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Aims and Scope

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

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

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Secretariat of The Medical Bulletin of Haseki
Adnan Adivar Caddesi, 34906 Haseki-Aksaray-Istanbul-Turkey
Phone: +90 212 529 44 00/1874
Fax: +90 212 530 84 23
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The Medical Bulletin of Haseki

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

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"Materials and methods" section should be presented in sufficient details to permit the repetition of the work. The statistical methods used should be clearly indicated.

Results should also be given in detail to allow the reproduction of the study.

The Discussion section should provide a correct and thorough interpretation of the results. The references should be directly related to the findings of the authors.

Study Limitation should be detailed in the section.

Conclusion section should provide highlighted and interpreted with the study's new and important findings.

Acknowledgements should be as brief as possible. Any support should be acknowledged in this section. (Acknowledgements should be only send with the "Cover Page".)

The excessive use of abbreviations is to be avoided. All abbreviations should be defined when first used by placing them in brackets after the full term. Abbreviations made in the abstract and in the text are taken into consideration separately. Abbreviations of the full terms stated in the abstract must be re-abbreviated after the same full term in the text.

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Editor of The Medical Bulletin of Haseki
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Adnan Adivar Caddesi, 34906 Haseki-Aksaray-Istanbul-Turkey
Phone: +90 212 529 44 00/1874
Fax: +90 212 530 84 23
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The Medical Bulletin of Haseki

Contents

Original Articles

Original Article

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The Effects of Low-intensity Resistance Training with Blood Flow Restriction Versus Traditional Resistance Exercise on Lower Extremity Muscle Strength, Walking Capacity, and Balance in Ischemic Stroke Survivors: A Study Protocol for the BFR-Stroke RESILIENCE Trial

Ishtiaq Ahmed*, Rustem Mustafaoglu**, Belgin Erhan***

*Istanbul University-Cerrahpasa, Institute of Graduate Studies, Department of Physiotherapy and Rehabilitation, Istanbul, Turkey

**Istanbul University-Cerrahpasa, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Istanbul, Turkey

***Istanbul Medeniyet University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey

Abstract

Aim: The purpose of this study will be to determine the effect of low-intensity resistance training with blood flow restriction (LIRT-BFR) on lower extremity muscle strength, balance, functional mobility, walking capacity, gait speed, anxiety, and depression in patients with stroke and to compare the results with high-intensity resistance training (HIRT).

Methods: This will be a two-arm, single-blinded, randomized controlled trial (RCT) in which 32 ischemic stroke survivors will be randomized into two groups: the LIRT-BFR group and the HIRT group. Both groups will perform 3 sets of 6 resistance training for 40 minutes, 3 days a week, in addition to aerobic exercise for 5 weeks. In the LIRT-BFR group, blood flow to the active muscle was restricted by a BFR band (tourniquet) placed at the proximal end of the lower limbs. The 10-meter walk test, five-time sit-to-stand test, timed up and go test, 6-minute walk test, and Barthel index test will be the primary outcome measures. The secondary outcome measures include depression, anxiety, gait speed, stride length, cadence, adherence to treatment intervention, and adverse events.

Conclusion: The results from this RCT will constitute an evidence-base for BFR training and its efficacy on lower limb strength, walking capacity, and balance performance in patients with stroke.

Keywords: Blood flow restriction, strength training, stroke, mobility, balance, depression

Introduction

Stroke is the leading neurological disease in the world that causes long-term disability (1,2). Worldwide, the incidence of stroke has increased by 70% in the last decade (3). In Europe, more than one million cases are reported each year, and nine million stroke survivors are alive right now (4). The annual estimated cost of stroke treatment in Europe is twenty-seven billion euros, and it is estimated to reach up to 184 billion dollars by 2030 (5). Therefore, it is necessary to develop an economical rehabilitation program that prevents or reduces long-term disability after stroke.

Stroke survivors may experience various problems, depending on the severity, like impaired mobility, balance, function, cognition, and psychological problems. Almost two-thirds of individuals with stroke have impaired mobility and functional limitations resulting from brain damage (6). The quality of life is also disturbed by the abnormal gait patterns of individuals with strokes. Individuals who have had a stroke can walk with capacity, which plays an important role in improving their quality of life. The reduced walking capacity of these patients may limit their social participation. Therefore, impaired walking capacity should be adequately addressed (7).

Address for Correspondence: Rustem Mustafaoglu,
Istanbul University-Cerrahpasa, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Istanbul, Turkey
Phone: +90 212 866 37 00 E-mail: rustem.mustafaoglu@iuc.edu.tr ORCID: orcid.org/0000-0001-7030-0787
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High-intensity exercise resulted in greater improvement in walking speed, stride length, and cadence compared with conventional gait training in chronic stroke patients (8). However, traditional high-intensity training (HIT) may cause increased blood pressure and arterial stiffness (9) and is not feasible for stroke patients with limited mobility. Therefore, a safer, feasible, and cost-effective training program for stroke patients with limited mobility is needed. Blood flow restriction (BFR) with resistance training may be an economic and time-efficient alternative to HIT to manage the risk factors of stroke and can also be useful in reducing stroke-related impairment effectively.

Karatsu training, or BFR, was first introduced as a common exercise in Japan, and some scientists considered it the "state of the art" exercise. During BFR training, the blood flow of the exercising muscle is restricted by placing the inflated tourniquets at the most proximal parts of the legs or arms (10). By restricting the blood flow to the limbs, the desired muscle group will work in an ischemic environment and can trigger a significant increase in hypertrophy/muscle mass, power, and strength (11) by recruiting the fast twitch muscle fibers (12).

Previous evidence from neurological studies has shown that BFR training can improve muscle strength, balance, walking capacity, and cognitive function in multiple sclerosis and incomplete spinal cord injury patients (11,13,14). A recent study showed that BFR training has improved brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) and the rate of perceived exertion in ischemic stroke patients (14). Similarly, a randomized controlled trial (RCT) reported a significant improvement in upper limb motor recovery and function in the BFR group compared with exercise training alone in stroke patients (15). Recently, it was found that the neurophysiological response of BFR in stroke patients was reported to have no significant difference between BFR and exercise groups after one session (16). Despite its beneficial effects, to the best of our knowledge, no study has investigated the effect of low-intensity resistance training with BFR (LIRT-BFR) on balance, muscle strength, walking capacity, and depression in patients with stroke. It is hypothesized that both LIRT-BFR and HIRT will yield a similar improvement in balance, muscle strength, walking capacity, and depression in patients with ischemic stroke. This RCT will compare the effects of a 5-week LIRT-BFR combined with aerobic training versus a 5-week HIRT combined with aerobic training on balance, muscle strength, walking capacity, and depression in stroke survivors.

Materials and Methods

Study Design and Ethical Approval

It will be a single-blinded, two-arm, parallel RCT, which will be conducted in accordance with the tenets of the Helsinki Declaration. The RCT has been designed according to the SPIRIT (17) and CONSORT (18) guidelines and has been approved by Non-Invasive Clinical Research Board of Istanbul University-Cerrahpasa on 02-02-2022 (protocol no:E-74555795-050.01.04-335759). This trial was prospectively registered at www.clinicaltrials.gov (identifier: NCT05281679). The SPIRIT schedule of study is shown in Figure 1.

The research will be carried out at the outpatient Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Istanbul University-Cerrahpasa. Written informed consent was provided by all the stroke survivors included in this study.

Participants and Eligibility Criteria

Patients with more than one month of stroke will be eligible for the study. All the participants will be evaluated to be in stable cardio-vascular condition, i.e., ACSM Class B (19). The inclusion criteria will be: (1) 18 to 75 years of age; (2) more than 1 month of stroke onset; (3) first-ever unilateral ischemic stroke (4) walking 10 meters independently with or without an assistive device; (5)

	STUDY PERIOD			
	Enrolment	Allocation	Post-allocation	
TIMEPOINT**	$-t_1$	0	T_0	T_1
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Allocation		X		
INTERVENTIONS:				
[LIRT-BFR]			X ⟷	X
[HIRT]			X ⟷	X
ASSESSMENTS:				
[Demographics variable]		X	X	X
[Primary outcome]			X	X
[Secondary Outcome]			X	X

Figure 1. Schedule of study
Primary outcomes: 10-meter walk test, five time sit-to-stand test timed up and go test, 6-MWT, and Barthel index test
Secondary outcomes: Anxiety and depression measured by the hospital anxiety and intervention, and adverse events

T0: Baseline; T1: Post-intervention (5 weeks), LIRT-BFR: Low-intensity resistance training-blood flow restriction

being an independent ambulator (Functional Ambulation category >3); and (6) modified Ashworth scale < grade I. The exclusion criteria were: (1) people with a history of mental/cognitive illness; (2) transient ischemic attack; (3) combination with peripheral neuropathy; (4) having resting blood pressure above 160/100 mmHg even after taking medications; (5) hemorrhagic stroke (6) cardiovascular comorbidity (heart failure, unstable angina, aortic stenosis, arrhythmias, hypertrophic cardio-myopathy, depression of ST-segment); (7) people with obvious cognitive impairments; (8) by-pass surgery in the last 3 months; (9) any musculoskeletal condition that resists or limits the participants from doing resistance training; and (10) people who have taken analgesics, dopamine, antipyretics, and any other drugs that can affect the function of the autonomic nerve system in the last 2 weeks.

Sample Size

Stata version 16.0 was used to determine the sample size by using the reported effect size of the 6-minute walk test (6-MWT) on patients with stroke in a prior study (20). The minimum sample size required to show a clinically significant difference of 55 meters in the 6-MWT [two-tailed type I error of 0.05; power of 90%; standard deviation (SD) of 40] was 13 per group. A total of 32 patients (16 in each group) will be recruited after considering a dropout rate of 20%.

Randomization

Participants will be randomly allocated to LIRT-BFR or HIRT without the BFR group. Microsoft Excel software will be used for the randomization. Specifically, a random number between 0 and 1 will be assigned to each group (distribution to groups was based on: 0 to <0.5 = HIRT group and 0.5 to <1 = LIRT-BFR group). The generated random numbers will be placed in a sealed envelope and kept in a container. An individual, with no other role in the study, will pull a sealed envelope out of a container to decide the distribution of participants. The envelopes will be designed to achieve the allocation of a 1:1 ratio of LIRT-BFR to HIRT groups. Group allocation will be blinded to the assessor to ensure group concealment. After the randomization process, the participants will receive information about the group they are allocated to. Figure 2 shows the distribution of patients.

Training Intervention

After the randomization process, patients in the LIRT-BFR and HIRT groups will undergo five weeks of treatment in the outpatient department. The HIRT group will receive high-load resistance training (40 min, 3 days/week), while the LIRT-BFR group will receive LIRT-BFR (40 min, 3 days/week). The duration of training will be 5 weeks for both groups. In addition to resistance training, all the participants will perform 20 min of aerobic training without BFR (treadmill and cycling training, 10 min each).

Determination of 1-repetition Maximum

During the first visit, the subjects will be familiarized with the use of test instruments and will be screened for one-repetition maximum (1-RM) tests, which are widely used to determine muscular strength and consist of the highest load that can be lifted in a single repetition through a full range of motion (14,21). After two minutes of warm-up, participants will choose, according to the range self-predictability, an initial weight (50-70%) of 1-RM. After each test, a 10-20% weight increment will be added until they reach the final limit (maximum load) that can be lifted once. A 3-5 minute recovery interval will be provided between the two tests, and the maximum weight lifted will be recorded as 1-RM (14).

