobin, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, CK: Creatinine kinase, cre: Creatinine, HBO: Hyperbaric oxygen, min-max: Minimum-maximum

There was a positive correlation between the time under the dent and the max CK level, number of hemodialysis sessions, length of stay in the ICU, duration of antibiotic treatment days, albumin replacement number, erythrocyte replacement number, first albumin level, min albumin level, and min Hb level (p=0.017, p=0.012, p=0.003, p=0.001, p=0.001, p=0.001, p=0.001, p=0.001, p=0.002 respectively) (Table 6).

Table 6. Correlation of time under the rubble with complications

		Duration under the rubble (hour)
First CK	r	0.203
	p	0.152
Max CK	r	0.332
	p	**0.017**
Total number of HD session	r	0.349
	p	**0.012**
Length of stay in ICU	r	0.404
	p	**0.003**
Duration of antibiotic treatment days	r	0.457
	p	**0.001**
Albumin replacement number	r	0.461
	p	**0.001**
Erythrocyte suspension replacement number	r	0.559
	p	**0.001**
First GFR	r	-0.268
	p	0.057
First cre	r	0.248
	p	0.079
First cre	r	0.181
	p	0.204
First albumin	r	-0.445
	p	**0.001**
First Hb	r	-0.122
	p	0.394
Min albumin	r	-0.588
	p	**0.001**
Min Hb	r	-0.417
	p	**0.002**

Spearman correlation analysis.
CK: Creatinine kinase, HD: Hemodialysis, ICU: Intensive care unit, cre: Creatinine, Hb: Hemoglobin, GFR: Glomerular filtration rate, Max: Maximum, Min: Minimum

DISCUSSION

CS affects almost all organs. It causes not only AKI but also sepsis, acute respiratory distress syndrome, disseminated intravascular coagulation, bleeding, hypovolemic shock, cardiac failure, arrhythmias, electrolyte disturbances, and psychological trauma (6,9,10). In our study, we mainly found AKI and electrolyte disturbance complications of CS.

It was determined that the most important cause of death after direct trauma in the earthquake was CS and related AKI (2,11,12). Fifty-one patients were diagnosed with CS in our hospital; the reason for this low number is that we were far from the earthquake zone and there were transportation difficulties. In addition, patients with better clinical condition who could handle the transport were referred to us.

In our hospital, 21 patients (41.18%) had AKI, but 10 required RRT. After the earthquake in Tangshan, 2-5% of all injured patients had CS (13). After the Kobe earthquake, CS was observed in 13.8 % of the patients who were hospitalized, and AKI developed in half of them (14). In the Marmara earthquake, 43,953 people were injured. Among the hospitalized patients, AKI related to the CS rate was 12%, and the RRT requirement rate was 9% (7). Numerical data on the Kahramanmaraş earthquake have not yet been created. The Disaster and Emergency Management Presidency (AFAD) has announced that there are nearly 50,000 deaths, but there is no clear data on patients with CS and AKI. Those who are admitted to our hospital are only a small part of them.

None of the patients who received RRT remained dependent on hemodialysis, and their renal function improved during follow-up. This may be because, as I mentioned, the patients who were admitted to our hospital were not clinically severe.

In our study, a positive correlation was observed between high CK and creatinine levels. Complications such as the rate of ICU requirement, erythrocyte replacement number, albumin replacement number, and duration of antibiotic treatment days were found more frequently in patients with AKI. Also, as expected, there was a positive correlation between time under the rubble length of stay in the ICU, CK elevation, number of hemodialysis sessions, antibiotic treatment days, albumin replacement number, and erythrocyte replacement number. This was not a surprise because many previous studies have shown that the severity of CS is associated with AKI, hypovolemic and septic shock, and electrolyte imbalance (2,12,15-18).

Early treatment is the most important thing in CS. Aggressive fluid repletion should be initiated before the extrication of entrapped subjects who are prone to develop CS.

Third spacing at the site of muscle injury worsens hypovolemia. Thus, patients with rhabdomyolysis may require massive amounts of fluid to trigger and maintain vigorous diuresis (15,19-23). Electrolyte disturbances are very common in these patients, and the common is hyperkalemia. Therefore, potassium monitoring should be performed carefully and evaluation should be made in terms of RRT in resistant hyperkalemia (6,23,24). In our hospital, kidney functions, electrolyte values, fluid requirement, and RRT requirement of the patients were strictly evaluated, and kidney function disorders improved during follow-up.

The limitations of our study are the small number of patients and the inability to transfer patients with CS who are in severe clinics due to transportation difficulties and distance from the earthquake zone.

CONCLUSION

CS can cause serious morbidity and mortality. Beginning to treat patients with CS quickly and following them closely is essential. Dialysis once a day may not be enough for patients with severe CS; therefore, the nephrologist should take an active role in the follow-up of these patients.

ETHICS

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2023-08-06, date: 17.04.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: G.E.S., M.Y., Design: G.E.S., M.Y., Data Collection or Processing: G.E.S., A.B.D., E.G., Analysis or Interpretation: G.E.S., Literature Search: G.E.S., A.B.D., Writing: G.E.S.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:7-14
DOI: 10.4274/BMJ.galenos.2023.2023.8-5

Research

Personalized Treatment Selection and Its Effects on Glycemic Control in Older Adults with Diabetes: A Single Center Experience

Yaşlı Diyabetli Yetişkinlerde Kişiye Özel Tedavi Seçimi ve Glisemik Kontrol Üzerine Etkileri: Tek Merkez Deneyimi

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ABSTRACT

Objective: As society ages, managing people with diabetes gains importance and becomes difficult because of accompanying diseases and complications. This study examined the effects of treatment changes in people with diabetes over 65.

Methods: The data of patients aged ≥65 who were followed up in the İstanbul University, İstanbul Faculty of Medicine between 2010 and 2017 were retrospectively analyzed. Demographic data, comorbidities, complications, and metabolic effects of treatment changes were evaluated.

Results: The study included 250 patients with a mean age of 72.0±6.6 years. Of the patients, 78.8% had hypertension, 58.4% had dyslipidemia, 32% had coronary artery disease, and 10% had chronic renal failure. The frequency of diabetic neuropathy was 26%, nephropathy 22.8%, and retinopathy 20.8%. The incidence of hypoglycemia was 16.4%. While oral antidiabetic drugs (OAD) alone decreased by 19%, 14% of these patients switched to OAD + basal insulin therapy and 4% to basal-bolus therapy during the follow-up period. With the addition of basal insulin to OAD, an additional 0.9% reduction in glycated hemoglobin (HbA1c) was achieved, and a further 1.2% reduction was achieved by switching to basal-bolus insulin.

Conclusion: Our study has shown that continuing the use of metformin in older adults with diabetes with preserved renal functions and adding insulin to their existing treatments when needed, despite all the reservations, provides an effective treatment by decreasing the HbA1c level. However, the lower-than-expected hypoglycemia frequency in our study may be due to the progressive age of diabetes and hypoglycemia unawareness due to accompanying autonomic neuropathy. Education of patients gains importance in this regard.

Keywords: Older adults with diabetes, glycemic control, hypoglycemia, personalized treatment

ÖZ

Amaç: Toplum yaşlandıkça, eşlik eden hastalıklar ve komplikasyonlar nedeniyle şeker hastalarının yönetimi önem kazanmakta ve zorlaşmaktadır. Bu çalışma 65 yaş üstü şeker hastalarında tedavi değişikliklerinin etkilerini incelemeyi amaçlamıştır.

Gereç ve Yöntem: İstanbul Üniversitesi, İstanbul Tıp Fakültesi'nde 2010-2017 yılları arasında izlenen 65 yaş ve üzeri hastaların verileri retrospektif olarak incelendi. Demografik veriler, komorbiditeler, komplikasyonlar ve tedavi değişikliklerinin metabolik etkileri değerlendirildi.

Bulgular: Çalışmaya ortalama yaşları 72,0±6,6 yıl olan 250 hasta dahil edildi. Hastaların %78,8'inde hipertansiyon, %58,4'ünde dislipidemi, %32'sinde koroner arter hastalığı ve %10'unda kronik böbrek yetmezliği vardı. Diyabetik nöropati sıklığı %26, nefropati %22,8, retinopati %20,8 idi. Hipoglisemi görülme sıklığı %16,4 olarak belirlendi. Tek başına oral antidiyabetik ilaçların (OAD) kullanımı %19 azalırken, bu hastaların %14'ünün takip döneminde OAD + bazal insülin tedavisine ve %4'ünün bazal bolus tedavisine geçtiği gözlendi. Glikozillenmiş hemoglobinde (HbA1c) OAD'ye bazal insülin ilavesiyle ek bir %0,9'luk azalma ve bazal-bolus insüline geçilmesiyle ise ilave %1,2'lik azalma sağlandı.

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Cite as: Çalıkoğlu F, Guzey D, Hacışahinoğulları H, Çakmak R, Kubat Üzüm A, Soyluk Selçukbiricik Ö, Gül N, Karşıdağ K, Yılmaz MT, Dinççağ N, Satman İ. Personalized Treatment Selection and Its Effects on Glycemic Control in Older Adults with Diabetes: A Single Center Experience. Med J Bakirkoy 2024;20:7-14

Received: 09.08.2023
Accepted: 02.10.2023

Sonuç: Çalışmamız, böbrek fonksiyonları korunmuş yaşlı diyabetlilerde tüm çekincelere rağmen metformin kullanımına devam edilmesinin ve gerektiğinde mevcut tedavilerine insülin eklenmesinin HbA1c değerini düşürerek etkili bir tedavi sağladığını göstermiştir. Ancak hipoglisemi sıklığının beklenenden düşük bulunması, ilerleyen diyabet yaşı ve eşlik eden otonom nöropatiye bağlı hipoglisemi farkındasızlığından kaynaklanıyor olabilir. Bu noktada hastaların eğitimi önem kazanmaktadır.

Anahtar Kelimeler: Yaşlılıkta diyabet, glisemik kontrol, hipoglisemi, kişiselleştirilmiş tedavi

INTRODUCTION

Diabetes, which is currently considered a global epidemic, affected 382 million people worldwide in 2013, and this number is expected to reach 592 million by 2035 (1). In the United States of America, while the diabetes rate in older adults over 65 years old is around 22-33%, it is estimated that this rate will increase with the aging of the current population (2). According to the TURDEP-I study conducted in 1997, the frequency of type 2 diabetes in all age groups in our society was found to be 7.2%, and in the TURDEP-II study completed in 2010, this rate increased to 13.7% (3,4). For individuals aged 65 years and over, it increased from 20% to 35% in these 13 years. In the period between these two studies, the onset of diabetes five years earlier will increase both diabetes and diabetes complications in the population aged 65 and over in the coming years. Diabetes in old age is closely related to cardiovascular diseases, macrovascular and microvascular complications, the risk of hypoglycemia causing increased mortality, and hospitalization rates. Both diagnosis and treatment are problematic in this age group because of functional impairments and different comorbidities of older adults (5). There are very few studies on diabetes management in older adults. The main reason for this is that physiological changes that occur with aging are difficult to adapt to studies involving young populations (6). This study aimed to examine the general approach to treatment and the clinical effects of changes for treating patients aged 65 years and over who applied to the Diabetes Polyclinic of İstanbul University, İstanbul Faculty of Medicine, Department of Endocrinology and Metabolic Diseases.

METHODS

Study Design

For this study, outpatient follow-up files of all patients who applied to the Diabetes Policlinic of İstanbul University, İstanbul Faculty of Medicine Endocrinology and Metabolic Diseases Department between 2010 and 2017 were retrospectively scanned with the diagnosis of type 2 diabetes. The data of patients aged 65 years and over who came for follow-up visits at least three times after their first admission and had treatment arrangements were evaluated. Data from patients who applied for two or fewer follow-up visits and who were younger than 65 years were not assessed. This study was approved by the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (decision no: 08, date: 02.04.2021) and was conducted in accordance with the Declaration of Helsinki Principles. Written informed consent was obtained from each participant.

Study Variables

Patients' age, gender, educational status, marital status, employment status, smoking and alcohol use habits, duration of diabetes, diabetes diagnosis type, comorbidities, drugs preferred for diabetes treatment and treatment of micro- and macrovascular complications, treatment changes made at each control, and changes in weight and biochemical parameters were collected.

According to the Turkish Endocrinology and Metabolism Association 2018 diabetes guideline, in older adults with diabetes, the A1C target should be <7.0-7.5% in healthy patients with a low risk of hypoglycemia, considering complications, comorbid diseases, and other risks. On the other hand, it is recommended to aim for A1C <8.0-8.5% in patients with high hypoglycemia and other risks and need of care (7). In the American Association of Clinical Endocrinology 2018 guideline, the glycated hemoglobin (HbA1c) target is recommended as ≤6.5% for most healthy older adults, especially those with intact cognitive and functional status. In line with the recommendations of these two guidelines, the patients' data included in the study were evaluated by classifying their HbA1c as ≤6.5%, 6.6-7.5%, 7.6-8.0%, and ≥8.1% (8).

Statistical Analysis

IBM SPSS 21.00 packaged software was used for data analysis. Descriptive statistics were used to evaluate the data. Categorized data are presented as frequency-percentage ratios, and quantitative data are presented as mean and standard deviation and compared using Student's t-test.

RESULTS

Between 2010 and 2017, the files of 7087 patients who were followed up in our center diagnosed with type 2 diabetes were scanned, and 250 people (138 women and 112 men) aged 65 years and over who had at least three follow-up visits between these dates were included in the study.

The mean age at the first application was 72.0±6.6 (65-89) years, the duration of diabetes was 13.8±7.9 (2-40) years, and the weight was 82.5±14.8 (40-128) kg (Table 1).

Hypertension was observed in 78.8% of patients, dyslipidemia in 58.4%, coronary artery disease in 32%, chronic renal failure in 10%, cerebrovascular disease in 7.2%, and cancer in 14.4%. It was determined that 10.8% had thyroid dysfunction, 3.6% had chronic obstructive pulmonary disease, and 2.8% had peripheral artery disease.

The malignancies seen were breast (32.4%), colon (11.8%), rectum (8.8%), thyroid papillary capillaries (5.8%), Hodgkin lymphoma (5.8%), chronic lymphocytic leukemia (5.8%), skin cancer (5.8%), lung (2.94%), endometrium (2.94%), and gastrointestinal (2.94%) cancers, as well as melanoma (2.94%), adrenal adenoma (2.94%), bladder (2.94%), prostate (2.94%), and vulva (2.94%) tumors.

Diabetic neuropathy was associated in 26% of the patients, nephropathy in 22.8%, and retinopathy in 20.8%. It was observed that there were diabetic feet in seven cases, and amputation was applied to 4 of them.

Of the patients, 48% complied with medical nutrition therapy, 25.6% regularly exercised, and 58.9% regularly measured their blood glucose at home.

Insulin use increased from 21.6% at the first visit to 49.2% at the last visit. Of the 232 patients whose hypoglycemia frequency was questioned, 83.6% reported that they were not, 4% were nocturnal, 2% during the day, and 3.2% reported hypoglycemia at any time of the day. In addition to hypoglycemia, no patient was admitted to the hospital with hyperosmolar non-ketotic coma or lactic acidosis, which can often be seen, especially in older adults.

The mean HbA1c of all patients at the first admission was 8.1±2.0% (4.8-14.8%), while 7.5±1.5% (4.3-14.0%) at the last visit ($p<0.001$) was found as. The biochemical characteristics of the patients at their first admission are presented in Table 2.

The number of patients at the first and last visit within the determined HbA1c ranges were 30.8% (n=77) and 29.2% (n=73) for HbA1c ≤6.5%, respectively; 18.8% (n=47) and 30.8% (n=77) for HbA1c 6.6%-7.5%; 3.6% (n=9) and 11.2% (n=28) for HbA1c 7.6-8.0%; and 46.8% (n=117) and 28.8% (n=72) for ≥8.1%. The number of patients using antidiabetic drugs that have the risk of causing hypoglycemia in the first application and last treatments and those who had hypoglycemia according to the HbA1c ranges is summarized in Table 3.

Table 1. Demographic characteristics of patients

Age (mean ± SD)	**72.06±5.55**	**Marital status (n%)**	
Gender		Married	159 (95.8)
Woman (n)	138 (55.2%)	Single	6 (3.6)
Man (n)	112 (44.8%)	Widow	1 (0.6)
Weight (kg)		**Smoking (n%)**	
Initial	82.57±14.86	Non-smoke	161 (67.1)
Final	81.63±14.86	Smoke	27 (11.3)
BMI (kg/m²)		Smober	52 (21.7)
Educational status (n%)		**Alcohol use (n%)**	
Illiterate	6 (2.9)	User	222 (92.5)
Primary school	105 (51.2)	Non-user	7 (2.9)
Secondary school	20 (9.8)	Quit	11 (4.6)
High school	38 (18.5)	**Diabetes duration (year)**	13.81±7.99
University	36 (17.6)	**Diabetes onset (n%)**	
Employment status (n%)		Acute hyperglycemia	8 (4.1)
Employee	21 (10.2)	DKA	1 (0.5)
Retired	117 (56.8)	3P	47 (24)
Housewife	68 (33.0)	OGTT	7 (3.6)
		Random	133 (67.9)

BMI: Body mass index, DKA: Diabetic ketoacidosis, 3P: Polyphagia, polyuria, polydipsia, OGTT: Oral glucose tolerance test, SD: Standard deviation

Table 2. Biochemical characteristics of the patients

HbA1c (%)			
Initial	8.17±2.04	Lipase (U/L)	41.64±25.71
Final	7.57±1.47	hsCRP (mg/L)	19.18±40.75
Glucose (mg/dL)	150.14±55.32	Total cholesterol (mg/dL)	193.63±43.47
Urea (mg/dL)	42.73±25.97	HDL (mg/dL)	47.33±15.74
Creatinine (mg/dL)	1.12±1.13	LDL (mg/dL)	114.36±34.74
Uric acid (mg/dL)	8.13±12.85	TSH (mIU/L)	3.90±12.29
AST (U/L)	20.76±9.98	Vitamin D (ng/mL)	27.72±25.79
ALT (U/L)	21.81±12.08	PTH (pg/dL)	67.44±47.31
GGT (U/L)	32.33±37.91	Calcium (mg/mL)	10.00±6.55
ALP (U/L)	74.40±27.32	Phosphorus (mg/dL)	3.48±0.57
Amylase (U/L)	77.88±36.20	Albumin (g/dL)	4.40±0.37

HbA1c: Glycated hemoglobin, AST: Aspartate transaminase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase, hsCRP: High-sensitivity C-reactive protein, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, TSH: Thyroid stimulating hormone, PTH: Parathyroid hormone

Table 3. Summary of the treatment changes of people using antidiabetic drugs at risk of hypoglycemia according to different HbA1c levels at the first application and the number of people with hypoglycemia

Anti-diabetic medication	**HbA1c ≤6.5% (n=77)**		**HbA1c 6.6-7.5% (n=47)**		**HbA1c 7.6-8.0% (n=9)**		**HbA1c ≥8.1% (n=117)**	
	Initial treatment	**Final treatment**	**Initial treatment**	**Final treatment**	**Initial treatment**	**Final treatment**	**Initial treatment**	**Final treatment**
Gliclazide (n, %)	12 (15.58)	34 (44.15)	5 (10.63)	6 (12.76)	2 (22.22)	1 (11.11)	17 (14.52)	17 (14.52)
Glimepride (n, %)	2 (2.59)	2 (2.59)	2 (4.25)	0 (0.00)	0 (0.00)	1 (11.11)	7 (5.98)	2 (1.70)
Repaglinide (n, %)	2 (2.59)	15 (19.48)	2 (4.25)	9 (19.14)	0 (0.00)	4 (44.44)	2 (1.70)	34 (29.05)
Nateglinide (n, %)	2 (2.59)	1 (1.29)	0 (0.00)	2 (4.25)	0 (0.00)	0 (0.00)	2 (1.70)	2 (1.70)
Basal insulin (n, %)								
Glargine	9 (11.68)	20 (25.97)	6 (12.76)	9 (19.14)	4 (44.44)	5 (55.55)	21 (17.94)	62 (52.99)
Detemir	0 (0.00)	4 (5.19)	1 (2.12)	5 (1.06)	0 (0.00)	2 (22.22)	1 (0.85)	7 (5.98)
NPH	0 (0.00)	2 (2.59)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.85)	2 (1.70)
Regular insulin (n, %)	3 (3.89)	7 (9.09)	2 (4.25)	3 (6.38)	3 (33.33)	2 (22.22)	7 (5.98)	22 (18.80)
Analog insulin (n, %)	1 (1.29)	4 (5.19)	1 (2.12)	1 (2.12)	1 (11.11)	0 (0.00)	6 (5.12)	6 (5.12)
Mixt insulin (n, %)	3 (3.89)	3 (3.89)	2 (4.25)	1 (2.12)	1 (11.11)	0 (0.00)	7 (5.98)	2 (1.70)
Hypoglycaemia (n, %)	**Initial**	**Final**	**Initial**	**Final**	**Initial**	**Final**	**Initial**	**Final**
Night	2 (2.70)	3 (4.60)	1 (2.40)	2 (2.70)	0 (0.00)	1 (3.70)	7 (6.50)	4 (5.90)
Daytime	1 (1.41)	1 (1.40)	1 (2.40)	1 (1.40)	0 (0.00)	0 (0.00)	3 (2.80)	1 (1.50)
Uncertain time	1 (1.41)	1 (1.40)	0 (0.00)	1 (1.40)	0 (0.00)	1 (3.70)	7 (6.50)	3 (4.40)
None	68 (94.52)	60 (92.30)	40 (95.20)	69 (94.50)	9 (100.0)	25 (92.60)	91 (84.30)	60 (88.20)

HbA1c: Glycated hemoglobin, NPH: Neutral protamine hormone

The general treatment distributions in the first and last visits of the patients and patients who received treatment according to the targeted HbA1c intervals are summarized in Figure 1 and Table 4.

While all patients with coronary artery and cerebrovascular disease used acetylsalicylic acid, only 24% of those with dyslipidemia used lipid-lowering medication. The HbA1c value of patients using oral antidiabetic (OAD) was found

to be 7.7±2.0% at the beginning and 7.1±1.2% at the last control. The distribution of the OADs used is shown in Figure 2. The most significant of the treatment changes was the addition of basal insulin to patients' treatment using OAD alone (n=23), an additional decrease of 0.9% in HbA1c, and a 1.2% additional decrease in basal-bolus insulin (n=10). HbA1c of 57 patients with nephropathy, whose mean age was 73.3±6.0, increased from 8.9±2.1% to 8.2±1.2% (p=0.033), weight 83.3±13, from 9 kg to 82.9±14.2 kg (p=0.570); HbA1c of 52 patients with retinopathy with a mean age of 72.7±5.8 years from 8.8±1.3% to 8.3±1.5% (p=0.136), and weight 85.1±15.1 kg to 84.3±15.4 kg (p=0.425); HbA1c of 65 patients with neuropathy with a mean age of 72.4±5.4 years from 8.2±1.8% to 7.8±1.4% (p=0.005), weight 83.3±15.9 kg

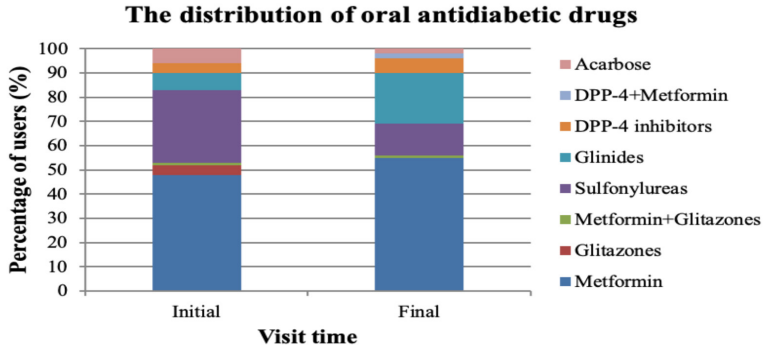

Figure 1. Treatment distribution in the first and last visits of the patients

Table 4. Summary of antidiabetic drug use and treatment changes according to different HbA1c levels at first admission

Anti-diabetic medication	HbA1c ≤%6.5 (n=77)		HbA1c 6.6-7.5% (n=47)		HbA1c 7.6-8.0% (n=9)		HbA1c ≥8.1% (n=117)	
	Initial treatment	Final treatment	Initial treatment	Final treatment	Initial treatment	Final treatment	Initial treatment	Final treatment
MNT (n, %)	35 (45.53)	10 (13.00)	16 (34.00)	4 (8.50)	2 (22.22)	0 (0.00)	44 (37.61)	8 (6.81)
OAD (n, %)	30 (39.0)	39 (50.61)	22 (46.81)	28 (59.61)	2 (22.22)	2 (22.22)	45 (38.52)	36 (30.82)
OAD + basal insulin (n, %)	4 (5.21)	14 (18.21)	2 (4.35)	7 (14.90)	0 (0.00)	5 (55.63)	4 (3.43)	39 (33.33)
Basal insulin (n, %)	2 (2.64)	2 (2.64)	1 (2.12)	3 (6.42)	0 (0.00)	0 (0.00)	5 (4.32)	4 (3.43)
Basal + bolus insulin (n%)	3 (3.92)	10 (13.00)	3 (6.42)	4 (8.53)	4 (44.44)	2 (22.22)	14 (12.00)	28 (23.91)
Mixt insulin (n, %)	1 (1.30)	0 (0.00)	0 (0.00)	0 (0.00)	1 (11.11)	0 (0.00)	4 (3.43)	0 (0.00)
OAD + mixt insulin (n, %)	2 (2.64)	2 (2.64)	2 (4.35)	1 (2.12)	0 (0.00)	0 (0.00)	1 (0.90)	2 (1.73)
Basal + bolus + mixt insulin (n, %)	0 (0.00)	0 (0.00)	1 (2.12)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

HbA1c: Glycated hemoglobin, OAD: Oral antidiabetic, MNT: Medical nutrition therapy

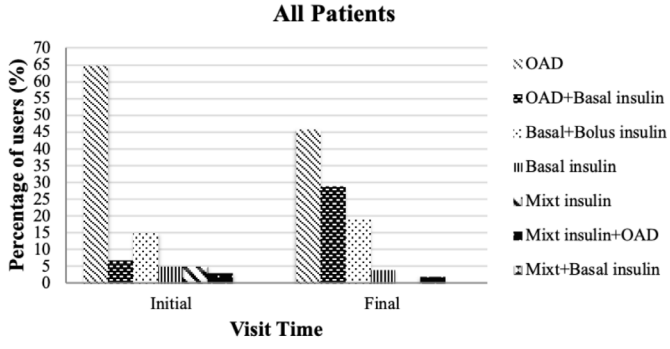

Figure 2. Summary of the distribution of oral anti-diabetics used in first application and final control
OAD: Oral antidiabetic

from 83.7±15.3 kg (p=0.604). The distribution of patients with microvascular complications according to the targeted HbA1c ranges is summarized in Table 5, and the distribution of preferred treatments is summarized in Figure 3.

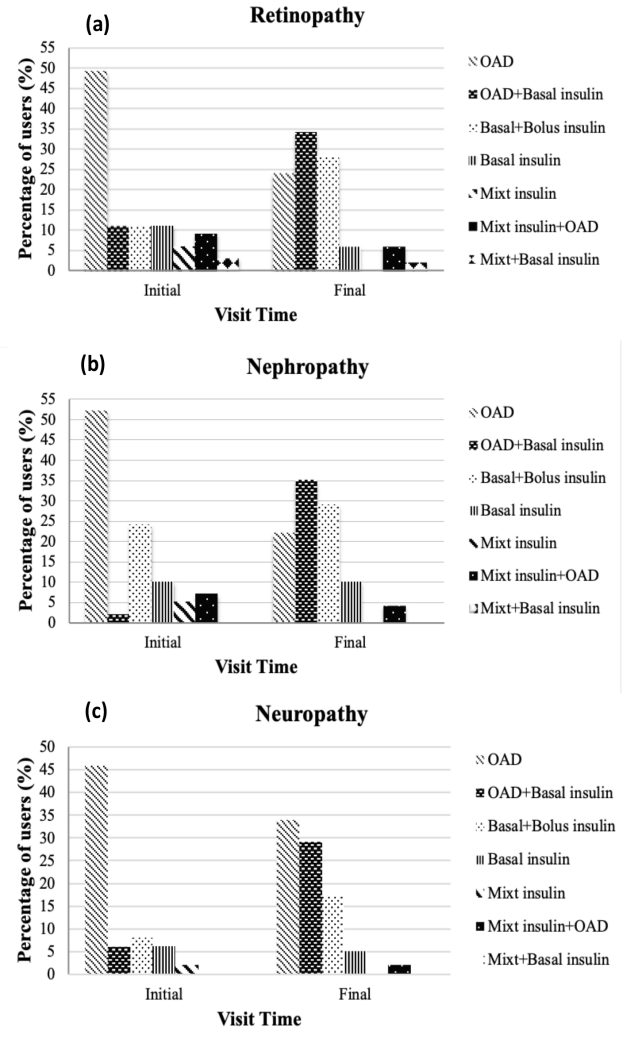

Figure 3. Distribution of selected treatments according to microvascular complications: (a) Retinopathy, (b) nephropathy, and (c) neuropathy
OAD: Oral antidiabetic

DISCUSSION

As the human lifespan increases, the prevalence of developing type 2 diabetes increases accordingly. Individuals with diabetes over the age of 65 years are at a similar risk to younger diabetes patients in terms of the risk of developing microvascular complications. However, their late detection of the disease also reduces their absolute risk. However, their absolute risk of macrovascular complications is significantly higher than that for young diabetics (2).

Our study revealed the necessity of re-evaluating and closely monitoring the treatment of all diabetic patients aged 65 years, especially those with comorbidities. In this way, both glycemic targets can be achieved, control of additional diseases can be achieved, and patients' quality of life can be increased (9).

Few data exist to make specific recommendations for the treatment of type 2 diabetes in older adults (10). However, patients over the age of 65 years have been included in many diabetes drug trials, including studies evaluating cardiovascular endpoints. Therefore, the approach to choosing initial, alternative, and combination therapies is similar in older and younger adults. All types of oral hypoglycemic drugs and insulin are effective in older patients, but each has some limitations. Most importantly, oral and injectable agents with a low risk of hypoglycemia should be used.

Increased risk of hypoglycemia and weight gain in the use of sulfonylureas (SU), which have an essential place in intensive treatment protocols in reducing the risk of microvascular complications, are two important problems to be considered (5) and may lead to severe consequences for the older adult population (11). Therefore, the American Geriatrics Association does not recommend the use of some drugs in the SU group, especially glibenclamide, in older adults (12). Our clinical approach in this regard was mostly the use of short-acting secretagogues, and the drugs of approximately 30% of the patients who used SU at their first application were replaced with repaglinide or

Table 5. Number of patients with different HbA1c levels and average age of patients with microvascular complications at first admission

Microvascular complication	HbA1c ≤6.5% (n=77)		HbA1c 6.6-7.5 (n=47)		HbA1c 7.6-8.0% (n=9)		HbA1c ≥8.1% (n=117)	
	Yes	No	Yes	No	Yes	No	Yes	No
Age (mean ± SD)	72.36±5.33		71.93±6.03		73.25±4.06		71.85±5.61	
Retinopathy (n, %)	7 (9.10)	70 (90.90)	6 (12.80)	41 (87.20)	2 (22.22)	7 (77.80)	37 (31.60)	80 (68.40)
Nephropathy (n, %)	10 (13.00)	67 (87.00)	7 (14.90)	40 (85.10)	3 (33.30)	6 (66.70)	37 (31.60)	80 (68.40)
Neuropathy (n, %)	19 (24.70)	58 (75.30)	10 (21.30)	37 (78.70)	2 (22.20)	7 (77.80)	34 (29.10)	83 (70.90)

HbA1c: Glycated hemoglobin, SD: Standard deviation

nateglinide. Short-acting secretagogues provide significant advantages in older adult patients because of the low risk of hypoglycemia and the fact that the dose can be easily changed according to the patient's number and amount of meals.

Metformin is the first-line diabetes therapy for all ages; it is effective and safe, inexpensive, and may reduce the risk of cardiovascular events and death. Metformin, recommended by the American Geriatrics Society and increased the usage rate from 48% to 55% in our outpatient clinic, improves the treatment results when added to the treatment of diabetics over 65 years of age who have no contraindications for use (12). Recent studies have shown that metformin can be safely used in patients with an estimated glomerular filtration rate of 30 mL/min/1.73 m^2. However, its use in patients with severe renal insufficiency is contraindicated. It should also be used cautiously in patients with hepatic dysfunction or congestive heart failure because of the increased risk of lactic acidosis. However, it is associated with weight loss, frailty, and lactic acidosis in older adults.

Metformin can also have both gastrointestinal side effects and decreased appetite, which can be problematic for some older people. Metformin reduction or discontinuation may be necessary for patients experiencing persistent gastrointestinal side effects (10). Weight loss is a common trigger factor for frailty and sarcopenia, with a high risk of being overlooked. Vitamin B12 deficiency is another nutritional deficiency often observed in patients receiving metformin treatment. Older adults are more prone to vitamin B12 deficiency because of various factors. In this context, clinicians should know when to cease metformin treatment in patients with malnutrition and/or frailty (13).

Insulin use is closely associated with hypoglycemia risk. While the patients' insulin use followed up in our study increased approximately twice, 83.6% of them stated that they did not experience any hypoglycemia, contrary to what was expected (11). The time of hypoglycemia was stated as 4% at night, 2% during the day, and 3.2% at any time of the day. In our study, the lower frequency of hypoglycemia than expected may be related to the inability to notice hypoglycemia due to advanced diabetes age and accompanying autonomic neuropathy. At this point, it is essential to educate patients about hypoglycemia and for physicians to ask patients about the frequency of hypoglycemia during visits.

Although the goals in managing hyperglycemia and diabetes complications in older people are similar to those of young people with diabetes, they should be determined by considering the presence of severe comorbidity, the state of their cognitive functions and functionality, the patient's life expectancy, and the risks of complications (10).

Glycemic control targets of older adult patients with normal functional and cognitive capacity and life expectancy (e.g. >10 years) long enough to allow for the use of treatment benefits should be as in young diabetes patients: A1c 7-7.5%, fasting and preprandial plasma glucose (PG) 80-130 mg/dL, night PG 90-150 mg/dL. Survival is shortened in older adult patients with multiple chronic diseases and mild to moderate cognitive dysfunction. In this group of patients, targets should be A1c 7.5-8%, fasting and preprandial PG 90-150 mg/dL, night PG 100-180 mg/dL. Glycemic and metabolic targets should be more flexible in older adult patients with advanced complications, accompanying major cardiac problems, short life expectancy, and fragile and limited functional or cognitive capacity. In these patients, recommendations are as follows: A1c 8-8.5%, fasting or preprandial PG 100-180 mg/dL, night-time PG 110-200 mg/dL (14).

In general, the average HbA1c values of our patients when they first came to the outpatient clinic were 8.17%, which was taken into the target range by decreasing 0.6% until the last control. The most appropriate treatments have been predominantly determined for patients with comorbidities, and their treatments have been customized. All patients were given medical nutrition therapy, medication use patterns, correct injection techniques for insulin users, and training on blood glucose measurement at home, and they were frequently called for follow-up visits. In older adult patients, a single daily dose of long-acting basal insulin may be preferred to maintain fasting blood glucose levels within the desired range. In cases where fasting glucose is close to normal limits and the HbA1c value is high, short-acting insulin can be added to the treatment. However, this multi-injection treatment, defined as basal + bolus, should not be used in patients with vision problems and dementia symptoms and who tend to miss or delay meals. Multiple insulin therapy can be a difficult option for older adults. In older adult patients with limited mobility and adjustment disorders. It can also cause hypoglycemia (9).

In this study, we found that the addition of basal insulin to OADs, which can be safer to achieve the glycemic target, is preferred, especially in patients with microvascular complications, neuropathy, nephropathy, and retinopathy. This intervention resulted in a significant decrease in HbA1c levels (from 8.7% to 8.0%, p=0.012), while providing nearly 3 kg of weight loss compared with the initial values. In contrast, basal + bolus therapy was the preferred treatment primarily in patients with microvascular complications,

especially retinopathy, in our outpatient clinic. While the patients' weight using basal + bolus increased by 1.5 kg, as expected, HbA1c values decreased by 0.4%.

Our study has both strengths and limitations. A few studies in the literature reveal both the current diabetes treatment of patients with type 2 diabetes aged 65 years and over and the results of reorganization in line with the recommendations and accompanying comorbidities. Our study fills a significant gap in this regard. On the other hand, our study's most significant limitation is that patients who applied before 2017 were included in the study, and their number was low. Therefore, the results of patients who used drugs with both weight-neutral and cardiovascular effects, such as SGLT-2 inhibitors introduced after this date, and those with a low risk of hypoglycemia, such as U-300 insulin, could not be included in the study. In addition, because the data of patients followed in a single center were evaluated in our study, it is not generalizable considering the living conditions in Türkiye. Finally, lifestyle changes, which have a significant place for treating diabetes, should also be considered when interpreting the results. From this point on, new studies are planned in our department, including more patients and evaluations, including today's applications.

CONCLUSION

Our study has shown that continuing the use of metformin in older adults with diabetes with preserved renal functions and adding insulin to their existing treatments when needed, despite all the reservations, provides an effective treatment by decreasing the HbA1c value. However, the lower than expected hypoglycemia frequency in our study may be due to the progressive age of diabetes and hypoglycemia unawareness due to accompanying autonomic neuropathy. Education of patients gains importance in this regard.