Low Intensity Resistance Training with the Blood Flow Restriction Group

The LIRT-BFR group will perform three sets of low-load resistance exercises, targeting the large muscles of the legs at 40% of their 1-RM. The resistance training protocol consists of 3 sets of 6 exercises (knee extension, hip flexion, extension and abduction, straight leg raise using a sandbag, leg press, and squat). Each set consisted of 10 repetitions of 1-RM with a 1-min recovery interval between sets and 3 min between exercises. Subsequent 1-RM testing procedures will be performed every week, where the weight load will be readjusted to 40% of 1-RM. Blood flow to the active muscles during LIRT-BFR training is restricted by a BFR band (tourniquet) placed at the proximal end of the lower limbs. When participants perform LIRT-BFR training, the proximal portion of their lower limb was compressed at 150-160 mmHg by a blood pressure cuff (22). The air pressure belt will be inflated before the exercise and will remain inflated during the one-minute intervals between the sets and will be deflated during the three-minute intervals between the exercises.

High-Intensity Resistance Training Without the Blood Flow Restriction Group

The HIRT group will perform 3 sets of high load resistance exercises, targeting the large muscles of the legs at 80% of 1-RM. The resistance training protocol consists of 3 sets of 6 exercises (knee extension, hip flexion, extension, and abduction, straight leg raise using a sandbag, leg press, and squat). Each set consisted of 10 repetitions of 1-RM, with a 1-minute rest interval between sets and a 3-minute rest interval between exercises. Subsequent 1-RM testing procedures will be performed every week, where the weight load will be readjusted to 80% of the 1-RM.

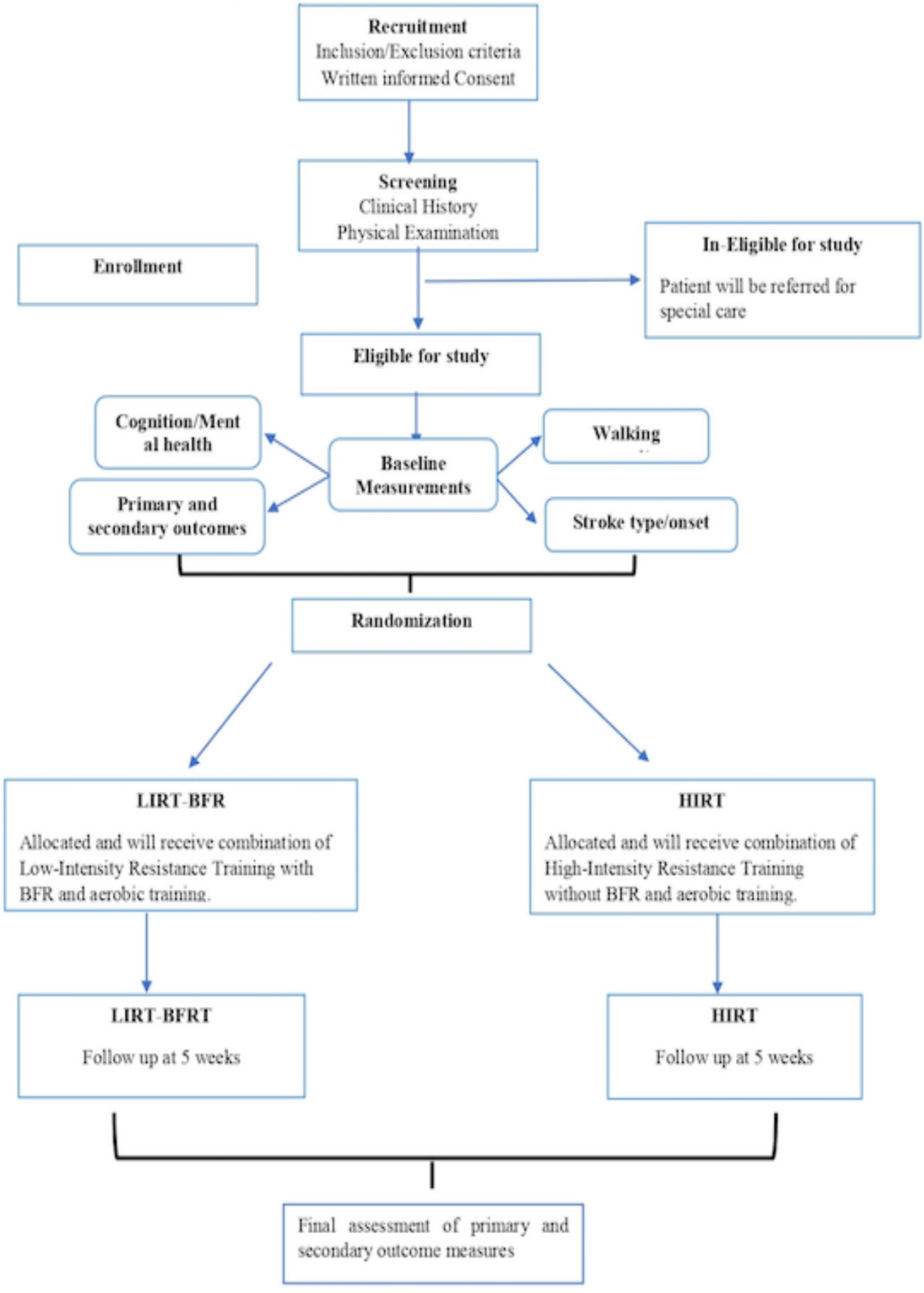

Figure 2. Flowchart of the study

Outcome Measures

The outcome measures will be obtained at baseline and post-intervention (5 weeks). After taking the baseline measurements, participants will be randomized by a therapist not involved in the recruitment, intervention, or assessment process of the study. All the outcome measurements will be obtained from an assessor who will be blinded to the group allocation. Patients will be instructed to avoid mentioning their treatment plan to the assessor. The accessor (physiotherapist) will be trained to ensure consistency in the assessment process and to ensure that the protocol is standardized. All the demographic measurements, location, type of stroke lesion, time post-stroke, and functional ambulation category score to determine the post-stroke functional ability will be collected at baseline. The 10-meter walk test, five-time sit-to-stand test, timed up and go test, 6-MWT, and Barthel index test will be the primary outcome measures. The secondary outcome measures will be anxiety and depression as measured by the hospital anxiety and depression scale, gait speed, stride length, cadence, adherence to treatment intervention, and adverse events. In addition to these outcome measures, blood pressure, heart rate, and oxygen saturation will be monitored daily during the intervention.

Primary Outcome Measures

Five time sit-to-stand test: Five time sit-to-stand test will be used to assess lower extremity muscle strength, balance, and risk of fall in stroke patients (23). The test measures the amount of time taken to complete five repetitions of the sit-to-stand task. The test was performed using a standard-height chair without an armrest and with a straight back (43-45 cm high). The patients will be instructed to, by keeping their arms folded across their chest, stand up and sit down as quickly as possible five times. The stop-watch will be started when the patient's back leaves the backrest of the chair and stop once the back touches the backrest of the chair for the fifth time (24).

10-meter walk test: The 10-m walk test will be used to determine the gait speed of walking. A 14-meter corridor will be used for the test, and patients will be allowed to use a walking aid if necessary. Patients will be instructed to walk comfortably. The stopwatch will be started at the 2nd meter and stopped when the patient reaches the 12th meter. After three tests, the average of the three tests will be recorded (20).

Timed up-go test: The timed up-go test is a functional mobility test used to assess dynamic balance, transfer, and gait. The patients will be instructed to stand up, with support for the arms, from a chair (46 cm high), walk for a short distance (3 m), turn, go back, and sit down as quickly as possible. The stopwatch will be used to measure the time it takes to perform these tasks from start to finish. The patients will be allowed to use their walking aids (25,26).

6-minute walk test: The walking distance will be measured by the 6-MWT, the most commonly used for measuring the functional exercise capacity of individuals after stroke (27). The patients will be instructed to walk as far as possible throughout the 30-meter course within 6 minutes by following the standardized instructions provided by the physiotherapist. Participants will be allowed by the physiotherapist to use an aiding device if necessary. The physiotherapist will guard the participants during the walk test but will not offer any assistance or support to the participants.

Barthel index (BI): The level of independence in functional activities is determined by the BI. It included ten items, and the score range between 0 and 20 points show complete dependence; between 21 and 61 points, severely dependent; between 62 and 90 points, moderately dependent; between 91 and 99 points, lightly dependent; and 100 points indicate complete independence (20,28).

Secondary Outcome Measures

Anxiety and depression: The hospital anxiety and depression scale, which is the most widely used scale in the clinical evaluation of stroke patients, will be used to measure anxiety and depression (29). It includes anxiety and depression subscales and consists of 14 items, 7 of which investigate depression and 7 of which investigate anxiety symptoms. Responses are evaluated in a four-point Likert format and scored between 0 and 3 (30).

Walking parameters: Walking time and number of steps during 10-meter walk test will be assessed to calculate gait speed (m/s), stride length (cm), and cadence (steps/min). After three trials, the average of the three trials is recorded as m/s (20).

Adherence: Adherence to the intervention program will be calculated as a percentage using the following formula:

$$\%Adherence = \frac{\text{No. of session attended}}{\text{Total number of sessions}} * 100$$

Adverse events: Participants will be advised to report any adverse or unexpected symptoms (change in blood pressure, heart rate, pain, etc.) to the physiotherapist. A logbook will be used to document any adverse or unexpected symptoms.

Statistical Analysis

The normality of data will be tested using the Shapiro-Wilk test of normality. The descriptive analysis will be reported as the mean and SD. Baseline data

will be collected at T0. Measurements will be repeated after five weeks of intervention (T1). To compare the normally distributed continuous demographic variables, the independent t-test will be used, and for not normally distributed continuous variables, the Mann-Whitney U test will be used. For categorical demographic variables, the chi-square with Yates' adjustment or Fisher's exact test will be used. If the data are normally distributed, we will use a parametric test (e.g., Paired samples t-test, Independent Samples t-test), whereas if the data are not normally distributed, we will use a non-parametric test (e.g., Wilcoxon signed-rank test, Mann-Whitney U test). The effect size is determined by Cohen's d coefficient value and was considered large (0.5), moderate (0.3), and small (0.1) (31). All the data will be analyzed using SPSS version 24.0 (SPSS Inc., Chicago, IL).

Discussion

Although resistance training is commonly used to treat stroke patients, HIRT is not only more intensive but also less safe and suited for long-term use. Högg et al. (32) reported that 26% of stroke patients reported joint pain after HIRT. LIRT-BFR improves muscle strength, balance, walking capacity, and cognitive function in neurological patients. The hypertrophy responses induced by LIRT-BFR are comparable to those produced by HIRT (33). Previous studies have determined the neurophysiological and hormonal response of BFR in stroke patients, and this will be the first RCT to evaluate the effects of LIRT-BFR on balance, lower limb muscle strength, walking capacity, and depression in stroke survivors. Another novel aspect of this study will be that it will not only determine the effect of LIRT-BFR but also compare the improvement achieved with HIRT. The marked expected improvement in lower extremity muscle strength, balance, walking capacity, and depression will allow stroke patients to have a more active lifestyle and will improve their quality of life. The important findings will provide clinicians and physiotherapists with the information they need to modify resistance training in stroke rehabilitation to maximize motor recovery, as well as encourage clinicians and physiotherapists to use BFR during stroke rehabilitation.