Acknowledgements: We would like to express our gratitude to the archives workers of the Diabetes Polyclinic of the Department of Endocrinology and Metabolic Diseases of the İstanbul University, İstanbul Faculty of Medicine for obtaining and arranging the patient files.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (decision no: 08, date: 02.04.2021) and was conducted in accordance with the Declaration of Helsinki Principles.

Informed Consent: Written informed consent was obtained from each participant.

Authorship Contributions

Surgical and Medical Practices: F.Ç., H.H., R.Ç., A.K.Ü., Ö.S.S., N.G., K.K., M.T.Y., N.D., İ.S., Concept: A.K.Ü., Ö.S.S., N.G., K.K., M.T.Y., N.D., İ.S., Design: A.K.Ü., Ö.S.S., N.G., K.K., M.T.Y., N.D., İ.S., Data Collection or Processing: F.Ç., D.G., H.H., R.Ç., Analysis or Interpretation: F.Ç., D.G., A.K.Ü., İ.S., Literature Search: F.Ç., A.K.Ü., İ.S., Writing: F.Ç., A.K.Ü., İ.S.

Conflict of Interest: We declare that no conflict of interest exists for any of the authors.

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:15-20
DOI: 10.4274/BMJ.galenos.2024.2023.12-1

Research

A Single Center Retrospective Study: Evaluation of Demographic Structure, Pain Characteristics, Early and Late Results, and Complications in 214 Trigeminal Neuralgia Patients Treated with Radiofrequency Thermocoagulation

Tek Merkezli Retrospektif Bir Çalışma: Radyofrekans Termokoagülasyon Yöntemi ile Tedavi Edilen 214 Trigeminal Nevralji Hastasının Demografik Yapısı, Ağrı Özellikleri, Erken ve Geç Dönem Sonuçları ile Komplikasyonlarının Değerlendirilmesi

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ABSTRACT

Objective: Gasser's ganglion blockade with radiofrequency thermocoagulation is a treatment option for trigeminal neuralgia. The aim of this study was to investigate the early and late treatment results of patients with idiopathic trigeminal neuralgia who underwent Gasser's ganglion blockade with percutaneous radiofrequency thermocoagulation and to evaluate the possibilities and limitations of this treatment method.

Methods: Between January 2005 and October 2020, 214 patients admitted to our clinic with a diagnosis of trigeminal neuralgia were included in this study. These patients were evaluated in terms of age, sex, involved side, involved branch, early intervention results, pain-free periods, and complications.

Results: Two hundred and seventy five procedures were performed in 214 patients. Of the patients, 125 (58.41%) were female and 89 (41.59%) were male. The mean age was 58.48±14.07 years. Pain was predominantly on the right side (61.68%). The most commonly involved trigeminal nerve branch group was V2-V3 (35.98%). The early success rate after radiofrequency thermocoagulation was 93.09%. At the end of the 36-month follow-up, 78.12% of the patients had no recurrence of pain.

Conclusion: Although there were some differences in the involved branch of the trigeminal nerve, the results were concentrated on V2 and V2-V3. Early results were consistent with those reported in the literature. When the late-term results were evaluated, differences were observed in the follow-up periods. The complications were consistent with those reported in the literature. In conclusion, radiofrequency thermocoagulation in trigeminal neuralgia is a safe, low complication rate, and recurrent treatment method with correct indication and application.

Keywords: Foramen ovale, facial pain, trigeminal neuralgia, radiofrequency thermocoagulation

ÖZ

Amaç: Radyofrekans termokoagülasyon yöntemi ile Gasser ganglion blokajı trigeminal nevralji için tedavi seçeneklerinden biridir. Bu çalışmanın amacı, perkütan radyofrekans termokoagülasyon ile Gasser ganglion blokajı uygulanan idiyopatik trigeminal nevraljili hastaların erken ve geç tedavi sonuçlarını araştırmak ve bu tedavi yönteminin olanaklarını ve kısıtlılıklarını değerlendirmektir.

Gereç ve Yöntem: Ocak 2005 ile Ekim 2020 tarihleri arasında kliniğimize trigeminal nevralji tanısı ile başvuran 214 hasta çalışmaya dahil edildi. Bu hastalar yaş, cinsiyet, tutulan taraf, tutulan dal, erken müdahale sonuçları, ağrısız dönemler ve komplikasyonlar açısından değerlendirildi.

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Cite as: Gündüz HB. A Single Center Retrospective Study: Evaluation of Demographic Structure, Pain Characteristics, Early and Late Results, and Complications in 214 Trigeminal Neuralgia Patients Treated with Radiofrequency Thermocoagulation. Med J Bakirkoy 2024;20:15-20

Received: 07.12.2023
Accepted: 01.03.2024

Bulgular: İki yüz on dört hastaya 275 prosedür uygulanmıştır. Hastaların 125'i (%58,41) kadın ve 89'u (%41,59) erkekti. Ortalama yaş 58,48±14,07 idi. Ağrı ağırlıklı olarak sağ taraftaydı (%61,68). En sık tutulan trigeminal sinir dal grubu V2-V3 (%35,98) idi. Radyofrekans termokoagülasyon sonrası erken başarı oranı %93,09 idi. Hastaların %78,12'sinde 36 aylık takip sonunda ağrı nüksü görülmedi.

Sonuç: Trigeminal sinirin tutulan dalında bazı farklılıklar olmasına rağmen, sonuçlar V2 ve V2-V3 üzerinde yoğunlaşmıştır. Erken dönem sonuçları literatür ile uyumlu idi. Geç dönem sonuçlar değerlendirildiğinde takip sürelerinde farklılıklar gözlendi. Komplikasyonlar literatürde bildirilenlerle uyumluydu. Sonuç olarak trigeminal nevraljide radyofrekans termokoagülasyon güvenli, komplikasyon oranı düşük, doğru endikasyon ve doğru uygulama ile tekrar uygulanabilir bir tedavi yöntemidir.

Anahtar Kelimeler: Foramen ovale, yüz ağrısı, trigeminal nevralji, radyofrekans termokoagülasyon

INTRODUCTION

The aim of this study was to analyze the early and late treatment results of patients with idiopathic trigeminal neuralgia (TN) who underwent Gasser ganglion blockade with percutaneous radiofrequency thermocoagulation (RFT) and to evaluate the possibilities and limitations of this treatment method. According to the third edition of the International Classification of Headache Disorders, TN is a disorder characterized by recurrent unilateral short electric shock-like pain limited to the distribution of one or more sections of the trigeminal nerve, with sudden onset and termination, and triggered by innocuous stimuli. It may develop for no obvious reason or may result from another diagnosed disorder (1,2).

The incidence of TN is 2 to 5 patients per 100,000 people (3-6). TN is evaluated in three etiological categories: 1) Idiopathic TN develops without any recognized cause; 2) classic TN occurs as a result of vascular compression of the trigeminal nerve root; and 3) secondary TN occurs due to a secondary cause such as multiple sclerosis or cerebellopontine angle tumor (7).

The first-step treatment of idiopathic TN is medical. Pain can be kept under control for a long time in this way, and even surgical intervention may not be needed (8). However, the effect of the drugs administered may decrease over time or side effects may develop. In this case, percutaneous methods or microvascular decompression in the presence of vascular compression may be considered. Percutaneous methods include radiofrequency thermocoagulation, glycerol rhizotomy, and balloon compression. Radiosurgery is another treatment method.

In 1913, Härtel (9) first described percutaneous access to Meckel's Cave through the foramen ovale for treating TN (10-12). In 1973, Sweet and Wepsic (13) used radiofrequency-based thermal energy to destroy preganglionic trigeminal rootlets in Meckel's cave.

METHODS

University of Health Sciences Türkiye, Prof. Dr. Mazhar Osman Psychiatric and Neurological Diseases Training and Research Hospital Ethics Committee approval was obtained for this study (decision no: 514, date: 12.01.2016).

The patients included in this study had the pain type defined by the International Headache Committee for typical TN. Patients with atypical headache were excluded from the study. In addition, patients with vascular compression of the 5th nerve on magnetic resonance imaging and those with secondary pain characteristics (intracranial tumor multiple sclerosis, etc.) were excluded from the study. The expert opinion of a neurologist was obtained for all patients who underwent intervention. First, it was ensured that drug treatment was administered under the control of a neurologist. Between January 2005 and October 2020, 275 interventions were performed in 214 patients who met these criteria. These patients were evaluated in terms of age, sex, involved side, involved branch, early intervention results, pain-free periods, and complications. Early results after RFT were evaluated according to the Barrow Neurological Institute (BNI) pain intensity scale (Table 1) (14).

Early postoperative outcomes and complications were documented for each intervention and not on a patient-by-patient basis. This is because multiple interventions may have been performed for the same patient. For standardization the follow-up period was limited to 36 months, and pain-free periods during this period were evaluated using Kaplan-Meier survival curves.

Statistical Analysis

The IBM SPSS version 22 statistical program was used to evaluate the mean values, standard deviations (SDs), percentages, and cumulative survival processes of the

Table 1. Barrow Neurological Institute pain intensity scale

Pain score	Definition
I	No trigeminal pain, no medication
II	Occasional pain, not requiring medication
III	Some pain, adequately controlled with medication
IV	Some pain, not adequately controlled with medication
V	Severe pain, no pain relief

results obtained. Microsoft Office Excel 2010 was used to create all graphs except the Kaplan-Meier survival curve.

Surgical Procedure

The patient is placed on the operating table in the supine position. The position is adjusted such that the orbital roofs and anterior clinoid processes overlap. Härtel's anatomical points are used for percutaneous application to Gasser's ganglion. The entry point is 2.5 cm lateral to the edge of the mouth. The #18 needle cannula is advanced along the medial aspect of the coronoid process of the mandible. It is advanced along the zygomatic arch and just medial to the pupil up to the intersecting plane 30 mm anterior to the external acoustic meatus. To prevent perforation of the buccal mucosa, the needle is aimed at the foramen ovale with a free hand technique with the index finger inside the mouth. This process was monitored by fluoroscopy (Figure 1).

After the needle has passed the foramen ovale in the correct position, cerebrospinal fluid can be seen coming from the distal end of the cannula. This observation is evidence that Meckel's cavity has been reached, but it must be confirmed using an electrode placed in the cannula. Sensory (2 MHz) and motor stimuli (75 MHz) are given to the area with the radiofrequency lesion generator connected to the electrode. The intervention is continued according to the results. Ineffective results may require repositioning of the needle. Simultaneously, the sensory stimuli we give show us whether the V1 branch of the trigeminal nerve is affected or not. Affection of the V1 branch may result in loss of the corneal reflex and consequently an increased risk of keratitis. Once localization is confirmed, a maximum of 70 °C heat can be applied for 1 min. The procedure can be repeated two or three times with 0.3 cm position changes, stimulus controls, and corneal reflex monitoring.

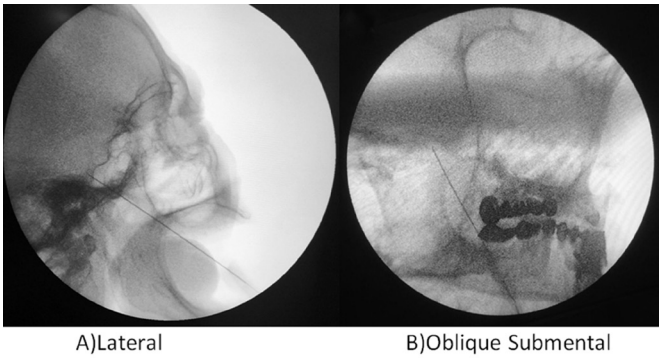

Figure 1. Trajectory of the catheter needle in lateral (A) and oblique submental (B) cranial radiograph images. Permission to publish the images was obtained from the authors of the accompanying article. The figure is based on original photographs from the author's archive (15)

RESULTS

Sex, Age, Painful Side, Involved Nerve Branch, Pain History

The patient group consisted of 125 (58.41%) females and 89 (41.59%) males. The age distribution was between 27 and 89 years. The mean age was 58.48±14.07 years. The mean symptom duration in patients with TN was 78.26 months (SD: ±86.13). Pain was on the right side in 132 (61.68%) and left side in 79 (36.92%) patients. Three (1.40%) patients complained of bilateral pain. When we analyzed the involved branch of the trigeminal nerve, we observed that 1 (0.47%) patient had V1, 48 (22.43%) patients had V2, 42 (19.63%) patients had V3, 16 (7.48%) patients had V1 and V2, 77 (35.98%) patients had V2 and V3, and 25 (11.68%) patients had V1, V2, and V3. In our retrospective study, we could not determine which branch was affected in 5 patients (2.34%) (Table 2). The duration of symptoms ranged from 2 to 720 months. The mean age at the onset of symptoms was 51.93 years (SD: ±14.55).

Early Results After the Interventions

Of the 214 patients who underwent RFT, 167 underwent one intervention (78.04%), 35 underwent two interventions (16.35%), 11 underwent three interventions (5.14%), and 1 underwent five interventions (0.47%) (Figure 2). After 275 procedures were performed in 214 patients, early results were evaluated according to the BNI pain intensity scale. Of the 275 procedures, 256 were considered grade 1, 2, and 3 (93.09%), and 19 procedures were considered grade 4 and 5 (6.91%). Of the 256 successful procedures, 164 were grade 1 (59.64%), 43 were grade 2 (15.64%), and 49 were grade 3 (17.82%). Of the 19 unsuccessful attempts, 14 were grade 4 (5.09%) and 5 were grade 5 (1.82%) (Figure 3).

Table 2. Demographic characteristics and pain localization distribution of patients with trigeminal neuralgia treated with percutaneous radiofrequency thermocoagulation

Characteristic	Value
Total patients (n=214)	
Age (years)	58.48±14.07 (27-89)
Sex, F:M	125 (58.41): 89 (41.59)
Affected side, R:L:B	132 (61.68%): 79 (36.92%): 3 (1.40%)
Involved branch	V1 (0.47%): V2 (22.43%): V3 (19.63%): V1-V2 (7.48%): V2-V3 (35.98%): V1-V2-V3 (11.68%): Unknown (2.34%)

Values are presented as mean values ± standard deviation (range) or number (%).
F: Female, M: Male, R: Right, L: Left, B: Bilateral

Follow-up and Recurrence of Pain

During the 36-month follow-up period, the mean pain-free period of 256 patients was 30.83 months. Of the 256 patients who were evaluated as BNI grade 1, 2, and 3, pain recurred in 37 (14.45%) patients within 1 to 12 months, 14 (5.47%) patients within 13-24 months, and 5 (1.95%) patients within 25-35 months. In total, 200 (78.12%) patients were pain free at the end of the 36th month (Figure 4).

Pain-controlled periods after 256 interventions that were considered successful were graphed using Kaplan-Meier survival curves (Figure 5).

Complications

After 275 procedures, 23 patients had intrabuccal haematoma (8.36%), 15 patients had corneal hypoesthesia and reflex loss (5.45%), 6 patients had masseter muscle weakness (2.18%), 6 patients had dysesthesia (2.18%), 1 patient had temporal muscle atrophy (0.36%), and 1 patient had a 1 cm RF lesion in the temporal lobe (0.36%) (Table 3).

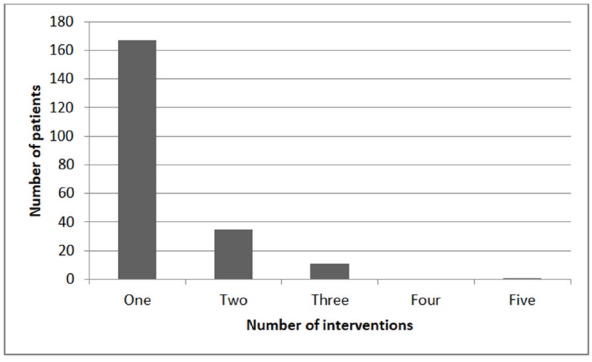

Figure 2. Number of interventions performed for each trigeminal neuralgia patient. The x-axis denotes number of procedures and the y-axis denotes number of patients

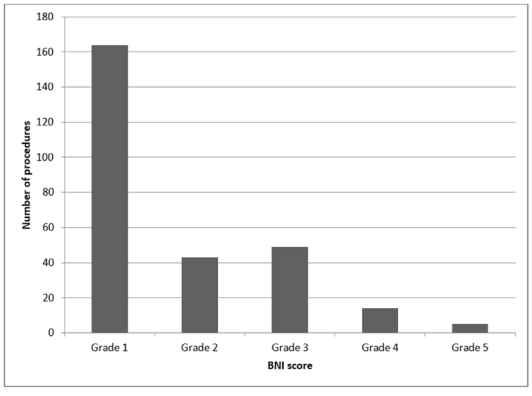

Figure 3. Early period results according to the Barrow Neurological Institute (BNI) pain intensity scale. The x-axis denotes BNI pain intensity score and the y-axis denotes number of procedures

DISCUSSION

Sex and Age

58.41% of our patients were female. In Bendtsen et al. (16), it was reported that TN affected 60% of women, although the cause was not clear (17,18).

In this study, the mean age was 58.48±14.07. The mean age range in the literature is 53-57 (17,18). However, although the mean age of the patients who applied to us was 58.48

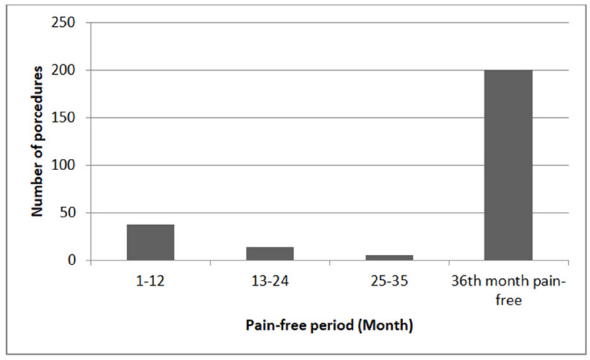

Figure 4. Pain recurrence at 36 months after 256 interventions. The x-axis denotes time and the y-axis shows number of procedures

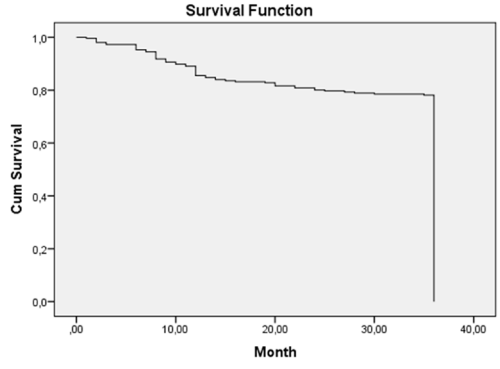

Figure 5. A graph showing Kaplan-Meier analysis of the pain-free survival rate of 256 successful surgical procedures with trigeminal neuralgia treated by radiofrequency thermocoagulation. The x-axis denotes pain-free survival in months and the y-axis denotes cumulative survival

Table 3. Complications occured due to intervention in 275 procedures

Complication	Total (n=275)
Intrabuccal hematoma	23 (8.36)
Corneal hypoesthesia and reflex deficit	15 (5.45)
Dysestesia	6 (2.18)
Masseter muscle weakness	6 (2.18)
Atrophy of temporal muscle	1 (0.36)
RF lesion in temporal lobe	1 (0.36)

Values presented as number (%). RF: Radiofrequency

years, the age distribution covered a wide range from 27 to 89 years. We should also consider a group of patients who had received medical treatment for a long time before surgical treatment or who had not been diagnosed with trigeminal treatment for a long time. Therefore, the mean date of onset of the complaints was 76.26 months before the patients were admitted to our clinic. In addition, the SD of these data was very large (SD: ±86.13). Taking all this into account, the age of onset of the disease was calculated as 51.93 years.

Painful Side and Involved Nerve Branch

According to the study by Son et al. (19) the most commonly involved side was the right side and the most commonly involved branch was V3. In the study by Maarbjerg et al. (18) the most commonly involved side was the right side and the most commonly involved branches were V2-V3. In this study, 61.68% of the patients had right-sided pain. The most commonly involved branches were V2-V3 branches (35.98%). When the literature is analyzed, right-sided dominance is evident. As for the involved branches, V3 or V2-V3 became dominant.

Early Post-intervention Results

After 275 interventions in 214 patients, 256 (93.09%) were evaluated in grades 1, 2, and 3 according to the BNI pain intensity scale. Grade 1 was completely painless, did not require medication, and included 164 procedures (59.64%). Grade 2 did not require medication, but occasional pain was present. Forty three interventions were performed in this group (15.64%). Grade 3 had occasional pain but could be controlled with medication. This group included 49 attempts (17.82%). Grades 4 and 5 were considered unsuccessful (19, 6.91%). In these groups, medication was required, and pain was not completely controlled. When the literature was reviewed, Son et al. (19) obtained BNI grade 1 results with a rate of 81.6%. Kanpolat et al. (20) reported an early pain relief rate of 97.6%. Taha et al. also reported a 99% result for the same category (21).

Follow-up and Recurrence of Pain

In this study, 36 months were set as the follow-up limit. Setting a fixed time limit was a methodological choice. Thus, we could standardize the follow-up period. No patient with whom we lost contact within 36 months was included in the study group. However, all patients whose pain recurred during this period and who underwent RFT were included in the study. After each intervention, the 36-month follow-up period was restarted.

During the 36-month follow-up period, the mean pain-free period was 30.83 months. Of the 256 patients who underwent RFT and received BNI grade 1, 2, and 3 results, 14.45% had pain within the first 12 months, 5.47% within 13-24 months, and 1.95% within 24-35 months. In addition, 78.12% of the patients were pain-free at the end of the 36th month. Taha et al. (21) reported a 15% recurrence of pain within the first 5 years. Kanpolat et al. (20) reported a 25% recurrence rate in 1-25 years of follow-up, and Nugent (22) reported a 23% recurrence rate in 4.7 years of follow-up.

Complications

Intrabuccal haemotoma (8.36%), corneal hypesthesia and reflex loss (5.45%), masseter muscle weakness (2.18%), dysesthesia (2.18%), temporal muscle atrophy (0.36%), and a 1 cm RFT lesion in the temporal lobe (0.36%) were observed after the interventions. The RFT lesion in the temporal lobe was detected by cranial computed tomography and magnetic resonance imaging examinations performed 6 h after the intervention due to nausea and vomiting. Within 12 h, the patient's complaints completely regressed. No progression was detected in the control imaging studies. Complications have also been reported in different studies. The most common complications in the study by Broggi et al. (23) were corneal reflex loss and masseter muscle weakness without keratitis. The most common complications were the same as those in the series of Kanpolat et al. (20).

In this study, hypesthesia was observed after RFT in almost all patients in the BNI grade 1, 2, 3. This hypesthesia was defined as "not disturbing and not troublesome" and this was explained to all patients before the intervention. Donnet et al. (24) described this condition as the cost of pain relief. Other sensory changes were defined as a complication under the name of dysesthesia.

A follow-up period longer than 36 months would have provided more detailed results.

One of the shortcomings of this study is that the effects of other diseases associated with TN were not monitored. Hypertension, diabetes, and thyroid disorders are highly likely to trigger TN. The effects of these comorbidities on disease characteristics and treatment outcomes may be different.

CONCLUSION

In this study, the early success rate was 93.09%. During the 36-month follow-up period, 78.12% of the patients did not experience recurrence of pain. RFT in TN is an effective, repeatable, and low-complication treatment method. However, it is necessary to understand its limitations well. The points to be considered during patient selection and intervention can be summarized as follows: 1) Avoid applying

RFT to atypical TN; 2) avoid applying lesion to V1 branch; 3) avoid high temperature and prolonged application; and 4) try to find the correct localization with radiological imaging and pre-lesion stimuli during the procedure.

ETHICS

Ethics Committee Approval: University of Health Sciences Türkiye, Prof. Dr. Mazhar Osman Psychiatric and Neurological Diseases Training and Research Hospital Ethics Committee approval was obtained for this study (decision no: 514, date: 12.01.2016).

Informed Consent: Retrospective study.

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:21-27
DOI: 10.4274/BMJ.galenos.2023.2022.1-12

Research

Evaluation of Eating Disorders, Eating Attitudes, and Triggers for Weight Gain in Bariatric Surgery Candidates with Childhood Obesity

Çocukluk Çağı Obezitesi Öyküsü olan Bariyatrik Cerrahi Adaylarında Yeme Bozuklukları, Yeme Tutumu ve Kilo Alma Tetikleyicilerinin Değerlendirilmesi

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ABSTRACT

Objective: Disordered eating among bariatric surgery candidates is common and associated with comorbid diseases. But the relationship with childhood stories is not known very well. Therefore, we sought to determine the properties of disordered eating and childhood obesity in bariatric surgery candidates.

Methods: The sample comprised 69 female and 16 male bariatric surgery candidates. Individuals were categorized as having childhood obesity or not. The groups consisted of 40 (33 female, 7 male) bariatric surgery candidates with childhood obesity and 45 (36 female, 9 male) bariatric surgery candidates without childhood obesity. All bariatric surgery candidates were examined by a psychiatrist for eating disorders. The eating attitude test was applied to all groups.

Results: 49.4% of the total 85 bariatric surgery candidates (n=42) identified any kind of trigger factor. Eating attitudes, rate of eating disorders, and trigger factors for morbid obesity were similar in both groups. The rate of type 2 diabetes was higher in bariatric surgery candidates without childhood obesity (57.8% vs. 30.0%, p=0.010). This group was older than bariatric surgery candidates with a childhood obesity story (41.8±7.7 vs. 33.6±9.1, p=0.000). There was no statistically significant difference between groups in familial obesity story (p=0.700).

Conclusion: The absence of a history of childhood obesity in bariatric surgery candidates appears to be associated with type 2 diabetes. Healthy eating habits and preventive measures for obesity must be put into practice.

Keywords: Bariatric surgery, childhood, eating disorder, obesity

ÖZ

Amaç: Bozulmuş yeme paterni bariyatrik cerrahi adaylarında oldukça sıktır ve komorbid hastalıklarla ilişkilidir. Ama çocukluk çağı obezitesi öyküsü ile ilişkisi pek bilinmemektedir. Bu nedenle bariyatrik cerrahi adaylarında bozulmuş yeme davranışıyla ilgili özellikleri ve çocukluk çağı obezitesi öyküsünü araştırmayı hedefledik.

Gereç ve Yöntem: Örneklem 69 kadın ve 16 erkek bariyatrik cerrahi adayını kapsamaktaydı. Katılımcılar çocukluk çağı obezite öyküsü olanlar ve olmayanlar şeklinde kategorize edildi. Gruplar çocukluk çağı obezitesi olan 40 (33 kadın, 7 erkek) bariyatrik cerrahi adayından ve olmayan 45 (36 kadın, 9 erkek) bariyatrik cerrahi adayından oluştu. Bariyatrik cerrahi adayları yeme bozuklukları açısından bir psikiyatrist tarafından değerlendirildi. Tüm gruplara yeme tutumu testi uygulandı.

Bulgular: Toplam 85 bariyatrik cerrahi adayının %49,4'ü (n=42) herhangi bir tetikleyici faktör tanımladı. Örneklemimizde yeme tutumu, yeme bozukluğu oranı ve morbid obeziteyi tetikleyen faktörler her iki grupta benzer bulundu. Tip 2 diyabet oranı çocukluk çağı obezitesi öyküsü olmayan bariyatrik cerrahi adaylarında daha yüksek bulundu (%57,8'e karşı %30,0, p=0,010). Bu grup çocukluk çağı obezitesi öyküsü olan bariyatrik cerrahi adayı grubundan daha yaşlıydı (41,8±7,7 vs. 33,6±9,1, p=0,000). Ailede obezite öyküsü açısından gruplar arasında belirgin bir istatistiksel farklılık yoktu (p=0,700).

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Cite as: Zengin Eroğlu M, Luş MG. Evaluation of Eating Disorders, Eating Attitudes, and Triggers for Weight Gain in Bariatric Surgery Candidates with Childhood Obesity. Med J Bakirkoy 2024;20:21-27

Received: 26.01.2022
Accepted: 04.04.2023

Sonuç: Bariyatrik cerrahi adaylarında çocukluk çağı obezite öyküsünün olmaması ile tip 2 diyabet ilişkili görünmektedir. Sağlıklı beslenme alışkanlıkları ve obeziteyi önleyici girişimler hayata geçirilmelidir.

Anahtar Kelimeler: Bariyatrik cerrahi, çocukluk çağı, yeme bozukluğu, obezite

INTRODUCTION

Recently, the prevalence of obesity has increased worldwide (1). Therefore, eating habits and eating disorders attracted clinicians' attention excessively. The relationship between eating disorders and obesity is often researched by clinicians (2,3). In particular, podiatrists and endocrinologists are interested in obesity and the development process of children. Eating disorders such as binge eating, unhealthy dieting, and purging are very common in obese adolescents (4).

The prevalence and incidence of eating disorders may vary across clinical samples and communities. Industrialization period, change in eating habits, city life, media, and cultural factors may affect the rate of eating disorders (5). Different factors have been blamed for eating disorders. Childhood trauma, obesity, high-level occupation of food and eating, over evaluation of weight and shape, restricted dieting, familial functionality, and familial story of eating disorders are related to the development of eating disorders (6).

As food and eating have a cultural and genetic basis, they interact and are passed on from generation to generation. In particular, the family environment has an important effect on the formation and progression of eating disorders. Abnormal eating attitude is a predictive factor of eating disorders (7). In the first years of life, people meet their nutritional needs by getting help from others. Usually, caregiver of baby is notably mother and other family members. Therefore, family circle is an important factor in eating and the development of eating habits through learning and genetic effects. A recent study from Türkiye draws attention to this issue and evaluates parents and grandparents' feeding practices on children (8). Obesity also has genetic aspects. Children with severe obesity and/or children with a family history of obesity are at risk of adult obesity (9).

In some cases, obesity is a process that starts in childhood and extends into adulthood. This process may reduce life expectancy due to the emerging risks of comorbid medical diseases [type 2 diabetes mellitus (DM), hypertension, cardiovascular diseases, non-alcoholic fatty liver disease, obstructive sleep apnea, dyslipidemia, some types of cancer, and menstrual irregularities] in childhood, adolescence, or adulthood. Some authors are assertive about childhood obesity and describe obesity as a "pediatric disease" (10). For this reason, bariatric surgery is being discussed as a treatment method and has started to be applied in a limited manner in properly selected adolescent cases (11).

In Türkiye, the risk of morbid obesity appears to be increasing on the contemporary cultural stage. Thus, bariatric surgery methods have become more popular and the number of bariatric surgery candidates (BSCs) is increasing day by day. From this point of view, we evaluated the relationship between childhood obesity story, eating disorders, and eating attitudes in BSCs. The relationship between childhood and disordered eating behavior in adult BSCs has not been adequately studied. Our main goal was to investigate whether childhood obesity makes a difference among BSCs. The hypothesis of this study is that eating disorders and unhealthy eating habits are more common in BSCs with childhood obesity.

METHODS

This study was approved by the Ethics Committee of University of Health Sciences Türkiye, Zeynep Kamil Women and Children Diseases Training and Research Hospital (decision no: 106, date: 27.06.2018). The research was conducted in accordance with the Helsinki Declaration as revised in 1989.

Procedures

BSCs admitted to University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital were evaluated at pre-surgical psychiatric interviews. The study was conducted during bariatric surgical procedures. All BSCs were examined by a general surgeon, dietitian, and endocrinologist before a psychiatrist. BSCs who agreed to participate in the study and gave written informed consent were consecutively included in the study. All patients were evaluated by the same psychiatrist in a single session. Session took about 50 minutes. First, the sociodemographic form, body mass index (BMI) calculation, and psychiatric examination were performed. Second, BSCs completed self-tests. Data about medical diseases were collected from patients' histories, medical records, and relatives of BSCs. Childhood obesity was noted according to patient's or relative's statements and could not be confirmed from patient files in all BSCs. Data about eating habits and triggers of obesity were collected with open-ended questions.

Participants

The inclusion criteria were super-obese patients (BMI >50 kg/m^2), morbidly obese (BMI >40 kg/m^2), or severely obese patients (BMI 35-40 kg/m^2) with at least one comorbid medical status. Exclusion criteria were being under the age of 18 years or older than 60 years, illiteracy, being visually handicapped, diagnosis of psychosis, mental retardation, history of neurologic diseases, for example dementia, or the presence of any condition affecting the ability to complete the assessment. Ninety-two BSCs were invited to participate in the study. One patient was excluded due to a diagnosis of mental retardation, and six patients were rejected from the study.

BSCs were divided into two groups: BSCs with childhood obesity stories and BSCs without childhood obesity stories.

Materials

Sociodemographic form: This form was developed for this study and included questions regarding gender, age, education level, marital status, employment status, eating disorders, family history of psychiatric disorders, medical diseases, medical treatment, childhood obesity etc. Forms were filled by a psychiatrist during the psychiatric examinations with the help of patients' or relatives' statements.

BMI: Height and weight were measured using a stadiometer and an electronic scale to calculate BMI.

Eating attitude test (EAT): EAT-40 was introduced by Garner and Garfinkel (12) and consisted of 40 items with a six-point (Always, Very Often, Often, Sometimes, Rarely, Never) likert scale. It was developed to identify adolescents with eating disorders and measure the symptoms of anorexia nervosa. It is a self-report test. For items 1, 18, 19, 23, 27, 39, "sometimes" 1 point, "rarely" 2 points, "never" 3 points, and "other options" 0 points. The total score of the scale is obtained by adding the scores obtained from each item of the scale. The cut-off score for the scale is 30. According to the evaluation scale of EAT-40, people with a score of "≥30" were described as "prone to eating behavior disorder". It was adapted to Turkish by Savaşır and Erol (13). The reliability coefficient of EAT-40 was 0.65. Internal consistency calculated by Cronbach's alpha was 0.70. High scores indicate higher level of pathology.

Night eating questionnaire (NEQ): This is a screening questionnaire developed by Allison et al. (14) and consists of 14 questions. It is a self-report test. The questionnaire includes questions about morning appetite and first food intake of the day, evening and night eating, rate of food intake after dinner, cravings, control over night eating behavior, difficulty falling asleep, frequency of waking up at night, and awareness and mood during night eating. The first nine questions in the questionnaire are answered by all participants. Participants who do not wake up at night or do not have a snack are warned not to continue in the next questions. Questions 10-12 are answered by the participants who have night awakenings, and questions 13 and 14 are answered by the participants who have night snacks. Total score ranges from 0 to 52. The cut-off point is 25. This was adapted by Atasoy et al. (15) to Turkish.

Current and/or past eating habits or eating disorders were detailed in the psychiatric examination. Psychiatric disorders were diagnosed by psychiatric examination based on the diagnostic and statistical manual of mental disorders-5 (16). Night eating syndrome was diagnosed by having ≥25 points in the NEQ. Emotional eating was evaluated with open-ended questions such as "Do you think that your overeating behavior is related to your feelings?" and "Do you have excessive eating because of positive/negative affects unrelated to meals or feeling hunger?". No questionnaire was used to evaluate emotional eating. Similarly, no questionnaire was used to evaluate grazing. It was asked to BSCs as "Graze eating is defined as repetitive, unplanned eating of small amounts of food throughout the day. Do you have these eating habits?"

Existence of childhood obesity was evaluated with an open-ended question of "Did you have childhood obesity before adolescence?" Trigger factors for obesity were asked with open-ended questions such as "Did you experience any rapid weight gain? What was the reason/trigger? Pregnancy delivery? Medication? Give up exercise? Loss (in term of psychiatric)? Other factors?".

Statistical Analysis

Data were analyzed with descriptive statistics such as frequency, percentage, average, and standard deviation using SPSS 15.0. The normal distribution assumption of all variables was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Demographic variables were compared between groups using the chi-square test (to compare whether there is a dependency between the variables) or independent t-tests (comparing means between two independent groups) as indicated. The Mann-Whitney U test was used for ordinal and nonparametric continuous variables. All statistical analyses were two-tailed and used a 0.05 level of significance.

RESULTS

Forty (33 female, 7 male) BSCs with childhood obesity and 45 (36 female, 9 male) BSCs without childhood obesity were included in this study. BSCs with childhood obesity were younger than BSCs without childhood obesity. There was a statistical difference in marital status between the two groups. The general characteristics of the groups are shown in Table 1.

There was no statistically significant difference between groups in familial psychiatric history (p=0.416). The rate of psychiatric history was statistically higher in BSCs without childhood obesity than in BSCs with childhood obesity (60.0% vs. 32.5% respectively, p=0.011). The rate of eating disorders was 37.5% in BSCs with childhood obesity and 42.2% in BSCs without childhood obesity (p=0.657). Also, no statistical difference was found between the groups in the distribution of past eating disorders (p=0.485).

The rate of eating disorders in BSCs with childhood obesity was 35% (n=14), and in BSCs without childhood obesity was 31.1% (n=14). Rates were similar in these groups (p=0.703). No statistical significant difference was found in the distribution of eating disorders types between groups (Table 2).

There was no statistically significant difference between groups in familial obesity history (p=0.700).

The rate of comorbid medical states was statistically higher in BSCs without childhood obesity than in BSCs with childhood obesity (84.4% vs. 52.5% respectively, p=0.001). The rate of type 2 DM was statistically higher in BSCs without childhood obesity than in BSCs with childhood obesity (57.8% vs. 30.0% respectively, p=0.010).

There was no statistically significant difference between the groups in hyperlipidemia, hypertension, thyroid disorders, polycystic over syndrome, and other medical status. There was no statistically significant difference between groups in multiple medical diseases (p=0.144).