Safety and Efficacy

This single-blinded RCT will provide valuable information about the safety and efficacy of BFR therapy in stroke rehabilitation. Previous studies in high-risk groups of patients, such as those with cardiovascular disease, stroke, etc., reported that BFR is safe and produces significant improvement (34). In addition, BFR training and HIT produced a similar effect on both systolic and diastolic blood pressure and heart rate in young individuals and older adults (35).

Study Limitations

This RCT will constitute an evidence-base for BFR training and its efficacy on lower limb strength, walking capacity, and balance performance in stroke patients. Secondly, the randomization is stratified by age and sex variables, which may influence the prognosis. Moreover, the accessor and the person who performs the randomization will be blinded to the group allocation. Finally, the sample size of this study was calculated to detect the minimum clinical difference, which will help detect the differences in outcome measures.

Our research has a few limitations. Although the accessor was blinded to the group allocation, due to training, we could not blind the patients and therapists for treatment allocation. Secondly, we don't know whether the current range of cuff pressure for BFR is suitable for stroke patients. The cuff pressure used in this study is based on BFR training in sub-acute stroke. Finally, the study will recruit only ischemic stroke patients, and the findings of this study might not apply to patients with hemorrhagic stroke.

Conclusion

Previous studies determined the effect of BFR training in stroke patients and could only report the improvement in BDNF and VEGF levels and could not report any physical function outcome. Therefore, this RCT will assess the effect of BFR with resistance training on physical function outcomes in ischemic stroke patients.

Ethics

Ethics Committee Approval: The ethical approval has been approved by the Non-Invasive Clinical Research Board of Istanbul University-Cerrahpasa on 02-02-2022 (protocol no: E-74555795-050.01.04-335759).

Informed Consent: Written informed consent was provided by all the stroke survivors included in this study.

Peer-reviewed: Internally peer-reviewed.

Authorship Contributions

Concept: I.A., R.M., B.E., Design: I.A., R.M., Data Collection and/or Processing: I.A., R.M., B.E., Analysis and/or Interpretation: I.A., R.M., Literature Research: I.A., Writing: I.A., R.M., B.E.

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

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Original Article

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Comparison of Different Strategies for Prevention of Catheter-Related Bladder Discomfort: A Randomized Controlled Trial

Fatma Ozkan Sipahioglu*, Filiz Karaca Akaslan*, Ozge Yamankilic Mumcu*, Reyhan Polat*, Fatih Sandikci**, Asli Donmez*

*University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Ankara, Turkey

**University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital, Clinic of Urology, Ankara, Turkey

Abstract

Aim: Catheter-related bladder discomfort (CRBD) is characterized by pain and a burning sensation in the suprapubic region caused by stimulation of type 3 muscarinic (M3) receptors. The aim of this study was to compare the effects of tramadol and dexmedetomidine on CRBD, which have inhibitory effects on the M3 receptor.

Methods: A total of 135 male patients with ASA I-II, aged between 18 and 70 years and scheduled to undergo elective retrograde intrarenal surgery between March and July 2020, were included in the study. Patients were randomized into three groups: tramadol (group T), dexmedetomidine (group D), and control (group C). Patients were evaluated for the incidence and severity of CRBD and postoperative pain at the postoperative 0th (t_0), 1st (t_1), 3rd (t_2), and 6th (t_3) hours.

Results: The incidence and severity of CRBD were lower in group D at t_1 than in the other groups ($p<0.05$). The incidence and severity of CRBD were similar between groups T and D, and they were significantly lower than those in group C at t_2 and t_3 ($p<0.01$). Postoperative pain levels were significantly lower in groups T and D than in group C at t_0 and t_1 ($p<0.01$). Postoperative recovery time was significantly longer in group D ($p<0.01$).

Conclusion: Both dexmedetomidine and tramadol are effective in preventing CRBD and in postoperative analgesia. Dexmedetomidine is more potent than tramadol in the early period; however, it may delay post-anesthesia recovery time.

Keywords: Dexmedetomidine, tramadol, urinary catheterization, complications

Introduction

Urinary catheterization is frequently performed in many surgeries, particularly urinary surgery. However, this intervention may cause a group of symptoms termed "catheter-related bladder discomfort" (CRBD), characterized by pain, a burning sensation in the suprapubic region, and a constant urge to urinate. CRBD increases the risk of postoperative complications by causing pain and agitation in the patient, delays the recovery period and increases the workload of health workers. Therefore, the prevention or treatment of CRBD at an early stage is essential.

Male sex and Foley catheter diameter (≥18F) are major risk factors for CRBD. Additionally, the type of surgery is also essential for CRBD, which is more common in urological or lower abdominal surgeries (1,2). Other reported risk factors are cesarean and urinary catheterization medical history, age <50 years, and absence of lubrication (3).

The main cause of urinary catheter-related discomfort is involuntary contractions of the detrusor muscle due to stimulation of muscarinic receptors, primarily type 3 receptors (M3 receptors). Several studies have shown that medical treatments including ketamine, tolterodine, oxybutynin, gabapentin, pregabalin, butylscopolamine,

Address for Correspondence: Fatma Ozkan Sipahioglu,
University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Ankara, Turkey
Phone: +90 553 136 28 75 E-mail: ftmozkan_uzmdr@yahoo.com ORCID: orcid.org/0000-0002-9350-2653
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chlorpheniramine, tramadol, and dexmedetomidine, and methods such as botulinum toxin injection, adjustment of the catheter balloon diameter, local infiltration, and regional anesthesia are effective in preventing CRBD (1,4-9). Muscarinic receptor antagonists such as oxybutynin, tolterodine, and ketamine are the main drugs used to treat CRBD (10-12). Gabapentin has been reported to be effective in preventing CRBD by regulating the afferent signal input from the bladder and excitability of the sacral reflex center (13). Hyosin N-butyl bromide, also known as scopolamine, treats CRBD effectively by stopping painful cramps and spasms with its anticholinergic effect (14). However, the search for the ideal agent for preventing CRBD continues since no definitive conclusions can be drawn for routine use due to the small number of samples, surgical differences, and some anticholinergic and sedative side effects.

In this study, we evaluated and compared the effects of intraoperatively administered tramadol and dexmedetomidine on the incidence and severity of CRBD and their side effects. We also examined their analgesic activity.

Materials and Methods

Compliance with Ethical Standards

This prospective randomized controlled study was conducted between March and July 2020 after obtaining ethical committee approval from University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital (date: 05.08.2019, approval number: 69/15). The protocol for this clinical trial was registered at ClinicalTrials.gov (NCT04314050).

Study Design

Internet-based randomization software (http://www.randomizer.org) was used to determine randomization assignments. Written informed consent was obtained from all patients. A total of 135 male patients with ASA I-II, aged between 18 and 70 years, scheduled to undergo elective retrograde intrarenal surgery (RIRS) and who would be undergoing a urinary bladder catheter were included in the study. Patients with preoperative double j stent and difficulty inserting the urinary catheter were excluded from the study. Moreover, patients with a history of bladder outlet obstruction, overactive bladder, neurogenic bladder, and patients with morbid obesity, liver or kidney insufficiency, diabetic neuropathy, chronic analgesic drug use, and cognitive impairment were excluded from the study.

To ensure standardization, we included only male patients and preferred one type of surgery. Urinary catheterization was performed using a 16-Fr Foley catheter with a lubricant gel and fixed to the leg without any traction-using sticking plaster. Additionally, as a routine practice of the urology clinic, a polyurethane 26 cm 4.7-F double j stent was applied to all patients after the RIRS operation.

The patients were randomized into three groups: tramadol (group T), dexmedetomidine (group D), and control (group C). No premedication was given. Standard general anesthesia with a laryngeal mask was applied to all patients, and 1 g paracetamol was administered intravenously (i.v.) for postoperative analgesia. After anesthesia induction, group D was infused with dexmedetomidine (Hipnodex™; Haver Pharma Drug Inc., Istanbul, Turkey) at a loading dose of 1 μg kg^{-1} (diluted in 100 ml of 0.9% saline-10 minute i.v. infusion) followed by a continuous infusion of 0.5 μg kg^{-1} h^{-1} at the end of the surgery. In group T, tramadol (Tramosel™; Haver Pharma Drug Inc., Istanbul, Turkey) 1.5 mg kg^{-1} diluted in 100 mL of 0.9% saline was given by slow infusion during the last 30 min of the surgery. No additional drugs were administered to the patients in the control group. The patients who were extubated at the end of the operation were transferred to the post-anesthesia care unit (PACU).

Patient Evaluation and Follow-up

The patients were evaluated using the Ramsay sedation scale (RSS) and the modified aldrete score (MAS) on admission to the PACU. The RSS is the most commonly used sedation scale in intensive care units and scores sedation at six levels (15). The ideal sedation level is two. Patients with a sedation scale of ≥4 were considered deeply sedated. MAS is used to check whether the patient is ready for discharge from the PACU after anesthesia. MAS assesses patients' motor activity, respiration, blood pressure, consciousness, and oxygenation over 10 points (16). Nine points are required for discharge from the PACU. Patients whose evaluation scores reached 9 points were transferred to the ward. The time from admission to PACU until MAS ≥9 was recorded as recovery time.

Patients who were informed about CRBD symptoms preoperatively were evaluated for the incidence and severity of CRBD at postoperative 0^{th} (t_0), 1^{st} (t_1), 3^{rd} (t_2), and 6^{th} (t_3) hours in the PACU and ward. The severity of CRBD was assessed in four grades: none, when patients did not complain of any CRBD; mild, when reported by patients only on questioning; moderate, when reported by patients on their own (without asking and any behavioral response); and severe, when reported by patients on their own along with behavioral responses (severely agitated) (5,17,18). Patients who complained of moderate or severe CRBD were considered CRBD-positive. As part of our routine clinical practice, we administered 20 mg

of hyoscine N-butyl bromide (Buscopan®, Sanofi Health Products Ltd, Istanbul, Turkey) as rescue therapy (19,20).

Patients were evaluated for postoperative pain using a numerical rating scale (NRS). The patient was asked to score their pain between 0 (no pain) and 100 points (worst imaginable pain) at t_0, t_1, t_2, and t_3 (21). Rescue dexketoprofen (Arveles, UFSA Pharmaceutical Industry and Trade Inc., Istanbul, Turkey) 50 mg was administered when the NRS was >60. Additionally, major adverse effects such as nausea, vomiting, dry mouth, and intraoperative hypotension or bradycardia were recorded.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS version 22.0, Chicago, IL, USA) was used for statistical analysis. P<0.05 was considered significant. The normality of continuous data was assessed using a one-sample Kolmogorov-Smirnov test. The homogeneity of variances was tested using Levene's test. Numerical variables were summarized as mean ± standard deviation (SD) or median (IQR), and categorical variables as frequencies and percentages. For the comparison of continuous variables, the Kruskal-Wallis test was used in the triple group comparison and the Mann-Whitney U test was used for paired group comparisons.

The sample size for the research was estimated on the basis of a preliminary experiment according to the incidence of CRBD in a range from 0.17 to 0.5 between the three groups. To obtain significance of α=0.05 and 90% power (1-β=0.9), the required sample size per group was at least 41. Considering the possibility of dropout, we included 135 patients in this study.

Results

During the study period, 169 patients were assessed for eligibility, and 34 were excluded (Figure 1), so 135 patients (45 in each group) were analyzed. Reasons for exclusion included history of bladder disease (n=10), refusal to participate (n=4), language barrier (n=5), cognitive disorder (n=6), and pre-existing catheter before surgery (n=9).

The demographic data of the patients was similar (Table 1). Among the three groups, there was no significant difference in the incidence and severity of CRBD at the first assessment (t_0) in the PACU (p=0.934 and p=0.467, respectively). However, they were significantly lower in group D at t_1 (p=0.0006 and p=0.032, respectively) than in the other groups. The incidence and severity of CRBD were similar between groups T and D (p=0.334 and p=0.708; p=0.557 and p=0.168, respectively) and were significantly lower than those in group C at t_2 and t_3 (p=0.0007 and p=0.005; p=0.002 and p=0.0001, respectively) (Figure 2, Table 2).

The median NRS scores were significantly lower in groups T and D than in group C at t_0 and t_1 (p=0.0001 and p=0.005, respectively), and they were similar in groups T and D (p=0.848 and p=0.365, respectively). There was no significant difference in NRS scores between the groups at t_2 and t_3 (p=0.910 and p=0.491, respectively) (Table 3).

The postoperative recovery time was significantly longer in group D than in the other groups (p=0.0001), and it was similar in groups T and C (p=0.075) (Table 3).

Deep sedation was not observed in these patients. No drug-related adverse effects were observed in any patient.

Discussion

We observed that tramadol was as effective as dexmedetomidine in reducing the frequency and severity of CRBD and postoperative pain. However, dexmedetomidine was more effective than tramadol in the early period.

Tramadol is a centrally acting, synthetic opioid analgesic with M1 and M3 muscarinic receptor inhibitory effects. In a previous study comparing the dose-response effect of tramadol, 1.5 mg kg^{-1} was reported to be more effective than 1 mg kg^{-1} in treating CRBD and reducing postoperative pain (17). Agarwal et al. (22) showed that 1.5 mg kg^{-1} i.v. tramadol, administered 30 min before extubation, decreased the incidence and severity of CRBD (50%) at all time points (0^{th}, 1^{st}, 2^{nd}, and 6^{th} hours) and provided a 20% reduction in postoperative fentanyl consumption. However, a recent study reported that butorphanol effectively lowered the CRBD score and reduced postoperative pain compared with 1.5 mg kg^{-1} of tramadol in non-urological surgery (23). However, the sedation score was higher in the butorphanol group.

In this study, we observed that tramadol did not affect the incidence and severity of CRBD in the first hour; still, it reduced the incidence and severity of CRBD by 17-31% in the 3^{rd} and 6^{th} hours postoperatively. Tramadol, consisting of two enantiomers [(+) tramadol, (-) tramadol], each with a different mechanism of action, turns into an active metabolite after metabolism. The pharmacokinetics and pharmacodynamics of tramadol can vary due to a delay of action depending on its transport from the plasma to the central nervous system and pharmacodynamic interactions between its two enantiomers and its active metabolites (24,25). Although the information about the onset of action and elimination half-life of the i.v. form of tramadol is not unclear, intramuscular injection and 30-minute i.v. infusion are considered bioequivalent in terms of systemic effects. Accordingly, it may take up to 1.5 h to reach the serum peak value for tramadol (26). As explained above, this may be because the drug cannot reach its serum peak level in the early period.

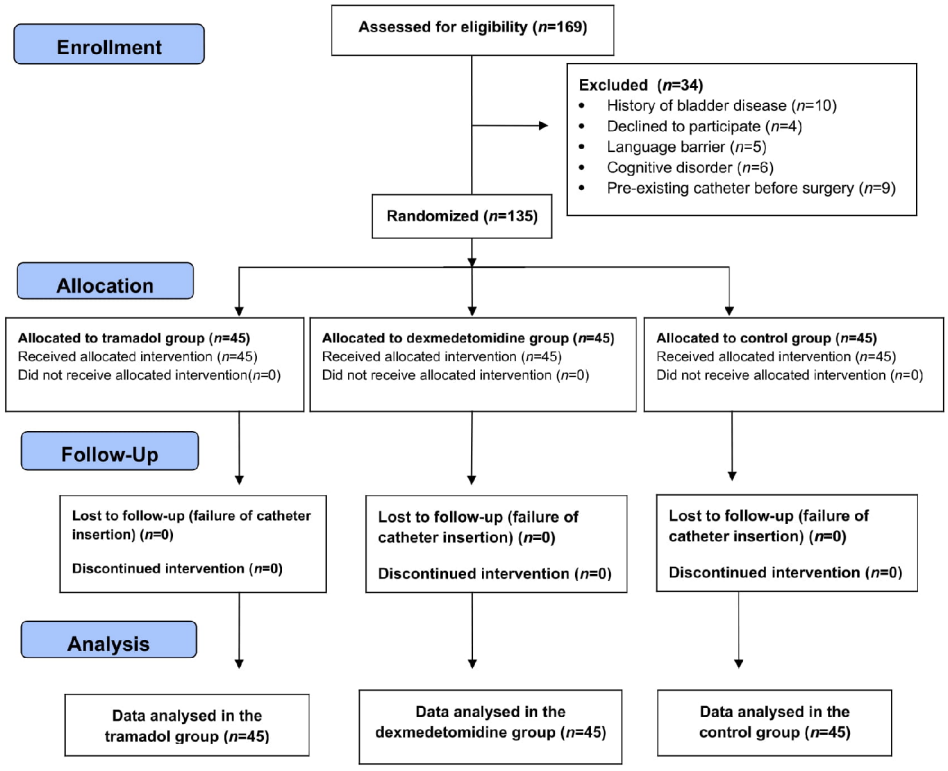

Figure 1. CONSORT diagram

Dexmedetomidine, a selective α-2 adrenoceptor agonist, has analgesic, sympatholytic, and sedative properties (27). The research by Takizuka et al. (28) found an inhibitory effect of dexmedetomidine on the M3 receptor; the impact of dexmedetomidine on CRBD has been the subject of research. Previous studies have shown that dexmedetomidine is effective in preventing CRBD and reducing the frequency and severity of CRBD, and is also effective in alleviating postoperative analgesia (18,29-32). A recent meta-analysis, which included seven studies on different types of surgery, concluded that intraoperatively administered dexmedetomidine reduced the frequency and severity of CRBD in the early postoperative period without having any serious side effects (33). Consistent with other studies, our results showed that intraoperatively administered dexmedetomidine effectively prevents CRBD and reduces the frequency and severity of CRBD by 20-33%.

A previous study comparing the effects of lidocaine and dexmedetomidine on CRBD prevention found that lidocaine and dexmedetomidine reduce the frequency of CRBD in the early period but have no effect on the severity of CRBD (34). Another study comparing dexmedetomidine with ketamine reported that both agents had similar analgesic effects on CRBD, but dexmedetomidine was more acceptable regarding its side-effect profile (35). In this study comparing dexmedetomidine and tramadol, we found that the two drugs had similar efficacy. However, dexmedetomidine is more effective than tramadol in the first hour, suggesting that its antimuscarinic effect is more significant than tramadol in the early period. This may be related to dexmedetomidine's being a selective

Table 1. Patients' demographic data

	Group T (n=45)	Group D (n=45)	Group C (n=45)	p-value
Age (year) (mean ± SD)	44±9	40±12	40±12	0.241*
ASA I/II (n)	17/28	16/29	18/27	0.910**
Stone size [median (IQR)]	10 (8-12)	10 (8-12)	10 (9-12)	0.460**

*: Anova test; **: Kruskal-Wallis test
IQR: Interquartile range, SD: Standard deviation

M3 receptor inhibitor. Furthermore, we consider that the antimuscarinic effect of dexmedetomidine is prolonged, as suggested by other studies, although the half-life of dexmedetomidine after infusion for 60 min has been reported to be approximately 30 min (33,36).

At the first evaluation (t_0) in the PACU, there was no significant difference between the groups regarding CRBD severity and frequency. However, the incidence of CRBD was low in all the groups at t_0. This may be due to ongoing anesthetic activity in the first postoperative minutes, as seen in a recent study that compared tramadol and tapentadol, an opioid-derived analgesic (37).

The incidence of CRBD varies between 47% and 90% (1,7,11,13,17,22,38). In contrast, Binhas et al. (39) reported the incidence of CRBD as 47% in a study investigating the incidence and risk factors of CRBD in patients requiring intraoperative urinary catheterization under general anesthesia. However, in their study of patients who underwent percutaneous nephrolithotomy, Agarwal et al. (12) reported the incidence of CRBD as 92% in the control group at the postoperative 2nd hour. The incidence of CRBD was 40% in the control group at t_1 and t_2 in this study. The reason for the low incidence compared to the general literature may be the inclusion of only moderate and severe symptoms of CRBD.

The patients were also assessed for postoperative pain at the same intervals. Similar to the results reported in the literature, both agents were effective for postoperative analgesia. In this study, the patients' pain levels were not very high because the surgical procedure is less painful than invasive procedures such as percutaneous nephrolithotomy.

Although previous studies have reported tramadol-related side effects such as nausea (56%), vomiting (40%), and dexmedetomidine-related side effects such as dry mouth (3%), nausea (11%), and rarely, hypotension and bradycardia attacks, no side effects were observed in this study (18,22,23,32,33). This may be because the tramadol was diluted and administered as a slow infusion and the dexmedetomidine infusion was short because of the short operation time.

There is no consensus on the effect of dexmedetomidine on postoperative recovery time; the general opinion is that it prolongs recovery time (29,40-42). The recovery period was significantly longer in the dexmedetomidine group than in the other groups. However, since the recovery time was limited to a maximum of 20 min, we considered that it would not pose a problem regarding patient safety.

Tramadol and dexmedetomidine can easily be administered and prevent CRBD without any side effects, making them superior to other treatments. This study may help establish a common intraoperative approach to prevent CRBD early, especially in patients at risk of CRBD.

Study Limitations

Firstly, the administration of drugs was arranged according to the end time of the operation. However, the inability to accurately predict the end time of the operation limited our study. Therefore, it would be appropriate to record the duration of the surgery. Secondly, we evaluated

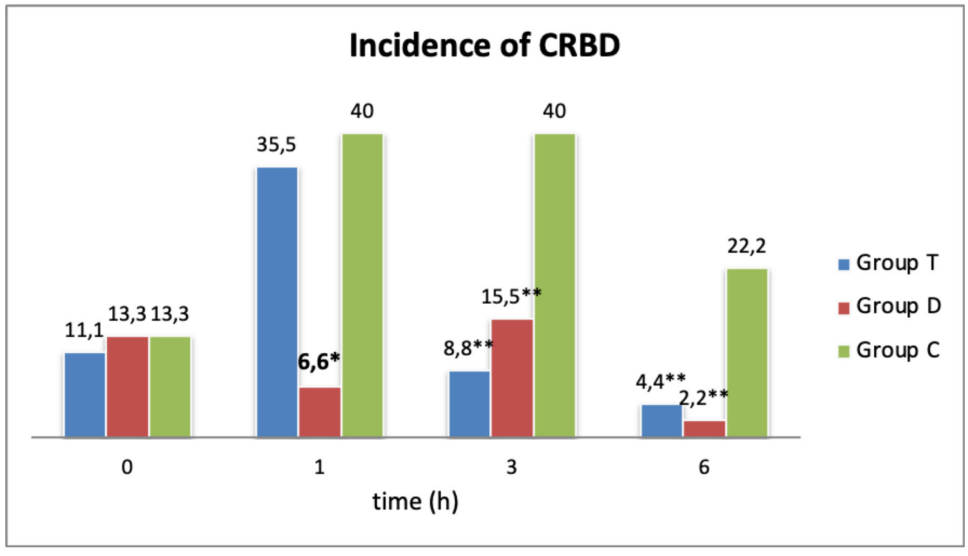

Figure 2. Incidence of CRBD. Dexmedetomidine is more effective in reducing the frequency of CRBD in the early period. Data are presented as n (%). Chi-square test; *p<0.001, for comparison between group D vs. groups T and C, **p<0.01, for comparison between groups T and D vs. group C and p>0.05 for comparison between group T vs. D