The rate of treatment for comorbid medical states was statistically higher in BSCs without childhood obesity than in BSCs with childhood obesity (75.6% vs. 50.0% respectively, p=0.015).

Of the total 85 BSCs (n=42) identified any kind of trigger factor. The rate of trigger for obesity occurrence was statistically higher in BSCs without childhood obesity than in BSCs with childhood obesity (60.0% vs. 37.5% respectively, p=0.038). Rate of trigger factors for obesity occurrence in total group were pregnancy-maternity (n=21) 24.7%, menopause (n=4) 4.7%, grief (n=1) 1.2%, other factors (retirement, sedentary life, medical treatment, medical status) (n=15) 17.6%. No statistical difference was found between the groups in the distribution of trigger types of occurrence for obesity (p=0.139).

Table 1. Sociodemographic properties of bariatric surgery candidates with and without childhood obesity

		Childhood obesity (+) (n=40) Mean, %	Childhood obesity (-) (n=45) Mean, %	p-value
Age*		33.6±9.1	41.8±7.7	**0.000**
BMI*		45.7±4.5	45.2±4.5	0.610
EAT*		24.7±8.3	23.3±8.27	0.427
Gender**	Male	17.5%	20.0%	0.769
	Female	82.5%	80.0%	
Marital status**	Single	42.5%	15.6%	**0.012**
	Married	55.0%	73.3%	
	Divorced	2.5%	11.1%	
Education level**	Primary school	12.5%	24.4%	0.547
	Secondary school	15.0%	11.1%	
	College	32.5%	31.1%	
	University	40.0%	33.3%	
Employment status**	Employed	40.0%	57.8%	0.835
	Unemployed	60.0%	42.2%	
Eating disorders**		35.0%	31.1%	0.703

BMI: Body mass index, EAT: Eating attitude test, *Independent sample t-test, **Chi-square tests, p<0.05

Table 2. Distribution of eating disorders among groups

	Childhood obesity (+), %	Childhood obesity (-), %	p-value
Bulimia	0.0%	2.2%	0.268
NES	2.5%	4.4%	
Binge eating disorder	7.5%	15.6%	
EE	2.5%	6.7%	
EE + NES	2.5%	0.0%	
Binge eating disorder + EE	2.5%	0.0%	
Binge eating disorder + NES	7.5%	2.2%	
Bulimia + NES	5.0%	0.0%	
Binge eating disorder + NES + EE	5.0%	0.0%	
Grazing	35.0%	22.2%	0.191

NES: Night eating syndrome, EE: Emotional eating, chi-square tests, $p<0.05$

95.3% of the total 85 BSCs (n=81) reported any kind of weight-loss attempt (diet, exercise, acupuncture and combined methods). There was no difference between the groups in the types of weight-loss attempt (p=0.583).

DISCUSSION

The major results of the study were higher rates of comorbid medical diseases, medical treatment, and psychiatric disorders in the BSC without childhood obesity group. When the other results of the study were reviewed, it was noticed that BSCs without childhood obesity were older than those with childhood obesity. Generally, being old brings some risks in terms of chronic medical diseases and psychiatric disorders. The relationships between obesity and several age-related diseases are poorly understood about causality and biological mechanisms (17-19). Risks of cardiovascular problems, hypertension, and metabolic problems increase with age (20). Our study results pointed to similar occasions.

In our study, type 2 DM stands out among other medical diseases. The rate of type 2 DM was higher in BSCs without childhood obesity. This was an unexpected result for our study. However, our study did not include medical records of childhood obesity data in all BSCs. Our results were mostly based on individual reports. Some data suggest that malnutrition in intrauterine life or early childhood predisposes patients to adult-onset diabetes (21). We do not have no data about malnutrition or cachexia in the childhood period of BSCs in our study. Also, many research results in the literature point to the high incidence of type 2 DM in the general population. Obesity is an important risk factors for type 2 DM. Old age is another risk factor for type 2 DM. The prevalence of type 2 DM increases with age in both male and female genders (22). Determinants such as older age, abdominal obesity, low physical activity, and hypertension have been discussed for hyperglycemia (23). Genetic factors are also effective in the occurrence of type 2 DM. Some genetic profiles, for example, Asian populations are more vulnerable to obesity and exhibit higher risks for type 2 DM under comparable living conditions than others (24).

In this study, eating attitudes of the BSCs were assessed using EAT. EAT scores, rate of eating disorders, distribution of eating disorders, and unhealthy eating habits did not differ between groups in our study. In BSCs with childhood obesity, an almost impaired eating attitude is assumed to be an acquired behavior in childhood. It seems that many chronic diseases or high rates of DM diagnosis may affect eating attitudes and disturb eating attitudes in BSCs. eating patterns, such as the amount of salt, sugar, or fat intake, are associated with many non-communicable diseases (25-27). Also, EAT mostly evaluates anorexia nervosa, and people with anorexia nervosa do not require bariatric surgery, but anorexia-like presentations may be seen after bariatric surgery (28). So both of two groups had cut-off scores in EAT (Table 1).

Obesity is caused by both genetic and environmental factors. Although no relationship was found between childhood obesity history and eating disorders in BSCs by this study, there is some related evidence in the literature. For example, emotional binge eating was found to be higher in obese children in a study (29). We believe that the recall factor of BSCs related to childhood obesity has affected our study results. Keeping childhood health records and childhood follow-up processes more stringent will make it easier for us to understand the relationship between childhood obesity

and adult obesity. The prevalence of obesity in childhood is increasing, and it is an important health problem in our country and all over the world (30). The most important causes of obesity in children and adolescents are the weight status of parents, lack of physical activity, and eating foods resulting in excessive energy intake. Among these factors, those related to behavioral attitudes seem to be more easily changed (31,32).

There is a gap in the literature regarding the relationship between childhood obesity and eating attitude in BSCs. Our study results reached some conclusions that shed light on this gap. This study has several limitations. First, the "childhood obesity" concept is mostly based on the declaration of BSCs. It was not documented from medical records in all BSCs. Some measures were self-reported; thus, the results may not reflect the participants' actual eating attitudes. Second, unknown total duration of obesity, unmatched age of groups, and unequal ratio of women to men are other limitations. Third, the small sample size and cross-sectional design are disadvantages of the study. Follow-up studies will illuminate the problem further. Thus, these factors limit the generalizability of the study results.

CONCLUSION

In conclusion, preventive methods such as lifestyle changes, high physical activity, and a healthy diet should be recommended to obese children. "Family" and "nursery" which personalize and teach us many things first, should bring us healthy eating habits. Preventive forethoughts are put into practice immediately in health and education politics.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Türkiye, Zeynep Kamil Women and Children Diseases Training and Research Hospital (decision no: 106, date: 27.06.2018). The research was conducted in accordance with the Helsinki Declaration as revised in 1989.

Informed Consent: BSCs who agreed to participate in the study and gave written informed consent were consecutively included in the study.

Authorship Contributions

Surgical and Medical Practices: M.Z.E., M.G.L., Concept: M.Z.E., M.G.L., Design: M.Z.E., Data Collection or Processing: M.Z.E., Analysis or Interpretation: M.Z.E., M.G.L., Literature Search: M.Z.E., M.G.L., Writing: M.Z.E., M.G.L.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:28-34
DOI: 10.4274/BMJ.galenos.2023.2022.6-1

Research

Correlation of Conjunctival Swab PCR Positivity with Nasopharyngeal Swab PCR Positivity in COVID-19 Patients

COVİD-19 Hastalarında Nazofariengeal Sürüntü PCR Pozitifliğinin Konjonktival Sürüntü PCR Pozitifliği ile Korelasyonu

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ABSTRACT

Objective: To evaluate the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the tear and conjunctival secretions of laboratory-confirmed coronavirus disease-2019 (COVID-19) patients.

Methods: A total of 152 consecutive COVID-19 patients, confirmed by real-time polymerase chain reaction (RT-PCR) test in nasopharyngeal swabs, were included. The conjunctival swabs were taken from both eyes by the same ophthalmologist in the first 24-36 hours after positive test results for COVID-19 in the nasopharyngeal swabs were detected.

Results: Of the 152 patients, 96 (63.15%) were male and 56 (36.85%) were female. The mean age was 39.36±13.15 years. Sixteen (10.5%) patients had symptoms or findings such as tearing, stinging, redness, pain, and burning in their eyes. RT-PCR tests for SARS-CoV-2 RNA in conjunctival swabs were positive in 13 (8.55%) of 152 COVID-19 patients.

Conclusion: This study showed that SARS-CoV-2 may be found in the conjunctival swabs of laboratory-confirmed COVID-19 patients, and ocular secretions may be a possible route for virus transmission.

Keywords: Conjunctival swab, COVID-19, nasopharyngeal swab, RT-PCR, SARS-CoV-2

ÖZ

Amaç: Laboratuvar onaylı koronavirüs hastalığı-2019 (COVİD-19) hastalarının gözyaşı ve konjonktival sekresyonlarında şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) varlığını değerlendirmektir.

Gereç ve Yöntem: Nazofaringeal sürüntüde gerçek zamanlı polimeraz zincir reaksiyonu (RT-PCR) testi ile doğrulanan ardışık yüz elli iki COVİD-19 hastası dahil edildi. Nazofarengeal sürüntülerde COVİD-19 için pozitif test sonuçları tespit edildikten sonraki ilk 24-36 saat içinde aynı oftalmolog tarafından her iki gözden konjonktival sürüntüler alındı.

Bulgular: Yüz elli iki hastanın 96'sı (%63,15) erkek, 56'sı (%36,85) kadındı. Ortalama yaş 39,36±13,15 idi. On altı (%10,5) hastanın gözlerinde yaşarma, batma, kızarıklık, ağrı, yanma gibi semptom veya bulgular vardı. Konjonktival sürüntülerde SARS-CoV-2 RNA için RT-PCR testleri, 152 COVİD-19 hastasının 13'ünde (%8,55) pozitif tespit edildi.

Sonuç: Bu çalışma, laboratuvarca doğrulanmış COVİD-19 hastalarının konjonktival sürüntülerinde SARS-CoV-2'nin bulunabileceğini ve oküler sekresyonların virüs bulaşması için olası bir yol olabileceğini göstermiştir.

Anahtar Kelimeler: Konjonktival sürüntü, COVİD-19, nazofaringeal sürüntü, RT-PCR, SARS-CoV-2

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Cite as: Özbaş M, Vural A, Demirayak B, Karabela Y, Karabela Ş, Zırtıloğlu S, Küçüksümer Y, Yiğit U, Kart Yaşar K. Correlation of Conjunctival Swab PCR Positivity with Nasopharyngeal Swab PCR Positivity in COVID-19 Patients. Med J Bakirkoy 2024;20:28-34

Received: 03.06.2022
Accepted: 04.04.2023

INTRODUCTION

Coronaviruses (CoV) of coronaviridae are single-strain ribonucleic acid (RNA) viruses that typically infect birds and mammals. These viruses usually cause mild common cold cases in humans. However, some rare CoV strains, such as Middle East respiratory syndrome CoV, severe acute respiratory syndrome coronavirus (SARS-CoV), and coronavirus disease-2019 (COVID-19), (2019-nCoV), known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may cause respiratory failure, which has an increased mortality risk (1).

In December 2019, an outbreak of infectious lethal pneumonia caused by a new strain of CoV (SARS-CoV-2) (2) was announced in Wuhan, China. Hence, the disease is named COVID-19 or coronavirus disorder-2019. The disease soon became a major global health issue (3,4), and the World Health Organization declared a pandemic on March 11, 2020.

SARS-CoV-2 is highly contagious. It is mainly transmitted through the inhalation of droplets or aerosols released by an infected person or through contact routes with infected fomites (5). Ocular tissues are easily exposed to infectious droplets and fomites during close contact with infected persons and contaminated hands. This may cause the conjunctiva to be a direct target of infected droplets (6). The ocular surface may be a route to spread and limit the disease, which needs to be clarified. Ophthalmic examination, in particular, may be a risk factor for contracting SARS-CoV-2 infection because patients are examined in closer proximity by an ophthalmologist. Direct contact with the eyes of patients may be unavoidable during an ophthalmic examination.

There are an increasing number of studies on viral RNA detection in ocular secretions (7-10). In addition, some studies have demonstrated that the conjunctiva can be an important entry point for respiratory viruses (11) and that infected tears can flow into the nasopharynx and reach the lower respiratory tract (8-12). The presence of the virus in ocular secretions is important to understand the possible different modes of transmission of the virus.

This study aimed to evaluate the presence of viral RNA in tear and conjunctival secretions (swabs) of laboratory-confirmed COVID-19 patients via real-time polymerase chain reaction (RT-PCR).

METHODS

One hundred and fifty-two patients who were diagnosed with COVID-19 with a positive nasopharyngeal swab real-RT-PCR test (Bioeksen, Türkiye) and admitted to our clinic were included in this prospective, observational study. In this study, patients younger than 18 years and those receiving treatment for COVİD-19 were excluded.

The tear and conjunctival secretion samples were taken from both eyes of the patients by the same ophthalmologist in the first 24-36 hours after the nasopharyngeal swab RT-PCR was detected as positive. The lower eyelid was pulled down to expose the conjunctival sac, and tears and conjunctival samples were collected using disposable swabs (iClean) without topical anesthesia. This procedure was repeated in the other eye. The sampling swab was then placed inside the disposable virus sampling tube containing a protective solution. The marked upper end of the swab was cracked, and the virus sampling tube was sealed. The sterile medical gloves and other personal protective equipment were changed between patients and prevent possible infection and contamination. All samples were stored in a 4 °C refrigerator and sent to the laboratory for RT-PCR analysis with in 2 hours.

The study protocol was approved by the University of Health Sciences Türkiye, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Researches Ethics Committee (decision no: 2020-12-33, date: 08.06.2020) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients included in the study.

RT-PCR Protocol

Detection of the species-specific RdRp (RNA dependent RNA polymerase) gene of COVID-19 was performed by genomic RNA isolation and subsequent qualitative RT-PCR. Tear samples of patients were collected in Biospeedy transfer tubes (Bioeksen, Türkiye) for genomic RNA isolation. The QIA Symphony DSP Virus/Pathogen kit and QIA Symphony isolation instrument (Qiagen, Germany) were used to obtain virus RNA from tear samples. A Biospeedy COVID-19 RT-qPCR detection kit (Bioeksen, Türkiye) was used in the qualitative RT-PCR study. The Bioeksen PCR Kit and Rotor-Gene Q Real-Time PCR instrument were used to provide RNA amplification for the isolated RNA samples. The CoV reaction setup and qPCR program are summarized in Table 1.

FAM/HEX (Patient channel/Internal control channel) channel proliferation curve images were examined for the interpretation of the results. Non-sigmoidal curves were considered negative. Quantitation cycle (Cq) was calculated. If Cq<38, the results were considered as positive and the results were interpreted according to Table 2.

Statistical Analysis

All data were analyzed using the Number Cruncher Statistical System (NCSS, Utah, USA). Data are described as means and standard deviations (mean ± SD), percentages, or medians. The distribution of the data was evaluated using the Kolmogorov-Smirnov test. Fisher-Freeman Halton: Pearson Q-square test and Fisher's Exact test were used to compare the qualitative data. P values 0.05 were considered statistically significant.

RESULTS

The demographics and defining characteristics of 152 COVID-19 patients and 13 patients (8.55%) with conjunctival swab PCR positive results are summarized in Table 3.

Defining characteristics include treatment types as inpatient or outpatient, existence of ocular complaints, and symptom status of the patients. There was no statistically significant difference between the treatment modalities of the patients whether they had eye complaints or whether they were asymptomatic or not, in terms of the presence of virus in the conjunctival swabs (Table 3).

One hundred and eleven (73.00%) of the 152 COVID-19-positive patients reported complaints (one or a few of fever, loss of taste and smell, chill, shivering, weakness, fatigue, cough, sore throat, back pain, and shortness of breath) at the time of admission to the hospital. Thirty-six (23.7%) patients had no complaint but had a history of contact with someone who was COVID-19 positive. Five (3.3%) patients were both asymptomatic and had no history of contact (Table 3). The demographics and defining characteristics of 13 conjunctival PCR-positive patients on a case-by-case basis are presented in Table 4. The status of PCR positivity of both samples taken from the nasopharynx and conjunctiva are also shown.

Two (15.4%) patients with positive conjunctival RT-PCR test were treated as inpatients with lung involvement. One patient had mild COVID-19 pneumonia and the other had moderate (intermediate) COVID-19 pneumonia radiologically. Four of the 11 outpatients underwent thorax computed tomography. Only one of the 4 patients who had thorax computed tomography had mild COVID-19 pneumonia findings.

In three patients, one or more of the following complaints were together: low back pain (lumbar pain), fever, cough, weakness, back pain, loss of taste and mell, and sore throat complaints (Table 4).

Table 1. Reaction setup and qPCR program

Reaction setup			qPCR program application protocol		
Component	**Addition order**	**Reaction**	**Cycle count**	**Temperature**	**Time**
2x prime script	1	10 µL	1	52 °C	5 min
Oligo mix	2	5 µL	1	95 °C	10 sec
Template nucleic acid	3	5 µL	40	95 °C	1 sec
Total reaction volume		20 µL		55 °C	30 sec
				FAM/HEX reading	

qPCR: Quantitative polymerase chain reaction

Table 2. Interpretation of SARS-CoV-2 results

Template	Non isolate		Positive control		Negative control		Interpretation
Target	**Wuhan RdRp**	**IC**	**Wuhan RdRp**	**IC**	**Wuhan RdRp**	**IC**	
State 1	Positive	Positive	Positive	Positive	Negative	Negative	SARS-CoV-2 positive
State 2	Negative	Positive	Positive	Positive	Negative	Negative	SARS-CoV-2 negative
State 3	Positive	Positive	Positive	Positive	Positive	Negative	Contamination: Re-experiment
State 4	Negative	Negative	Positive	Positive	Negative	Negative	Extraction/inhibition trouble: Dilute the nucleic acid isolate to 1/10, re-experiment.
State 5	Negative	Negative	Negative	Negative	Negative	Negative	Reactive trouble: The reagents are refreshed by contacting the supplier and re-experiment.

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, IC: Internal control, RdRp: RNA dependent RNA polymerase

Table 3. Distributions of defining characteristic

		All cases (n=152)	Conjunctival swab PCR (+) (n=13)	Conjunctival swab (-) PCR (+) (n=139)	p-value
Age (year)	Min-max (median)	19-72 (9.88)	21-59 (9.88)	19-72 (39)	
	Avr ± SD	39.29±13.19	42.15±12.01	39.61±13.41	
	19-40	92 (60.5)	-	92 (66.2)	[a]**0.001****
	41-60	49 (32.2)	7 (43.8)	42 (30.2)	
	>61	11 (7.2)	6 (46.2)	5 (3.6)	
Gender	Male	97 (63.8)	8 (61.5)	89 (64.0)	[b]**0.415**
	Female	55 (36.2)	5 (38.5)	50 (36.0)	
Treatment type	Inpatient	9 (5.9)	2 (15.4)	7 (5.1)	[c]**0.173**
	Outpatient	143 (94.1)	11 (84.6)	131(94.9)	
Ocular complaints	Existent	16 (10.5)	2 (15.4)	14 (10.1)	[c]**0.629**
	Non	136 (89.5)	11 (84.6)	125 (89.9)	
Patient complaints	Asymptomatic	41 (27.0)	4 (26.7)	37 (26.6)	[c]**0.749**
	Symptomatic	111 (73.0)	9 (73.3)	102 (73.4)	

[a]Fisher Freeman Halton test, [b]Pearson chi-square test, [c]Fisher Exact test,**p<0.01
Avr ± SD: Average ± standard deviation, min-max: Minimum-maximum, PCR: Polymerase chain reaction

Table 4. Positive conjunctival PCR tests

Patient no	Age	Gender	Patient complaint	Ocular complaint	Treatment type	PCR test	
						Nasopharynx	Conjunctiva
1	57	F	Low back pain (lumbar pain)	-	Outpatient	+	+
2	39	M	Fever, cough	-	Outpatient	+	+
3	43	F	Weakness, cough	-	Outpatient	+	+
4	39	M	Loss of taste and smell, weakness	+	Inpatient	+	+
5	59	F	Weakness, fatigue	-	Outpatient	+	+
6	31	M	Sore throat	-	Outpatient	+	+
7	32	M	Asymptomatic	-	Outpatient	+	+
8	52	F	Sore throat, cough, weakness	-	Outpatient	+	+
9	39	F	Cough, weakness, back pain	-	Inpatient	+	+
10	31	F	Asymptomatic	-	Outpatient	+	+
11	21	M	Asymptomatic	-	Outpatient	+	+
12	59	M	Muscle pain, cough	-	Outpatient	+	+
13	46	M	Asymptomatic	+	Outpatient	+	+

PCR: Polymerase chain reaction, M: Male, F: Female

DISCUSSION

SARS-CoV-2 is a highly contagious virus that is mainly spread by respiratory droplets, person-to-person contact (13) and contact with contaminated objects or surfaces. There is limited and controversial evidence of SARS-CoV-2 transmission by other routes.

It has been shown that the conjunctiva may be an infection source and the virus may be transmitted by the ocular route. Ocular inflammation findings related to COVID-19 were reported to have a prevalence ranging from 5% to 8% in some studies (14,15). There have been several studies on the isolation of SARS-CoV-2 from blood, saliva, and stool (16).

The ocular surface and conjunctiva are tissues in direct contact with the outdoor environment. Therefore, whether the new CoV will cause an eye infection or pass through the ocular surface is a issue that ophthalmologists focus on. It should not be ignored that SARS-CoV-2 can infect both the eyes and surrounding tissues. The virus may use ocular tissues as an extra route of transmission. However, the main reason is contamination of the conjunctival epithelium with infectious droplets and body fluids (6). In particular, hand–eye contact increases the risk of viral infection.

The enzymes angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) are believed to be the key proteins for entry of 2019-nCoV into host cells (17). Besides the studies indicating that ACE2, the main receptor for SARS-CoV-2, is not significantly expressed, a very low expression, in conjunctival samples of healthy and diseased people (18), there are studies showing that ACE2 receptors were located in non-pigmented epithelial cells of the ciliary body, corneal endothelial and epithelial cells, conjunctival epithelial cells, and trabecular meshwork cells in the anterior segment the expression of ACE2 in cornea and conjunctiva tissue of the eye (19). In addition, recent studies have reported the expression of ACE2 in the cornea and conjunctiva tissue of the eye (20). Studies have shown the overexpression of the ACE2 receptor gene in the human conjunctiva and cornea together with the TMPRSS2 protein (20,21). The presence of ACE2 and TMPRSS2 in the corneal limbal cells could explain the affinity of SARS-CoV-2 to this tissue and its existence in the tear (21). In agreement with the literatüre SARS-CoV nucleic acid can be detected in the ocular secretions of patients with SARS (7). Recently, Wuhan ophthalmologists detected viral nucleic acid in the conjunctival swab samples of laboratory-confirmed COVID-19 patients (22).

The possible infection of SARS-CoV-2 via the conjunctival route is a debated issue. Recent studies have reported that SARS-CoV-2 may be transmitted through mucous membranes, including the conjunctiva (23). These studies highlight the necessity for further research to investigate the possible transmission of SARS-CoV-2 through the conjunctival route, especially considering the recent findings that all COVID-19 patients have conjunctival congestion and ocular complaints (14,15). Ocular surface involvement characteristics include unilateral or bilateral bulbar conjunctival hyperemia, chemosis, follicular reaction of the palpebral conjunctiva, epiphora, and mild edema of the eyelids (24).

In a meta-analysis conducted by Sarma et al. (12) conjunctivitis findings were reported in only 3.75% of patients, and the positive rate for virus in the tear sample was found to be 1.949%. Zhang et al. (25) detected only 1 (0.9%) of the conjunctival swab samples of 102 COVID-19 patients (laboratory-confirmed 72 patients) with a positive result for the virus. In another study by Atum et al. (26) from 40 hospitalized COVID-19 patients, the PCR test of conjunctival swab samples collected in the first 3 days of their hospitalization was found to be positive for 3 (7.5%) of them. Mahmoud et al. (27) found a higher rate of SARS-CoV-2 RT-PCR positive tests in the conjunctival swab samples of COVİD-19 patients (8/28 patients-28.57%). Xia et al. (28) analyzed 2 conjunctival secretion samples taken at 2-3 days intervals after 7.33±3.82 days after the onset of symptoms from 30 patients with COVID-19. One of whom also complained of conjunctivitis. The SARS-CoV-2 RNA was found only in the tear and conjunctival secretion sample of a patient (3.3%) with conjunctivitis complaints. Li et al. (29) found that 4 patients (8.2%) were positive for SARS-CoV-2 RNA in a conjunctival swab sample by RT-PCR in their study, which included 49 COVID-19 patients without ocular symptoms. In contrast to those studies, in a study carried out by Deng et al. (30) including 114 COVID-19 patients, they found that no PCR test was positive for the virus in the conjunctival swab samples taken in 11±6.3 days.

In our study, 16 (10.52%) of 152 patients had ocular complaints. The RT-PCR test for SARS-CoV-2 was found to be positive in the conjunctival swab samples of 2 out of 16 patients. SARS-CoV-2 RNA was found in the conjunctival RT-PCR test in a total of 13 patients. Two of the 13 patients were among those with ocular complaints. The other 11 patients were among those without eye complaints. The conjunctival RT-PCR test was positive in 12.5% of COVID-19 patients with ocular complaints. Virus RNA was found in the conjunctival RT-PCR test in 11 (7.35%) of 136 patients without ocular complaints. Our results were similar to those of the previous studies mentioned above.

Briefly, in all these studies, the rate of patients with evidence of viral particles in the tear or conjunctival secretions remained between 0% and 7.5%, except for the study by Mahmoud et al. (27). They found it to be 28.57%, and this high rate may be due to various factors such as race difference, hygiene practices, and the fact that all of the included patients were inpatients.

However, conditions such as tests belonging to different manufacturers used in the studies, test techniques, patients included in the study (inpatient or outpatient, stil receiving treatment), sample sizes, differences in test sampling techniques, and intake times have an effect on the results of the studies.

In our study, the conjunctival swab samples were taken in the first 24 h after the nasopharyngeal RT-PCR tests were declared positive. Conjunctival swab samples were taken earlier than those in the aforementioned studies and from numerous patients before starting their treatment. Most of the patients were outpatients. We found an RT-PCR positivity rate of 8.55% in conjunctival swab samples from patients with confirmed diagnosis of SARS-CoV-2.

In regard to the present study results, COVID-19 RNA may be found in the conjunctival secretions and tears of COVID-19 patients with or without ocular symptoms, and the virus can be transmitted by the ocular route. The presence of SARS-CoV-2 RNA in the tear and conjunctival secretions was not associated with the presence of generalor ocular symptoms.

Various anatomical features indicate that the eye is a potential site for viral infection and a gateway for respiratory infection. The nasolacrimal system provides an important anatomical route between the ocular and respiratory systems (31). Therefore, the virus colonizing the conjunctiva can infect the upper and lower respiratory tracts.

This study has some limitations. First, only one conjunctival swab was obtained from each patient. The other limitation was that the patients did not know the first day of their complaints (some patients were also asymptomatic) during the RT-PCR test.

CONCLUSION

In agreement with some previous studies, we have detected that the conjunctival/eye secretions of COVID-19 patients, even if they are asymptomatic, may be a source of infection and transmission for medical professionals and other people. Ocular symptoms are rarely seen in COVID-19 patients. The eye may be not only a potential virus replication site but also an alternative route of virus transmission from the ocular surface to the respiratory and gastrointestinal tracts.

Acknowledgement: This study was funded by TÜSEB. Statistical analyses were performed by Emire Bor. Proofreading was performed by Filiz Özbaş.

ETHICS

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Researches Ethics Committee (decision no: 2020-12-33, date: 08.06.2020) and adhered to the tenets of the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all patients included in the study.

Authorship Contributions

Surgical and Medical Practices: M.Ö., Concept: M.Ö., Y.K., Ş.K., S.Z., K.K., Design: M.Ö., A.V., B.D., Ş.K., Ya.K., U.Y., K.K., Data Collection or Processing: M.Ö., A.V., B.D., Y.K., Ş.K., S.Z., K.K., Analysis or Interpretation: M.Ö., B.D., Y.K., Ş.K., U.Y., K.K., Literature Search: M.Ö., A.V., S.Z., Ya.K., Writing: M.Ö., A.V., B.D., U.Y.

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

Financial Disclosure: This study was supported by the TUSEB.

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Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:35-41
DOI: 10.4274/BMJ.galenos.2023.2022.11-1

Research

Is Ischemic Stroke Declines During the COVID-19 Pandemic?

COVİD-19 Pandemisinde İskemik İnmeler Azaldı mı?

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ABSTRACT

Objective: A decrease in the number of ischemic strokes has been reported during the coronavirus disease-2019 (COVID-19) pandemic period. The aim of this study was to determine the effect of COVID-19 and associated risk factors on the number of ischemic strokes in hospitalizations during the COVID-19 period.

Methods: This cross-sectional study was conducted using hospital records. Data of patients who underwent a COVID-19 real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test between 2020 and 2021 were included. In addition to RT-PCR test results, the diagnosis of ischemic stroke and known risk factors for ischemic stroke (gender, age, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, hypercholesterolemia, congestive heart failure, coronary artery disease, peripheral vascular disease, chronic kidney disease) were evaluated.

Results: According to the inclusion criteria, 25,522 patient records were included in the analysis. There were 123 (0.6%) acute ischemic stroke patients among 19,051 COVID-19-negative patients and 23 (0.4%) among 6471 positive patients. Among the covariates, age and diabetes have a significant effect on acute ischemic stroke. In path analysis, the negative direct effect of RT-PCR positivity on acute ischemic stroke was reversed through the mediator variable effect of diabetes and age. Patients with diabetes and higher age have an increased risk of acute ischemic stroke if they have COVID-19.

Conclusion: Evidence is not satisfactory to determine the effect of COVID-19 on ischemic stroke. Reports of a decrease in the number of hospitalizations due to ischemic stroke are accumulating. This result may be due to the direct effect of COVID-19, the lack of recognition of clinical symptoms, or the decrease in hospital admissions of patients without a severe clinical picture. In the presence of accompanying risk factors such as age and diabetes that will aggravate the stroke clinic, the reducing effect of COVID-19 on the number of ischemic strokes disappears.

Keywords: COVID-19, ischemic stroke, COVID-19 testing, ischemic stroke: diagnosis, ischemic stroke: epidemiology, pandemic

ÖZ

Amaç: Yeni koronavirüs hastalığı-2019 (COVİD-19) pandemi döneminde iskemik inme sayısında azalma bildirilmiştir. Çalışmanın amacı, COVİD-19 döneminde hastaneye yatışlarda COVİD-19 ve ilişkili risk faktörlerinin iskemik inme sayısı üzerindeki etkisini belirlemektir.

Gereç ve Yöntem: Bu kesitsel çalışma hastane kayıtları üzerinden yapıldı. 2020-2021 tarihlerinde COVİD-19 gerçek zamanlı ters transkriptaz-polimeraz zincir reaksiyonu (RT-PCR) testi yaptırmış hasta verileri dahil edildi. RT-PCR test sonuçlarına ek olarak, iskemik inme tanısı, iskemik inme için bilinen risk faktörleri (cinsiyet, yaş, diabetes mellitus, kronik obstrüktif akciğer hastalığı, hipertansiyon, hiperkolesterolemi, konjestif kalp yetmezliği, koroner arter hastalığı, periferik vasküler hastalık, kronik böbrek hastalığı) değerlendirildi.

Bulgular: Dahil etme kriterlerine göre 25.522 hasta kaydı analize dahil edildi. 19.051 COVİD-19 negatif arasında 123 (%0,6), 6471 pozitif hasta arasında 23 (%0,4) akut iskemik inme hastası vardı. Ortak değişkenler arasında yaş ve diyabetin akut iskemik inme üzerinde önemli bir etkisi olduğu belirlendi. Path analizinde, RT-PCR pozitifliğinin akut iskemik inme üzerindeki olumsuz doğrudan etkisi, diyabet ve yaşın aracı değişken etkisi ile tersine çevrilmiştir, diyabetli ve daha ileri yaştaki hastalarda COVİD-19 varsa akut iskemik inme riski artmıştır.

Sonuç: COVİD-19'un iskemik inme üzerindeki etkisine karar vermek için kanıtlar tatmin edici değildir. İskemik inme nedeniyle hastaneye yatış sayısında azalma raporları birikmektedir. Bu sonuç, COVİD-19'un doğrudan etkisi olabileceği gibi, klinik semptomların tanınmaması veya ciddi bir klinik tabloya sahip olmayan hastaların hastaneye başvurularının azalmasından da kaynaklanabilir. İnme kliniğini ağırlaştıracak yaş ve diyabet gibi eşlik eden risk faktörlerinin varlığında COVİD-19'un iskemik inme sayısını azaltıcı etkisi ortadan kalkar.

Anahtar Kelimeler: COVİD-19, iskemik inme, COVİD-19 testi, iskemik inme: tanı, iskemik inme: epidemiyoloji, pandemic

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Cite as: Ocak Ö, Şahin EM, Toraman Ç. Is Ischemic Stroke Declines During the COVID-19 Pandemic?. Med J Bakirkoy 2024;20:35-41

Received: 06.11.2022
Accepted: 23.04.2023

INTRODUCTION

The causative agent of coronavirus disease-2019 (COVID-19), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a new type of coronavirus known as a positive polarity, single-stranded, enveloped RNA virus with the potential to invade neurological tissues (1). Many neurological diseases and neurological complications related to these diseases have been reported. In a case series of 214 patients from China, 36.4% reported neurological complications in addition to systemic symptoms (2).

Neurological complications may result from a systemic response to infection or from the direct effects of the virus. Direct spread of the virus to the nervous system, immune system disorder, renin-angiotensin system, and neurological damage caused by systemic disorder are thought to be effective mechanisms (3).

Cases of ischemic and hemorrhagic stroke have been reported in patients with COVID-19. Stroke pathogenesis is associated with increased fibrinogen, low platelet levels, coagulopathy, and increased D-dimer levels. The cytokine storm observed in COVID-19 infection can cause prothrombotic activation and microvascular thrombosis. In autopsy studies of infected patients, viral inclusions were detected in endothelial cells, and it has been reported that ischemic events may develop directly due to endothelial damage (4).

The frequency of stroke during the pandemic period can be evaluated from two different perspectives: in the whole community and in patients diagnosed with COVID-19. In different series reported so far, the frequency of stroke in COVID-19 cases with a definitive diagnosis and requiring hospital inpatient care varies between 2.8% and 5.4% (2,5).

Most of the cases reported in the literature are diagnosed with ischemic stroke (6). However, the retrospective nature of these studies, limited number of cases, and lack of detailed clinical and neuroradiological features are important points to consider when evaluating these data. Another noteworthy situation is that stroke is seen more frequently in COVID-19 cases with a moderate and severe clinical course. Initial observations have shown that the presence of ischemic or hemorrhagic stroke is associated with poor prognosis during COVID-19 infection (2).

In the general population, it has been reported that the frequency of stroke decreases, especially in admissions to emergency services. Considering the data of the last five years in Italy, which has experienced the devastating effects of the COVID-19 pandemic, in a center where an average of 51 new ischemic stroke cases per month is observed, surprisingly, only six ischemic stroke cases were admitted between February 21 and March 25, 2020. While 21% of the strokes admitted in the pre-pandemic period were ischemic strokes due to large vessel occlusion, only one ischemic stroke due to cardioembolic large vessel occlusion was recorded during the pandemic period (7).

The aim of this study was to determine the number and effects of COVID-19 on ischemic strokes during the pandemic period on the records of our hospital, which is a regional tertiary health center.

METHODS

This study was conducted with the approval of the Clinical Research Ethics Committee of the Çanakkale Onsekiz Mart University (decision no: 2022-03, date: 02.02.2022). The study was conducted on hospital records by including the data of patients who had COVID-19 polymerase chain reaction (PCR) test (positive or negative results, both will be examined).

In this cross-sectional study, data from patients who underwent COVID-19 PCR testing between 2020 and 2021 at Çanakkale Onsekiz Mart University Hospital were included in the review. In addition to the diagnosis of acute ischemic stroke (AIS), patient characteristics and disease diagnoses that pose a risk for this disease were compiled from the patient records, and arrangements and analyses were made in accordance with the purpose of the study.

Research Variables

In this study, the prevalence of AIS and the effect of exposure to COVID-19 on AIS in the determined period were examined. In addition, the possible effects of AIS risk factors and the change in these possible effects due to exposure to COVID-19 have also been examined.

These variables can be classified as

- Output variable: AIS,
- Exposure variable: COVID-19 (as positive or negative according to the RT-PCR result),
- Variables Potentially Affecting AIS and the covariate with COVID-19:

Gender, age, previous cerebrovascular disease (p-CVD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), hypertension (HT), hypercholesterolemia (HCL), congestive heart failure (CHF), coronary artery disease (CAD), peripheral vascular disease (PVD), and chronic kidney disease (CKD).

Patient Population

The criteria for inclusion in the data file are as follows:

- The patient underwent a COVID-19 PCR test.
- The patient's COVID-19 PCR result was reported as positive or negative.
- The patient was 18-years-old or older.
- Knowing whether the patients have had an AIS.
- Gender, age, and CVD, DM, COPD, HT, HCL, CHF, CAD, PVD, and CKD diagnostic information of the patients were present.

The number of patients included in the analysis according to the inclusion criteria was 25,522. The distribution of patient characteristics according to the variables listed above is presented in Table 1.

Statistical Analysis

Data analysis was carried out in two steps.