CRBD: Catheter-related bladder discomfort

Table 2. Severity of CRBD					
		t_0	t_1	t_2	t_3
Group T n (45)	**No**	17	11	17	32
	Mild	23	18	24	11
	Moderate	4	11	4	2
	Severe	1	5	0	0
Group D n (45)	**No**	18	15	17	25
	Mild	21	27	21	19
	Moderate	4	2	7	1
	Severe	2	1	0	0
Group C n (45)	**No**	24	14	10	12
	Mild	15	13	17	23
	Moderate	4	9	14	8
	Severe	2	9	4	2
p-value	*	0.467	**0.032**	**0.005**	**0.0001**
	**	0.972	**0.015**	0.708	0.168
	a	0.272	0.883	**0.003**	**0.0001**
	β	0.301	0.031	**0.010**	**0.001**

Dexmedetomidine and tramadol decrease the severity of CRBD
CRBD: Catheter-related bladder discomfort, t_0: 0 h, t_1: 1 h, t_2: 3 h, t_3: 6 h postoperatively
*: Kruskal-Wallis test for comparison between three groups
**: Mann-Whitney u test for in comparison between group T vs. D
a: Mann Whitney test for in comparison between group T v.s C
β: Mann-Whitney u test for in comparison between group D vs. C
Bold values denote statistical significance at the p<0.05 level

Table 3. Patients' postoperative pain scores (NRS) and post-anesthesia recovery times				
	Group T	**Group D**	**Group C**	**p-value**
t_0	10 (10-10)	10 (10-10)	10 (10-30)	**0.0001*** 0.848**
t_1	10 (10-30)	10 (10-40)	30 (10-50)	**0.005*** 0.365**
t_2	30 (10-40)	20 (10-40)	20 (10-40)	0.910*
t_3	10 (10-20)	10 (10-30)	20 (10-30)	0.491*
Recovery time (min)	10 (10-15)	15 (15-20)	10 (10-15)	**0.0001**[a] 0.075**

Dexmedetomidine may delay post-anesthesia recovery time
NRS: Numeric rating scale; t_0: 0 h, t_1: 1 h, t_2: 3 h, t_3:6 h postoperatively
NRS and recovery time expressed as median (Interquartile range)
*: Kruskal-Wallis test for comparison between groups T and D vs. group C
**: Mann-Whitney U test for comparison between groups T vs. D
a: Kruskal-Wallis test for comparison between group D vs. groups T and C

only the efficacy of tramadol and dexmedetomidine in preventing CRBD. The dose-response relationship and efficacy of the treatment were not evaluated. Finally, it was difficult for the patients to differentiate between postoperative surgical pain and CRBD. We considered that acetaminophen, which we used for postoperative analgesia, may have masked the CRBD symptoms, although its effect on relieving postoperative CRBD has not been reported.

Conclusion

Intraoperative tramadol and dexmedetomidine administration are useful agents for the prevention and treatment of CRBD and postoperative analgesic activity. The effect of dexmedetomidine on CRBD is more potent than that of tramadol in the early period. However, dexmedetomidine may delay post-anesthesia recovery time.

Ethics

Ethics Committee Approval: Ethical committee approval was obtained from University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital (date: 05.08.2019, approval number: 69/15).

Informed Consent: Written informed consent was obtained from all patients.

Peer-reviewed: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.O.S., A.D., Design: F.O.S., A.D., Data Collection and/or Processing: F.K.A., O.Y.M., R.P., F.S., Analysis and/or Interpretation: F.O.S., F.K.A., Literature Research: O.Y.M., F.S., Writing: F.O.S., R.P., A.D.

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

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Original Article

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Investigation of the Change in the Incidence of Neural Tube Defects in the Eastern Black Sea Region of Turkey by Years and its Relationship with Folic Acid Use: A Case-control Study

Omer Demir*, Hidayet Sal**, Mirac Ozalp***, Murat Topbas****

*Karadeniz Technical University Faculty of Medicine, Department of Gynecology and Obstetrics, Trabzon, Turkey

**Arakli Bayram Halil State Hospital, Clinic of Gynecology and Obstetrics, Trabzon, Turkey

***University of Health Sciences Turkey, Istanbul Prof. Dr. Cemil Tascioglu City Hospital, Clinic of Gynecology and Obstetrics, Istanbul, Turkey

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

Abstract

Aim: This study aimed to determine the change in neural tube defects (NTD) incidence in Trabzon, a province of the Eastern Black Sea region, and evaluate the efficiency of folic acid use on NTD.

Methods: The present study was a retrospective case-control study. The case group of the study consisted of those diagnosed with fetal NTD in the intrauterine period between 2015 and 2020. The control group were selected by matching the ages in the case group with ± two standardized years. The total number of births in the province was obtained from the Turkish Statistical Institute data, and the NTD incidence was determined accordingly.

Results: Between the aforementioned years, the number of cases who had NTD-complicated pregnancies and were delivered in our clinic was 88. When the use of folic acid before and in the first trimester of pregnancy was compared, a statistically significant difference was determined between the groups ($p<0.001$). The use of folic acid during pregnancy was similar in both groups ($p=1$).

Conclusion: Neural tube defects is a preventable condition by using folic acid before and during the first trimester of pregnancy. Hence, the importance of using folic acid in family planning and prenatal counseling should not be forgotten.

Keywords: Black Sea, case-control study, folic acid, neural tube defects, pregnancy

Introduction

Neural tube defects (NTDs) occur congenitally between the embryological third and fourth weeks due to abnormal central nervous system development (1). NTD is rare and has a prevalence of 1 in 1,200 among live births in the United States and between 1 in 1,000 and 3-5 in 1,000 worldwide (2).

There are various factors in NTD etiology, such as drug exposure, geographical and ethnic differences, chromosomal abnormalities, single-gene disorders, folic acid deficiency, and family history of NTD (3). Pioneering studies on NTD by Smithells et al. (4) emphasized the importance of vitamin intake during pregnancy. Subsequently, a randomized, double-blind, placebo-controlled study by the MRC Vitamin Study Research Group in 1991 demonstrated that supplementation of 4 mg of folic acid daily resulted in a threefold reduction in the risk of NTD relapse (5). Today, NTD formation can be prevented at a significant rate of 15.5%-58% with maternal folic acid supplementation (6). The recommendation of folic acid use is the most critical part of preconception counseling regarding NTD prevention in family planning (7).

Although NTD incidence in Turkey varies between 3-5.8 per 1,000 according to the region, it is accepted as

Address for Correspondence: Omer Demir,
Karadeniz Technical University Faculty of Medicine, Department of Gynecology and Obstetrics, Trabzon, Turkey
Phone: +90 533 626 77 77 E-mail: itf.omerdemir@gmail.com ORCID: orcid.org/0000-0003-4376-8733
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3 per 1,000 on average (8,9). In a guideline published by the Ministry of Health in Turkey in 2002, it was stated that all women of reproductive age should take daily folic acid supplementation during the preconception period and during the first trimester of pregnancy (10). The highest NTD frequency was observed in Northern and Eastern Anatolia in the previous studies and the lowest in Western Anatolia (11). The effect of Chernobyl on NTD has been discussed in prior studies examining the change in NTD incidence over the years in Trabzon province of the eastern Black Sea region (12).

At the time of these past studies performed in our clinic (12), folic acid supplementation had not been provided in Turkey. The present study aimed to determine the change in the incidence of NTD in Trabzon, a province of the Eastern Black Sea region, and to evaluate the efficiency of folic acid use on NTD.

Materials and Methods

Compliance with Ethical Standards

The ethical approval was obtained from the Karadeniz Technical University Faculty of Medicine Local Ethics Committee to perform the study (2020/266).

Study Design

The study was designed as a retrospective case-control study. The case group of the study consisted of those diagnosed with fetal NTD in the intrauterine period between 2015 and 2020 in the Department of Obstetrics and Gynecology of Karadeniz Technical University Hospital. The cases in the control group were selected by matching the ages in the case group with ± two standardized years. These controls were chosen from patients without any risk factors and did not require folic acid use due to any medical disease or condition or during pregnancy.

By matching the cases according to their ages, an equal number of cases were selected within the specified years, and the control group was formed.

The Gynecology and Obstetrics Clinic of our faculty hospital is a tertiary reference clinic in the Eastern Black Sea Region (provinces within this region include Rize, Artvin, Trabzon, Giresun, Ordu, Gumushane, and Bayburt) where fetal anomaly screenings are performed. The perinatology unit of this clinic is the primary perinatology center in the Eastern Black Sea Region. Like other similar studies, data for this study was collected from birth records and hospital automation systems. In this context, all NTD diagnoses (anencephaly, acrani, exencephaly, spina bifida, hydrocephalus, cephalocele, meningocele, meningomyelocele, encephalocele, iniencephaly, craniostosis, Arnold Chiari malformation) were reviewed from the hospital automation system to determine the incidence of NTD. The total number of births in the province was obtained from the Turkish Statistical Institute data, and NTD incidence was determined accordingly.

The incidence was calculated by dividing the number of births with NTD by the total number of births in the province in that year. Obviously, this will not give a direct NTD incidence because although our faculty hospital is the primary perinatology center in the province, the fact that the number of births with NTD in other hospitals in the province is unknown, making it an indirect incidence study. However, since most fetuses with anomalies were evaluated and delivered in our faculty, the total number of births in the province was considered the total number of births.

The cases in both the case and control groups were those who were born in our hospital regardless of their residence. As a result, possible sampling errors were attempted to be avoided.

After the cases were extracted from the records, they were called individually, and their pregnancies complicated by NTD were questioned. The use of folic acid before pregnancy, the use of folic acid in the first trimester of pregnancy, and whether they used folic acid-containing vitamins during pregnancy were asked and noted. Additionally, although they were available in the hospital records, their medical and drug use histories were also queried.

Statistical Analysis

The SPSS 21 program designed for Windows was used for the statistical analysis. All continuous variables were presented as mean and SD values, while categorical variables were expressed as percentages of the total group. A p-value of <0.05 was considered statistically significant, and all statistical tests were planned by comparing the two groups. An independent samples t-test compared categorical variables in the two groups. The chi-square test was used to compare cases and control groups, and the estimated risk was determined. Odds ratio analyses were performed, and the effect of folic acid use on NTD incidence was determined.

Results

Between the aforementioned years, the number of patients who had NTD-complicated pregnancies and were delivered in our clinic was 88. Considering the distribution of these cases by year, there were ten complicated pregnancy deliveries with NTD in 2015, while 12 deliveries occurred in 2020. The change in the incidence of NTD according to the number of births in Trabzon province by year was as presented in Figure 1. The highest incidence of NTD in the years indicated was in 2017, at 2 per 1,000 (Figure 1).