Step 1: This step is structured in two stages. In the first stage, the relationships between AIS, which is the output variable, and gender, age, p-CVD, DM, COPD, HT, HCL, CHF, CAD, PVD, and CKD, which may have possible effects, were examined. In the second stage, gender, age, p-CVD, DM, COPD, HT, HCL, CHF, CAD, PVD, and CKD were accepted as covariate variables, and the relationship between COVID-19 exposure and AIS was examined. These analyses are modeled using logistic regression (8).

Step 2: Path analysis was performed in data analysis in this step. Significant relationships from the logistic regression analysis were used as preliminary information. As detailed in the findings section, the three variables that had a significant impact on AIS were DM, age, and COVID-19. The effect of COVID-19 on AIS was modeled by path analysis of DM and age mediator variables. Path analysis is an approach to model explanatory relationships between observed variables. The defining feature of path analysis models is the absence of hidden variables. Path analysis models are special cases of structural equation models (9). Since the variables in the model are categorical and there is no normal distribution expectation, the estimations were made using the "Asymptotic Distribution Free" method.

RESULTS

COVID-19 and Ischemic Stroke

AIS was diagnosed in 123 (0.6%) of the total 19,051 COVID-19-negative patients. AIS was diagnosed in 23 (0.4%) of 6471 COVID-19-positive patients. The rate of AIS diagnosis in COVID-19-positive patients is significantly lower than that in COVID-19-negative patients.

Analysis

Step 1: The impact of COVID-19 on AIS was modeled by logistic regression. Gender, age, p-CVD, DM, COPD, HT, HCL, CHF, CAD, PVD, and CKD variables, which may have possible effects on AIS, were taken as covariate variables,

Table 1. Patient characteristics

Gender	Male 13,147 (51.5%)	Female 12,375 (48.5%)
Age	Mean =44.2	Standard deviation =17.3
COVID-19 (RT-PCR)	Negative 19,051 (74.6%)	Positive 6471 (25.4%)
Clinical conditions	**Present n (%)**	**Not-present n (%)**
Acute ischemic stroke	146 (0.6%)	25,376 (99.4%)
Previous cerebrovascular disease	1411 (5.5%)	24,111 (94.5%)
Hypertension	3749 (14.7%)	21,773 (85.3%)
Diabetes mellitus	3529 (13.8%)	21,993 (86.2%)
Coronary artery disease	1179 (4.6%)	24,343 (95.4%)
Congestive heart failure	436 (1.7%)	25,086 (98.3%)
Chronic obstructive pulmonary disease	471 (1.8%)	25,051 (98.2%)
Hypercholesterolemia	3135 (12.3%)	22,387 (87.7%)
Peripheral vascular disease	1732 (6.8%)	23,790 (93.2%)
Chronic kidney disease	444 (1.7%)	25,078 (98.3%)

COVID-19: Coronavirus disease-2019, RT-PCR: Real-time reverse-transcriptase polymerase chain reaction

and the effect of COVID-19 on AIS was remodeled with them. The results are presented in Table 2.

According to the analysis results, COVID-19 disease is effective against AIS [odds ratio (OR): 1.82, p=0.008]. Of the total 19,051 COVID-19-negative patients, 18,928 (99.4%) were AIS-negative, whereas 123 (0.6%) were AIS-positive. Of the 6471 COVID-19-positive patients, 6448 (99.6%) were AIS-negative, whereas 23 (0.4%) were AIS-positive. As COVID-19 reverted to a positive diagnosis, AIS-positive diagnosis showed a decrease 0.2%, and this decrease is significant.

In addition, when modeled with the COVID-19 covariate variables gender, age, p-CVD, DM, COPD, HT, HCL, CHF, CAD, PVD, and CKD, a small increase from the COVID-19 coefficient (from B=0.600 to B=0.622) but shows the same effect on AIS with a similar significance level (OR: 1.86, p=0.007).

Among the variables gender, age, p-CVD, DM, COPD, HT, HCL, CHF, CAD, PVD, and CKD, whose possible effects were examined and considered as covariate variables, age (OR: 1.08, p<0.0001) and DM (OR: 0.53, p=0.002) has a significant effect on AIS.

Age has a significant effect on AIS. The probability of developing AIS increases with age.

Table 2. Relationships between AIS and COVID-19

Variables	B	OR (95% CI)	p-value
Step 1			
COVID-19	0.600	1.82 (1.17-2.85)	**0.008**
Step 2			
COVID-19	0.622	1.86 (1.19-2.93)	**0.007**
Gender	0.280	1.32 (0.94-1.86)	0.105
Age	0.072	1.08 (1.06-1.09)	**<0.0001**
p-CVD	16.971	23456229.28 (0)	0.986
DM	-0.633	0.53 (0.36-0.79)	**0.002**
COPD	-0.108	0.89 (0.44-1.83)	0.766
HT	-0.141	0.87 (0.57-1.34)	0.519
HCL	0.148	1.16 (0.70-1.92)	0.565
CHF	0.033	1.03 (0.51-2.08)	0.927
CAD	0.034	1.03 (0.59-1.82)	0.909
PVD	0.208	1.23 (0.68-2.23)	0.491
CKD	-0.311	0.73 (0.37-1.46)	0.376

COVID-19: Coronavirus disease-2019, AIS: Acute ischemic stroke, OR: Odds ratio, CI: Confidence interval, p-CVD: Previous cerebrovascular disease, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, HT: Hypertension, HCL: Hypercholesterolemia, CHF: Congestive heart failure, CAD: Coronary artery disease, PVD: Peripheral vascular disease, CKD: Chronic kidney disease

Of the 21,993 DM-negative patients, 21,895 (99.6%) were AIS-negative, whereas 98 (0.4%) were AIS-positive. While 3481 (98.6%) of the total 3529 DM-positive patients were AIS negative, 48 (1.4%) were AIS positive. As patients had a DM diagnosis, the probability of a positive diagnosis of AIS increased by 1.0%.

Step 2: Logistic regression gave an idea about the variables that were significantly correlated with AIS. AIS and COVID-19, age, and DM are associated variables. Among these variables, the explanatory levels were examined by path analysis. In path analysis, it is possible to use internal and external variables and mediator variables. As stated by Baron and Kenny (10), the full mediator effect reduces the relationship between the explanatory variable and the explained variable to zero. The path analysis performed was modeled as shown in Figure 1. Estimates of the modeling in the path analysis are presented in Table 3.

In direct effects, DM and age increased AIS positivity (p<0.05). Again, as a direct effect, as COVID-19 turns positive, AIS becomes negative, and this effect is significant (p<0.05). However, the effect of COVID-19 on AIS was reversed through the mediator variable effects of DM and age. Therefore, as COVID-19 positive, it tends to be AIS positive. In this case, patients with DM and age risk increased their risk of AIS if they received COVID-19.

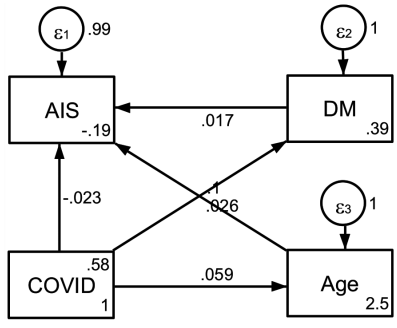

Figure 1. Model of relationships and mediator effect between AIS, COVID-19, age, and DM

COVID-19: Coronavirus disease-2019, AIS: Acute ischemic stroke, DM: Diabetes mellitus

Table 3. Estimates of Path analysis

Effects	Coefficient	p-value
Direct effect		
DM → AIS	0.0047	0.008
Age → AIS	0.0005	<0.0001
COVID-19 → AIS	-0.0041	<0.0001
Indirect effect		
COVID-19 → DM, Age → AIS	0.0012	<0.0001

DISCUSSION

The sociological effects of the pandemic, which are added to the effects of the COVID-19 infection process, bring many unknowns and discussions. Different results have been reported in terms of the incidence of AIS after COVID-19, and the issue has not yet been clarified.

In this study conducted on tertiary hospital records, it was determined that there was a significant decrease in ischemic stroke cases after the diagnosis of COVID-19. According to our results, the number of patients diagnosed with AIS during the pandemic period was significantly lower in patients with COVID-19. While performing the analyses, the decrease was shown to be evident in patients without additional risk factors. This decreasing effect due to COVID infection is not observed when DM and advanced age, which are seen to pose a risk for strokes, are present in the patient population examined. This result suggests that the comorbidity of advanced age and comorbid diseases caused an increase in AIS during the COVID-19 pandemic or that only severe patients were admitted to the hospital during the pandemic period.

According to the definition of the World Health Organization, a stroke is the sudden loss of function of a part of the brain or the entire brain, lasting for 24 h or more (11). Many views have been proposed regarding the pathophysiological mechanisms related to the development of stroke during COVID-19 infection. The uncontrollable cytokine storm observed in severe cases can lead to multi-organ failure. Activation of the microthrombotic pathway, particularly with destructive pathological mechanisms mediated by the endothelial system, may cause stroke. In infected cases, there is a tendency for thrombosis due to increased D-dimer, fibrinogen, and C-reactive protein (CRP) levels. In addition, inflammatory markers and inflammatory cytokines, such as tumor necrosis factor-α, interleukin-2 (IL-2) receptor, and IL-6, were increased. In particular, the role of IL-6 in stroke has not been clarified. Studies have reported that increased IL-6 levels adversely affect the volume of infarcts in the brain and the long-term outcome (12). In a laboratory study, IL-6 was shown to increase angiogenesis after stroke (13).

Viral inclusion structures were detected in the endothelial cells in postmortem examinations of infected patients. Thus, ischemic events may develop because of direct endothelial damage and widespread endothelial inflammation (14). Widespread microvascular thrombosis is seen with prothrombotic activation together with the cytokine storm that also occurs in COVID-19 infection, and D-dimer levels are found to be high in these patients (7). However, there is a decrease in fibrinogen values and thrombocytopenia (4).

Italian researchers have additionally hypothesized a pathophysiologic mechanism behind this decreased stroke occurrence, based on the controversial role of IL-6 in stroke (15). There is experimental evidence that IL-6, which is elevated in severe COVID-19, has a neuroprotective effect and enhance angiogenesis. The alternate explanations proposed are based on the thrombocytopenia encountered even in patients with mild COVID-19 (12). It is likely that low platelets prevent the formation of large clots in the intracranial circulation (16). Lastly, widespread mitigation measures, which have minimized the prevalence of influenza in the community, could have decreased the negative impact of the flu on cardiovascular disease and stroke. Further research into the cause of the observed associations is warranted (17).

In a different study, a reduction of 39% was observed in patients undergoing imaging with a preliminary diagnosis of stroke (18). A study comparing the pandemic period with the same period of the previous year reported a 36.4% decrease in stroke admissions (19). While the number of mild and moderate strokes with TIA decreased during the pandemic period, there was no significant change in the number of severe strokes and intraparenchymal hemorrhages (20).

In a study based on data from 227 hospitals, a decrease was reported in the number of stroke-related therapeutic interventions during the COVID-19 era. This study showed that a decline in stroke admissions resulted in fewer patients being treated with thrombolysis in 2019 than in 2020. Similarly, it has also been shown that patients who are not hospitalized lose their chances of receiving appropriate secondary prevention treatments for carotid revascularization, antiplatelet therapies, lipid-lowering therapies, anticoagulation for atrial fibrillation, and blood pressure management (21).

This decrease in stroke cannot be fully explained by sociodemographic factors. Measures such as restriction of free movement to control the rate of the pandemic, encouraging not going to emergency services except in very urgent situations, and the tendency not to apply to the emergency services due to the fear of being infected can partly explain the decrease in the number of strokes recorded.

Many risk factors have been identified in stroke. Unchangeable risk factors include age, gender, race, low birth weight, genetic factors, and modifiable risk factors include HT, heart diseases, DM, high blood cholesterol and lipids, smoking, asymptomatic carotid stenosis, familial

Mediterranean anemia, hormonal therapy after menopause, diet, obesity, and physical activity (22).

Dysregulation of the natural immune response in the background of chronic diabetes, endothelial dysfunction, and impaired barrier structure cause proinflammatory hypercoagulability, the formation of infections, and their more severe course (23). When cellular mechanisms triggered by COVID-19 and diabetes-specific pathological changes come together, the likelihood of a cytokine storm resulting in organ damage in individuals with diabetes increases exponentially.

IL-6, fibrinogen, ferritin, D-dimer, and CRP levels were found to be significantly higher in individuals with diabetes infected with COVID-19 than in non-diabetic subjects (24). A report of 72,314 cases of COVID-19 published by the Chinese Center for Disease Control and Prevention showed that mortality in people with diabetes (7.3%) is about three times higher than that in people without diabetes (2.3%) (25). This may explain why stroke risk factors such as diabetes are indicators of poor prognosis in patients with COVID-19 infection and an increase in AIS in COVID-19.

Infections are the primary cause of death in 1/3 of individuals aged 65 years and over and contribute to death in many older adults. They also have a significant impact on morbidity in older adults, exacerbating underlying diseases and leading to increased secondary risk and functional decline in the elderly (26). As the immune system ages, increased susceptibility to infections, cancer, and autoimmune disorders occurs. In a national study of 88,747 US veterans tested for SARS-CoV-2 infection between February 28 and May 14, 2020, those testing positive had a 4.2-fold risk of mechanical ventilation and a 4.4-fold risk of death compared with those testing negative. Among those who tested positive for SARS-CoV-2, older age was the strongest risk factor associated with hospitalization, mechanical ventilation, and mortality (27).

In studies conducted in China, the most common comorbidities in patients with COVID-19 were found to be HT (23.2%) and DM (10.9%) (28,29). Yang et al. (30) reported in a meta-analysis that the most common comorbidities were HT, DM, cardiovascular diseases, and respiratory system diseases. In this study, it was stated that the advanced age group and comorbidity of the patients may be associated with the serious disease picture (30).

In the English National Audit cohort, the risk ratio of COVID-19 death for type 1 diabetes was 3.51 and that for type 2 diabetes was 2.03. When adjusted for age, sex, and diabetes duration, people who developed fatal or critical care unit-treated COVID-19 on average had worse profiles for almost every clinical measure examined; they were more likely to have other comorbidities and evidence of diabetic microvascular disease (31).

In this study, the risk of COVID-19 and comorbid risk factors for AIS were evaluated. The fact that individuals with COVID-19 are older and the comorbidity of pre-existing DM disease is an unfavorable predictive factor for the occurrence of AIS in patients with COVID-19.

CONCLUSION

In terms of stroke, both the social effects of the pandemic and the process of COVID-19 infection bring many unknowns. There are insufficient evidence to determine whether there are fewer or more stroke patients due to COVID-19. The current results of these studies are contradictory. However, patients with COVID-19 may develop a new stroke, and the presence of other systemic and neurological symptoms of COVID-19 may complicate the diagnosis of stroke. Stroke symptoms are often noticed by another family member, friend, or someone outside the home before they are noticed by the patient himself. During the pandemic period, clinical findings may have been missed in patients with AIS, and applications may have decreased or been delayed because of strict measures to stay at home, individuals' avoidance of contact for fear of being infected, or living alone.

In this study, it was determined that COVID-19 infection decreased hospital admissions in AIS. It has been suggested that the older age of individuals with DM and COVID-19 as a comorbid disease causes AIS or that hospital admission increases because of more severe clinical findings and hospital care is required in this group.

The main limitation of our study seems to be that the study was conducted on data from a single center, the hospital worked as a private pandemic hospital during the COVID-19 pandemic, and the decrease in the number of applications other than COVID-19 patients during this period. Comprehensive studies and aggregate analyses are expected to yield definitive conclusions on the subject.

ETHICS

Ethics Committee Approval: This study was conducted with the approval of the Clinical Research Ethics Committee of the Çanakkale Onsekiz Mart University (decision no: 2022-03, date: 02.02.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: Ö.O., E.M.Ş., Ç.T., Design: Ö.O., E.M.Ş., Ç.T., Data Collection or Processing: Ö.O., E.M.Ş., Analysis

or Interpretation: Ö.O., E.M.Ş., Ç.T., Literature Search: Ö.O., E.M.Ş., Ç.T., Writing: Ö.O., E.M.Ş., Ç.T.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:42-47
DOI: 10.4274/BMJ.galenos.2023.2022.5-12

Research

Prevalence and Prognostic Significance of Anemia in Lymphoma

Lenfomada Aneminin Prevalansı ve Prognostik Önemi

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ABSTRACT

Objective: Anemia is common in cancer patients and has adverse effects on prognosis. In this study, we investigated the prevalence, etiological causes, and effects of anemia on the prognosis of patients with lymphoma.

Methods: We analyzed 153 newly diagnosed lymphoma cases. The hemoglobin (Hb) cut-off value for the diagnosis of anemia was set as Hb <12 g/dL in women and Hb <13 g/dL in men. Cases with anemia were classified as mild (Hb =10 g/dL-normal value), moderate (Hb =8-9.9 g/dL), and severe (Hb <8 g/dL) anemia. The relationship between the presence and degree of anemia and the revised international prognostic index (r-IPI) score, Eastern Cooperative Oncology Group performance score, Ann Arbor stage, presence of B symptoms, bulky mass, extra-nodal involvement, and life status was evaluated.

Results: Anemia was detected in 82 (53.6%) patients, and the most common cause of anemia was chronic disease anemia (30.5%). There was no significant relationship between the presence of anemia and the presence of bulky mass, r-IPI score, performance score, or Ann Arbor stage. A significant correlation was found between the degree of anemia and the presence of extranodal involvement and B symptoms (p<0.001, p=0.01, respectively). A significant correlation was found between the presence and degree of anemia and overall survival (p=0.011, p<0.001, respectively).

Conclusion: Anemia is common in Hodgkin and diffuse large B-cell lymphoma patients and is associated with some worse prognostic factors. Therefore, further studies examining more cases and including patients in all non-Hodgkin lymphoma subgroups are needed to better understand the importance of anemia in lymphoma cases.

Keywords: Anemia, diffuse large B-cell lymphoma, Hodgkin lymphoma, prognosis, prevalence

ÖZ

Amaç: Anemi kanser hastalarında sık görülür ve prognozu olumsuz etkiler. Bu çalışmada lenfoma hastalarında aneminin prevalansını, etiyolojik nedenlerini ve prognoz üzerindeki etkilerini araştırmayı amaçladık.

Gereç ve Yöntem: Yeni tanı almış 153 lenfoma olgusunu inceledik. Anemi tanısı için hemoglobin (Hb) eşik değeri kadınlarda Hb <12 g/dL, erkeklerde Hb <13 g/dL olarak kabul edildi. Anemisi olan olgular hafif (Hb =10 g/dL-normal değer), orta (Hb =8-9,9 g/dL) ve şiddetli (Hb <8 g/dL) anemi olarak sınıflandırıldı. Anemi varlığı ve derecesi ile revize edilmiş uluslararası prognostik indeks (r-IPI) skoru, Eastern Cooperative Oncology Group performans skoru, Ann Arbor evresi, B semptom varlığı, hacimli kitle, ekstra nodal tutulum ve yaşam durumu arasındaki ilişki değerlendirildi.

Bulgular: Seksen iki (%53,6) olguda anemi saptandı ve aneminin en sık nedeni kronik hastalık anemisiydi (%30,5). Anemi varlığı ile hacimli kitle varlığı, r-IPI skoru, performans skoru, Ann Arbor evresi arasında anlamlı bir ilişki yoktu. Anemi derecesi ile ekstranodal tutulum ve B semptomlarının varlığı arasında anlamlı bir ilişki bulundu (sırasıyla p<0,001, p=0,01). Anemi varlığı ve derecesi ile genel sağkalım arasında anlamlı bir korelasyon bulundu (sırasıyla p=0,011, p<0,001).

Sonuç: Hodgkin ve diffüz büyük B-hücreli lenfoma hastalarında anemi sıktır ve bazı kötü prognostik faktörlerle ilişkilidir. Bu nedenle lenfoma olgularında aneminin öneminin daha iyi anlaşılabilmesi için daha fazla olguyu inceleyen ve Hodgkin dışı lenfomanın tüm alt gruplarındaki hastaları içeren ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Anemi, diffüz büyük B-hücreli lenfoma, Hodgkin lenfoma, prognoz, prevalans

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Cite as: Sincan G, Kılıç AF, Sincan S, Erdem F. Prevalence and Prognostic Significance of Anemia in Lymphoma. Med J Bakirkoy 2024;20:42-47

Received: 30.05.2022
Accepted: 23.04.2023

INTRODUCTION

Anemia is a decrease in the erythrocyte mass or hemoglobin (Hb) value from the normal range according to age and gender (1). It is defined by the World Health Organization as <12 g/dL in women, <13 g/dL in men, and <11 g/dL in pregnant women (2). The prevalence of anemia was reported to be 22.8% in the population in 2019 (3). However, the prevalence of anemia in cancer patients is 30%-90% (4). One of the most important reasons for this variability in the prevalence of anemia in cancer patients is the different Hb cut-off values accepted for anemia. In cases with Hodgkin lymphoma (HL), the prevalence of anemia is 7% when Hb <9 g/dL is accepted as anemia, and it is 86% when Hb <11 g/dL is accepted (4). The European Cancer Anemia Research Group reported the prevalence of anemia (Hb <12 g/dL) as 52.5% in lymphoma and multiple myeloma cases (5).

The most important cause of anemia in cancer patients is increased inflammatory mediators such as tumor necrotizing factor-alpha, interleukin (IL)-1, IL-6, and tumor necrotizing factor gamma (6). These mediators cause shortening of erythrocyte lifespan, impaired iron utilization, suppression of erythropoietin (EPO) secretion, inadequate response of bone marrow precursor cells to EPO, and inhibition of erythroid precursor cells. Therefore, chronic disease anemia is a common cause of anemia in lymphoma cases. The causes of anemia in lymphoma cases are nutritional anemia, autoimmune hemolytic anemia (AIHA), anemia associated with bleeding caused by tumor tissue, anemia secondary to bone marrow infiltration, and chemotherapy treatment. Anemia is associated with poor prognosis in patients with lymphoma (7). In addition, it worsens the quality of life of cancer patients due to fatigue, decreased exercise capacity, and cognitive functions. Anemia treatment positively affects both the quality of life of cancer patients and their response to cancer treatment (8,9). However, only approximately 40% of cancer patients with anemia receive anemia treatment (6). In this study, we investigated the prevalence, causes, and prognostic significance of anemia.

METHODS

In our study, 153 cases of newly diagnosed HL and diffuse large B-cell lymphoma (DLBCL) followed up in our clinic were examined. Ethical approval was obtained from the Atatürk University Faculty of Medicine Clinical Researches Ethics Committee for this study (decision no: 50, date: 30.09.2021). In addition, written informed consent was obtained from the participants.

Patients who were pregnant at the time of diagnosis and were treated for anemia, had a history of blood transfusion, were diagnosed with congenital anemia, and had active infection were excluded from this study. The diagnosis and classification of lymphoma cases were made by histopathological examination according to the 2016 criteria of the World Health Organization. HL with anemia cases who received adriamycin, bleomycin, vinblastine, and deticine chemotherapy and DLBCL with anemia cases who received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone treatment were included in our study. Bone marrow biopsy was performed in all patients.

Anemia was accepted as Hb <12 g/dL in women and Hb <13 g/dL in men. Patients with anemia were divided into 3 groups according to their Hb values: severe (Hb <8 g/dL), moderate (Hb =8-9.9 g/dL), and mild (Hb =10 g/dL-normal value) grade anemia. Cases with low serum iron levels increased iron-binding capacity and low ferritin levels were considered to have iron deficiency anemia. Patients were accepted as having B12 deficiency anemia if serum vitamin B12 <200 µg, folic acid deficiency anemia if folate level <4 µg, anemia secondary to bone marrow involvement if bone marrow infiltration, AIHA if the direct Coombs test was positive with laboratory findings of hemolysis.

The files of all patients were reviewed retrospectively and age, gender, hemogram parameters (mean corpuscular volume, mean corpuscular Hb and mean corpuscular Hb concentration), lactate dehydrogenase (LDH), iron, iron-binding, ferritin, vitamin B12, folate, and reticulocyte levels, direct and indirect Coombs tests, bone marrow infiltration status, revised international prognostic index (r-IPI) score of DLBCL cases, Eastern Cooperative Oncology Group (ECOG) performance score, and Ann Arbor stage were recorded. When determining the r-IPI score, 1 point was given for each parameter if age >60, LDH value higher than normal, ECOG score ≥2, Ann Arbor stage 3 or 4, and area of extranodal involvement >1. The cases were divided into 3 groups according to their total scores (0 points = very good, 1-2 points = good, and ≥3 points = poor risk group).

Statistical Analysis

Data were evaluated using SPSS software (version 21.0, Chicago, USA). Categorical variables are given as percentages and continuous variables as mean ± standard deviation. The independent t-test was used to determine the difference between the two groups if there was a normal distribution, and the Mann-Whitney U test was used in the other groups. One-way analysis of variance was used to compare the three groups. Survival curves were evaluated

using the Kaplan-Meier method. The log-rank test was used to determine univariate relationships between progression-free survival and prognostic variables, and multivariate analysis tests were performed using the cox proportional hazards model. P-value <0.05 for all analyses was considered statistically significant.

RESULTS

In this study, 153 cases followed up in our clinic with the diagnoses of HL (n=40) and DLBCL (n=113) were examined. Anemia was detected in 82 (53.6%) patients (20 patients with HL, 62 patients with DLBCL). The mean age of our patients with anemia was 50.32±18.73 years; 37 (45.1%) patients were female and 45 (54.9%) were male. The age and gender distribution of the groups with and without anemia were similar (p=0.8 and p=0.6, respectively). The most common cause of anemia in our cases was chronic disease anemia, and other causes of anemia are shown in Table 1.

The hemogram parameters, LDH, and β2 microglobulin levels of the groups with and without anemia are reported in Table 2. The presence of bulky mass, extranodal involvement status, presence of B symptoms, r-IPI score (for DLBCL cases), ECOG score, and Ann Arbor stage in the groups with and without anemia are indicated in Table 3.

Fifty-eight (70.7%) patients had mild anemia, 18 (22%) had moderate anemia, and 6 (7.3%) had severe anemia. The relationship between the degree of anemia and clinical parameters such as disease stage, IPI score (in DLBCL cases), ECOG score, extranodal involvement, presence of B symptoms, and bulky mass are shown in Table 4.

The mean follow-up period was 37.91±7.45 months. Three of the patients with mild anemia, 10 with moderate anemia, and 6 with severe anemia died during the follow-up period. Six patients died in the without anemia group. A significant correlation was found between the presence and degree of anemia and overall survival (p=0.011, p<0.001, respectively) (Figures 1, 2, respectively). The results of univariate and multivariate analyses of some factors affecting survival are shown in Table 5.

Table 1. Anemia causes our cases

Type of anemia	HL, n (%)	DLBCL, n (%)	Total, n (%)
Chronic disease anemia	6 (30%)	19 (30.6%)	25 (30.5%)
Anemia secondary to bone marrow infiltration	5 (25%)	14 (22.6%)	19 (23.2%)
Autoimmune hemolytic anemia	4 (20%)	13 (21%)	17 (20.7%)
Iron deficiency anemia	2 (10%)	7 (11.3%)	9 (11%)
Multifactorial anemia	2 (10%)	5 (8%)	7 (8.5%)
Vitamin B12 deficiency anemia	1 (5%)	4 (6.5%)	5 (6%)

HL: Hodgkin lymphoma, DLBCL: Diffuse large B-cell lymphoma

Table 2. Hemogram parameters, LDH, and β2 microglobulin levels of anemia and non-anemia groups

Parameters	Group					p-value
	Group with anemia				Group without anemia	
	Mild	Moderate	Severe	Total		
Hb (g/dL)	11.42±0.78	9.18±0.49	7.9±0.86	10.67±1.41	14.58±1.42	<0.001
Hct (%)	35.12±2.75	28.53±2.36	25±3.77	32.93±4.44	43.88±3.92	<0.001
MCV (fL)	82.01±9.36	82.11±6.61	87.83±8.63	82.45±8.82	85.4±4.41	0.01
MCH (pg)	26.59±2.68	26.11±3.12	27.33±3.38	26.54±2.81	28.14±1.93	<0.001
MCHC (g/dL)	31.95±1.59	31.5±1.5	31±1.78	31.78±1.59	32.8±1.51	<0.001
RBC (10^6/μL)	4.23±0.46	3.47±0.49	2.86±0.54	3.97±0.64	5.09±0.46	<0.001
LDH (IU/L)	366.38±329.8	544.28±521.69	242.83±62.54	397.14±376.78	307.23±164.62	0.067
β2 (μg/mL)	2.86±0.64	3.47±0.49	4.24±0.46	4.74±0.89	3.97±0.64	<0.001

Hb: Hemoglobin, Hct: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RBC: Red blood cell, LDH: Lactate dehydrogenase, B2: β2 microglobulin

Table 3. Bulky mass, extranodal involvement, B symptoms, r-IPI score, ECOG score, and Ann Arbor stage of anemia and non-anemia groups

Parameters	Anemia group n (%)	Non-anemia group n (%)	p-value
Bulky mass	14 (17%)	7 (9.9%)	0.15
Extranodal involvement	9 (11%)	5 (7%)	0.23
Presence of B symptoms	38 (46.3%)	25 (35.2%)	0.10
r-IPI score			
Very good	28 (34.1%)	23 (32.4%)	
Good	30 (36.6%)	29 (40.8%)	0.73
Bad	24 (29.3%)	19 (26.8%)	
ECOG performance score			
ECOG 1	27 (32.9%)	17 (23.9%)	
ECOG 2	34 (41.5%)	35 (42.3%)	0.57
ECOG 3	16 (19.5%)	16 (22.5%)	
ECOG 4	5 (6%)	3 (4.2%)	
Ann Arbor stage			
Stage 1	15 (18.3%)	6 (8.5%)	
Stage 2	26 (31.7%)	27 (38%)	0.39
Stage 3	29 (35.4%)	24 (33.8%)	
Stage 4	12 (14.6%)	14 (19.7%)	

r-IPI: Revised international prognostic index score, ECOG: Eastern Cooperative Oncology Group

Table 4. The relationship between the degree of anemia and disease stage, IPI score, ECOG score, extranodal involvement, presence of B symptoms, and bulky mass

Parameters	Anemia grade			p-value
	Mild n (%)	Moderate n (%)	Severe n (%)	
Ann Arbor stage				
Stage 1	12 (20.7%)	3 (16.7%)	0 (0%)	
Stage 2	17 (29.3%)	7 (38.9%)	2 (33.3%)	0.73
Stage 3	19 (32.8%)	7 (38.9%)	3 (50%)	
Stage 4	10 (17.2%)	1 (5.6%)	1 (16.7%)	
r-IPI score				
Very good	22 (37.9%)	4 (22.2%)	2 (33.3%)	
Good	24 (41.4%)	4 (22.2%)	2 (33.3%)	0.73
Bad	12 (20.7%)	10 (55.6%)	2 (33.3%)	
ECOG score				
ECOG 1	21 (36.2%)	4 (22.2%)	2 (33.3%)	
ECOG 2	25 (43.1%)	7 (38.9%)	2 (33.3%)	0.63
ECOG 3	10 (17.2%)	5 (27.8%)	1 (16.7%)	
ECOG 4	2 (3.4%)	2 (11.1%)	1 (16.7%)	
B symptoms				
Present	14 (24.1%)	18 (100%)	6 (100%)	<0.001
Absent	44 (75.9%)	0 (0%)	0 (0%)	
Bulky mass				
Present	10 (17.2%)	2 (11.1%)	2 (33.3%)	0.45
Absent	48 (82.8%)	16 (88.9%)	4 (66.7%)	
Extranodal involvement				
Present	1 (1.7%)	4 (22.2%)	4 (66.7%)	0.01
Absent	57 (98.3%)	14 (77.8%)	2 (33.3%)	

r-IPI: Revised international prognostic index score, ECOG: Eastern Cooperative Oncology Group

DISCUSSION

Anemia is common in patients with lymphoma (10). In a study conducted in India, the prevalence of anemia was reported to be 42.4% in patients with lymphoma (7). In our study, this rate was 53.4% and which was higher than the study conducted in India. While Moullet et al. (10) reported the prevalence of anemia as 32% in patients with NHL, Morel et al. (11) reported this rate as 35.3%. In our study, anemia prevalence was 40.3% in DLBCL cases, which was higher than that reported in the literature. The reason for this situation may be the difference in the number of cases in the studies or the inclusion of only DLBCL cases in our study. Yasmeen et al. (12) examined 422 lymphoma cases and reported the prevalence of anemia as 53.23% in cases with HL and 40.3% in cases with DLBCL. We found the prevalence of anemia in HL cases to be similar to that reported by Yasmeen et al. (12), and it was higher than the rate reported by Yasmeen et al. (12) in our DLBCL cases. This may be due to the small number of cases in our study. In another study, 422 patients with solid organ malignancy were examined, and the prevalence of anemia was reported as 29%. In this study, it was stated that 83.5% of the cases had mild- moderate anemia (13). In our study, mild to moderate anemia was found in 92.7% of the cases. This rate was higher than the anemia prevalence in cases with solid organ malignancy. This may be because bone marrow infiltration is more common in lymphoma cases than in solid organ malignancies.

Ghosh et al. (7) examined 316 cases consisting of patients with chronic lymphocytic leukemia, HL, and NHL and reported the prevalence of anemia as 42.4%. Of these cases, 71.7% had chronic disease anemia, 39.1% had iron deficiency anemia, 21.7% had vitamin B12 and/or folic

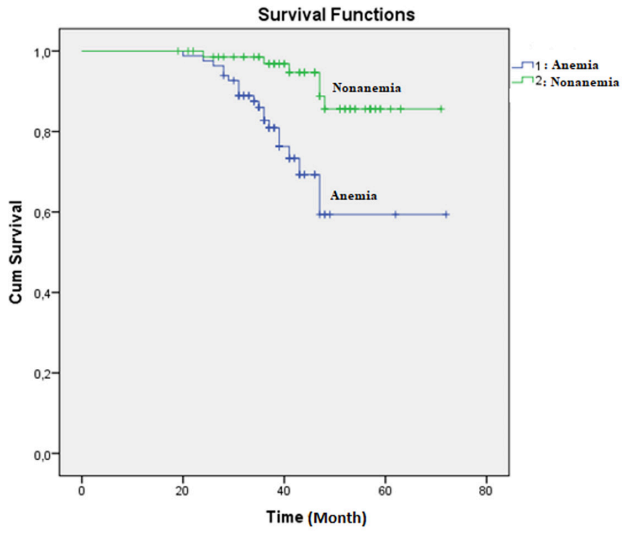

Figure 1. The correlation between the presence of anemia and overall survival

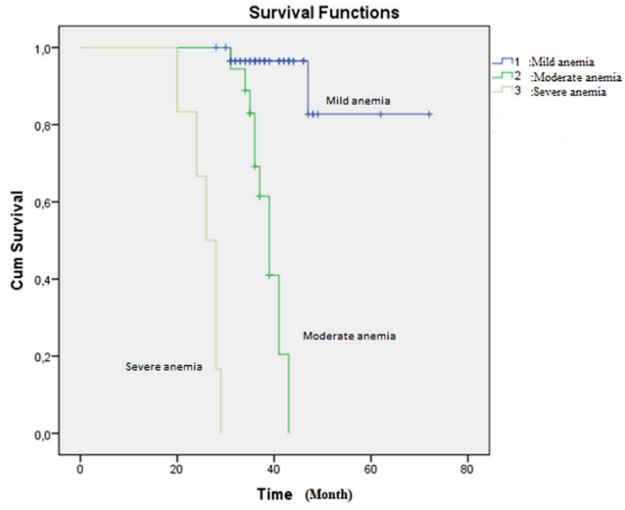

Figure 2. The correlation between degree of anemia and overall survival

Table 5. The results of univariate and multivariate analyzes of some factors affecting the survival

Parameters	HL		DLBCL	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Univariate analyses				
Age >40 (HL group) Age >60 (DLBCL group)	1.02 (0.51-1.15)	0.04	1.06 (0.32-1.35)	0.03
Sex	0.79 (0.68-1.31)	0.08	0.39 (0.29-1.61)	0.6
Elevated lactose dehydrogenase	1.34 (0.82-1.68)	0.04	1.44 (0.72-2.18)	0.02
ECOG performance status ≥2	0.65 (0.38-1.51)	0.2	1.21 (0.28-2.18)	0.04
Presence of bulky mass	0.97 (0.28-2.51)	0.04	0.69 (0.23-2.11)	0.06
Presence of B symptoms	1.49 (0.38-1.51)	0.02	0.95 (0.38-1.51)	0.04
Ann Arbor stage ≥3 (DLBCL) Ann Arbor stage =4 (HL)	0.31 (0.24-2.38)	0.3	1.23 (0.94-2.28)	0.04
Extranodal sites ≥2	0.74 (0.41-1.92)	0.4	1.2 (0.84-1.82)	0.02
BM involvement	1.32 (0.98-2.31)	0.01	1.18 (0.49-2.17)	0.03
Number of nodal areas ≥3	1.34 (1.1-2.24)	0.04	1.26 (0.86-1.77)	0.03
Presence of anemia	1.23 (0.92-2.35)	0.01	1.29 (0.78-1.65)	0.02
Presence of moderate or severe anemia	0.97 (0.57-1.47)	0.001	1.25 (0.87-1.92)	0.002
Multivariate analysis				
Presence of anemia	1.39 (0.71-1.43)	0.02	1.22 (0.84-1.46)	0.02
BM involvement	1.35 (0.69-2.22)	0.04	1.38 (0.92-1.83)	0.03
Presence of moderate or severe anemia	1.25 (0.83-2.1)	0.001	1.12 (0.91-1.86)	0.02

HL: Hodgkin lymphoma, DLBCL: Diffuse large B-cell lymphoma, BM: Bone marrow, ECOG: Eastern Cooperative Oncology Group, HR: Hazard ratio, CI: Confidence interval

acid deficiency anemia, 10.9% had AIHA, and 40% had anemia secondary to bone marrow infiltration. In addition, multifactorial anemia was in 39.1% of the patients. Yasmeen et al. (12) determined that the most common cause of anemia in patients with lymphoma was chronic disease anemia (33.1%). They reported that anemia secondary to bone marrow infiltration was 27.17%, iron deficiency anemia was 7.6%, vitamin B12 deficiency anemia was 1.6%, and

AIHA was 0.54%. In our study, the most common cause of anemia was chronic disease anemia, and the second most common cause was anemia secondary to bone marrow infiltration. The frequencies of chronic disease anemia and bone marrow infiltration-related anemia in our study were consistent with the results of Yasmeen et al.'s study (12). The frequency of anemia of chronic disease was lower in our cases than in the study by Ghosh et al. (7) This may be because of the small number of cases in our study.

AIHA is seen in 7-10% of lymphoma cases (14). The cause of AIHA is chronic antigenic stimulation. Zhou et al. (15) examined 20 cases with concomitant AIHA and NHL (15). They reported that AIHA is most commonly associated with angioimmunoblastic T-cell lymphoma. In our study, the frequency of AIHA was higher than that reported in the literature. This may be because we included only HL and DLBCL cases in our study.

Yasmeen et al. (12) reported a relationship between anemia and disease stage in lymphoma. In addition, this relationship has been reported in other studies (7,16). In our study, no correlation was found between the stage of the disease and the presence and degree of anemia. We found a relationship between the presence of anemia and the level of LDH, which is a prognostic marker in patients with lymphoma. We also determined a correlation between the severity of anemia and the presence of extranodal involvement and B symptoms. Anemia has been reported as a negative prognostic marker in patients with NHL (15,17). Moullet et al. (10) examined 1077 cases with NHL and considered anemia as Hb ≤12 g/dL for men and women over 50 years and Hb ≤11 g/dL for women aged 50 years. They stated that anemia is an unfavorable prognostic factor for overall survival and progression-free survival. In our study, we found a relationship between overall survival and the presence and degree of anemia.

CONCLUSION

Anemia, which is a treatable condition, is frequently observed in patients with lymphoma. It has adverse effects on patient prognosis. Therefore, careful evaluation of lymphoma cases in terms of anemia and early diagnosis and treatment of anemia may contribute positively to disease surveillance.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the Atatürk University Faculty of Medicine Clinical Researches Ethics Committee for this study (decision no: 50, date: 30.09.2021).

Informed Consent: Written informed consent was obtained from the participants.

Authorship Contributions

Surgical and Medical Practices: G.S., S.S., F.E., Concept: G.S., A.F.K., S.S., Design: G.S., A.F.K., S.S., F.E., Data Collection or Processing: G.S., A.F.K., Analysis or Interpretation: G.S., S.S., Literature Search: A.F.K., S.S., Writing: G.S., A.F.K., S.S., F.E.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:48-54
DOI: 10.4274/BMJ.galenos.2023.2023.1-8

Research

Factors Predicting Mortality in Methyl Alcohol Intoxication: A Retrospective Clinical Trial

Metil Alkol İntoksikasyonunda Mortaliteyi Öngören Faktörler: Retrospektif Bir Klinik Çalışma

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ABSTRACT

Objective: Methyl alcohol, which is quite cheap compared to ethyl alcohol, can be used to produce imitated alcohol. For this reason, cases of methyl alcohol intoxication can be observed from time to time. Although it is rare, it is an emergency that needs to be diagnosed and treated early because of its high mortality.

Methods: In this study, 22 patients aged ≥18 years who were admitted to the intensive care unit (ICU) due to methyl alcohol intoxication between 2015 and 2022 were included. The patients were divided into 2 groups, survivor and non-survivor, and compared retrospectively in terms of factors predicting mortality.

Results: Except for one of the 22 patients included in the study, all patients developed methyl alcohol intoxication because of the use of imitated alcohol. Only one patient had a history of using perfume for suicidal purposes. Of the patients who developed methyl alcohol intoxication, 13 (59%) were in the non-survivor group and 9 (41%) were in the survivor group. While the rate of invasive mechanical ventilation needed before the ICU was 55.6% in the survivor group, it was 100% in the non-survivor group, and there was a statistically significant difference between them ($p<0.017$). In the non-survivor patient group, blood HCO_3 and pH levels were found to be significantly lower after ICU admission ($p=0.002$, $p=0.008$). At the same time, blood creatinine, potassium, and total bilirubin levels were significantly higher ($p=0.002$, $p=0.007$, $p<0.035$). Acute physiology and chronic health evaluation-II and sequential organ failure assessment scores after ICU admission were also significantly higher in the non-survivor group than in the survivor group ($p=0.005$, $p=0.035$).

Conclusion: It was determined that in patients who died due to methyl alcohol intoxication, deeper metabolic acidosis and irreversible multi-organ failure developed during the period until ICU admission. The acute physiology and chronic health evaluation-II and sequential organ failure assessment scores were both effective in predicting mortality.

Keywords: Methyl, alcohol, intoxication, mortality

ÖZ

Amaç: Etil alkole göre oldukça ucuz olan metil alkol, dolandırıcılar tarafından sahte alkol üretiminde kullanılabilmektedir. Bu nedenle zaman zaman metil alkol zehirlenmesi olguları görülebilmektedir. Nadir görülmekle birlikte mortalitesinin yüksek olması nedeniyle erken teşhis ve tedavi edilmesi gereken acil bir durumdur.

Gereç ve Yöntem: Bu çalışmada 2015-2022 yılları arasında metil alkol intoksikasyonu nedeniyle yoğun bakım ünitesine (YBÜ) yatırılan ≥18 yaş 22 hasta çalışmaya dahil edildi. Hastalar sağ kalan ve sağ kalmayan olmak üzere 2 gruba ayrılarak mortaliteyi öngören faktörler açısından retrospektif olarak karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen 22 hastadan biri dışında tüm hastalarda sahte alkol kullanımı nedeniyle metil alkol intoksikasyonu gelişti. Sadece bir hastada intihar amaçlı parfüm kullanma öyküsü vardı. Metil alkol intoksikasyonu gelişen hastaların 13'ü (%59) sağ kalmayan grupta, 9'u (%41) sağ kalan grupta yer aldı. Sağ kalan grubunda YBÜ öncesi invaziv mekanik ventilasyon ihtiyacı oranı %55,6 iken, sağ kalmayan grupta %100'dü ve aralarında istatistiksel olarak anlamlı fark vardı (p=0,017). Sağ kalan grupta YBÜ'ye yatış sonrası kan HCO_3 ve pH düzeyleri istatistiksel olarak anlamlı derecede düşük bulundu (p=0,002, p=0,008). Aynı zamanda kan kreatinin, potasyum ve total bilirubin düzeyleri istatistiksel olarak anlamlı

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Cite as: Aslan M, Özel Bilgi D. Factors Predicting Mortality in Methyl Alcohol Intoxication: A Retrospective Clinical Trial. Med J Bakirkoy 2024;20:48-54

Received: 11.01.2023
Accepted: 29.05.2023

derecede yüksekti (p=0,002, p=0,007, p<0,035). YBÜ'ye kabulü sonrası akut fizyoloji ve kronik sağlik değerlendirmesi-II ve sıralı organ yetmezliği değerlendirmesi skorları da sağ kalmayan grupta sağ kalan gruba göre istatistiksel olarak anlamlı derecede yüksek bulundu (p=0,005, p=0,035).

Sonuç: Metil alkol intoksikasyonu nedeniyle mortal seyreden hastalarda YBÜ kabulüne kadar geçen sürede daha derin metabolik asidoz ve geri dönüşümsüz çoklu organ yetmezliği geliştiği belirlendi. Akut fizyoloji ve kronik sağlık değerlendirmesi-II ve sıralı organ yetmezliği değerlendirmesi skorlarının her ikisi de mortaliteyi öngörmede etkilir.

Anahtar Kelimeler: Metil, alkol, intoksikasyon, mortalite

INTRODUCTION

Although methyl alcohol intoxication is a rare condition, it should be diagnosed and treated early because of its high mortality. Even 8-10 mL of methanol taken from the body is toxic. Approximately 25-30 mL of methanol can lead to intoxication that can cause permanent blindness, and ingestion of 1 mL/kg or 100 mL of methanol is fatal (1,2). Methyl alcohol is a product that is generally used for industrial purposes, and it often causes poisoning by taking it for suicidal purposes or by accident. Windshield washer fluid, gas line antifreeze, carburetor cleaner, copier fluid, perfumes, and many other industrial substances contain methyl alcohol (3). In addition, because it is cheap, it can be used by fraudsters in the production of imitated alcohol, as is seen in our country, and can cause intoxication cases from time to time. Because methyl alcohol is a colorless and odorless substance, it is not possible to distinguish it from ethyl alcohol when taken orally.

Methyl alcohol intoxication often occurs after oral ingestion but can also occur through inhalation and skin absorption. Methyl alcohol is quickly absorbed from the gastrointestinal tract after oral administration and reaches peak blood concentrations within 30-60 min. Once absorbed, methyl alcohol has a volume of distribution similar to that of body water. They are then metabolized in the liver or excreted renally. The metabolism of methyl alcohol to formic acid leads to increased anion gap metabolic acidosis. Afterwards, formic acid ultimately inhibits oxidative phosphorylation, which then leads to anaerobic respiration and thus an increase in lactate levels (2,4-6). Although the clinical signs and symptoms related to methyl alcohol intoxication may start in as little as 40 minutes, they can last up to 72 hours. This period depends on the type of exposure, amount, and taking it together with its antidote, ethanol (2,7).

Although blood levels should be checked for a definitive diagnosis of methyl alcohol intoxication, this is not possible in every center. Visual impairment, hyperosmolarity, and increased anion gap metabolic acidosis are the most important findings of methyl alcohol intoxication. Along with these findings, a history of consumption of products containing methyl alcohol and the exclusion of other factors likely to cause metabolic acidosis with an increased anion gap can be used in the diagnosis of methyl alcohol intoxication (4,5). For treating methyl alcohol intoxication, the administration of ethyl alcohol or fomepizole is the first basic step of treatment. The affinity of ethyl alcohol to the alcohol dehydrogenase enzyme is 10-20 times higher than that of methyl alcohol, and 100 mg/dL blood level of ethyl alcohol almost stops the metabolism of methyl alcohol (8). The half-life of methyl alcohol, which is 14-30 h alone, can be extended to 43-96 h with ethyl alcohol (4). However, although fomepizole has 500-1000 times more affinity for alcohol dehydrogenase than ethyl alcohol, its cost is high and cannot be obtained in every center. Slowing down the metabolism of methyl alcohol is important in terms of slowing down the rate of increase in the serum level of toxic metabolites that will occur and allowing them to be removed by hemodialysis without irreversible damage to the body. All alcohols can be easily removed from the body by hemodialysis because they have low molecular weight, low body distribution volume, and are not bound to proteins (5,7,9).

In our study, we aimed to examine the factors predicting mortality in patients hospitalized in the intensive care unit (ICU) due to methyl alcohol intoxication as a primary cause. Second, we aimed to look at the change in the annual number of ICU admissions and the length of stay in the ICU due to methyl alcohol intoxication. In addition, we aimed to show the pathognomonic findings of methyl alcohol intoxication.

METHODS

Design and Study Population

The study was conducted retrospectively on patients over the age of 18 with a diagnosis of methyl alcohol intoxication admitted to the ICU between 01.10.2015 and 01.10.2022. Other toxic alcohol intoxications, patients under 18 years of age, and pregnant women were excluded from the study (Figure 1).

The study was conducted in full accordance with local Good Clinical Practice guidelines and current legislation. Ethical approval was obtained from the Ethics Committee of the

University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision number: 2022-21-14, date: 07.11.2022).

Data Collection

Study data were obtained retrospectively from the 'ImdSoft-Metavision/QlinICU Clinical Decision Support Software' system. A history of visual impairment, cardiac arrest, need for invasive mechanical ventilation (IMV), and intermittent hemodialysis (IHD) application were recorded before ICU admission. Then, demographic (gender, age, weight, height, body mass index), comorbidity, clinical findings, complications, laboratory, in-hospital mortality and other data of the patients after ICU admission were obtained from the decision support system and recorded. Acute physiology and chronic health evaluation-II (APACHE-II), sequential organ failure assessment (SOFA) and Charlson comorbidity index (CCI) scores were calculated using the patients' available data at ICU admission (Supplement Table).

Protocol

Patients who apply to our emergency department because of the suspicion of methyl alcohol intoxication and whose general clinical condition is poor are immediately consulted. Because the blood methyl alcohol level and routine blood osmolarity could not be measured in our center, the diagnosis of the patients who applied to our emergency department with the suspicion of methyl alcohol intoxication was as follows:

- A history of substance intake that may contain methyl alcohol before coming to the emergency department and strong clinical suspicion.
- Increased anion gap metabolic acidosis (pH <7.30, HCO_3<15, anion gap >15, base deficit <-3) during follow-up to the emergency department.

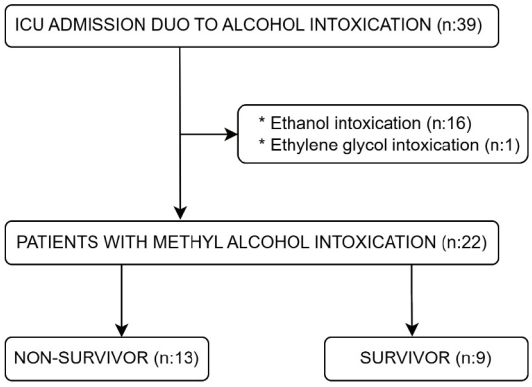

Figure 1. Study flowchart
ICU: Intensive care unit

- It was established by excluding other possible causes of increased anion gap metabolic acidosis (ethylene glycol intoxication, salicylic acid intoxication, paracetamol intoxication, lactic acidosis, diabetic ketoacidosis, other).

After the patients came to the emergency room, blood and urine toxic panels were studied to differentiate other possible toxic causes. Afterwards, an intravenous (IV) infusion of 10% ethyl alcohol at 1-2 mL/kg/h (followed by 7.5-8 mL/kg IV loading in 1 hour) was administered. The target blood level of ethyl alcohol was more than 100 mg/dL. In addition, 1-2 mL/kg $NaHO_3$ and 1000-2000 cc crystalloid IV bolus administration were applied to correct metabolic acidosis (in those with pH <7.30).

It was thought that urgent hemodialysis should be applied in cases with increased anion gap (>30 mEq/L) or base deficit (<-15), visual impairment, renal failure, and refractory metabolic acidosis (pH <7.25). If these patients did not need IMV support because of hemodynamic instability and coma, ICU was accepted after IHD was applied first and continuous renal replacement therapy (CRRT) support was continued. Otherwise, ICU was accepted without applying IHD, and CRRT application was initiated. Ethanol infusion was increased to 2-3 mL/kg/h to maintain a serum ethanol level more than 100 mg/dL during hemodialysis. Hemodialysis treatment was continued until metabolic acidosis improved.

To increase the metabolism of formic acid, 50 mg/day folic acid was administered enterally until metabolic acidosis resolved.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to determine whether the data were normally distributed. Categorical variables are given as frequency (n) and percentage (%), numerical variables mean ± standard deviation or median with interquartile range. Independent-samples t-test was used to compare the quantitative variables with normal distribution between the two groups. Mann-Whitney U test was used for comparisons between two groups of quantitative variables that did not show normal distribution. Fisher's Exact test was used to compare categorical variables. Statistical significance was set as $p<0.05$.

RESULTS

Between 2015 and 2022, 22 patients admitted to the ICU because of methyl alcohol intoxication were evaluated. The majority of these patients [59% (n=13)] were intoxication cases accepted in 2021 (Figure 2). One of these patients

developed intoxication because of voluntarily ingesting perfume. All the other patients were intoxicated because of imitated alcohol consumption.

One-month in-hospital mortality was 59% (n=13) in 22 patients included in the evaluation (Table 1). The patients were analyzed in terms of factors predicting mortality in 2 groups as survivor (n=9) and non-survivor (n=13). There was no statistically significant difference between the two patient groups in terms of demographic data and CCI score (Table 1).

The need for IMV support before ICU was 55.6% (n=5) in the survivor group and 100% in the non-survivor group, with a statistically significant difference between them (p=0.017). Again, 3 patients (23.1%) in the non-survivor patient group and 1 patient (11%) in the survivor patient group had a history of cardiac arrest before ICU admission, but the difference between them was statistically insignificant. However, no statistically significant difference was observed in terms of the development of visual impairment and IHD use before ICU (Table 1).

APACHE-II and SOFA mortality scores after ICU admission in the non-survivor group were significantly higher than those in the survivor group (p=0.005, p=0.035). At the same time both blood creatinine, potassium, and total bilirubin levels were higher and blood pH and HCO_3 levels were lower in the non-survivor group (p=0.002, p=0.007, p<0.035). There was no statistically significant difference between the two groups in terms of other laboratory parameters (Table 1).

Total ICU hospitalization time was found to be statistically lower in the non-survivor patient group than in the survivor group [3 (2-5.5), 6 (4.5-15.5)] (Table 1).

Bilateral basal ganglia bleeding, which is a pathognomonic finding for methyl alcohol intoxication, was detected in one patient from the non-survivor group (Figure 2).

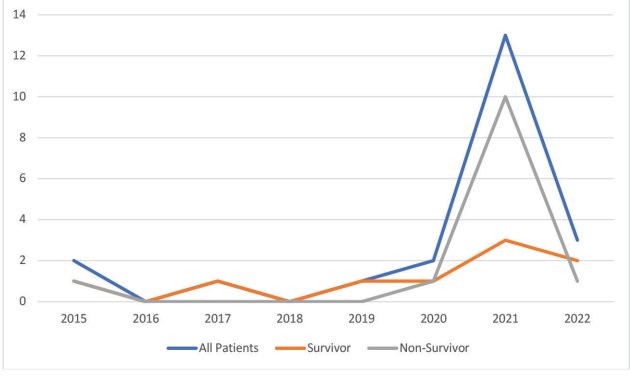

Figure 2. The number of methyl alcohol intoxication cases in the last 8 years

Table 1. Demographic and clinical characteristics of patients

	Non-survivor (n=13)	Survivor (n=9)	p-value
Age	47±13	48±13	0.863
Male, n (%)	8 (61.5)	7 (77.8)	0.648
Body mass index	24.3±2.3	25.5±3.7	0.373
CCI	1 (0-2)	1 (0-2)	0.7
Before ICU, n (%)			
Invasive MV need	13 (100)	5 (55.6)	0.017*
Cardiac arrest	3 (23.1)	1 (11)	0.61
Defect of vision	5 (38.5)	5 (55.6)	0.666
IHD use	1 (7.7)	4 (44)	0.116
SOFA score	9 (8.5-10)	8 (6-9)	0.035*
APACHE-II	28±5	20±6	0.005*
Urea (mg/dL)	36 (22-57)	21 (16-35.3)	0.089
Creatinine (mg/dL)	1.8±0.7	0.94±0.34	0.002*
Total bilirubin (mg/dL)	1.2 (0.85-1.5)	0.6 (0.44-2.1)	0.035*
AST (U/L)	66 (41-230)	135 (33-196)	0.815
ALT (U/L)	41 (25-110)	33.6 (11.3-66)	0.367
Na (mmol/L)	139±9	137±5	0.511
K (mmol/L)	5.3±1.2	4±0.7	0.007*
Cl (mmol/L)	110±7	110±5	0.725
Procalcitonin (ng/mL)	0.14 (0.06-0.34)	1.3 (0.22-2.6)	0.160
CRP (mg/L)	3.3±2.5	9±7.5	0.057
pH	6.78 (6.71-6.9)	7.11 (6.85-7.27)	0.008*
PCO_2 (mmHg)	36±14	29±10	0.171
PO_2 (mmHg)	179±64	148±74	0.3
SO_2 (%)	96 (96-98)	98 (88-99)	0.316
HCO_3 (mmol/L)	5 (4.5-6.2)	9.1 (6.5-13.5)	0.002*
Base deficit (mmol/L)	-27.9±9.9	-21.7±7	0.124
Lactate (mmol/L)	9.6±4.7	5.8±4.7	0.077
Glucose (mg/dL)	198±133	106±76	0.079
WBC (x10^9/L)	24.5±9.5	19.5±10.8	0.264
Hematocrit (%)	44±6	40.1±8.5	0.221
Platelet (x10^9/L)	289±86	220±86	0.097
ICU time (day)	3 (2-5.5)	6 (4.5-15.5)	0.034*

ICU: Intensive care unit, CCI: Charlson comorbidity index, MV: Mechanical ventilation, IHD: , SOFA: Sequential organ failure assessment, APACHE-II: Acute physiology and chronic health evaluation-II, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, WBC: White blood cell Fisher's Exact test [n(%)], independent-samples t-test (mean ± standard deviation), Mann-Whitney U test [median (interquartile range)], *p<0.05

DISCUSSION

The mortality rate of our study was found to be slightly higher than that of other studies. In various studies on methyl alcohol intoxication, the mortality rate varies between 20% and 55%, depending on factors such as the amount of methyl alcohol intake of the patient, the duration of admission to the hospital, concomitant ethanol intake, and different geographical regions (10-14). As in many centers, because blood methyl alcohol level was not measured in our center, its relationship with mortality could not be evaluated. The critical period between the onset of symptoms and hospitalization may be too extended because the unconsciousness and other symptoms that develop due to methyl alcohol intoxication after imitated alcohol intake are similar to the symptoms that develop after ethanol intake. In a retrospective study conducted on 383 people who died due to methyl alcohol intoxication between 2002 and 2010 in Türkiye, 64.7% (n=248) of these deaths died at home, 7.5% (n=29) died in open areas, 9.9% (n=38) died in other areas, and only 12.8% (n=49) died in the hospital (15). In our patients, although it could not be detected clearly, they had a history of methyl alcohol intake 1 day or more, and their admission to the hospital was quite delayed. Therefore, we believe that our mortality rate is higher. The fact that the need for IMV on arrival at the hospital is so high and that some of them even reached the level of cardiac arrest shows that these patients are quite late for treatment.

Visual impairment, which is a finding specific to methyl alcohol intoxication and can be permanent, was observed in 5 patients in each group. In fact, the number of patients with visual impairment may be higher than this because many patients who come to our emergency department have severe unconsciousness and because routine eye examinations are not performed by an ophthalmologist. In a retrospective study conducted in 2022, the rate of visual impairment was found to be 70% in patients with methyl alcohol intoxication who applied to the emergency department (16).

Although the number of patients who underwent IHD before ICU admission was higher in the survivor group, it did not make a statistically significant difference. The lack of statistical difference may be due to the low sample size. IHD application before ICU could be performed in patients who did not need IMV and who were hemodynamically stable. Hemodialysis removes both methanol and toxic metabolites (formic acid) from the blood and thus corrects the acid-base disorder (17). Even though we performed CRRT immediately in all our patients admitted to the ICU, IHD is the first choice as it provides a shorter time to remove methyl alcohol and toxic metabolites (18). The late arrival to the hospital after methyl alcohol intake may have caused us to not benefit sufficiently from hemodialysis.

The APACHE-II and SOFA scores, which are the scores used to predict mortality in critical illnesses, are higher in the non-survivor group in methyl alcohol intoxication and can be used to predict mortality. Blood creatinine, potassium, and total bilirubin levels measured at hospital admission are also higher in the non-survivor group and can be used to predict mortality. Although the blood potassium level was higher in the non-survivor group, it was within the upper limits of normal (5.3±1.2). This elevation may have resulted from renal failure or metabolic acidosis. These results show how severe the toxic picture is during ICU admission in the non-survivor patient group. Formic acid is formed because of methyl alcohol intoxication; it has a direct toxic effect on all organs, mainly on the eyes, brain, kidneys, and liver (2,17).

In the non-survivor patient group, blood HCO_3 and pH values were quite low, and there was deeper metabolic acidosis. In a retrospective study, it was found that a pH value of ≤6.9 was strongly associated with mortality (19). We believe that both blood HCO_3 and pH values should be used to predict mortality.

The total length of stay in the ICU was found to be statistically shorter in the non-survivor group than in the survivor group. At the same time, the median value of the total hospitalization period in the non-survivor patient group is as short as '3 days', which shows how fast death due to methyl alcohol intoxication occurs.

Bilateral basal ganglia hemorrhage, a pathognomonic finding due to methyl alcohol intoxication, was detected in the non-survivor group (Figure 3) (20). However, clear statistical data could not be obtained because not all patients underwent routine cranial imaging.

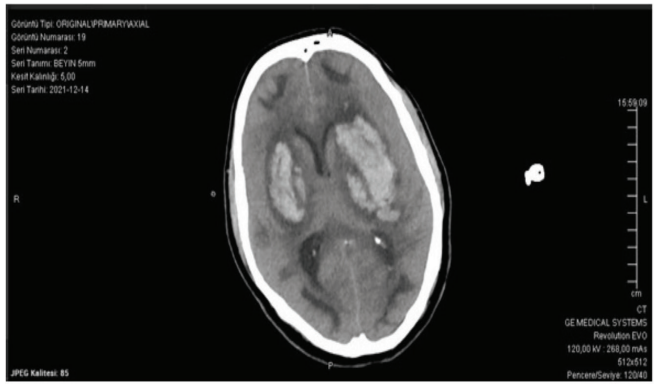

Figure 3. Bilateral basal ganglia bleeding in a methyl alcohol intoxication patient

The most important limitations of our study are that it was single-centered, the sample size was small, and the blood levels of methyl alcohol, which is the gold standard for diagnosis, could not be measured. In addition, in cases of methyl alcohol intoxication due to imitated alcohol intake, the timing of methyl alcohol intake could not be precisely determined because of late detection and admission to the hospital. However, a positive aspect of our study was that the necessary tests could be performed to detect other possible toxic or non-toxic causes that may cause metabolic acidosis with increased anion gap in these patients. Apart from this, the use of the 'ImdSoft-Metavision/QlinICU Clinical Decision Support Software' decision support system was another advantage for the security of research data.

CONCLUSION

The depth of metabolic acidosis, the need for an invasive mechanical ventilator in the early period, acute renal injury, hyperbilirubinemia, and high SOFA and APACHE-II scores are the most important factors predicting mortality in patients who develop methyl alcohol intoxication.

In patients who develop methyl alcohol intoxication due to imitated alcohol use, the possibility of irreversible organ damage in terms of survival is high when the intoxication is recognized. Therefore, it is crucial for state administrators to take measures to prevent fraudsters from producing imitated alcohol and to increase consumers' awareness of this issue.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision number: 2022-21-16, date: 07.11.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.A., D.Ö.B., Concept: M.A., Design: M.A., D.Ö.B., Data Collection or Processing: M.A., Analysis or Interpretation: M.A., Literature Search: M.A., Writing: M.A., D.Ö.B.

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

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

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Supplement Table

1. Charlson comorbidity indexes of the patients; It was calculated by entering patient data from the https://www.mdcalc.com/calc/3917/charlson-comorbidity-index-cci website.
2. SOFA scores of the patients; It was calculated by entering patient data from the https://www.mdcalc.com/calc/691/sequential-organ-failure-assessment-sofa-score website.
3. APACHE-II scores of the patients; It was calculated by entering patient data from the https://www.mdcalc.com/calc/1868/apache-ii-score website

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:55-61
DOI: 10.4274/BMJ.galenos.2023.2023.5-5

Research

Developmental Hip Dysplasia Screening in Child Health Follow-up and Risk Factors Assessment Review

Çocuk Sağlığı Takibinde Gelişimsel Kalça Displazisi Taraması ve Risk Faktörleri Değerlendirmesi

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ABSTRACT

Objective: Developmental dysplasia of the hip (DDH) is the most common skeletal dysplasia. For early diagnosis, screening is recommended. The aim of our study was to determine the incidence of DDH and type IIa hips among infants, evaluate the risk factors for DDH, and review the studies on the same topic that were conducted in Türkiye.

Methods: For this retrospective descriptive study, the records of all infants who were followed up between December 2014 and May 2015 by a "Child Health Follow-up Outpatient Clinic" were investigated for DDH. A total of 300 infants constituted the study group. Risk factors for DDH, including gender, being first born, birth weight and height, maternal age, mode of delivery, multiple births, skeletal deformity, oligohydramnios, breech presentation, swaddling, positive family history, and examination findings related to DDH were extracted from the files. Missing information was gathered by phone from parents.

Results: The incidence of DDH was 0.3%. The rate of immature hip was 16.7%. Immature hip and positive family history, swaddling, and left hip involvement had a statistically significant relationship. In the follow-up, only one case developed hip dysplasia, and 98% of cases with immature hips returned to normal at the end of the third month.

Conclusion: Immature hips may resolve without requiring intervention. Infants who are swaddled and have a positive family history of DDH should be carefully monitored. Left side involvement of immature hips is an important risk factor for DDH.

Keywords: Developmental dysplasia of the hip, screening, risk factors

ÖZ

Amaç: Gelişimsel kalça displazisi (GKD) en sık görülen iskelet displazisi olarak bilinmektedir. Erken teşhis için tarama yapılması önerilir. Çalışmamızın amacı bebeklerde GKD ve tip IIa kalça görülme sıklığını belirlemek, GKD için risk faktörlerini değerlendirmek ve aynı konuda Türkiye'de yapılmış çalışmaları gözden geçirmektir.

Gereç ve Yöntem: Bu retrospektif tanımlayıcı çalışma için, Aralık 2014-Mayıs 2015 tarihlerinde "Çocuk Sağlığı İzlem Polikliniği" tarafından izlenen tüm bebeklerin kayıtları GKD açısından incelendi. Toplam 300 bebek çalışma grubunu oluşturdu. GKD için risk faktörleri olan cinsiyet, ilk doğum, doğum kilosu ve boyu, anne yaşı, doğum şekli, çoğul doğum, iskelet deformitesi, oligohidramnios, makat geliş, kundaklama, pozitif aile öyküsü ve GKD ile ilgili muayene bulguları dosyalardan elde edildi. Eksik bilgiler velilerden telefonla toplanmıştır.

Bulgular: GKD insidansı %0,3 olarak saptandı. İmmatür (olgunlaşmamış) kalça oranı %16,7 idi. İmmatür kalça ve pozitif aile öyküsü, kundaklama ve sol kalça tutulumu arasında istatistiksel olarak anlamlı bir ilişki vardı. Takipte sadece bir olguda kalça displazisi gelişti ve olgunlaşmamış kalça olgularının %98'i üçüncü ayın sonunda normale döndü.

Sonuç: Bebeklerde immatür kalça müdahale gerektirmeden düzelebilir. Kundaklanmış ve ailesinde GKD öyküsü olan bebekler dikkatle izlenmelidir. Ayrıca immatür kalçanın sol taraf tutulumu GKD için önemli bir risk faktörü oluşturmaktadır.

Anahtar Kelimeler: Gelişimsel kalça displazisi, tarama, risk faktörleri

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Cite as: Aydın F, Gür E, Kural B, Sayılı U, Adaletli İ. Developmental Hip Dysplasia Screening in Child Health Follow-up and Risk Factors Assessment Review. Med J Bakirkoy 2024;20:55-61

Received: 23.05.2023
Accepted: 28.08.2023

INTRODUCTION

Developmental dysplasia of the hip (DDH) encompasses a range of hip abnormalities in which the femoral head and acetabulum fail to develop and articulate anatomically (1). DDH is asymptomatic during infancy and early childhood; thus, screening by periodic physical examination after birth and the use of radiographic imaging, especially ultrasound, is crucial in early detection (2). To reduce the exposure of babies to radiation, hip ultrasound is the method for the identification of hip dysplasia just before the ossification of the femoral head (3). A risk-based screening program for DDH was started in Türkiye in 2013 as a pilot study and then became a nationwide practice in 2014. All neonates with a family history of DDH up to second-degree relatives, first-born girl of the family oligohydramnios multiple pregnancy, breech presentation, foot deformities, congenital muscular torticollis, plagiocephaly, scoliosis, pelvic obliquity, and adduction contracture of the hip are referred for ultrasound scanning (4).

Still, there is no consensus on the exact timing of and indications for ultrasonography (USG) among expert groups (5). In the literature, ultrasound screening for DDH is recommended after the fourth week of life (day 22 and beyond) (6). Imaging advancements have created uncertainty, particularly in the first few months of life, regarding whether minor degrees of anatomic and physiologic variability are clinically significant or even abnormal (2). Hips with a slightly shallow acetabulum and rounded bony rim before 3 months of age are classified as Graf type IIa and considered developmentally immature (7). Some mild cases of DDH (and the immature hip) may resolve without intervention (1). Therefore, a different definition was made by Peled et al. (8), who defined "true DDH as a hip that underwent a subsequent treatment".

The aim of this study was to determine the incidence of DDH and type IIa hips among infants. In addition, we aim to evaluate the risk factors for DDH and review the results of studies on this topic, which were conducted in Türkiye.

METHODS

The study was conducted by retrospectively examining the medical records of infants admitted to the Child Health Follow-up Outpatient Clinic of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine during the neonatal period between December 2014 and May 2015.

Selection and Identification of Cases

Infants whose hip ultrasound scans were performed by İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Radiology between 4 and 6 weeks of life and those who regularly came to routine controls for at least nine months were eligible to join the study. Infants with neural tube defect anomalies, genetic syndromes, neuromuscular diseases, and preterm infants were excluded. At each child's health follow-up visit, parental counseling for child care is provided. Back positioning of the infant during sleep, spending some time on the tummy, and putting on comfortable clothes for the infant is advised. It is also suggested that the diaper be placed waist high (above the spina iliaca) by leaving at least two fingers distance between the diaper and the baby's abdomen in a comfortable way. Swaddling is not recommended. In this study, all infants were investigated by physical examination for DDH. Limitations of hip abduction and positive Galeazzi sign (an obvious short leg) were sought as clinical findings. Ortolani and Barlow tests were performed on infants up to three months of age at every visit. Sonographic examinations and classifications were performed along with the Graf technique (3). Graf classification type IIb and higher hips were considered dysplastic hips in our study to calculate the prevalence of DDH.

The following DDH risk factors were extracted from the files: gender, birth weight and height, being first born, maternal age, breech presentation, mode of delivery, multiple birth, oligohydramnios, swaddling, skeletal deformity, positive family history, and examination findings related to DDH. Missing information such as swaddling of babies was collected from parents by phone calls.

Statistical Analysis

IBM® SPSS® Statistics for Windows version 21.0. (IBM Corp., Armonk, N.Y., USA) was used for statistical analysis. For descriptive analyses, categorical data were expressed as percentage and (n), continuous data were expressed as mean and standard deviation if they showed normal distribution, and median (minimum-maximum) if they did not show normal distribution. Normal distribution was determined by the coefficient of variation, histogram, and normality tests. In the comparison of the numerical data of the two independent groups, Student's t-test was used if normal distribution conditions were met. Parameters with non-normal distribution were assessed using the Mann-Whitney U test. The chi-square test and Fisher's Exact test were employed in the analysis of categorical variables. Findings were assessed with 95% confidence interval (CI), with $p<0.05$ level of significance. We also conducted binary logistic regression analyses to evaluate the independent risk factors for type IIa hips. The univariate and multivariate (Backward:LR) methods were used for logistic regression analysis.

The study was initiated following the approval of the Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, dated 03.05.2016 and decision numbered A-16.

RESULTS

Three hundred infants were included in the study. The study included 125 girls (41.7%) and 175 boys (58.3%). The mean birth weight was 3137.03±557.23 gr, and the mean birth height was 49.69±2.68 cm. The mean age of mothers was 30.77±5.76 years. The risk factors that were sought for the study and the results are given in Table 1. Four infants had pes equinovarus deformity (1.3%). No pathological findings related to DDH were detected in the physical examinations of the infants.

The hip USG performed at the fourth week after birth of 300 infants identified 250 hips as type I hips (normal) and 50 hips as type IIa (immature) hips. Control hip USGs were performed at the sixth week after birth, and 45 of the immature hips revealed normal hip USG results, while five of them (1.6%) were classified as type IIa (Figure 1). Orthopedic follow-ups were planned, and at the end of the third month, only one baby's hip progressed to type IIb, whereas the other four babies' hip developments were evaluated as normal. The recovery rate of type IIa hips was 98%. One baby, who progressed to type IIb, was followed up by the orthopedic clinic, and a Pavlik bandage was applied. The incidence of DDH was 0.3% in the study, and the rate of immature hip was 16.7%. The distribution of immature hips and side involvement are given in Table 2. A significant difference was found between type IIa hip and left hip involvement (p=0.040). At the age of nine months, hip examinations of all babies were evaluated as normal in the study group.