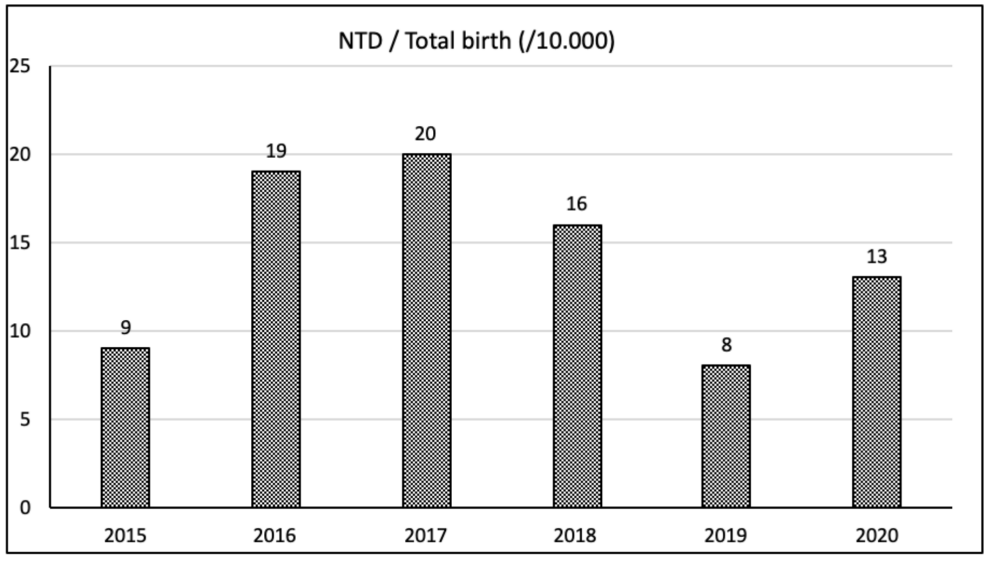

Figure 1. Change of NTD incidence by years
NTD: Neural tube defect

In the comparative analysis of the groups, there was no statistically significant difference in terms of age parameter (p=0.863) between the case and control groups regarding folic acid use. When the use of folic acid before and in the first trimester of pregnancy was compared, a statistically significant difference was determined between the groups (p<0.001). The use of folic acid during pregnancy was similar in both groups (Table 1).

The percentages of reducing the NTD risk by using folic acid before and in the first trimester of pregnancy were 91.2% and 91%, respectively (Table 2).

Discussion

According to the current study data, NTD incidence between 2015 and 2020 in Trabzon, where our clinic, the tertiary perinatology center of the Eastern Black Sea region of Turkey, is located, is between 0.8-2 per 1,000.

Table 1. Comparative analysis of the groups' mean age and folic acid use rates

	Case Group Pregnancy complicated with NTD (n=88)	Control Group Pregnancy uncomplicated with NTD (n=88)	p-value
Age	27.7±5.6	27.8±2.6	0.863'
Folic acid use before pregnancy	4 (4.5%)	31 (35.2%)	**0.000^**
Folic acid use in the first trimester of pregnancy	24 (27.3%)	64 (72.7%)	**0.000^**
Folic acid use during pregnancy (all trimesters)	18 (20.5%)	18 (20.5%)	1^

NTD: Neural tube defect
': Independent samples t-test, ^: The chi-square test

Table 2. The degree of effect of folic acid use on the NTD rate

	Case Group Pregnancy complicated with NTD (n=88)	Control Group Pregnancy uncomplicated with NTD (n=88)	p-value	OR	95% Confidence Interval	
					Lower	Upper
Folic acid use before pregnancy	4 (4.5%)	31 (35.2%)	**0.000'**	**0.088**	0.029	0.262
Folic acid use in the first trimester of pregnancy	24 (27.3%)	64 (72.7%)	**0.000'**	**0.090**	0.044	0.182

NTD: Neural tube defect
': The chi-square test and Odds ratio analysis

We observed that the use of folic acid before pregnancy prevented NTD by 91.2%, and its use in the first trimester by 91%. Consequently, the use of folic acid before and in the first trimester of pregnancy is found to be quite effective in preventing NTD. This effect is thought to be due to the contribution of folic acid to DNA formation between the third and fourth embryological weeks of neural tube development. The use of folic acid after the first trimester of pregnancy does not affect preventing NTD.

Neural tube defects occurs at a rate of 1-2 per 1,000 births in the world (13). The NTD rate is higher in countries with low or no folic acid use. In India, where the use of folic acid is uncommon, NTD incidence ranges from 6.5 to 8.2 per 1,000 births (stillbirths and live births) (14). In a Canadian study showing that the NTD rates decreased with the use of folic acid, the periods before and after the use of folic acid were compared. While NTD rates increased from 1986 to 1995, there was a decrease in NTD rates from 1995 to 1999 due to folic acid use (15). In Scotland, the fortification of cereal products with folic acid has been shown to reduce the incidence of NTD to 1.17 per 1,000 births (16). The average incidence of NTD in Trabzon between 2015 and 2020 was 1.44 per 1,000. This rate is similar to that in countries with folic acid use (13,16).

Folic acid use reduces NTDs, and all women of reproductive age should consume at least 400 µg folic acid per day to protect against NTDs (5). It is used at higher doses in high-risk groups (5,17). Low adherence to treatment, inability to receive preconceptional counseling due to unplanned pregnancies, low awareness of folic acid use, and stopping food supplementation due to unproven harm by European governments (18) stand out as the most critical problems in NTD prevention (19). Nevertheless, folic acid supplementation has been identified as the best approach to improving blood folate levels at a population level and has been mandated in several countries (10,20). Turkey also recommended using folic acid in the periconceptional period and the first trimester of pregnancy in 2002 to prevent NTD (10). In a study performed in Barcelona, a decrease in the prevalence of neonatal NTD was observed with primary prevention programs such as periconceptional folic acid supplementation (21). In our current study, we obtained results that support the previous studies. We have determined that the use of folic acid in the preconceptional period and the first trimester of pregnancy is quite efficient in preventing NTD. This study concluded that the risk of NTD decreased by 91.2% with the use of folic acid in the preconceptional period and by 91% with the use of folic acid in the first trimester of pregnancy. We revealed that the use of folic acid after the first trimester of pregnancy did not change the incidence of NTD ($p>0.05$). Several studies in the literature have reported that folic acid use throughout pregnancy has no effect on NTD and may affect homocysteine metabolism and the development of pre-eclampsia (22,23).

In our country, folic acid started to be used during pregnancy after the 2000s (10). When the studies before the 2000s were examined in a comparative analysis of the country's data and EUROCAT records (24), NTD rates were found to be high in Turkey (25). This is thought to be due to the later use of folic acid in the country compared to European countries. In Europe in the early 1980s, the incidence of NTD was much higher in the British Isles than in continental Europe (26), while the incidence of NTD in Turkey was very high even compared with rates in the British Isles in the 1980s (27). Mocan et al. (28) examined the population of Ankara, which was 3,235,637 in 1990, with the surrounding districts and villages. Before 1987, the incidence of NTD was 3.83 per 1,000 births (28). Some researchers have reported an NTD incidence of 1.5-2.6 per 1000 births in Turkey. The NTD rate in eastern Turkey has been reported as 4.5 (25). Himmetoglu et al. (29) reported that the overall incidence of congenital anomalies was 1.11%, and the incidence of NTD was 0.27% in their study population. Tunçbilek et al. (11) observed that 66 out of a total of 21,907 live births and stillbirths had NTDs. The incidence rate of NTDs was 30.1 per 10,000 births.

There are also studies after the 2000s when folic acid started to be used in our country. In 2000, the incidence of NTD was found to be 1.5 per 1,000 births in a study conducted by Mandiracioğlu et al. (30) in Izmir, western Turkey. Again, in a study performed in Afyonkarahisar, located in the west of the country, the incidence of NTD was 3.59 in 1,000 total pregnancies in 2004 (9). In a study conducted in Van province in eastern Turkey (31), the NTD rate was found to be 26 per 1,000 births between 2012 and 2015, and 13 per 1,000 births in another study between 2016 and 2018 (32). The authors considered that the slightly higher NTD rates than the actual rates were due to the low socioeconomic level and because the patients only applied to the hospital for delivery or in the late stages of pregnancy (31,32). In this study, the incidence of NTD in northeast Turkey has varied between 0.8 and 2 per 1,000 in the last five years. This rate is similar to the years after starting to use folic acid in Turkey and is lower than before the 2000s. The NTD rate in the northeast is similar to that in the west and has lower rates than in the east. We think that factors such as socioeconomic level, awareness of folic acid use, and regular follow-up of pregnancy may have caused this difference. We would like to emphasize once again how vital the use of folic acid is in preventing NTD.

Folic acid deficiency causes hypomethylation of DNA, insufficient DNA repair, and increased chromosomal breakage (3). One study revealed that folic acid deficiency increases spontaneous chromosome damage and interacts synergistically with ionizing radiation (33). Radiation causes congenital disabilities due to the ability of radioisotopes to bind to fetal cells, tissues, and DNA (34). The risk of radiation-induced anencephaly is increased in rat zygotes (34,35). Four radioactive fallouts have occurred to date: Hiroshima and Nagasaki (1945); Marshall Islands (1952), Chernobyl (1986), and Fukushima (2011). Many results, including researchers from our country, have been reported about the NTD formation of radioactive fallout after the Chernobyl disaster (12,14,28,36,37). However, the EUROCAT working group in Europe did not confirm the relationship between NTD and radiation (38). There are publications stating that NTD rates have increased due to the effect of radiation on the coast of Turkey facing the Black Sea (Bursa and Trabzon provinces) (12,37). By 1993, these high NTD rates in Turkey were attributed to interpretation errors and small hospital data sets (39). However, after the 2011 Fukushima disaster, the incidence of anencephaly and spina bifida in the western states of the USA increased by 13% compared to the pre-disaster period (40,41). In this context, the fact that two studies on the subject (12,37) were performed in the same hospital in the province of Trabzon, where our study was also conducted, fills a crucial gap in the literature with our current study. In the first study using Mocan et al. (37) in 1990, they stated that the continuing high incidence of NTD and anencephaly in 1988 and 1989 compared to previous years was probably due to the consumption of radioactive foods, especially tea, by the local people in this region. Again, in the second article published by the same team in 1992 (12), they continued the previous study from 1989 to the end of 1999 and stated the incidence of NTD as 6.16 per 1,000 births. They stated that the higher NTD rate might be because the records kept in the period from the previous study to this day were recorded more carefully (12).

In our current study, the mean NTD incidence (between 2015 and 2020) was 1.44 per 1,000 births, while the mean NTD incidence in the pre-Chernobyl period (between 1981 and 1986) was reported as 2.12 per 1,000 births, and 4.98 per 1,000 births in the post-Chernobyl period (between 1987-1990) (12,37). Considering the average NTD rate of 3.08 per 1,000 births between 1981 and 1990, this rate has dropped to the range of 0.8-2 after folic acid use. We can consider that folic acid reduces NTD rates once again. With these three NTD incidence studies performed in the same province between the 1980s and the 2010s, it is concluded that radiation does not have a long-term effect on creating NTD. The efficiency of folic acid use in this cannot be ignored. This brings to mind, "Is it possible that the reason why the long-term effects of Chernobyl do not continue is the use of folic acid?" which begs the question.

Study Limitations

Although our hospital is the reference center of the region regarding fetal anomalies, the fact that infants with NTD may have been delivered in other hospitals in the province or at home is unknown, and therefore a clear incidence cannot be given, and the retrospective design of the study can be considered a limitation of the study. The fact that it revealed the change in NTD incidence in the region after many years and the effect of folic acid on NTD incidence in our region, which is thought to have long-term effects of radiation, are also the study's strengths.

Conclusion

Neural tube defects is a preventable condition with the use of folic acid before and during the first trimester of pregnancy. Accordingly, the importance of using folic acid in family planning and prepregnancy counseling should not be forgotten. The NTD incidence in Trabzon, the reference center of the Eastern Black Sea Region, is similar to Turkey and world data. The effect of Chernobyl-related radiation on the incidence of NTD in the long term cannot be clearly demonstrated due to the use of folic acid, but it is concluded that the use of folic acid is also protective against a possible long-term effect of radiation.

Ethics

Ethics Committee Approval: The ethical approval was obtained from the Karadeniz Technical University Faculty of Medicine Local Ethics Committee to perform the study (2020/266).

Informed Consent: The present study was a retrospective case-control study.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: O.D., H.S., M.T., Design: O.D., M.T., Data Collection and/or Processing: O.D., H.S., M.O., Analysis and/or Interpretation: O.D., H.S., M.O., M.T., Literature Research: O.D., H.S., M.O., M.T., Writing: O.D., H.S., M.O., M.T.

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Original Article

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Comparison of Incidence and Clinical Outcomes of COVID-19 among Healthcare Workers in the Pre-vaccination and Post-vaccination Periods: A Real-world Impact Study

Serkan Surme*,**, Betul Copur*, Osman Faruk Bayramlar***, Gulsah Tuncer*, Yusuf Emre Ozdemir****, Filiz Pehlivanoglu*, Gonul Sengoz*

*University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey

**Istanbul University-Cerrahpasa, Institute of Graduate Studies, Department of Medical Microbiology, Institute of Graduate Studies, Istanbul, Turkey

***Bakirkoy District Health Directorate, Clinic of Public Health, Istanbul, Turkey

****University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey

Abstract

Aim: Real-life data on the effect of coronavirus disease-2019 (COVID-19) vaccination is limited. We aimed to compare the incidence of COVID-19 among healthcare workers (HCWs) in the pre-vaccination and post-vaccination periods during the COVID-19 pandemic and identify associated factors for COVID-19 development.

Methods: In this single-center and cross-sectional study, HCWs employed in a tertiary care hospital were included. Pre-vaccination (14 October, 2020 and 14 January, 2021) and post-vaccination periods (1 March, 2021 and 1 June, 2021) were compared. A subgroup analysis was performed on HCWs without a previous history of COVID-19. Additionally, univariate regression analysis of COVID-19 development in the post-vaccination period was performed.

Results: Of 2,922 HCWs, 2,096 (71.7%) were vaccinated. The incidence of COVID-19 was higher in the pre-vaccination period (16.3%) than in the post-vaccination (6.6%) ($p<0.01$). In the subgroup analysis, the incidence of COVID-19 was 16.6% in the pre-vaccination period and 8.1% in the post-vaccination period ($p<0.01$). Previous history of COVID-19 ($p<0.01$) and double-dose vaccination ($p<0.01$) were associated with a decreased risk of COVID-19 development.

Conclusion: This study demonstrates the real-life impact of COVID-19 vaccination in reducing disease development and preventing poor clinical outcomes in a setting where the vaccination rate among HCWs was fairly low.

Keywords: COVID-19, vaccination, incidence, healthcare workers

Introduction

The coronavirus diseases-2019 (COVID-19) pandemic had a magnificent impact on global health, especially on healthcare workers (HCWs). Researchers from Turkey and all around the world made a great effort to better understand the epidemiology, clinical features, risk factors, and predictors of poor clinical outcomes, including the need for hospital admission, intensive care unit (ICU) transfer, and in-hospital death (1-3).

Nevertheless, treatment of and prevention against COVID-19 are still under research (4,5). Vaccination is one of the most effective methods of preventing infectious

Address for Correspondence: Gulsah Tuncer,
University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey
Phone: +90 543 579 94 09 E-mail: gulsah_durak_51@hotmail.com ORCID: orcid.org/0000-0002-9841-9146
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diseases and the poor clinical outcomes that accompany them. Also, there is evidence that CoronaVac, which is an inactivated whole-virion severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) vaccine, is safe and effective against COVID-19 (6). A randomized clinical efficacy trial has demonstrated that COVID-19 vaccination decreased the risk of COVID-19 development and COVID-19 related poor outcomes (7). However, there are a limited number of vaccine studies on the real-life experiences of preventing COVID-19 development, related hospitalization, and mortality among HCWs.

Therefore, we compared the incidence and clinical outcomes of COVID-19 among HCWs in the pre-vaccination and post-vaccination periods during the COVID-19 pandemic. Additionally, factors affecting the development of COVID-19 in the post-vaccination period were analyzed.

Materials and Methods

Compliance with Ethical Standards

All procedures performed in this study were in accordance with the ethical standards of the Declaration of Helsinki. This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 96-2022, date: 11.05.2022) and the Advisory Board on Coronavirus Research of the Republic of Turkey Ministry of Health Written informed consent was waived because of the retrospective nature of this study.

Study Design

In this single-center and cross-sectional study, HCWs employed in a tertiary care hospital were enrolled. Demographic features, clinical characteristics, and outcomes of HCWs with COVID-19 were recorded via data-sheets from follow-up forms. The vaccination status of all HCWs was collected via the hospital electronic medical record system.

The pre-vaccination period was defined as the 3-month period before the first vaccination was started (between October 14, 2020 and January 14, 2021). The post-vaccination period was defined as the 3-month period from 15 days after the second dose of vaccination (between 1 March, 2021 and 1 June, 2021).

The primary outcome was the development of COVID-19. The secondary outcome was a composite endpoint including hospital admission, ICU transfer, and in-hospital death. To detect the differences in the primary and secondary outcomes between the two periods, pre-vaccinated and post-vaccinated periods were compared. Additionally, a subgroup analysis was performed on HCWs without a previous history of COVID-19. The incidence rates of COVID-19 in the community and in HCWs in our study group were compared. Community-related data were obtained from the Republic of Turkey Ministry of Health's Coronavirus Information Platform (8). Prior to November 25, 2020, data were determined by proportioning patient data based on the symptomatic COVID-19 incidence rate. Moreover, HCWs with and without COVID-19 in the post-vaccination periods were compared to identify protective factors for developing COVID-19.

Statistical Analysis

Categorical parameters were represented as frequencies (n) and percentages (%), whereas quantitative parameters were represented as median and interquartile ranges. The chi-square test or Fisher's exact test were used to compare categorical data. The Kolmogorov-Smirnov test was used for normal distribution analysis. The Independent sample t-test was applied for normally distributed variables, while the Mann-Whitney U test was performed for variables without normal distribution. A univariate regression analysis for developing COVID-19 was performed. A p-value less than 0.05 was considered significant. Odds ratios (OR) with 95% confidence intervals (CI) were determined. The analyses were performed using IBM SPSS-21 (Statistical Package for Social Sciences, IL, USA).

Results

A total of 2922 HCWs were enrolled in this study. Of these, 1,179 (40.3%) were males. The mean age was 33.3±9.5 years. Overall, the vaccination rate in the study group during the first 3 months of the vaccination program was 71.7%. The single-dose and double-dose vaccination rates were 22.9% (n=668) and 48.9% (n=1428), respectively. Demographic characteristics of HCWs according to vaccination status are represented in Table 1.

Of 2,922 HCWs, 476 (16.3%) had COVID-19 in the pre-vaccination period, whereas 193 (6.6%) had COVID-19 in the post-vaccination period ($p<0.01$). Clinical deterioration as a secondary outcome occurred in 22 (0.8%) HCWs in the pre-vaccination period, whereas 11 (0.4%) HCWs had poor clinical outcomes in the post-vaccination period ($p=0.06$) (Table 2).

In the subgroup analysis, after excluding HCWs with a previous history of COVID-19 in the last 3 months, the incidence of COVID-19 was 16.6% in the pre-vaccination period and 8.1% in the post-vaccination period ($p<0.01$) (Table 3).

The weekly and cumulative incidence rates showed the positive impact of the COVID-19 vaccination program in preventing COVID-19 development among HCWs in

our study group. While the concurrent lockdown might have influenced our results, these same trends did not occur either during the previous lockdown among HCWs in our hospital or during the current lockdown at the community level. The weekly incidence rates of COVID-19 in the community and HCWs in our study group are demonstrated in Figure 1. The cumulative incidence rates of COVID-19 in the community and HCWs in our study group are demonstrated in Figure 2.

When we evaluated the factors affecting the development of COVID-19 in the post-vaccination period, previous history of COVID-19 (OR: 0.01, CI: 0.00-0.17,

Table 1. Demographic characteristics of healthcare workers according to the vaccination status in the first 3-month period

Parameters	Total (n=2,922)	Unvaccinated (n=826)	Single-dose vaccinated (n=668)	Double-dose vaccinated (n=1,428)
Age (mean ± SD)	33.3±9.5	33.5±10.1	32.3±9.0	33.6±9.4
Sex				
Male, n (%)	1,179 (40.3)	338 (40.9)	271 (40.6)	570 (39.9)
Female, n (%)	1,743 (59.7)	488 (59.1)	397 (59.4)	858 (60.1)
Comorbid diseases, n (%)	758 (25.9)	176 (21.3)	154 (23.1)	428 (30.0)
HT, n (%)	442 (15.1)	101 (12.2)	92 (13.8)	249 (17.4)
DM, n (%)	270 (9.2)	65 (7.9)	49 (7.3)	156 (10.9)
CAD, n (%)	137 (4.7)	34 (4.1)	27 (4.0)	76 (5.3)
Asthma/COPD, n (%)	32 (1.1)	5 (0.6)	8 (1.2)	19 (1.3)
Pre-vaccination COVID-19 history, n (%)	534 (83.7)	326 (63.7)	47 (94.9)	161 (90.1)
Pre-vaccination COVID-19 history (last 3 months), n (%)	58 (2.0)	26 (3.1)	13 (1.9)	19 (1.3)
Pre-vaccination COVID-19 history before the last 3-month, n (%)	476 (16.3)	300 (36.3)	34 (5.1)	142 (9.9)

HT: Hypertension, DM: Diabetes mellitus, CAD: Chronic artery disease, COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, COVID-19: Coronavirus disease-2019

Table 2. Comparison of pre-vaccination and post-vaccination periods in terms of COVID-19 development and the clinical deterioration

Parameters	Pre-vaccination period (n=2922)	Post-vaccination period (n=2922)	
	n (%)	n (%)	p-value
COVID-19			
Yes	476 (16.3)	193 (6.6)	**<0.01**[*]
No	2,446 (83.7)	2,729 (93.4)	
COVID-related hospitalization			
Yes	22 (0.8)	11 (0.4)	0.06[*]
No	2,900 (99.2)	2,911 (99.6)	
Need for ICU admission			
Yes	1 (0.03)	1 (0.03)	1.00[†]
No	2,921 (99.97)	2,921 (99.97)	
In-hospital death			
Yes	0 (0)	1 (0.03)	0.09[†]
No	2,922 (100)	2,921 (99.97)	
Composite end-point[a]			
Yes	22 (0.8)	11 (0.4)	0.06[*]
No	2,920 (99.2)	2,911 (99.6)	

[a]: Composite end-point includes COVID-19 related hospitalization, need for ICU admission, and in-hospital death, [*]: Chi-square test, [†]: Fisher's exact test. Bold values represent statistical significance at the level of p<0.05. The incidence of COVID-19 was significantly higher in the pre-vaccination period (16.3%) than in the post-vaccination period (6.6%).
ICU: Intensive care unit, COVID-19: Coronavirus disease-2019

p<0.01) and double-dose vaccination against COVID-19 (OR: 0.37, CI: 0.27-0.52, p<0.01) as well as comorbid diseases, including diabetes mellitus (OR: 0.30, CI: 0.13-0.68, p=0.01) and chronic artery disease (OR: 0.31, CI: 0.10-0.97, p=0.03) were associated with a decreased risk of the disease development (Table 4).