A comparison of risk factors and hip types is given in Table 3. There was no relationship between immature hip

Table 1. Distribution of risk factors in the study group

Risk factors	Number of infants (%)
Gender	
Girl	125 (41.7)
Boy	175 (58.3)
First born child of the family	
Yes	131 (43.7)
No	169 (56.3)
Multiple pregnancy	
Yes	27 (9)
No	273 (91)
Breech position	
Yes	2 (0.7)
No	298 (99.3)
Mode of delivery	
Cesarean section	230 (76.7)
Vaginal	70 (23.3)
Skeletal deformity	
Yes	4 (1.3)
No	296 (98.7)
Family history of DDH	
Yes	17 (5.7)
No	283 (94.3)
History of swaddling	
Yes	28 (9.3)
No	272 (90.7)
History of oligohydroamnios in pregnancy	
Yes	15 (5)
No	285 (95)

DDH: Developmental dysplasia of the hip

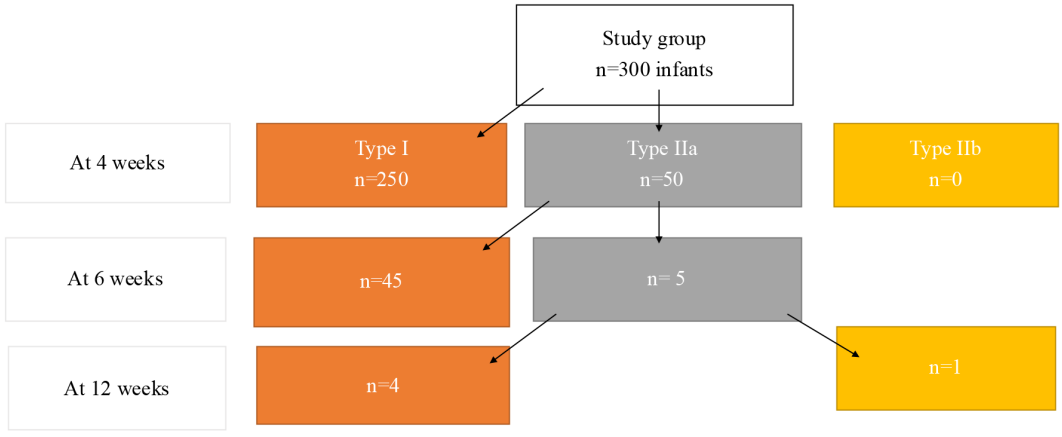

Figure 1. Initial and follow-up hip ultrasonography results of the group according to Graf classification

Table 2. The distribution of immature hips and side involvement

	Type IIa hips	Type I hips	p-value
Right hip	22 (7.3)	278 (92.7)	**0.040**
Left hip	37 (12.3)	263 (87.7)	

and gender, birth weight, birth height, first birth, mode of delivery, older maternal age (25 and older), multiple births, skeletal deformity oligohydramnios, or breech presentation (p>0.05). When we reviewed babies born at 4000 g and above, 12 (4.8%) babies with normal hips and 5 (10%) babies with immature hips were detected. There was no significant relationship between high birth weight and maturity of hips (p>0.05).

Immature hips were detected in 13.6% of infants who swaddled. There was a significant difference between swaddling and immature hips (p<0.001). In the study group, 52.9% of infants had a positive family history. There was a significant difference between positive family history and immature hips (p<0.001).

In the study, 50 babies (100 hips) were classified as immature hips (type IIa) at 4-week-old USG screenings. Nine of them (18%) had bilateral hip involvement, whereas 13 (26%) had right hip involvement and 28 had left hip involvement (56%). In the univariate logistic regression analysis, gender, first born child of the family, multiple pregnancy, breech position, mode of delivery, and skeletal deformity were not associated with type IIa hips. History of swaddling and family history were found to be related to type IIa hips. In the multivariate logistic regression analysis, a history of swaddling [Exp (B): 3.978, 95% CI: 1.648-9.601, p=0.002] and family history of DDH [Exp (B): 4.078, 95% CI: 1.362-12.211, p=0.012] were found to be risk factors for type IIa hips (Table 4).

Table 3. Comparison of risk factors and hip types

Risk factors	Type I hips n (%) (n=250)	Type IIa hips n (%) (n=50)	p-values
Gender			
Girl	105 (42)	20 (40)	0.793
Boy	145 (58)	30 (60)	
First born child of the family			
Yes	108 (43.2)	23 (46)	0.716
No	142 (56.8)	27 (54)	
Multiple pregnancy			
Yes	21 (8.4)	6 (12)	0.417
No	229 (91.6)	44 (88)	
Breech position			
Yes	1 (0.4)	1 (2)	0.306
No	249 (99.6)	49 (98)	
Mode of delivery			
Cesarean section	191 (76.4)	39 (78)	0.807
Vaginal	59 (23.6)	11 (22)	
Skeletal deformity			
Yes	3 (1.2)	1 (2)	0.520
No	247 (98.8)	49 (98)	
Family history of DDH			
Yes	8 (3.2)	9 (18)	**<0.001**
No	242 (96.8)	41 (82)	
History of swaddling			
Yes	15 (6)	13 (26)	**<0.001**
No	235 (94)	37 (74)	
History of olygohydroamnios in pregnancy			
Yes	13 (5.2)	2 (4)	1
No	237 (94.8)	48 (96)	

DDH: Developmental dysplasia of the hip

Table 4. Risk factors related to type IIa hips

	Univariate regression			Multivariate regression (Backward:LR)		
	Exp (B)	95% CI	p-value	Exp (B)	95% CI	p-value
Gender (ref: girl)	1.086	0.585-2.017	0.793	-	-	-
First born child of the family	1.120	0.609-2.061	0.716	-	-	-
Multiple pregnancy	1.487	0.568-3.895	0.419	-	-	-
Breech position	5.082	0.313-82.625	0.253	-	-	-
Mode of delivery (ref: vaginal delivery)	1.095	0.528-2.273	0.807	-	-	-
Skeletal deformity	1.680	0.171-16.491	0.656	-	-	-
History of swaddling	5.505	2.425-12.493	<0.001	3.978	1.648-9.601	0.002
Family history of DDH	6.640	2.423-18.20	<0.001	4.078	1.362-12.211	0.012

CI: Confidence interval, DDH: Developmental dysplasia of the hip

Table 5. Summary of studies from Türkiye related to DDH investigation

Reference	Year	Number of patients	Incidence of DDH	Age group	Family history of DDH	Breech	Sex	First born	Swaddling	Other evaluated DDH risk factors
Ömeroğlu et al. (11)	1999	150	11.0%	Av. 3.9 mo	Yes	Yes	NA	NA	NA	Limitation of abduction, pili asymmetry were found to be significant in DDH cases.
Akman et al. (12)	2007	403	3.4%	Av. 6.4 mo (4 w.-10 mo)	No	No	No	No	No	Olygohidroamnios was associated with DDH. In correlation analysis, there was a correlation between female gender and swaddling.
Dogruel et al. (13)	2008	3541	4.71%	4-6 w.	Yes	Yes	Yes/female	No	Yes	Caesarean section, skeletal anomaly, olygohidyromamnios, low birth weight and prematurity did not yield as significant risk factors.
Tosun et al. (14)	2010	310	21.0%	0-9 mo.	No	No	No	Yes	No	The presence of pes calcaneovalgus, birth weight over 4 kg, limitation of abduction was found to be significant in DDH cases.
Guner et al. (15)	2012	265	11.7 %	4 w.	Yes	No	Yes /female	NA	Yes	Consanguineous marriage is a significant factor.
Güler et al. (16)	2016	4782	9.9%	1 mo.	No	No	Yes/female	Yes	No	Vaginal birth, torticollis and foot deformities were not significant.
Saglam et al. (17)	2017	1025	0.29%	1.7±1.3 mo.	NA	NA	Yes/female	No	NA	….
Kural et al. (18)	2019	9758	0.2%	NA	No	Yes	Yes/female	No	NA	Multiple pregnancy, torticollis, limitation of abduction, Ortolani and Barlow manuvuers were significant.
Ömeroğlu et al. (19)	2019	952	NA	33-45 days	Yes	Yes	NA	No	Yes	Family history, swaddling and oligohydramnios were found to be the three significant risk factors correlated with a higher rate of unstable/decentred hip(s) (Graf types D/III/IV) in patients with DDH.
Demir et al. (20)	2020	4551	3.71%	80.3±20.3 days	Yes	No	No	No	No	Prematurity, oligohydramnios.

Av: Average, mo: Month/months, w: Week/weeks, NA: Not applicable, DDH: Developmental dysplasia of the hip

DISCUSSION

The risk-based screening experience of DDH is presented in this study. After the widespread use of hip USG, the detection rate of immature hips has increased, and close follow-up is required. The rate of immature hip was 16.7% in our study, whereas positive family history and swaddling were detected as risk factors. In addition, left hip involvement was identified to be related to the immature hip.

In the literature, the rates of immature hips in newborn populations vary between 2.3% and 45% (9). Although the spontaneous normalization rate in type IIa hips is reported to be high, dysplasia may persist or worsen in 5-10% of cases (7). In our study, only one patient proceeded to type IIb hip. Therefore, we calculated the true DDH rate as 0.3%. In Türkiye, there were many studies related to the incidence of DDH. The incidence rate varies between 0.2% and 21%; thus, it may depend on the screening method and definition of DDH and population (Table 5).

The definition of family history in DDH varies across screening programs. In the United Kingdom, hip problems of first-degree family members (this includes baby's parents or siblings, who have had a hip problem that started as a baby or young child that needed treatment) is defined as a family risk factor (10). In the screening program conducted in Türkiye, DDH cases up to second-degree relatives are defined as family history risk factors (4). In our study, we used this definition, and a family history of DDH was found to be a risk factor for immature hips. In Table 5, the studies from Türkiye carried out on different dates related to the investigation of DDH risk factors are given (11-20). Considering the family history used in the studies, there is a need for meta-analysis studies on whether family history is a risk factor in Türkiye or not.

Traditional swaddling involves wrapping the newborn from shoulder to hip or all the way to the foot for a certain period with the hips in extension and adduction and knees in extension (19). In the child health follow-up, swaddling was not recommended in the study group. Contrary to this recommendation, swaddling was detected in 9.3% of infants and was defined as a risk factor for immature hips. A prospective study that investigated the effect of swaddling on the development of DDH found that infants who were swaddled had 2.65 times greater odds of developing DDH (15). Also, swaddling was associated with a higher rate of unstable/decentred hip(s) in patients with DDH (19).

DDH can be unilateral or bilateral. In our study, type IIa was observed in the left hip in 37 of the cases, and it was statistically significant. In many studies, the occurrence of DDH was significantly higher on the left side than on the right side of the body (21). In the literature, this phenomenon was explained due to an adducted position of the left leg of the fetus against the mother's sacrum in the uterus (22). Çekiç et al. (23), conducted a study with 1186 newborns. Only 10 newborns with type IIa hips did not improve to type Ia and worsened to other types. Eighty percent of these cases were seen in left hip involvement (23). We emphasize that left-sided involvement of immature hips is an important risk factor for DDH.

Our study had some limitations. Missing information, such as history of swaddling, was gathered by phone and was based on parents' recall. This may cause recall bias. Preterm infants were not included.

CONCLUSION

In the DDH screening program, it is important to determine the rate of immature hips and the true rates of DDH. The immature hips may resolve without requiring intervention, but infants who are swaddled and have a positive family history of DDH should be carefully monitored. Left side involvement of the immature hip may need additional attention for DDH.

ETHICS

Ethics Committee Approval: The study was initiated following the approval of the Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, dated 03.05.2016 and decision numbered A-16.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: F.A., E.G., B.K., İ.A., Concept: F.A., E.G., U.S., İ.A., Design: F.A., E.G., U.S., İ.A., Data Collection or Processing: F.A., U.S., Analysis or Interpretation: F.A., E.G., B.K., U.S., İ.A., Literature Search: F.A., B.K., Writing: F.A., E.G., B.K., U.S., İ.A.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:62-71
DOI: 10.4274/BMJ.galenos.2023.2023.8-15

Research

Difficulties Experienced by Surgical Team Members with Operating Room COVID-19 Personal Protective Equipment

Cerrahi Ekip Üyelerinin Ameliyathane COVİD-19 Kişisel Koruyucu Ekipmanlarla Yaşadığı Zorluklar

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ABSTRACT

Objective: During the pandemic, operating theaters were considered high-risk areas because of aerosol-generating procedures and devices. Therefore, the surgical team members had to wear multi-component high-level personal protective equipment to prevent occupational exposure. In the current study, we evaluated the side effects of operating room coronavirus disease-2019 (COVID-19) personal protective equipment.

Methods: A descriptive and cross-sectional study was conducted with 203 participants. Side effects in six thematic areas (respiration, vision, hearing-communication, thermal stress, movement-occupational skills, neurocognitive-psychological) were evaluated using a questionnaire and face-to-face interview.

Results: The mean age was 32.6±8.4; 55.7% were women and 43.8% were doctors. Respiratory, vision, hearing, and communication limitations were determined as 91.6%, 94.1%, 61.6%, and 93.6%, respectively. Those who reported an increase in sweating, warmth, thirst and skin problems were 96.1%, 95.1%, 91.6% and 85.2%, respectively. Restrictions in movements and sense of touch were 88.2% and 80.3%, respectively. Decreased visual quality and psychological tolerance and increased thermal stress and sweating were higher in physicians ($p<0.05$). Hearing limitation was higher in nurses ($p<0.05$).

Conclusion: The results showed that the members of the surgical team experienced serious difficulties while working with the operating room COVID-19 personal protective equipment, and that they were not prepared for strategies to deal with these problems. There must be a balance between the protective effects of this equipment and the user side effects. It is recommended that efforts should be focused on designing and producing new user-friendly and suitable equipment for employee health.

Keywords: Operating room, COVID-19, personal protective equipment, side effects

ÖZ

Amaç: Pandemi döneminde ameliyathaneler, aerosol üreten prosedürler ve cihazlar nedeniyle yüksek riskli alanlar olarak kabul edildi. Bu nedenle, cerrahi ekip üyeleri, mesleki maruziyeti önlemek için çok bileşenli üst düzey kişisel koruyucu ekipman giymek zorunda kaldı. Bu çalışmada, ameliyathane koronavirüs hastalığı-2019 (COVİD-19) kişisel koruyucu ekipmanlarının yan etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Tanımlayıcı ve kesitsel nitelikteki çalışma, 203 katılımcıyla yürütüldü. Altı tematik alandaki (solunum, görme, işitme-iletişim, termal stres, hareket-mesleki beceriler, nörokognitif-psikolojik) yan etkiler anket ve yüz yüze görüşme yöntemiyle değerlendirildi.

Bulgular: Ortalama yaş 32,6±8,4; %55,7'si kadın, %43,8'i doktordu. Solunum, görme, işitme ve iletişim kısıtlılıkları sırasıyla %91,6, %94,1, %61,6 ve %93,6 olarak belirlendi. Terleme, sıcaklık, susuzluk ve deri problemlerinde artış bildirenlerin oranı sırasıyla %96,1, %95,1, %91,6, %85,2 bulundu. Hareketlerde ve dokunma duyusunda kısıtlamalar %88,2 ve %80,3 idi. Görme kalitesinde azalma, psikolojik toleransta azalma, termal stres ve terlemede artış hekimlerde daha yüksekti ($p<0,05$). Hemşirelerde işitme kısıtlılığı daha fazlaydı ($p<0,05$).

Sonuç: Bu çalışmanın sonuçları, cerrahi ekip üyelerinin ameliyathane COVİD-19 kişisel koruyucu ekipmanları ile çalışırken ciddi zorluklar yaşadıklarını ve bu sorunlarla baş etme stratejilerine hazırlıklı olmadıklarını göstermiştir. Bu ekipmanların koruyucu etkileri ile kullanıcı yan etkileri arasında bir denge olmalıdır. Çalışan sağlığına uygun, kullanıcı dostu yeni ekipmanların tasarlanması ve üretilmesine ağırlık verilmesi önerilir.

Anahtar Kelimeler: Ameliyathane, COVİD-19, kişisel koruyucu ekipman, yan etkiler

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Cite as: Turgut Eser M, Aygün M. Difficulties Experienced by Surgical Team Members with Operating Room COVID-19 Personal Protective Equipment. Med J Bakirkoy 2024;20:62-71

Presented in: This study was presented as a summary paper at the International Zeugma Scientific Research Congress' on 20 February 2023.

Received: 24.08.2023
Accepted: 17.10.2023

INTRODUCTION

During the coronavirus disease-2019 (COVID-19) pandemic, healthcare workers had to use varying levels of personal protective equipment (PPE) depending on the work area and risk exposure level. The viral transmission routes of severe acute respiratory syndrome coronavirus 2 are respiratory droplets, close contact, and possible splashing (1,2). In this respect, operating rooms are considered high-risk areas due to aerosol-producing procedures and devices and require high-level PPE in the pandemic (1,3,4).

For surgical team members who routinely work with standard PPE such as surgical masks and caps, overshoes, gown, and gloves, and guidelines specific to operating rooms, including COVID-19 PPE donning and doffing instructions have rapidly developed (3,5,6). Components such as N95 masks or air-purifying respirators, a surgical mask on top of the N95, protective coveralls that also cover the head, full face shield, double or triple gloves, and boots were added to the basic operating room PPE (2,3,5-7).

In the process, the tolerability of this PPE by healthcare workers and the side effects caused by it were also tested. It was observed that working with these multilayered PPEs for long periods had many adverse physical, ergonomic, cognitive, and psychological effects on healthcare workers (8-10).

In this study, we primarily aimed to evaluate the adverse effects of COVID-19 PPE in six thematic areas (respiratory, visual, hearing-communication, thermal stress, movement-occupational skills, neurocognitive-psychological) on surgical team members consisting of surgeons, operating room nurses, anesthesiologists, and anesthesia technicians. We also collected information about the employees' levels of knowledge to cope with these adverse effects and their compliance with this PPE. In the future, there will be pandemics or chemical etc. exposures that require the use of PPE. Therefore, it is necessary to develop new PPE with high protective properties, but at the same time user-friendly and with reduced side effects. The study's results may contribute to the side effects that should be focused on when developing such equipment.

METHODS

Study Design

This descriptive and cross-sectional study was conducted in University of Health Sciences Türkiye, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital between November 2021 and February 2022.

Sample and Setting

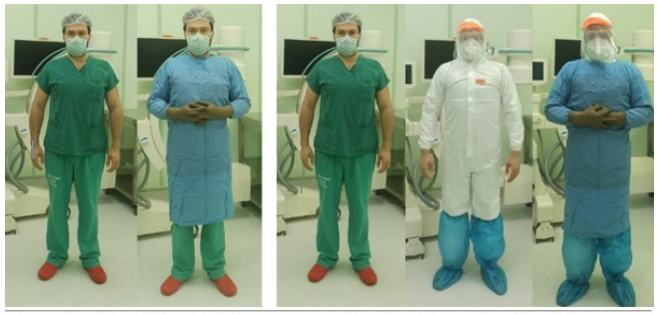
The study was conducted on surgeons, operating room nurses, anesthesiologists, and anesthesia technicians working in 24 operating rooms of the relevant hospital using a purposive sampling method. Inclusion criteria were as follows: being a surgical team member, having experience participating in surgical interventions with "Operating Room COVID-19 PPE" during the pandemic process, and volunteering to participate in the study. Employees on temporary duty, leave, or reporting during the period when the study data were collected were excluded from the study. The study was conducted with 203 participants.

During the pandemic, the COVID-19 PPE-wearing protocol shown in Figure 1 was applied in the operating rooms of the hospital where the study was conducted. These components were as follows: two-piece operating room uniform + surgical cap + overshoes + N95 mask and surgical mask on top of it + full face shield + coveralls covering the whole body including the head + boots/protective shoes up to the knee over the coveralls + sterile gown + 2 or 3 layers of sterile gloves.

Data Collection Tools

The research data were collected through face-to-face interviews and self-reports using a form consisting of three sections.

The first part included the personal and professional characteristics of the participants. The second part determined the adverse effects of operating room COVID-19 PPE on surgical team members. The researchers created the questions in this section on the basis of the



Operating Room Standard PPE	Operating Room COVID-19 PPE
Two-piece operating room uniform	Two-piece operating room uniform
Surgical cap	Surgical cap
Surgical mask	N95 mask + Surgical mask
Surgical overshoes	Surgical overshoes
Sterile surgical gown	Liquid impermeable protective coverall, covering the whole body including the head
Sterile gloves	Full face shield
	Liquid-proof protective overshoes/boots up to the knee over the coveralls
	Sterile surgical gown
	2 - 3 layers of sterile gloves

Figure 1. Operating room standard and COVID-19 PPE components

COVID-19: Coronavirus disease-2019, PPE: Personal protective equipment

potential risks determined by the literature review and anecdotes of personnel with operation experience with these PPEs (8,11,12). The form consisted of six thematic areas (respiratory, visual, hearing-communication, thermal stress, movement-occupational skills, neurocognitive and psychological) and 23 questions. Impact level was evaluated as "No = It didn't make a change" and "Yes = It had a negative impact." The third section was "Operating Room COVID-19 PPE" related to training, other experiences and opinions. In this section, questions about the knowledge and compliance of the participants regarding the use of PPE, the status of receiving additional training to cope with side effects, and the institutional opportunities provided were included, and the answers were evaluated as yes/no.

Ethical Permissions

For the methodology and data collection form of the study, ethical approval was first obtained from the Ministry of Health COVID-19 Scientific Research Evaluation Commission (08.04.2021/decision no: T16-58-10) and then from Biruni University Non-Interventional Research Ethics Committee (decision no: 2021/51-07, date: 21.05.2021) in accordance with the rules during the pandemic period. Permission was obtained from the institution where the study would be conducted (25.11.2021/decision no: 12). The purpose of the study was explained to the participants, and their informed consent was obtained. This study was conducted in accordance with the principles of the Helsinki Declaration.

Statistical Analysis

Statistical Package for the Social Sciences v.24.0 (SPSS - IBM Corporation, New York, NY, USA) was used for statistical analyses. Frequency, percentage distribution, mean, and minimum-maximum values were analyzed for descriptive analyses. The chi-square test, a parametric method, was used to compare the data according to the groups. The results were evaluated at a 95% confidence interval and $p<0.05$ significance level.

RESULTS

The mean age of the 203 surgical team members who participated in the study was 32.66±8.48 years; 55.7% were female, 43.8% were physicians, and 47.8% of the group had >20 operations with these PPEs (Table 1).

Table 2 shows participant feedback on the effects of N95 + surgical masks on respiratory quality and the effects of visors on visual quality. Those who stated that their respiratory quality was negatively affected were 91.6% (n=186). Regarding symptoms that may develop due to respiratory limitation, 32% of participants reported anxiety, 24.6% reported dizziness, 29.6% reported dyspnea, and 7.4% reported lightheadedness. 94.1% (n=191) of the participants said that their quality of vision had decreased. In this area, 89.2%, 54.7%, and 29.6% reported fogging, light reflection, and visual field narrowing due to full face shields, respectively.

Data on hearing-communication, thermal stress, movement-occupational skills, and neurocognitive-psychological effects of COVID-19 PPE in the operating room are presented in Table 3. 61.6% (n=125) reported a decrease in hearing quality, and 93.6% (n=190) reported problems with communication within the team while working with this equipment. Those reporting increased sweating, warmth, and thirst with these PPE components were 96.1%, 95%, and 91.6%, respectively. Those who reported skin problems due to thermal effects were 85.2%. Those who reported decreased mobility with these PPE were 88.2% (n=179), and those who reported limitations in occupational hand skills such as dissection/instrumentation were 75.9% (n=154). Those who reported decreased tactile sensitivity due to using two or three layers of gloves were 80.3% (n=163). There were 70.0% (n=142) who reported decreased

Table 1. Personal and occupational characteristics of the participants (n=203)

Variables		n (%)
Age	20-35	143 (70.4)
	36-50	52 (25.6)
	>51	8 (3.9)
Gender	Female	113 (55.7)
	Male	90 (44.3)
Occupation	Doctors	89 (43.8)
	Nurses	67 (33.0)
	Anesthesia technicians	47 (23.2)
Operating room experience (years)	0-1	45 (22.2)
	2-4	47 (23.2)
	5-10	48 (23.6)
	>10	63 (31.0)
Operation experience with COVID-19 PPE (number)	<3	27 (13.3)
	4-8	29 (14.3)
	9-14	34 (16.7)
	15-20	16 (7.9)
	>20	97 (47.8)

COVID-19: Coronavirus disease-2019, PPE: Personal protective equipment

reaction speed in performing occupational skills and 79.8% (n=162) who reported that the processes related to tasks are prolonged. 79.3% (n=161) reported decreased physical tolerance. 78.8% (n=160) of participants reported decreased concentration, attention, and perception associated with PPE use, 82.3% (n=167) reported increased headaches, 40.4% (n=82) reported problems with decision-making and forgetfulness, and 85.2% (n=173) reported decreased psychological tolerance (patience).

Complaints of decreased visual quality, increased thermal stress and sweating, and reduced psychological tolerance were higher in physicians than in other occupational groups ($p<0.05$). Hearing limitation was more elevated in nurses than in the other two occupational groups ($p<0.05$) (Table 4, Figure 2). Reports of skin problems and decreased physical and psychological tolerance were higher in men than in women ($p=0.001$, $p<0.05$, $p<0.05$, $p<0.05$, respectively). There was no difference between genders regarding respiratory limitation, thermal stress, increased sweating, and thirst ($p>0.05$). There was no statistically significant difference between the age groups regarding respiratory limitation, fatigue, and physical and psychological tolerance problems experienced by the participants regarding PPE use ($p>0.05$).

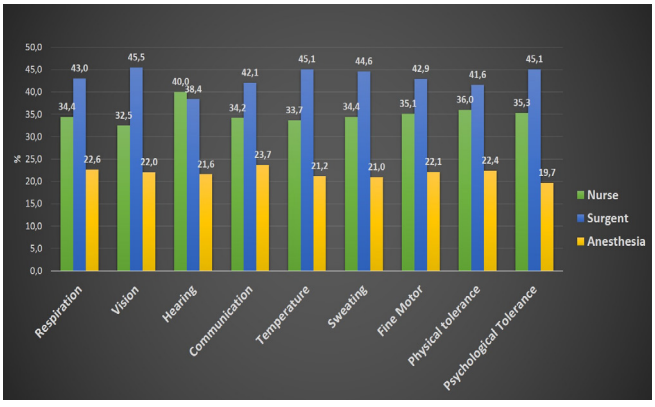


Figure 2. Distribution of operating room COVID-19 PPE-related problems by occupations

COVID-19: Coronavirus disease-2019, PPE: Personal protective equipment

The majority of the participants stated that they did not receive any additional training on breathing with an N95 mask, appropriate head movements to improve vision quality, prevent balance problems, prevent dehydration, and reduce speech-hearing and communication problems (85.2%, 91.6%, 90.6%, 76.8%, respectively). The number of those who stated that they had the opportunity to shower and rest outdoors after an operation with these PPEs was low (13.3% and 9.9%, respectively) (Table 5).

60.1% of the participants reported that the ideal operation time to work efficiently in surgical operations using PPE was less than 2 h. When the level of avoidance of wearing PPE was evaluated depending on the problems they experienced, 59.2% of the participants stated that they showed avoidance behavior (28.1% partially, 31.1% completely).

DISCUSSION

This study examined the difficulties experienced by surgical team members familiar with using standard surgical PPE when working with operating room COVID-19 PPE, which consists of many components and layers. The results of this study, reflecting the subjective experiences of the participants in defined PPE conditions, show that

Table 2. Effects of operating room COVID-19 PPE on respiration and vision (n=203)

Problems with operating room COVID-19 PPE					Yes n (%)	No n (%)
Respiratory limitation (the effects of the N95 mask + surgical mask and shield worn over it on the breathing)	My respiratory quality decreased n (%)	186 (91.6)	Symptoms experienced due to sensation of respiratory limitation associated with PPE components*	Anxiety	65 (32.0)	138 (68.0)
				Dizziness	50 (24.6)	153 (75.4)
	It did not make a difference n (%)	17 (8.4)		Dyspnea	60 (29.6)	143 (70.4)
				Lightheadedness	15 (7.4)	188 (92.6)
Visual limitation (the effects of breathing with masks and of the shields used in the scope of PPE on vision quality)	My quality of vision decreased n (%)	191 (94.1)	Visual effects of masks and shields*	Fogging	181 (89.2)	22 (10.8)
				Light reflection	111 (54.7)	92 (45.3)
	It did not make a difference n (%)	12 (5.9)		Narrowing of the visual field	60 (29.6)	143 (70.4)

*Multiple options. COVID-19: Coronavirus disease-2019, PPE: Personal protective equipment

surgical team members experienced severe difficulties and limitations in the areas of respiration, vision, hearing-communication, thermal stress, mobility-occupational skills, and neurocognitive-psychological impact. They were also unprepared for strategies to reduce these challenges.

Effect of Operating Room COVID-19 PPE on Respiratory Quality

During the pandemic, the use of N95 masks was mandatory to prevent droplet contamination caused by aerosol-generating procedures and surgical smoke. Surgical mask (to prevent N95 mask from blood etc. and prolong its use) and full face shields (to protect eyes) have been added to this combination (5,6). Experimental studies indicate that masks cause CO_2 and moisture to accumulate in the mask, increasing respiratory resistance, making breathing difficult, and reducing air exchange (13-15). In the current study, >90% of the participants stated that they experienced a feeling of limitation in breathing due to this PPE. Symptoms such as anxiety, dizziness, dyspnea, and lightheadedness that may be associated with respiratory limitation were reported at lower rates. Similar to our study results, in a study conducted on surgeons, 67% reported respiratory problems related to prolonged use of the N95 mask, and surgeons reported feeling dyspnea, especially during prolonged operations (12). In a study evaluating the effects of masks on oxygen saturation (SpO_2), a significant decrease in SpO_2 (97.5% vs. 94%) and complaints such as shortness of breath and dizziness were observed in surgeons using N95 masks covered with surgical masks (16). Another study conducted on intensive care healthcare workers showed that the N95 mask caused a significant decrease in SpO_2 and an increase in dyspnea scores (17). In the same study, 60% of the participants reported dyspnea as a side effect of PPE. In another study on dental healthcare workers, the baseline SpO_2 value decreased significantly from 98.6% to 97.0% after 4 h of N95 mask use (18).

Table 3. Effects of operating room COVID-19 PPE on hearing-communication, thermal, movement-occupational skills, and neurocognitive-psychological domains (n=203)

Problems with operating room COVID-19 PPE		Yes n (%)	No n (%)
Limitations in hearing and communication (restriction in hearing and communication due to the use of N95 mask + surgical mask + face shield + coveralls)	Decreased hearing quality	125 (61.6)	78 (38.4)
	Decreased quality of communication within the team	190 (93.6)	13 (6.4)
Thermal problems (thermal effects caused by the combination of upper and lower uniform + coveralls + sterile surgical gown + shoes up to the knee)	Increased sweating	195 (96.1)	8 (3.9)
	Increase in the feeling of warmth	193 (95.1)	10 (4.9)
	Increased sensation of thirst	186 (91.6)	17 (8.4)
	Skin problems	173 (85.2)	30 (14.8)
Movement and occupational skills-related problems (the effects of the combination of upper-lower uniform + coveralls + sterile surgical gown + shoes up to the knee + double/triple gloves on movements)	Decreased mobility	179 (88.2)	24 (11.8)
	Limitation in hand skills (dissection, instrumentation, etc.)-fine motor movements	154 (75.9)	49 (24.1)
	Limitation on tactile sensation-sensitivity (associated with double/triple glove use)	163 (80.3)	40 (19.7)
	Decreased reaction speed in performing professional skills	142 (70.0)	61 (30.0)
	Prolongation of professional tasks and processing times	162 (79.8)	41 (20.2)
	Decreased physical tolerance-loss of strength	161 (79.3)	42 (20.7)
	Feeling an increased level of fatigue	193 (95.1)	10 (4.9)
Neurocognitive-psychological effects (neurocognitive-psychological effects of all PPE components)	Decreased concentration, attention, and perception	160 (78.8)	43 (21.2)
	Increased headache	167 (82.3)	36 (17.7)
	Difficulty in making decisions, forgetfulness	82 (40.4)	121 (59.6)
	Decreased psychological tolerance (endurance, patience)	173 (85.2)	30 (14.8)

COVID-19: Coronavirus disease-2019, PPE: Personal protective equipment

Table 4. Comparison of side effects operating room COVID-19 PPE's between occupational groups (n=203)

PPE related problems		Nurse n (%)	Surgent n (%)	Anesthesia technician n (%)	χ2 p
Limitation of respiration	It didn't make a difference	3 (17.6)	9 (52.9)	5 (29.4	χ2=1.990 p=0.370
	The quality of my breathing has decreased	64 (34.4)	80 (43.0)	42 (22.6)	
Limitation of vision	It didn't make a difference	5 (41.7)	2 (16.6)	5 (41.7)	χ2*=4.553 **p=0.037**
	The quality of my vision has decreased	62 (32.5)	87 (45.5)	42 (22.0)	
Limitation in hearing	It didn't make a difference	17 (21.8)	41 (52.6)	20 (25.6)	χ2*=7.360 **p=0.025**
	The quality of my hearing has decreased	50 (40.0)	48 (38.4)	27 (21.6)	
Communication breakdown	It didn't make a difference	2 (15.4)	9 (68.2)	2 (15.4)	χ2*=3.248 p=0.178
	Our quality of communication within the team has decreased	65 (34.2)	80 (42.1)	45 (23.7)	
Feeling of warmth	It didn't make a difference	2 (20.0)	2 (20.0)	6 (60.0)	χ2*=8.071 **p=0.027**
	My temperature sensation increased	65 (33.7)	87 (45.1)	41 (21.2)	
Sweating	It didn't make a difference	0 (0.0)	2 (25.0)	6 (75.0)	χ2*=10.241 **p=0.002**
	It increased my sweating	67 (34.4)	87 (44.6)	41 (21.0)	
Limitation in occupational hand skills - fine motor movements	It didn't make a difference	13 (26.5)	23 (46.9)	13 (26.5)	χ2=1.280 p=0.527
	Restricted my ocupational hand skills/ movements	54 (35.1)	66 (42.9)	34 (22.1)	
Physical tolerance	It didn't make a difference	9 (21.4)	22 (52.4)	11 (26.2)	χ2=3.242 p=0.198
	I have experienced my power diminishing	58 (36.0)	67 (41.6)	36 (22.4)	
Psychological tolerance	It didn't make a difference	6 (20.0)	11 (36.7)	13 (43.3)	χ2=8.409 **p=0.015**
	My psychological tolerance (endurance, patience) decreased	61 (35.3)	78 (45.1)	34 (19.7)	

χ2= Pearson chi-square, χ2*= Fisher Exact test, p<0.05. COVID-19: Coronavirus disease-2019, PPE: Personal protective equipment

Table 5. Training and precautions to reduce the side effects of operating room COVID-19 PPEs (n=203)

Items	Yes n (%)	No n (%)
Have you received additional training on the problems caused by the N95 mask and how to breathe while using this mask?	30 (14.8)	173 (85.2)
Have you received additional training on appropriate head movements to improve the quality of vision and prevent balance problems?	17 (8.4)	186 (91.6)
Have you received additional training to prevent PPE-related dehydration?	19 (9.4)	184 (90.6)
Has the operating room temperature been decreased to reduce the thermal stress associated with PPE in your operations?	54 (26.6)	149 (73.4)
Have precautions such as speaking face-to-face and slowly, repeating orders, etc., been taken within the team to reduce hearing and communication problems?	47 (23.2)	156 (76.8)
Has your department set a maximum value for the length of stay in operation to reduce the adverse effects of PPE on the staff and established routines such as changing the surgical team at the end of this period?	41 (20.2)	162 (79.8)
After surgical operations using PPE in your department, is rest time and opportunity provided to the personnel in an oxygen-rich area (e.g., open-air), and is it routinely used?	20 (9.9)	183 (90.1)
Does the staff have the opportunity to shower after surgical operations using PPE in your unit?	27 (13.3)	176 (86.7)

COVID-19: Coronavirus disease-2019, PPE: Personal protective equipment

Effect of Operating Room COVID-19 PPE on Visual Quality

Masks and full face shields may lead to decreased quality of vision with effects such as fogging, light reflection, and narrowing of the visual field and may complicate procedures (8). In our study, almost all participants reported deterioration in visual quality due to breathing with masks and using goggles/full-face shields. In this context, the biggest complaint was fogging of the shield surface by exhaled air. The complaint of decreased visual quality was significantly higher among physicians than among nurses and anesthesia technicians. Clear visualization of the surgical field is one of the factors affecting the success of the operation; therefore, it is understandable that surgeons are more sensitive to this issue. In studies conducted on surgeons (11,12,19,20), the adverse effects of PPE on visual quality were reported at varying rates of 58%, 63%, 82%, and 95%, respectively. Some experimental study results indicate that full-face shields narrow the surgical field of view in operations that require a microscope and that the surgical field of view is important for safe surgery (21,22).

Effect of Operating Room COVID-19 PPE on Hearing and Communication

Speech intelligibility and quality communication between healthcare workers are essential to fulfill their duties quickly and safely. The combination of N95 mask + surgical mask + full face shield may impair speech intelligibility by silencing the voice, and cap + suit hood may impair hearing (8). This effect, which impairs hearing and understanding of speech, may be more intense with operating room noise. In our study, most surgical team members stated that their hearing quality decreased, and almost all indicated difficulty in intra-team communication. The problem of hearing limitation was higher in operating room nurses than in physicians and anesthesia technicians. Experimental studies suggest that the mechanical barrier created by masks and shields has a negative effect on speech intelligibility and worsens speech recognition scores (23,24). In a study conducted on surgeons, those who reported impaired communication in relation to PPE were close to our results by 82% (20). However, communication impairment feedback was lower than our results in some previous studies 64%, 54%, 48%, and 46%, respectively) (11,12,18,19).

Thermal Effects of COVID-19 PPE in the Operating Room

A balance between heat gain and loss in the human body is needed to ensure thermal comfort. During the pandemic period in the operating rooms where the study was conducted, a protocol change was made against the risk of contamination, such as wearing a top and bottom uniform + coveralls covering the head and whole body in polyethylene structure + sterile surgical gown + plastic overshoes up to the knee. These multilayered liquid-air impermeable PPE components trap sweat and hot air between the wearer's clothing and body. They may cause thermal stress by preventing heat loss through radiation evaporation convection (2,8). In the current study, almost all surgical team members reported increased sensations of heat, sweating, and thirst, and a significant number of them also reported skin problems. Thermal stress and increased sweating were significantly higher in physicians than in nurses and anesthesia technicians. The fact that they had to perform a surgical operation with these PPEs and under powerful lighting may have had more intense thermal effects on the surgeons. The results confirmed the strong effect of COVID-19 PPE on healthcare workers' perception of thermal stress, which is in line with the results obtained from similar studies (12,25-27). For example, in a study by Saeed et al. (12) on surgeons, heat regulation problems were 67%, and participants reported that increased sweat caused skin irritation. In a study by Tabah et al. (25) on 4879 healthcare workers, 51% reported thermal effects and 47% reported thirst as an adverse effect of PPE. In another study, 78% of healthcare workers reported that they experienced thermal stress perception (26). In the same study, 35.6% described their thermal sensations as hot and 52.4% described them as scalding while working with PPE; thirst was reported by 58% and sweating by 70% (26). In a focus group analysis study, healthcare workers said they sweat much with this PPE, even with minimal effort, and feel like they are on a steamship (27). An experimental study found a significant increase in body temperature (36.40 vs. 37.05) and significant increase in surface temperature measured by thermal imaging (24.5 vs. 26.9 °C) compared with baseline values in healthcare workers performing routine tasks for 1 h in coveralls (28). The researchers concluded that COVID-19 PPE causes significant thermal stress affecting human performance (28).

Effect of Operating Room COVID-19 PPE on Motor Functions

Intraoperative tasks require combined cognitive, visual, and motor skills. Multilayered clothing and gloves may cause effects such as limitation of movement and difficulty in technical skills, and working with these PPEs may lead to a decrease in physical strength with the accumulation of all adverse effects (8). In the study, surgical team members reported high rates of decreased mobility (88%), decreased occupational skill reaction speed (70%), decreased physical tolerance (79%), and increased fatigue (95%) based on their

experience working with COVID-19 PPE. When the results of similar studies were analyzed, the reported increase in physical fatigue was 70% in one study (17). In comparison, the negative effect of PPE on comfort was reported as 92.6% in the study by Alarfaj et al. (20) and 60.7% in the study by Saeed et al. (12). The restriction of movement caused by these PPE components may lead to prolonged task and procedure times. In this study, 79% of the participants reported that it took longer to perform occupational tasks. Supporting this result, a study found that cecal intubation (4.27 vs. 4.88 minutes) and total procedure times (9.08 vs. 11 minutes) were significantly longer with COVID-19 PPE than with standard PPE (29). In this study, 75% of the participants reported limitations in occupational hand skills and 80% in tactile sensation. In an experimental study, double glove use in laparoscopic surgery increased incision errors (20.4 mm^2 vs. 16.9 mm^2) compared with single glove use (30). Unlike our results, in the Yánez Benítez et al. (11) study, 54% of the participants said that their surgical performance was affected, and in the Saeed et al. (12) study, those who stated that the dissection quality was affected were lower, such as 32%. In the study by Alarfaj et al. (20), over half of the surgeons said their instrument use technical skills were unaffected.

Neurocognitive-psychological Effects

Working with these PPEs, especially for prolonged periods, may impair cognitive performance secondary to respiratory, visual, hearing, and thermal effects (8). In the current study, side effects such as decreased concentration, psychological tolerance, and increased headache were reported at high rates. The decrease in tolerance-patience level was significantly higher in physicians than in other surgical team members. This difference was probably related to the fact that the primary responsibility and difficulty in performing a surgical operation was on the surgeons. Supporting our results, a previous study showed that the use of N95 significantly increased headache (59% vs. 15%), attention deficit (50% vs. 15%), and concentration problems (62% vs. 18%) compared with surgical masks (31). In our study, the effect of PPE on decision making/forgetfulness was reported at a low level (40%). In parallel with this result, the effect of PPE on decision making was reported as 48% in one study (11) and 27% in another study (20).

In the study, the participants were also questioned about their training to cope with the problems that may be experienced due to PPE. Most participants stated that they did not receive additional training on strategies to minimize side effects and did not have the opportunity to shower and rest outdoors after surgery. These results suggest that employees were not prepared to reduce the adverse impact of PPE and that the organization could not provide a suitable working environment and rest periods due to the pandemic conditions. Similar to this result, only 50% of the participants reported that they were trained to use this PPE and that training on the appropriate use of this equipment was lacking (19). In the literature, there are suggestions such as consciously controlling the breathing depth rate and focusing on slow-regular breathing to prevent respiratory problems due to masks (8). Users should remember that they should slowly turn their heads right- left/up- down in one axis to reduce the limited field of vision due to all face shields and to prevent dizziness (8). There are suggestions to increase speech intelligibility in the presence of a mask, such as speaking louder, repeating critical commands, reducing simultaneous conversations and additional noise, and using surgical hand signals (8,32). To minimize thermal stress, if there is no risk of hypothermia for the patient, it is recommended to reduce the operating room temperature, use cooling clothing, reduce the time spent working with PPE, or make staff change, adequate fluid intake, and regular measurement of body temperature (8,28). Employees should also be reminded to resist the urge to wipe their sweat.

All these undesirable physical, ergonomic, and cognitive effects may not only decrease the performance of surgical team members but also reduce their compliance with PPE. In this context, it is remarkable that more than half of the participants stated that they avoid wearing these PPEs because of the problems they experienced.

This study is specific in terms of evaluating the side effects of "operating room COVID-19 PPE" on all surgical team members and examining all side effects, not limited to a single effect area. The study's limitations are that it was single-centered, and the results were based on the combination of PPE and the participants' subjective evaluations. In future studies, it is recommended to assess these side effects comparatively in larger sample groups, with physiological parameters, and with different PPEs.

CONCLUSION

PPE, which is used to protect against biological, chemical, thermal, mechanical, and radiological hazards, should have a high protective effect, be easy to put on and take off, and be comfortable. In addition, it should not have side effects that reduce the performance of the users and impair their health.

The results showed that the multi-component, multilayered, heavy, and bulky PPE used in the pandemic is not suitable for intraoperative areas. Operating room COVID-19 PPEs have caused restrictions on many areas such as breathing,

vision, hearing, movement, and technical skills, increased the problems related to thermal stress, and reduced the psychological tolerance levels of the users. It was also found that surgical team members did not know the strategies to cope with these effects and tended to avoid using PPE because of the severity of these adverse effects.

Considering future pandemics, the results of this and similar studies should be taken as a serious warning about areas that require improvement to protect the health and well-being of healthcare workers. studies should be conducted toward designing equipment that will eliminate the identified problems. Therefore, scientists, engineers, and manufacturers must increase their efforts to develop new user-friendly, safe, and effective PPEs using existing technologies. In the design of this new PPE, there is expected to be a balance between the protective effects of this equipment and the serious adverse effects it may have on users.

*This study was produced from the master's thesis of Merve Turgut Eser.

ETHICS

Ethics Committee Approval: Ethical approval was first obtained from the Ministry of Health COVID-19 Scientific Research Evaluation Commission (08.04.2021/decision no: T16-58-10) and then from Biruni University Non-Interventional Research Ethics Committee (decision no: 2021/51-07, date: 21.05.2021) in accordance with the rules during the pandemic period. Permission was obtained from the institution where the study would be conducted (25.11.2021/decision no: 12).

Informed Consent: The purpose of the study was explained to the participants, and their informed consent was obtained.

Authorship Contributions

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

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:72-78
DOI: 10.4274/BMJ.galenos.2024.2023.10-3

Research

Autologous Platelet-rich Plasma Intrauterine Perfusion Improves the Fertility Outcome by Correcting the Thin Endometrium due to Clomiphene Citrate

Otolog Trombosit Açısından Zengin Plazma İntrauterin Perfüzyonu, Klomifen Sitrat Nedeniyle İnce Endometriyumu Düzelterek Doğurganlık Sonucunu İyileştirir

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ABSTRACT

Objective: The primary aim of this study was to investigate the effects of autologous intrauterine platelet-rich plasma (IU-PRP) infusion during ovulation induction with clomiphene citrate (CC) on endometrial thickness (EMT) and clinical pregnancy in patients with polycystic ovary syndrome (PCOS) and thin endometrium. The secondary outcome was to detect possible transformations in oligomenorrheic cycles after PRP.

Methods: This study was conducted on 35 anovulatory PCOS patients aged between 22 and 29 years who applied for infertility treatment. The patients had a thin endometrium in their past history. EMT 7 mm was considered thin endometrium. The diagnosis of PCOS was made according to the revised Rotterdam criteria. A total of 35 patients were divided into two groups according to whether they received PRP or not. Twenty patients received CC plus PRP treatment, whereas 15 patients received CC treatment alone. Patients in both groups were administered CC at a dose of 100 mg/day for 5 days, starting from the 3rd day of progesterone-related withdrawal bleeding. Follicular development and EMT were recorded using transvaginal ultrasonography. In cases with EMT <7 mm, approximately 0.5-1 mL of autologous PRP was infused with the IUI catheter, four days after CC treatment, i.e., on the ninth day of the cycle. EMT was measured and recorded again 3 and 6 days after PRP. Timed intercourse was recommended for cases with a follicle with a mean diameter of at least 16-18 mm. The biochemical and clinical pregnancy rates of both groups were recorded.

Results: Both groups were similar in terms of participant age and body mass index. All participants in the CC plus PRP group were successfully infused with autologous PRP on the ninth day of the cycle. The serum estradiol, testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and LH/FSH ratios of both groups were similar. Biochemical pregnancy and clinical pregnancy rates of the CC plus PRP group were significantly higher than those of the CC alone group ($p<0.03$ and $p<0.02$, respectively). Although clinical pregnancy was detected in 5 individuals in the PRP group (25%), clinical pregnancy was recorded in 2 individuals in the CC alone group (13.3%). There was no significant change in the oligo/anovulatory cycle patterns of patients with and without PRP. EMT values on the sixth (4.96±2.11 mm vs. 4.68±2.47 mm, $p<0.37$) and eighth days were similar between the two groups (5.11±3.10 mm vs. 5.29±3.01 mm, $p<0.51$). Compared with the CC alone group, the EMT values measured both at day 12 (6.34±1.09 mm vs. 5.47±3.90 mm, $p<0.02$) and at day 15 (7.44±2.60 mm vs. 6.23±2.70 mm, $p<0.01$) in the PRP group were found to be significantly higher.

Conclusion: IU-PRP infusion in PCOS patients with thin endometrium who underwent ovulation stimulation with CC significantly increased both EMT and clinical pregnancy rates.

Keywords: PCOS, PRP, autologous, endometrial thickness, clinical pregnancy

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Cite as: Özyurt R, Bulutlar E, Yılmaz MB. Autologous Platelet-rich Plasma Intrauterine Perfusion Improves the Fertility Outcome by Correcting the Thin Endometrium due to Clomiphene Citrate. Med J Bakirkoy 2024;20:72-78

Received: 16.10.2023
Accepted: 06.02.2024

ÖZ

Amaç: Bu çalışmanın temel amacı ince endometriyuma sahip polikistik over sendromu (PKOS) hastalarında ovulasyon indüksiyonu sırasında klomifen sitrat (KS) ile otolog intrauterin trombositten zengin plazma (IU-PRP) infüzyonunun endometriyal kalınlık (EMT) ve klinik gebelik üzerine etkilerini araştırmaktır. İkincil sonuç, PRP sonrası oligomenoreik döngülerdeki olası dönüşümleri tespit etmektir.

Gereç ve Yöntem: Bu çalışma, infertilite tedavisi için başvuran, yaşları 22-29 arasında değişen 35 anovulatuar PKOS hastası üzerinde gerçekleştirildi. Hastaların geçmiş anamnezlerinde ince endometriyum mevcuttu. Endometriyal kalınlığın 7 mm'nin altında olması ince endometriyum olarak kabul edildi. PKOS tanısı revize edilmiş Rotterdam kriterlerine göre konuldu. Toplam 35 hasta PRP alıp almamalarına göre iki gruba ayrıldı. Yirmi hastaya KS artı PRP tedavisi uygulanırken, 15 hastaya yalnızca KS tedavisi uygulandı. Her iki gruptaki hastalara progesterona bağlı çekilme kanamasının 3. gününden itibaren 5 gün süreyle 100 mg/gün dozunda KS verildi. Foliküler gelişim ve endometriyal kalınlık transvajinal ultrasonografi ile kaydedildi. Endometriyal kalınlık <7 mm olan olgulara KS tedavisinden dört gün sonra yani siklusun dokuzuncu gününde IUI kateteri ile yaklaşık 0,5-1 mL otolog PRP infüze edildi. EMT, PRP'den 3 ve 6 gün sonra tekrar ölçüldü ve kaydedildi. Ortalama çapı en az 16-18 mm olan folikül olgularında zamanlı ilişki önerildi. Her iki grubun biyokimyasal ve klinik gebelik oranları kaydedildi.

Bulgular: Her iki grup da katılımcı yaşı ve vücut kitle indeksi açısından benzerdi. KS artı PRP grubundaki tüm katılımcılara döngünün dokuzuncu gününde başarıyla otolog PRP uygulandı. Her iki grubun serum östradiol, testosteron, luteinize edici hormon (LH), folikül stimülan hormon (FSH) ve LH/FSH oranları benzerdi. KS artı PRP grubunun biyokimyasal gebelik ve klinik gebelik oranları, yalnızca KS grubuna göre anlamlı derecede yüksekti (sırasıyla p<0,03 ve p<0,02). PRP grubunda 5 kişide (%25) klinik gebelik tespit edilirken, sadece KS grubunda 2 kişide (%13,3) klinik gebelik kaydedildi. PRP uygulanan ve uygulanmayan hastaların oligo/anovulatuar siklus paternlerinde anlamlı bir değişiklik olmadı. Altıncı gün (4,96±2,11 mm vs. 4,68±2,47 mm, p<0,37) ve sekizinci gündeki EMT değerleri iki grup arasında benzerdi (5,11±3,10 mm vs. 5,29±3,01 mm, p<0,51). Yalnızca KS grubuyla karşılaştırıldığında, EMT değerleri hem 12. günde (6,34±1,09 mm vs. 5,47±3,90 mm, p<0,02) hem de 15. günde (7,44±2,60 mm vs. 6,23±2,70 mm, p<0,01) PRP grubunda anlamlı olarak yüksek bulunmuştur.

Sonuç: KS ile ovulasyon stimülasyonu uygulanan ince endometriyumlu PKOS hastalarında uygulanan IU-PRP infüzyonu hem endometriyal kalınlığı hem de klinik gebelik oranlarını anlamlı derecede artırmaktadır.

Anahtar Kelimeler: PKOS, PRP, otolog, endometriyal kalınlık, klinik gebelik

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common (5-8%) multisystemic endocrine and metabolic disorder in women of reproductive age. Its incidence may be up to 13% according to the population studied (1,2). The presence of at least two of the criteria for oligoovulation and/or anovulation, biochemical or clinical evidence of hyperandrogenism, and polycystic ovarian morphology is sufficient to diagnose PCOS (3). Although most women with PCOS experience oligomenorrhea or amenorrhoea due to anovulatory cycles, both heavy and irregular bleeding can sometimes occur. Although oligo-ovulation is accepted as the main cause of infertility in patients with PCOS, even assisted reproductive techniques do not satisfactorily increase the decreased pregnancy outcomes in patients with PCOS (4). These data suggest that anovulation alone is not responsible for subfertility in PCOS. In connection with the last sentence, increased early pregnancy loss in women with PCOS suggests that parameters such as endometrial dysfunction, obesity, and hyperandrogenemia also affect the fertility status of patients (5).

The PCOS endometrium differs from the healthy endometrium in terms of histomorphology, steroid receptors and coactivators, and receptivity modulators. Therefore, the receptive status of the endometrium is often not suitable for implantation, and endometrial dysfunction in addition to oligoanovulation also contributes to subfertility. In PCOS, progesterone-dependent changes in the endometrium do not occur because of oligo-ovulation or anovulation. Increased androgen-estrogen conversion in peripheral tissue and increased free estradiol and testosterone levels due to hyperinsulinemia may cause unpredictable bleeding in the absence of progesterone. The endometrium of women with PCOS exhibits increased expression of ERα and AR compared with healthy controls (6,7). Differences in receptor expression in PCOS patients may be related to unopposed estrogen elevation. Both circulating portions of estrogen and progesterone and differences in receptor expression prevent the opening of the implantation window in PCOS. On the other hand, the PCOS endometrium fails to produce a physiological response to progesterone, which is an important evidence of progesterone resistance (8). In summary, decreased progesterone levels and receptor expression defects in patients with PCOS lead to the presence of unopposed estrogen, leading to disruption of the normal menstrual cycle and subfertility. Most PCOS patients present with oligo- or amenorrhoea although there is rarely heavy bleeding due to increased estrogen levels.

In the absence of ovulation and progesterone, the endometrium does not undergo secretory transformation and is constantly exposed to estradiol. However, although this rarely leads to excessive bleeding and hyperplasia, in most PCOS cases, menstrual cycle intervals are prolonged and become oligomenorrheic. Although making the cycles ovulatory with medical agents restarts the menstrual cycle,

the picture of amenorrhoea reappears when the treatment is stopped. Platelet-rich plasma (PRP), because of its regenerative potential, is more widely used in reproductive medicine, as it is in every field of medicine (9,10). Although there are studies showing improvement in fertility outcome after the use of intraovarain or intraendometrial PRP in reproductive medicine, most of them are studies with low level of evidence due to both design, PRP standardization, and inhomogeneous participant population (9,10). A thin endometrium is defined as an endometrial thickness (EMT) of 7 mm or less on the day of hCG or embryo transfer (11). The number of studies investigating the effects of PRP application on EMT and fertility outcome in an infertile patient population is quite limited. Although EMT varies in different phenotypes of PCOS, the incidence of a thin endometrium is higher in women with PCOS where hyperandrogenemia is dominant (12). In patients who have ovulation induction with clomiphene, the EMT is further thinned. The primary aim of this study was to investigate the effects of autologous intrauterine PRP (IU-PRP) application during ovulation induction with clomiphene citrate (CC) on EMT and fertility outcomes in patients with PCOS with thin endometrium (<7 mm) resistant to adjuvant treatments. The secondary outcome was to detect possible transformations in oligomenorrheic cycles after PRP.

METHODS

This study was conducted on 35 anovulatory PCOS patients, aged between 22 and 29 years, who applied to our gynecology and obstetrics clinic for infertility treatment. The patients had a history of a thin endometrium in their previous treatment history. EMT 7 mm was considered thin endometrium. The diagnosis of PCOS was made according to the revised Rotterdam criteria. Those who met at least two of the criteria for amenorrhoea/oligomenorrhea with chronic anovulation, clinical and/or biochemical evidence of hyperandrogenism, and ultrasonographic appearance of PCOS were accepted as having PCOS. The diagnosis of anovulation was confirmed by the patient's history and hormonal measurements. From the anamnesis of the patients, it was noted that adjuvant treatments, such as oral or patch-form estrogen supplementation, low-dose aspirin, and vaginal sildenafil, were applied to increase the EMT, but they did not benefit.

It was explained to the patients that PRP treatment is not a routine practice for the treatment of infertility and for increasing the thickness of the endometrium. It was emphasized that there were studies that reported positive results in EMT and fertility outcome after PRP, and studies that reported no benefit. The study was initiated after obtaining permission from the Clinical Research Ethics Committee of Zeynep Kamil Gynecology and Pediatrics Training and Research Hospital (decision no: 14, date: 11.01.2023). In addition, an informed volunteer consent form was obtained from all patients regarding the procedure to be performed. Twenty patients who accepted PRP and 15 patients who did not were divided into two groups and included in the CC treatment protocol. CC (Serophene, Serono, Roma, Italy) was administered to the patients in both groups for 5 days, starting from the 3rd day of progesterone-induced withdrawal bleeding at a dose of 100 mg/day. The patients were called for control on the sixth and eighth days of treatment. Follicular development and EMT were recorded using transvaginal ultrasonography (TV-USG). IU-PRP infusion was planned for cases with EMT <7 mm on the eighth day of follow-up. Endometrial PRP infusion was applied to the patients in the PRP group, four days after the 5-day CC treatment, i.e., on the ninth day of the cycle. In the CC alone group, PRP was not applied. In the TV-USG examination after PRP, both EMT and follicle diameter were measured. Timed intercourse was recommended for cases with a follicle with a mean diameter of at least 16-18 mm. The biochemical and clinical pregnancy rates of both groups were recorded. Clinical pregnancy was defined by the presence of an intrauterine gestational sac confirmed by TV-USG.

Autologous PRP Preparation and Endometrial Infusion

Autologous PRP was prepared from each patient following a two-stage centrifugation using autologous blood. On the 9th day of ovulation stimulation with CC, 15 mL of venous blood was drawn into a syringe containing acid citrate A anticoagulant solution and immediately centrifuged at 300 rpm for 5 min. In the first procedure, red blood cells were removed from the medium. Subsequently, the plasma was centrifuged again at 700 rpm for 17 min and autologous PRP was obtained. Platelet activation was achieved by adding $CaCl_2$ and human thrombin. Activated PRP was finally centrifuged at 3000 rpm for 20 min, and the supernatant was collected. The collected pellets contained erythrocyst- and leukocyte-free PRP. Approximately 0.5-1 mL of PRP was infused with the IUI catheter into the endometrial cavity of the patient in the lithotomy position, accompanied by ultrasonography. No anesthesia or sedation was used during PRP infusion (13). EMT was measured and recorded again 3 and 6 days after PRP infusion.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences software 18.0 for Windows package

software (SPSS). Normality of data was examined using the Kolmogorov-Smirnov test. Mean values were calculated for data showing abnormal distribution and compared with the non-parametric Mann-Whitney U test. Categorical data are described either by number of cases or percentages. Categorical variables were presented as percentage values and compared using the chi-square/Fisher's Exact test. Continuous variables were analyzed using the Mann-Whitney U test. The results are presented as mean ± standard deviation. For all tests, p-value <0.05 was considered statistically significant.

RESULTS

Demographic, hormonal, and reproductive parameters of the CC plus PRP and CC alone groups are presented in Table 1. Both groups were similar in terms of participant age and body mass index. All participants in the CC plus PRP group were successfully infused with autologous PRP on the ninth day of the cycle. No PRP application was applied to the CC alone group. Serum estradiol, testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and LH/FSH ratios of both groups were similar. CC doses and administration times were similar in both groups. Biochemical pregnancy and clinical pregnancy rates of the CC plus PRP group were significantly higher than those of the CC alone group (p<0.03 and p<0.02, respectively). Although clinical pregnancy was detected in 5 individuals in the PRP group (25%), clinical pregnancy was recorded in 2 individuals in the CC alone group (13.3%). No significant change was observed in the oligo/anovulatory cycle patterns of patients with and without PRP.

A detailed presentation of the change in the EMT values of the PRP and CC alone groups is shown in Table 2. EMT values on the sixth (4.96±2.11 mm vs. 4.68±2.47 mm, p<0.37) and eighth days were similar between the two groups (5.11±3.10 mm vs. 5.29±3.01 mm, p<0.51). EMT was not evaluated because PRP was performed on the ninth day. Compared with the CC alone group, the EMT values measured both at day 12 (6.34±1.09 mm vs. 5.47±3.90 mm, p<0.02) and at day 15 (7.44±2.60 mm vs. 6.23±2.70 mm, p<0.01) in the PRP group were found to be significantly higher.

DISCUSSION

Implantation in mammals is a very complex process that requires coordinated cross-talk between the blastocyst and endometrium through molecular pathways. Before implantation, the endometrium must be exposed to adequate levels of estrogen and progesterone to make it susceptible to blastocyst invasion. Ovarain sex steroids exert their effects on the endometrial epithelium and decidualized stromal cells through mediator molecules and immune cells. Peripheral blood-derived immune

Table 1. Comparison of demographic and fertility outcome parameters of PCOS patients in CC plus PRP and CC alone groups

Parameters	CC plus PRP	CC alone	p-values*
N	20	15	-
Age (yrs)	26.2±5.43	25.4±4.30	0.462
BMI (kg/m^2)	25.3±5.44	25.8±4.98	0.351
IU-PRP, n (%)	20 (100%)	0 (0)	NA
Total testosterone (ng/dL)	41.7±7.88	43.6±5.01	0.339
Estradiol (pg/mL)	49.3±5.49	50.3±7.20	0.544
LH (mIU/mL)	8.32±2.09	9.13±3.76	0.701
FSH (mIU/mL)	5.67±2.91	5.67±2.10	0.673
LH/FSH ratio	1.46	1.61	0.09
CC dose and duration	100 mg/day, five days	100 mg/day, five days	NA
Endometrila thickness on 6th day of CC treatment	4.96±2.11	4.68±2.47	0.729
PRP time	9th day of the cycle	No PRP	NA
Cycle pattern change after PRP	No (anovulatory)	No (anovulatory)	NA
Biochemical pregnancy, n (%)	6 (30%)	3 (20%)	0.03
Clinical pregnancy, n (%)	5 (25%)	2 (13.3%)	0.02

Data presented as means ± standard deviation. PCOS: Polycystic ovary syndrome, BMI: Body mass index, IU-PRP: Intrauterine platelet rich plasma, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, CC: Clomiphene citrate, *p<0.05

Table 2. Comparison of endometrial thickness values of CC alone and CC plus PRP groups

CC plus PRP					CC alone (without PRP)				
6th*	8thμ	9th	12th#	15thΣ	6th	8th	9th	12th	15th
4.96±2.11	5.11±3.10	IU-PRP was applied	6.34±1.09 3rd day of PRP	7.44±2.60 6th day of PRP	4.68±2.47	5.29±3.01	No IU-PRP	5.47±3.90	6.23±2.70

*The 6th day EMT value of the PRP group was similar to the CC alone group (p<0.37). μThe 8th day EMT value of the PRP group was similar to the CC alone group (p<0.51). #The 12th day EMT value of the PRP group was significantly higher than the CC alone group (p<0.02). ΣThe 15th day EMT value of PRP group was significantly higher than CC alone group (p<0.01).
CC: Clomiphene citrate, IU-PRP: Intrauterine platelet rich plasma, EMT: Endometrial thickness

cells, leukocytes, and platelets mediate the effects of estrogen and progesterone. These effects are mediated by paracrine mechanisms and prepare the endometrium for implantation by regulating the release of growth factors and cytokines. This multi-molecular pathway results in endometrial decidualization, proliferation in epithelial and stromal cells, increased synthesis of receptivity modulators, and provision of an end-point receptive endometrium (14,15). However, pre-implantation reactions at the histomorphological, molecular, and genomic levels in the endometrium can keep the endometrium in the receptive phase within a period of approximately 6 days. Although the endometrium exhibits these cyclic changes regularly in most women of reproductive age, implantation failure remains the most frequent and serious problem in assisted reproductive techniques (16). Therefore, it is critical to determine whether the endometrium is in the receptive phase before implantation and to choose a treatment approach accordingly. Endometrial receptivity tests developed for this purpose in the last decade have not been routinely used because of their invasive nature and low sensitivity and specificity. EMT measurement with ultrasonography, an old but effective marker, remains the only non-invasive and reproducible method available to evaluate the receptive endometrium.

In the ultrasonographic evaluation of the endometrium, a prediction can be made about endometrial receptivity by evaluating echogenicity and thickness. In addition to the hypoechogenic appearance in sonographic evaluations performed on the day of ovulation or hCG, the detection of an EMT of 7 mm or more strongly supports the presence of a receptive endometrium (17). However, pregnancy has also been reported in hyperechogenic endometriums with a thickness of approximately 4 mm (18). Although the presence of high EMT is not always compatible with receptivity status, the chance of pregnancy is lower in women with thin endometrium. A value of <7 mm, measured on the day of ovulation or hCG, is considered as thin endometrium and means that the success rate for implantation is low (11). PCOS is an endocrine cause of subfertility with ovulatory dysfunction, receptivity defect, and thin endometrial development. Although EMT is normal in some PCOS phenotypes, a thin endometrium is more common, especially in PCOS phenotypes with hyperandrogenemia (12). In particular, in cycles using CC for ovulation induction, EMT is seen to be more thinned (19). Although EMT has been increased with methods such as sildenafil citrate, aspirin, and mechanical endometrial injury, the results are heterogeneous (20). There is no study design using PRP to increase EMT in patients with PCOS using CC for ovulation stimulation. This is the first clinical study investigating the effects of PRP on EMT and fertility outcome in patients with PCOS who could not conceive due to thin endometrium in previous cycles. EMT values of both groups were similar before PRP application. We found that EMT measurements performed 3 and 6 days after IU-PRP application increased significantly. Similarly, both biochemical and clinical pregnancy rates in the PRP group increased significantly compared with the control group. Because the oligo-anovulatory cycle patterns of both groups did not change, we can argue that PRP has a phase-specific effect and has no long-term and clear effect on ovulatory functions.

One of the possible reasons for the significant increase in EMT and clinical pregnancy rates in PCOS patients administered PRP compared with control PCOS patients is the regenerative effects of PRP on the endometrium. PRP is a platelet product that is free from leukocytes and erythrocytes. In addition to many growth factors in PRP, anti-inflammatory and pro-inflammatory molecules create a suitable microenvironment for implantation by regulating decidualization and redox reactions (13,21). In animal studies, treatment of mating-induced endometrial inflammation with PRP infusion supports the immunomodulatory and anti-inflammatory role of PRP (22). The decrease in endometrial development and blood flow due to CC may have been caused by the intense cytokine and growth factor

content of PRP. Increased expression of receptivity genes in PRP-treated animals suggests that a similar effect may occur in patients with PCOS treated with PRP (19,23). The presence of intense interleukin, tumour necrosis factor-α, and interferon-α in PRP may regulate clomiphene-induced endometrial developmental defects and decreased blood flow. The fact that an increase in both EMT and endometrial vascularization was reported in Power Doppler analysis studies performed after PRP is an important evidence of the net effect of PRP on vascular demodulation (24).

In addition to studies reporting improvement in EMT and fertility outcome after IU-autologous PRP infusion (10), there are also studies reporting that PRP has no effect on EMT and implantation (21,25). Although the regenerative effect of PRP has been demonstrated in a murine model of endometrial damage, no human studies have investigated the effect of PRP on receptivity modulators (26). Our study is clinically important in terms of presenting the first clinical data reporting that clomiphene-induced thin endometrial growth is improved with PRP. However, the low number of cases and the application of PRP once is an important handicap. Multiple infusions of autologous PRP may reveal the relationship between EMT and clinical pregnancy rates more clearly. The lack of standardization of the PRP preparation methods may be the main reason for the difference in the results. Applying the buffy coat obtained using only two-stage centrifugation to the endometrial cavity is not a real PRP. Because leukocytes are not removed from the environment in such infusions, we cannot determine whether the effect on the endometrium is due to leukocytes or cytokines. Similarly, the administration of PRP without activation limits its effectiveness. Activated PRP infusion should also be performed quickly and without release of platelet contents. In our study, activated PRP was infused as soon as it was prepared. The fact that the participants were PCOS patients using CC and serial EMT measurements is critical in determining PRP efficacy.

CONCLUSION

In conclusion, autologous IU-PRP increases both EMT and clinical pregnancy rates in patients with PCOS with thin endometrium due to CC. However, the application of IU-PRP did not cause a significant change in the oligo/anovulatory cycle patterns of the patients. We can make a clearer judgment about the effectiveness of PRP in PCOS using case-controlled studies with multiple PRP applications.

Acknowledgment: We thank the participants, anonymous reviewers, and section editor for their excellent criticism of the article.

ETHICS

Ethics Committee Approval: The study was initiated after obtaining permission from the Clinical Research Ethics Committee of Zeynep Kamil Gynecology and Pediatrics Training and Research Hospital (decision no: 14, date: 11.01.2023).

Informed Consent: In addition, an informed volunteer consent form was obtained from all patients regarding the procedure to be performed.

Authorship Contributions

Surgical and Medical Practices: R.Ö., E.B., Concept: R.Ö., E.B., M.B.Y., Design: R.Ö., E.B., Data Collection or Processing: R.Ö., E.B., M.B.Y., Analysis or Interpretation: R.Ö., E.B., Literature Search: R.Ö., E.B., M.B.Y., Writing: R.Ö., E.B.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:79-84
DOI: 10.4274/BMJ.galenos.2023.2022.1-13

Research

Comparison of Two Different Techniques in Macular Hole Surgery: 12-month Results of Clinical Practice

Makula Deliği Cerrahisinde İki Farklı Tekniğin Karşılaştırılması: 12 Aylık Klinik Uygulama Sonuçları

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ABSTRACT

Objective: To examine and compare the outcomes of complete internal limiting membrane (ILM) peeling and inverted ILM flap techniques in patients with idiopathic full-thickness macular holes.

Methods: Sixteen eyes of 16 patients operated on with the standard complete ILM peeling technique were included in group 1, and 12 eyes of 12 patients who had vitrectomy with the inverted ILM flap technique were included in group 2. Baseline and postoperative month 3, 6, and 12 best-corrected visual acuity (BCVA) data and spectral-domain optical coherence tomography (OCT) images were examined. Macular hole closure, foveal contour formation, ellipsoid zone integrity on OCT images, and BCVA improvement were analyzed.

Results: The macular hole closure rate was 62.5% in group 1 and 91.7% in group 2, but the difference between the groups was not significant (p=0.18). An improvement was seen in BCVA after surgery in group 1, but the difference was not significant compared with the pre-operative BCVA (p=0.28). In group 2, the improvement from baseline BCVA at postoperative month 12 was significant (p=0.016).

Conclusion: The macular hole closure rate was over 90% in the eyes that were operated on with the inverted ILM flap technique. BCVA was improved after surgery in both groups, and a significant improvement from baseline BCVA was seen at postoperative month 12 with the inverted ILM flap technique.

Keywords: Internal limiting membrane peeling, inverted internal limiting membrane flap, macular hole, optical coherence tomography, visual improvement

ÖZ

Amaç: İdiyopatik tam kat makula deliği olan bireylerde tam iç limitan membran (İLM) soyulması ve ters İLM flep tekniklerinin sonuçlarını incelemek ve karşılaştırmaktır.

Gereç ve Yöntem: Standart İLM soyma tekniği ile ameliyat edilen 16 hastanın 16 gözü grup 1'e, ters İLM flep tekniği ile vitrektomi uygulanan 12 hastanın 12 gözü grup 2'ye alındı. Başlangıç ve ameliyat sonrası 3. ay, 6. ay ve 12. ay en iyi düzeltilmiş görme keskinliği (EİDGK) verileri ve spektral-domain optik koherens tomografi (OKT) görüntüleri incelendi. Makula deliği kapanması, foveal kontur oluşumu, OKT görüntülerinde elipsoid zon bütünlüğü ve EİDGK'deki iyileşme analiz edildi.

Bulgular: Makula deliği kapanma oranı grup 1'de %62,5 ve grup 2'de %91,7 idi; ancak gruplar arasındaki fark anlamlı değildi (p=0,18). Grup 1'de cerrahi sonrası EİDGK'de iyileşme görüldü ancak ameliyat öncesi EİDGK ile karşılaştırıldığında fark anlamlı değildi (p=0,28). Grup 2'de, postoperatif 12. ayda, başlangıca göre EİDGK'deki iyileşme anlamlıydı (p=0,016).

Sonuç: Ters İLM flep tekniği ile opere edilen gözlerde makula deliği kapanma oranı %90'ın üzerinde idi. Ameliyattan sonra her iki grupta da EİDGK düzeldi ve ters İLM flep tekniği ile postoperatif 12. ayda başlangıca göre EİDGK'de anlamlı bir iyileşme görüldü.

Anahtar Kelimeler: İnternal limitan membran soyma, ters internal limitan membran flebi, makula deliği, optik koherens tomografi, görsel iyileşme

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Cite as: Akarsu Açar ÖP, Sonbahar O, Zırtıloğlu S, Onur İU. Comparison of Two Different Techniques in Macular Hole Surgery: 12-month Results of Clinical Practice. Med J Bakirkoy 2024;20:79-84

Received: 30.01.2022
Accepted: 04.04.2023

INTRODUCTION

Full-thickness macular hole (FTMH) is a defect of retinal tissue on the macula that especially affects the foveola and fovea (1). Macular holes are usually idiopathic, and women in the 7th and 8th decades are more commonly affected (2-4). Tangential or anteroposterior traction of the posterior cortical vitreous on the fovea is accepted to be the cause of idiopathic FTMHs (1,3-6).

In 1991, Kelly and Wendel (7) used modern vitrectomy techniques for the treatment of idiopathic FTMH and reported that the macular holes closed in 58% of their patients. Since then, with advances in surgery such as the internal limiting membrane (ILM) peeling technique during vitrectomy, the macular hole closure rate has increased to over 90% (8-13).

Michalewska et al. (14) showed that the results obtained with the inverted ILM flap technique in large macular holes (≥400 µm) were more satisfactory than those obtained with the complete ILM peeling technique. With the inverted ILM flap technique, covering the macular hole with the inverted ILM flap allowed early closure of the hole. Thereafter, they also reported nearly 100% anatomical success in myopic macular holes using the same technique (15).

Functional improvement was associated with the integrity of the ellipsoid zone (EZ) and the external limiting membrane (ELM) (16-20). Optical coherence tomography (OCT) has been found useful in the detailed analysis of macular holes before surgery and in the evaluation of both anatomical closure and integrity of the retinal layers that affect the visual prognosis after surgery (16).

In this study, we aimed to examine and compare the surgical and functional results of these two techniques in eyes with idiopathic FTMHs.

METHODS

We performed this retrospective, observational study at University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ophthalmology Clinic after obtaining approval from the Clinical Researches Ethics Committee (decision no: 2020-02-15, date: 20.01.2020). The study adhered to the tenets of the Declaration of Helsinki and we obtained informed consent from all participants.

The records of the patients who underwent surgery with the diagnosis of idiopathic FTMH between January 2015 and January 2021 were retrospectively evaluated. FTMHs with retinal detachment, patients with lamellar, traumatic, or myopic macular holes, history of uveitis, glaucoma, or any other retinal diseases, previous ocular surgery except phacoemulsification, and less than 12 months follow-up were excluded.

The patients were examined in two groups. Group 1 included patients who were operated on with the standard complete ILM peeling technique; group 2 included patients who had pars plana vitrectomy (PPV) using the temporal inverted ILM flap technique.

Age, gender, operated eye, axial length of the eye, lens status, and detailed ophthalmological examination data of both groups were obtained from patient records. Baseline and postoperative month 3, 6, and 12 best-corrected visual acuity (BCVA) data were recorded, and the logarithm of minimal angle of resolution (logMAR) values were used for statistical analysis.

Spectral-domain OCT device (RTVue-100, Optovue Inc., Fremont, US) images in the patient records were analyzed at baseline and at postoperative months 3, 6, and 12. The minimum macular hole diameter was measured from the baseline OCT image. Postoperative month 3, 6, and 12 OCT images were examined to analyze macular hole closure, foveal contour formation, and EZ integrity (Figure 1).

The same experienced vitreoretinal surgeon (U.O.) performed a standard 3-port 23-gauge PPV. Patients with cataracts underwent combined PPV, phacoemulsification, and intraocular lens implantation surgery. In both groups, a mixture of brilliant blue G and trypan blue (Membrane Blue Dual, DORC, Netherlands) was used to stain ILM and then aspirated with a backflush needle. The epiretinal membranes were peeled away before ILM.

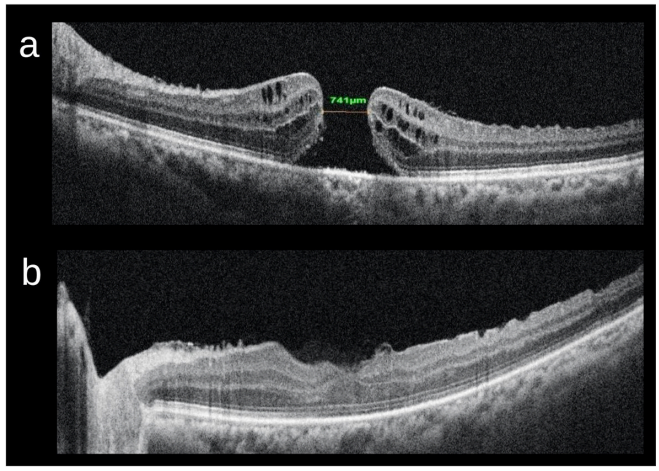

Figure 1. a) Preoperative spectral-domain optical coherence tomography (SD-OCT) image of a patient with a minimum 741 µm macular hole diameter. b) Postoperative month 12 SD-OCT image of the same patient who was operated on with the inverted internal limiting membrane flap technique. Macular hole was closed. Foveal contour formation and the integrity of both the external limiting membrane and the ellipsoid zone could be seen

In the ILM peeling group, ILM was removed completely by approximately 2 disk diameters around the macular hole in a circular pattern using ILM peeling forceps. In group 2, ILM peeling was performed in a manner similar to the study of Michalewska et al. (14). After inverting the ILM flap, the macular hole was covered with this, and an air-fluid exchange and then a 20% SF6 gas-air exchange were performed. After surgery, maintaining a prone position for at least three days was advised to all subjects.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 21.0 (SPSS, Inc, Chicago, IL, USA). The distribution of the data was evaluated using the Kolmogorov-Smirnov test. Parametric data were analyzed using Student's t-test and One-Way repeated ANOVA. Analysis of the non-parametric data and comparison of the groups were performed using the Mann-Whitney U test. The baseline characteristics of age between the groups were compared using an independent t-test, and gender was compared using the chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

Twenty-eight patients who underwent surgery for FTMH were included in this retrospective and observational study. There were 16 eyes of 16 patients that were operated with the standard complete ILM peeling technique in group 1 and 12 eyes of 12 patients that were operated with the inverted ILM flap technique in group 2. The baseline characteristics of patients in both groups are given in Table 1.

Phacovitrectomy was performed in 3 eyes (18.75%) in group 1 because of lens opacification in the baseline examination, and vitrectomy alone was performed in all eyes in group 2. No major complications were seen in both surgical procedures, but 1 eye in group 1 and 3 eyes in group 2 required cataract surgery during the follow-up. In all 4 eyes, cataract surgery was performed 10 months after vitrectomy, and no complications were observed.

The macular hole closure rate was 68.75% at postoperative month 3 and 56.25% at postoperative month 6 in group 1, whereas it was 91.7% at postoperative months 3 and 6 in group 2. The foveal contour formation rate was 68.75% at postoperative month 3 and 56.25% at postoperative month 6 in group 1, whereas it was 91.7% at postoperative month 3 and 83.3% at postoperative month 6 in group 2. Restoration of the EZ rate was 50% at postoperative month 3 and 43.75% at postoperative month 6 in group 1, whereas it was 58.3% at postoperative month 3 and 41.7% at postoperative month 6 in group 2. Surgical and functional results of the groups at postoperative month 12 are given in Table 2.

BCVA was 0.98±0.46 logMAR units at postoperative month 3 and 0.86±0.50 logMAR units at postoperative month 6 in group 1, whereas it was 0.80±0.35 logMAR units at postoperative month 3 and 0.78±0.37 logMAR units at postoperative month 6 in group 2. An improvement was seen in BCVA after surgery in group 1, but the difference was not significant compared with the pre-operative BCVA (p=0.28). In group 2, the improvement from baseline BCVA at postoperative month 12 was found significant (p=0.016). Figure 2 shows the changes in BCVA (logMAR) from baseline to 12 months postoperatively for both groups.

DISCUSSION

The results of our study showed a macular hole closure rate of over 90% in patients who had vitrectomy with the

Table 1. Baseline characteristics

Variables	Group 1 (n=16) ILM peeling technique	Group 2 (n=12) Inverted ILM flap technique	p-value
Age (mean ± SD)	69.2±4.8	67.2±5.3	0.29[t]
Gender (female/male)	11/5	6/6	0.44[x²*]
Eye (right/left)	10/6	6/6	0.78[x²**]
Lens (phakic/pseudophakic)	11/5	8/4	0.90[x²]
Axial length (mm) (mean ± SD)	23.20±0.69	23.28±0.84	0.48[m]
Minimum hole diameter (µm) (mean ± SD)	468.63±181.97	520.67±170.39	0.48[m]
Foveoschisis (n)	16	11	0.42[x²]
Preoperative BCVA (logMAR) (mean ± SD)	1.02±0.42	1.02±0.38	0.43[m]

[t]: Independent t-test, [x²]: Chi-square test, [x²*]: Chi-square test (Fisher's Exact test), [x²**]: Chi-square test (Yates' correection), [m]: Mann-Whitney U test
ILM: Internal limiting membrane, SD: Standard deviation, BCVA: Best-corrected visual acuity, logMAR: Logarithm of minimal angle of resolution

Table 2. Results of the groups at postoperative month 12

Variables	Group 1 (n=16) ILM peeling technique	Group 2 (n=12) Inverted ILM flap technique	p-value
Hole closure rate (%)	62.5%	91.7%	0.18[x²]
Foveal contour formation (%)	68.8%	91.7%	0.35[x²]
Restoration of ellipsoid zone (%)	43.8%	58.3%	0.70[x²]
Mean BCVA logMAR (mean ± SD) /median	0.84±0.53	0.78±0.47/0.70	0.23[m]

[x²]: Chi-square test; [m]: Mann-Whitney U test
ILM: Internal limiting membrane, BCVA: Best-corrected visual acuity, SD: Standard deviation, logMAR: Logarithm of minimal angle of resolution

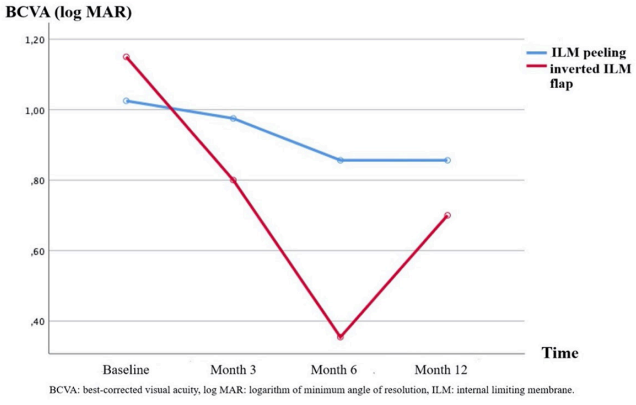

Figure 2. Changes in best-corrected visual acuity (BCVA) from baseline to 12 months postoperatively for both groups. An improvement was seen in BCVA after surgery in both groups. In group 1, the difference in BCVA from baseline to postoperative month 12 was not significant (p=0.28). The improvement in BCVA from baseline to postoperative month 12 was found significant in group 2 (p=0.016)

inverted ILM flap technique, whereas it was 62.5% in patients who underwent vitrectomy with the complete ILM peeling technique. Michalewska et al. (15) were the first to use the inverted ILM flap technique in patients with large idiopathic FTMHs and reported a 98% macular hole closure rate while it was 88% in patients who had surgery with the standard complete ILM peeling technique. In addition, recent studies have shown that the inverted ILM flap technique is more efficient than the complete ILM peeling technique, especially in myopic holes and large (>400 µm) FTMHs (14,21-23). In their retrospective study, Rizzo et al. (21) examined the results of two techniques involving large patient groups and found that the anatomical success rate of the inverted ILM flap technique was 95.6% and that of the ILM peeling technique was 78.6% in large macular holes (p=0.001). They also reported an 88.4% anatomical success rate with the inverted ILM flap technique and a 38.9% rate with the ILM peeling technique in patients with myopic holes (p=0.001). In our study, the mean axial length of patients was 23.20±0.69 mm in group 1 and 23.28±0.84 mm in group 2. The minimum baseline hole diameter was 468.63±181.97 µm in in patients who underwent surgery with the complete ILM peeling technique and 520.67±170.39 µm in in patients who underwent surgery with the inverted ILM flap technique. Although it appeared larger in the inverted ILM flap technique group, the difference in the baseline minimum macular hole diameter between the groups was not significant (p=0.48). Despite having a higher macular hole closure rate with the inverted ILM flap technique (91.7%), the difference from the complete ILM peeling technique (62.5%) was not significant (p=0.18). We suggest that the difference may be significant with larger groups, as in the study by Rizzo et al. (21).

Previous studies have shown that the evaluation of the integrity of EZ, ELM, and outer segments of foveal cone photoreceptors on OCT images is important in the determination of visual recovery after macular hole surgery (17,20,24). In addition, it was suggested that the restoration of the foveal retinal tissues might continue over time, and because of this process, postoperative BCVA might improve during the follow-up period (25). Ooka et al. (20) studied 43 eyes of 43 patients at months 1, 3 and 6 after macular hole surgery and found that the correlation of BCVA and foveal sensitivity with defects on both EZ and ELM were significant at all postoperative exams.

It is known that the proliferation of Müller cells is activated by the inverted ILM flap tissue. The restoration of the outer retinal tissues was induced by the activated Müller cells, and as a result, both the macular hole closure rate and the final BCVA improved (14,26). A meta-analysis by Shen et al. (23) comparing the efficacy of two surgical techniques in large macular holes showed a significant improvement in BCVA at postoperative month 3 in patients who had vitrectomy with the inverted ILM flap technique compared with patients who underwent complete ILM peeling surgery (p<0.00001). However, the difference in BCVA between the groups was not significant during the longer follow-up period. Silva et al. (27) reported the 8-year experience results of their retrospective study analyzing EZ recovery and improvement in BCVA after macular hole surgery with the inverted ILM technique. They showed that 80% of their patients had ≥0.3

logMAR units of BCVA improvement, and the final BCVA in the patients with closed holes after surgery was better in eyes that had good EZ integrity than in eyes with EZ defects (p=0.003). In our study, the foveal contour formation rate at postoperative month 12 was higher (91.7%) in subjects who underwent vitrectomy with the inverted ILM flap technique than in those who underwent vitrectomy with the standard ILM peeling technique (68.8%). Restoration of the EZ was seen in 58.3% of the subjects who underwent surgery with the inverted ILM flap technique and in 43.8% of the eyes who underwent surgery with the standard ILM peeling technique at postoperative month 12. BCVA improved in both groups after surgery, and the final BCVA was 0.84±0.53 logMAR units in group 1 and it was 0.78±0.47 logMAR units in group 2. We believe that despite the improvement, these relatively low final visual acuity results might be related to the relatively low EZ restoration rates. The improvement from baseline to 12^{th} months after surgery was only significant in the inverted ILM flap technique group (p=0.016). We suggest that the small sample size of our study could affect these results and that different results may be obtained with larger groups. In addition, we think that the improvement in BCVA may continue over time by the restoration of the EZ, as shown in previous reports (14,26).

Cataract progression can be seen after vitreoretinal surgery, and combined phacovitrectomy can be considered in phakic patients (27). In this study, cataract surgery was required for one eye in group 1 and three eyes in group 2 during the follow-up period after vitrectomy.

This study had several limitations. First, this was a retrospective study, and the sample size of the groups was small. This could affect the power of our results; therefore, a prospective study including larger patient groups is necessary to confirm the findings of this study. Another limitation is that the 12-month follow-up time could be inadequate and more informative results could be obtained after a longer follow-up period. Lastly, phacovitrectomy was performed for only 3 eyes in group 1, and in the follow-up period, cataract surgery was needed for four eyes. Considering that combined surgery for the phakic eyes could affect the postoperative recovery process.

CONCLUSION

In conclusion, both surgical techniques could be performed for treating FTMHs without any complications. Similar to the previous studies, the macular hole closure rate was over 90% in the eyes that were operated on with the inverted ILM flap technique. BCVA was improved after surgery in both groups, and a significant improvement from baseline BCVA was seen at postoperative month 12 with the inverted ILM flap technique. OCT could be accepted as a useful device for both diagnosis and follow-up of patients and could provide predictive data about the anatomical and functional healing process.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Researches Ethics Committee (decision no: 2020-02-15, date: 20.01.2020).

Informed Consent: We obtained informed consent from all participants.

Authorship Contributions

Surgical and Medical Practices: Ö.P.A.A., İ.U.O., Concept: Ö.P.A.A., O.S., İ.U.O., Design: Ö.P.A.A., O.S., İ.U.O., Data Collection or Processing: O.S., S.Z., Analysis or Interpretation: Ö.P.A.A., S.Z., Literature Search: Ö.P.A.A., Writing: Ö.P.A.A.

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

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

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Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:85-91
DOI: 10.4274/BMJ.galenos.2023.2022.12-1

Research

Is the Internet Sufficient and Trustworthy for Torticollis Parents? Evaluation of Online Information for Torticollis

Tortikollis Ebeveynleri için İnternet Yeterli ve Güvenilir mi? Tortikollis için Çevrimiçi Bilgilerin Değerlendirilmesi

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ABSTRACT

Objective: The purpose of this study was to assess the readability and quality of torticollis-related web content.

Methods: The top 3 browsers were determined. The 2 reviewers structured their websites according to type. Each one's quality was determined based on whether or not it conformed to the Health On the Net (HON) code as well as using some scoring tools such as the DISCERN score, Journal of American Medical Association (JAMA) benchmark, and Global Quality score (GQS). To evaluate readability, the Flesch-Kincaid grade level (FKGL) was applied.

Results: Sixty websites were identified. The categories were as follows: 12 (20%) academic, 26 (43.3%) medical, 13 (21.7%) physician, and 9 (15%) commercial. The DISCERN, JAMA, GQS, FKGL, and Torticollis-Specific Content (TSC) scores of the academic category were significantly higher than those of the other categories. Websites with a HON code had considerably higher DISCERN, JAMA, GQS, and TSC scores than those without it ($p<0.05$).

Conclusion: Most material on the websites reviewed in this study was of low quality. Despite the higher quality of academic resources, the material was challenging to comprehend. The current study can aid in the evaluation of information that may be important for preserving equilibrium in patient-doctor relationships.

Keywords: Torticollis, internet, search engine, information

ÖZ

Amaç: Bu çalışmanın amacı, tortikolis ile ilgili çevrimiçi bilgilerin içeriğini ve okunabilirliğini değerlendirmektir.

Gereç ve Yöntem: En sık kullanılan 3 internet tarayıcısı belirlendi. İki yorumcu, web sitelerini türe göre kategorize etti. Her birinin kalitesi, Health On the Net (HON) kodunun varlığına ve yokluğuna göre ve ayrıca DISCERN puanı, Amerikan Tıp Derneği Dergisi (JAMA) kıyaslaması ve Küresel Kalite skoru (GQS) dahil iyi bilinen puanlama sistemleri kullanılarak değerlendirildi. Okunabilirliği değerlendirmek için Flesch-Kincaid derece düzeyi (FKGL) kullanıldı.

Bulgular: Altmış web sitesi belirlendi. Kategorilerin dağılımı 12 (%20) akademik, 26 (%43,3) medikal, 13 (%21,7) hekim, 9 (%15) reklam şeklindeydi. Akademik kategorisinin DISCERN, JAMA, GQS, FKGL ve Torticollis-Specific Content (TSC) puanları diğer kategorilere göre anlamlı olarak yüksek bulunmuştur. HON kodu olan web sitelerinin DISCERN, JAMA, GQS ve TSC puan değerleri, HON kodu olmayanlara göre anlamlı derecede yüksekti ($p<0,05$).

Sonuç: Bu çalışmada incelenen web sitelerindeki materyallerin çoğu düşük kalitedeydi. Akademik kaynakların daha yüksek kalitesine rağmen, materyallerini anlamak zordu. Mevcut çalışma, hasta-doktor ilişkilerinde dengenin korunması için önemli olabilecek bilgilerin değerlendirilmesine yardımcı olabilir.

Anahtar Kelimeler: Tortikollis, internet, arama motoru, bilgi

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Cite as: Yalın M, Key S. Is the Internet Sufficient and Trustworthy for Torticollis Parents? Evaluation of Online Information for Torticollis. Med J Bakirkoy 2024;20:85-91

Received: 09.12.2022
Accepted: 12.06.2023

INTRODUCTION

Even parents of children and adolescents use the Internet as a crucial source of knowledge and a platform for buying and selling personal experiences. For most countries, the internet serves as the primary way of sharing health information (1). Because of inaccurate or incomplete information, this could make the whole process and treatment more challenging. Adults trust browsers to help them identify convenient websites, and most adults believe that the data provided on these websites is reliable (2). In addition, up to 90% of consumers think that the health data they find online is dependable (3). For parents of pediatric orthopedic outpatients as well, this trend appears to make sense. Seventy-four percent of parents indicated they would propose that others use the internet for medical information (4).

The Latin words "torus" (twisted) and "collum" (neck) are the source of the name "torticollis". Torticollis is a disorder in which the sternocleidomastoid muscle becomes shorter, which causes the head to tilt to one side and the chin to rotate in the opposite direction. Torticollis is a common disorder that occurs in individuals of all ages, from newborns to adults (5). It is a symptom of a deeper disease process but does not imply a definitive disease; therefore, if it persists or is combined with other signs, further study should be conducted (6).

The literature revealed that websites about common pediatric orthopedic diseases differ considerably in their quality and content (7). We hypothesized that the content and quality of online information related to torticollis would be acceptable and sufficient. We also hypothesized that the readability of the online data would be comprehensible. To the best of our knowledge, no printed report evaluating the online data for torticollis was conducted. Hence, in the current study, we evaluated the readability, content, and quality of online resources for torticollis.

METHODS

Google, Yahoo!, and Bing, the three most popular browsers, were used to search the internet using the expression 'torticollis'. Google is the most popular browser among them, followed by Bing and Yahoo! (8). The scans were performed on the same day (August 20, 2022), and all search engine cookies were removed before scanning. Websites that appeared to be duplicates or charged a fee for information access were excluded, and 60 websites were determined. The initial step in the study was to identify the types of websites. We divided the websites into academic, physician, medical, and commercial categories.

Methods of Assessment

The DISCERN instrument, the Flesch-Kincaid grade level (FKGL), the Global Quality score (GQS), the Journal of American Medical Association (JAMA) benchmark, the Torticollis-Specific Content (TSC) score (Table 1), and the availability of the Health On the Net (HON) accreditation were used to evaluate all of the selected websites. Two reviewers assessed each resource, and any disagreements in their evaluations were examined.

DISCERN has become a reliable and verified scoring tool for assessing the value of printed public health information online (9). It comprises 16 questions, with each question

Table 1. Torticollis content score

Wry neck
Cervical dystonia
Congenital muscular torticollis
Physical therapy
Sternocleidomastoid muscle
Ultrasonography
Spasmodic torticollis
Surgery
Prognosis
Splinting
Stretching
Congenital abnormalities
Traumatic brain injury
Selective peripheral denervation
Decreased neck movement
Tremor in head
Cervical range of motion
Cervical mass
Congenital oculer torticollis
Magnetic resonance imaging
Indication
Deep brain stimulation
X-ray
Electromyogram
Pain
Acquired torticollis
Physical examination
Infant
Trouble in breastfeeding
Klippel-Feil syndrome

worth one point out of five, with 80 being the highest possible score for a website. DISCERN was created in 1999 by a group of experts and was tested on specialists and care providers (10).

The JAMA benchmark criteria evaluate websites based on four criteria: authorship, attributions, disclosure, and currency (11). Each criterion received one point, with the highest score of four points awarded for this evaluation. GQS, which employs a five-point metric to measure the value of a website, was applied to each one. The evaluations ranked the platform's quality of information and its possible benefits to the patient (12).

Among the several methods for testing readability, FKGL and Flesch-Kincaid Reading Ease score (FKRS) are the most commonly cited (13,14). The FKGL of a written document implies that an individual having reading skills similar to those of a graduate from that 'academic level' would be able to read and comprehend the provided content. The FKRS determines how simple it is to understand a given topic, with scores ranging from 0 (unreadable) to 100 (very easy to read) (15). As in prior studies (16-18), the text from each website was copied to a Microsoft Word (Redmond, Washington) document to obtain FK scores.

Moreover, for quality, the status of the HON code was noted. The HON Foundation is an independent organization that was founded in 1996 to set ethical guidelines for the publication of medical information available on the Internet. It is the most frequently used web-based medical information dependability code (19).

Finally, a TSC score was developed to determine the actual content of the websites (Table 1). This necessitated a dispute between two senior orthopedic surgeons who specialized in pediatric orthopedics. Each of the predefined words related to symptoms, diagnostic instruments, and treatment preferences was awarded one point. There were no points given if the term was not mentioned. Sites were ranked between 0 and 30, with an overall score of 30 signifying the highest quality of content.

Statistical Analysis

For statistical analysis of the study findings, the IBM SPSS Statistics 22 (IBM SPSS, Türkiye) application was employed. While analyzing the data, the Shapiro-Wilks test was employed to assess the parameters' compliance with the normal distribution. In addition to descriptive statistical models, the Kruskal-Wallis test was employed in the comparison of quantitative data to compare parameters that did not exhibit normal distribution, and Dunn's test was performed to determine which group was concerned about the discrepancy. The Mann-Whitney U test was used to determine the two groups of parameters that did not have a normal distribution. To examine the associations between parameters that did not comply with normal dispersion, Spearman's rho correlation analysis was used. To determine the levels of agreement among observers, the lower and upper ranges of the intraclass correlation coefficient were determined. The significance was determined at the $p<0.05$ level.

RESULTS

First, 60 websites were determined according to their sources: 20% were academic, 21.7% were physician, 43.3% were medical, and 15% were commercial (Figure 1). The average scores of the assessment tools are shown in Table 2.

Statistically significant differences in the DISCERN, JAMA, GQS, FKGL, FKRS, and TSC scores were detected between the categories ($p=0.000$; $p<0.05$). In the post hoc evaluations conducted to determine the categories from which the significance originated, the DISCERN score ($p_1=0.020$; $p_2=0.000$; $p_3=0.000$; $p<0.05$), the JAMA score ($p_1=0.012$; $p_2=0.000$; $p_3=0.000$; $p<0.05$), the GQS score ($p_1=0.012$; $p_2=0.000$; $p_3=0.000$; $p<0.05$), the FKGL score ($p_1=0.001$; $p_2=0.000$; $p_3=0.000$; $p<0.05$), and the TSC score ($p_1=0.018$; $p_2=0.000$; $p_3=0.000$; $p<0.05$) of the academic category were found to be significantly higher than those of the physician, medical, and commercial categories. The FKRS score of the academic category was found to be significantly lower than that of the physician, medical, and commercial categories ($p_1=0.002$; $p_2=0.000$; $p_3=0.000$; $p<0.05$) (Table 3).

We observed a 93.5% statistically significant positive correlation between the DISCERN and JAMA scores ($p=0.000$, $p<0.05$). A positive and statistically significant relationship was also identified at the 65.2% level between the DISCERN and FKGL scores and at the 91.4% level

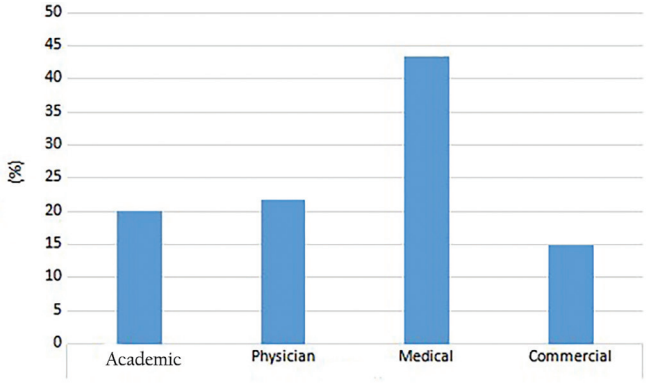

Figure 1. Distribution of websites according to sources

between the DISCERN and TSC scores (p=0.000, p<0.05) (Table 3) (Figure 2). In addition, a positive, 71.1%, and statistically significant correlation was found between the TSC and FKGL scores (p=0.000; p<0.05) and a negative, 72.3%, and statistically significant correlation was found between the FKRS and TSC scores (p=0.000; p<0.05) (Figure 3).

Table 2. Minimum, maximum, mean and standard deviation values of the assessment tools

	Min-max	Mean ± SD
DISCERN reviewer 1	17.6-64	34.72±12.48
DISCERN reviewer 2	17.6-64	36.8±12.96
DISCERN score	18.4-64	12.96±12.64
JAMA reviewer 1	1-4	1.97±0.97
JAMA reviewer 2	1-4	2.23±1.14
JAMA score	1-4	2.1±1.04
GQS reviewer 1	1-4	2.17±1.14
GQS reviewer 2	1-5	2.33±1.24
GQS score	1-4.5	2.25±1.17
FKGL	3.9-12	9.21±2.23
FKRS	6.6-80.8	46.63±19.54
TSC	5-30	19.38±7.92

Min-max: Minimum-maximum, SD: Standard deviation, JAMA: Journal of American Medical Association, GQS: Global Quality score, FKGL: Flesch-Kincaid grade level, FKRS: Flesch-Kincaid Reading Ease score, TSC: Torticollis-Specific Content

In addition, while 78.3% of websites did not have a HON code, 21.7% of them did. The DISCERN, JAMA, GQS, and TSC score values of websites with a HON code were found to be significantly higher than those without one (p<0.05). However, there appeared to be no significant difference in FKGL and FKRS scores between websites with and without a HON code (p>0.05) (Table 4).

DISCUSSION

The internet is a fast, efficient, and unidentified source of health-related data. Finding comprehensive information, on the other hand, is complicated. Patients frequently use commercial websites to look for relevant data and are more likely to assess a website's reliability based on its concept appearance instead of the origin of the data (20).

The findings of this study, based on analyses performed with standard assessment instruments, show that websites that are easily reachable to someone seeking information on the topic of torticollis are often of low quality. These findings are consistent with earlier orthopedic research on information quality (7,21,22). Torticollis parents encounter

Table 3. Evalution of scores by category and evaluation of correlation between assessment tools

		DISCERN score	JAMA score	GQS score	FKGL	FKRS	TSC
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Category	Academical	51.04±7.36	3.5±0.52	3.88±0.43	11.87±0.32	20.62±7.81	28.08±2.43
	Physician	38.24±9.12	2.31±0.83	2.46±1.03	9.12±2.06	45.87±18.81	21.31±5.66
	Medical	31.84±10.4	1.67±0.76	1.75±0.78	8.49±2.02	54.83±14.95	17±7.38
	Commercial	22.88±7.68	1.17±0.35	1.22±0.51	7.83±1.74	58.7±10.25	11.89±5.88
	p[1]	**0.000***	**0.000***	**0.000***	**0.000***	**0.000***	**0.000***
JAMA score	r	0.935	-	-	-	-	-
	p[2]	0.000*	-	-	-	-	-
GQS score	r	0.934	0.953	-	-	-	-
	p[2]	0.000*	0.000*	-	-	-	-
FKGL	r	0.652	0.660	0.659	-	-	-
	p[2]	0.000*	0.000*	0.000*	-	-	-
FKRS	r	-0.653	-0.664	-0.668	-0.953	-	-
	p[2]	0.000*	0.000*	0.000*	0.000*	-	-
TSC	r	0.914	0.878	0.891	0.711	-0.723	-
	p[2]	0.000*	0.000*	0.000*	0.000*	0.000*	-

[1]Kruskal-Wallis test, [2]Spearman Rho correlation analysis, *p<0.05, SD: Standard deviation, JAMA: Journal of American Medical Association, GQS: Global Quality score, FKGL: Flesch-Kincaid grade level, FKRS: Flesch-Kincaid Reading Ease score, TSC: Torticollis-Specific Content

anxiety and stress associated with the diagnosis and ongoing physical therapy intervention, in addition to the usual stress factors experienced by parents of newborns (23). Although torticollis is not a life-threatening or persistent condition, all parents have concerns about its diagnosis, treatment, and possible impact on the child's well-being and growth (24). Families with children suffering from orthopedic issues can obtain information from various sources, including online journals, personal accounts, and commercial websites. The peer review process before publication in medical journals carefully controlled information dissemination; however, in the new era of the Internet, everyone with an Internet connection and device can post information (4). This could lead to misdirection, particularly for patients seeking information on any health issue.

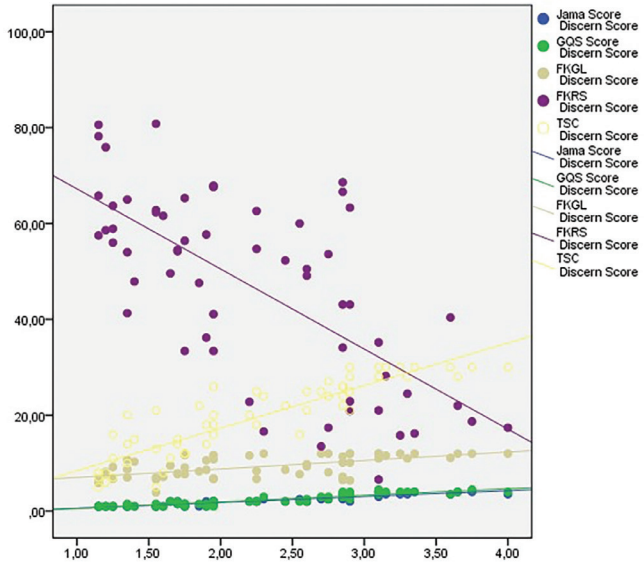

Figure 2. Relationship of DISCERN score to other scores

JAMA: Journal of American Medical Association, GQS: Global Quality score, FKGL: Flesch-Kincaid grade level, FKRS: Flesch-Kincaid Reading Ease score, TSC: Torticollis-Specific Content

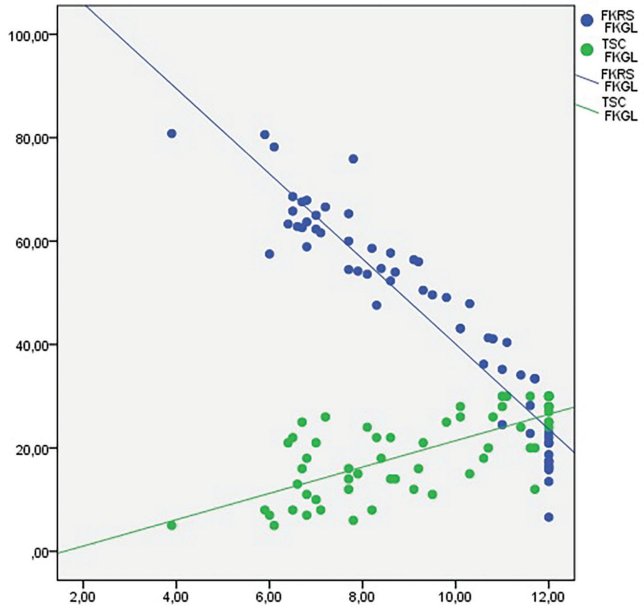

Figure 3. Relationship of TSC scores to FKGL scores and FKRS scores

FKGL: Flesch-Kincaid grade level, FKRS: Flesch-Kincaid Reading Ease score, TSC: Torticollis-Specific Content

In the current study, the DISCERN, JAMA, GQS, FKGL, and TSC scores of the academic category were found to be significantly higher than those of the other categories, as previously reported in the literature (21,25). The sample considered in this study had an average DISCERN score of 35.68±12.64. This finding is consistent with previous research (26,27), which identified that the quality of information accessible on websites is low. Although academic resources have higher scores, this low average score could be due to websites failing to state the aim of their content and providing referenced, accurate data in their text.

The mean JAMA benchmark score was 2.1±1.04 out of 4, which was similar to previous studies (22). The low JAMA scores could be attributed to the fact that most websites excluded any references or resources. We discovered a positive correlation between the JAMA benchmark criteria and DISCERN scores (p=0.000; p<0.05). This might be because the two DISCERN score questions are linked to the availability of references and the date of publication, which are both essential parts of the JAMA benchmark criteria score.

This study demonstrated that the average FKGL and FKRS scores were 9.21±2.23 and 46.63±19.54, respectively. These data suggest that the FKGL result is approximately 3.5 points

Table 4. Evaluation of scores based on the presence of HON code

	HON		
	Absent	Present	p-value
	Mean ± SD	Mean ± SD	
DISCERN score	33.12±12	45.12±11.04	0.004*
JAMA score	1.93±1	2.73±0.95	0.012*
GQS score	2.04±1.14	3±0.98	0.006*
FKGL	9.23±2.31	9.12±2.02	0.808
FKRS	46.19±20.18	48.18±17.7	0.747
TSC	18.17±7.93	23.77±6.38	0.020*

Mann-Whitney U test, *p<0.05, SD: Standard deviation, JAMA: Journal of American Medical Association, GQS: Global Quality score, FKGL: Flesch-Kincaid grade level, FKRS: Flesch-Kincaid Reading Ease score, TSC: Torticollis-Specific Content, HON: Health On the Net

higher than the sixth grade reading level proposed by the AMA and the National Institutes of Health (28). This result is similar to the findings of other studies that have evaluated the readability of information available on the Internet (29,30). The FKRS score obtained in this study signifies that the online data was "difficult to read", implying that patients must have nearly high school level English qualifications to adequately comprehend the content of the information available on the internet.

Similar to the literature (31,32), the quality of online papers with a HON code was higher, supporting the idea that the content of websites with a HON code can be relied on to provide higher quality data. In this study, 78.3% of websites did not have a HON code, whereas 21.7% did. The content evaluated about websites with a HON code had significantly higher DISCERN, JAMA, GQS, and TSC scores than those without a HON code ($p<0.05$). Nevertheless, no statistically significant difference in FKGL and FKRS scores was observed between websites with and without HON codes.

Because the content score used in this study was constructed from information provided by two pediatric surgeons, it may not be thorough overall. This study entirely focused on web-based paper products, but patients may also use audio-visual devices to gather information, which was not assessed in the current study. Because of the internet's ongoing evolution, search results or ranking positions may frequently change. The information quality on online platforms apart from the three most popular browsers was not evaluated in this study.

CONCLUSION

Despite a rise in the number of useful sites, most material on the websites reviewed in this study was of low quality, which agrees with previous studies. Despite the higher quality of several websites, particularly academic resources, their material was challenging to comprehend. This is, to the best of our knowledge, the first study of its kind on torticollis. In this regard, the current study can aid in the evaluation of information that may be important for preserving equilibrium in patient-doctor relationships.

ETHICS

Ethics Committee Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent: The study does not require patient consent.

Authorship Contributions

Surgical and Medical Practices: M.Y., S.K., Concept: M.Y., S.K., Design: M.Y., S.K., Data Collection or Processing: M.Y., S.K., Analysis or Interpretation: M.Y., S.K., Literature Search: M.Y., S.K., Writing: M.Y.

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

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

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