Discussion

In this study, we presented a detailed analysis of vaccination profiles in 2,922 HCWs employed in a tertiary care teaching hospital, which is one of the pandemic epicenters in Istanbul, Turkey, and compared pre-vaccination and post-vaccination periods in terms of

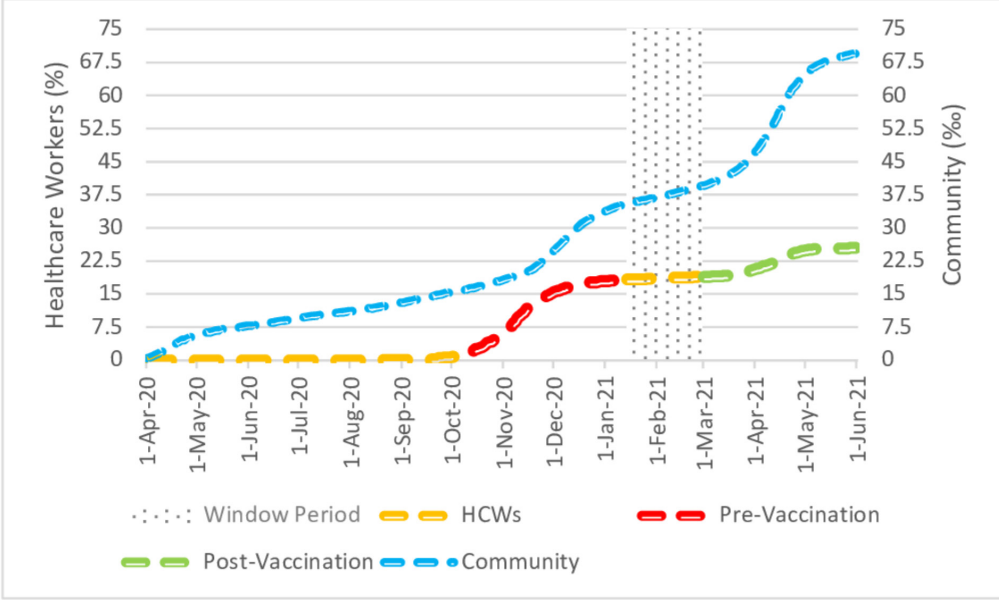

Figure 1. The cumulative incidence rates of COVID-19 in the community and HCWs

COVID-19: Coronavirus disease-2019, HCW: Healthcare workers

Table 3. Subgroup analysis of pre-vaccination and post-vaccination periods in terms of COVID-19 development and the clinical deterioration after exluding healthcare workers with previous history of COVID-19

Parameters	Pre-vaccination period (n=2,864)	Post-vaccination period (n=2,370)	
	n (%)	n (%)	p-value
COVID-19			
Yes	476 (16.6)	193 (8.1)	**<0.01***
No	2,388 (83.4)	2,177 (91.9)	
COVID-19 related hospitalization			
Yes	22 (0.8)	11 (0.5)	0.17*
No	2,842 (99.2)	2,359 (99.5)	
Need for ICU admission			
Yes	1 (0.03)	1 (0.04)	1.00†
No	2,863 (99.97)	2,369 (99.6)	
In-hospital death			
Yes	0 (0)	1 (0.04)	0.45†
No	2,864 (100)	2,369 (99.6)	
Composite end-point*			
Yes	22 (0.8)	11 (0.5)	0.17*
No	2,842 (99.2)	2,359 (99.5)	

*: Composite end-point includes COVID-19 related hospitalization, need for ICU admission, and in-hospital death, *: Chi-square test, †: Fisher's Exact test. Bold values represent statistical significance at the level of p<0.05. In the subgroup analysis after excluding HCWs with a previous history of COVID-19 in the last 3 months, the incidence of COVID-19 was significantly higher in the pre-vaccination period (16.6%) than in the post-vaccination period (8.1%).
ICU: Intensive care unit, COVID-19: Coronavirus disease-2019, HCW: Healthcore workers

the incidence and clinical outcomes of COVID-19. We analyzed the early impact (first 3 months) of the COVID-19 vaccination among HCWs. Therefore, the effect of COVID-19 vaccination on the risk of infection and clinical deterioration among HCWs was determined. Additionally, protective factors for the risk of COVID-19 development in the post-vaccination period were identified.

In a phase-3 efficacy trial, the efficacy of CoronaVac against SARS-CoV-2 infection was 50.7% (9). One retrospective study including HCWs in Brazil demonstrated

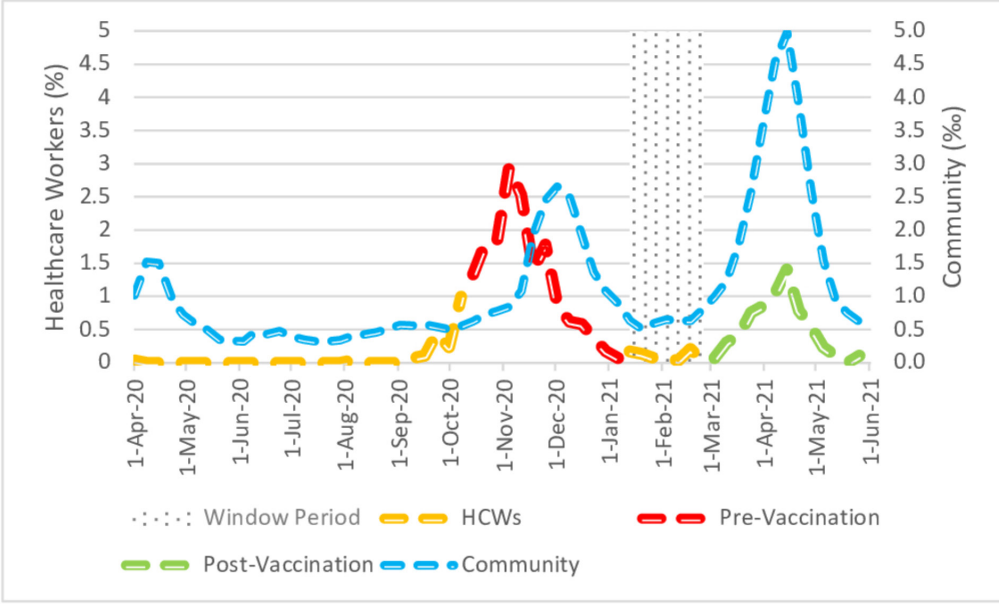

Figure 2. The weekly incidence rates of COVID-19 in the community and HCWs

COVID-19: Coronavirus disease-2019, HCW: Healthcare workers

Table 4. Univariate regression analysis for COVID-19 development in the post-vaccination period

Parameters		Presence		Absence		OR	CI	p-value
		n	%	n	%			
Sex								
Male		68	5.8	1,111	94.2	0.79	0.58-1.07	0.13
Female		125	7.2	1,618	92.8			
Comorbidity	Yes	38	5.0	720	95.0	0.68	0.48-0.99	**0.04**
	No	155	7.2	2,009	92.8			
DM	Yes	6	2.2	264	97.8	0.30	0.13-0.68	**0.01**
	No	187	7.1	2,465	92.9			
HT	Yes	23	5.2	419	94.8	0.75	0.48-1.17	0.20
	No	170	6.9	2,310	93.1			
COPD	Yes	2	6.3	30	93.8	0.94	0.22-3.97	0.94
	No	191	6.6	2,699	93.4			
CAD	Yes	3	2.2	134	97.8	0.31	0.10-0.97	**0.03**
	No	190	6.8	2,595	93.2			
Double-dose vaccination	Yes	53	3.7	1,375	96.3	0.37	0.27-0.52	**<0.01**
	No	140	9.4	1,354	90.6			
Previous history of COVID-19	Yes	0	0.0	534	100.0	0.01	0.00-0.17	**<0.01**
	No	193	8.1	2,195	91.9			

Bold values represent statistical significance at the level of p<0.05. Previous history of COVID-19 and double-dose vaccination against COVID-19 as well as comorbid diseases including diabetes mellitus and chronic artery disease were associated with decreased risk of the disease development.
HT: Hypertension, DM: Diabetes mellitus, CAD: Chronic artery disease, COPD: Chronic obstructive pulmonary disease, COVID-19: Coronavirus disease-2019, OR: Odds ratio, CI: Confidence interval

that while vaccination with CoronaVac was associated with a 0.5-fold decreased risk, the adjusted effectiveness was 36.8% of the double-dose vaccination against COVID-19 (10). Rovida et al. (11) showed that unvaccinated patients were transferred to the ICU more frequently (29.2%) than vaccinated patients (3.7%) among HCWs. In a community-based observational study, the efficacy of booster doses with various vaccines against the development of symptomatic COVID-19 was between 78.8% and 96.5% (12). In a recent impact-study conducted in Turkey, mortality was observed less frequently in patients who had COVID-19 in the post-vaccination period compared to those with COVID-19 in the pre-vaccination period (13). In a retrospective study in Denmark, the risk of hospitalization and mortality rate were significantly lower in vaccinated patients with solid organ transplants than in unvaccinated patients (14). In an Italian study, vaccinated patients had a less severe disease than unvaccinated patients, although vaccinated patients were older and had higher comorbidities (15). At the same time, McNamara et al. (16) demonstrated that vaccination programs decreased the risk of COVID-19 development, visits to emergency departments, and hospitalization among older adults.

Jara et al. (17) reported that the adjusted vaccine effectiveness was 65.9% for COVID-19 development, 87.5% for COVID-19 related hospitalization, 90.3% for preventing ICU admission, and 86.3% for preventing death. A retrospective real-life Turkish study that included HCWs found waning immunity in HCWs vaccinated with CoronaVac and the researchers reported that the unadjusted and adjusted effectiveness for preventing COVID-19 development was 47% and 39%, respectively (18). In our study, the incidence of COVID-19 was lower in the post-vaccination period compared to the pre-vaccination period. Moreover, COVID-19 vaccination and previous history of COVID-19 were found as protective factors for the disease's development. Additionally, HCWs with comorbid diseases had COVID-19 less frequently. This could be due to the high compliance of the HCWs with comorbid diseases. In this study, poor clinical outcomes occurred less frequently in the post-vaccination period compared to the pre-vaccination period.

In a study that included HCWs in India, the vaccine effectiveness against COVID-19 development was about 44% and 89% for partially and fully vaccinated HCWs, respectively. Haas et al. (19) demonstrated that the incidence of COVID-19 and related poor outcomes declined with the increased vaccination rate. In a study from the United States, they detected a significant decline (about 50%) in the daily COVID-19 cases in the 21-25 day post-period after the initial doses of vaccination (20). Another study comparing the pre- and post-vaccination periods in the United States found that as the vaccination rate increased, COVID-19 and related-poor clinical outcomes decreased. Additionally, the researchers revealed that older adults had the highest vaccination rate and a greater decline (up to 66%) was observed in the older adults (21). In the study by De Faria et al. (22), the effectiveness two weeks after the second dose of CoronaVac among HCWs was 50.7%. Toniasso et al. (23) reported that the incidence of COVID-19 decreased by 65% in people with a previous history of COVID-19 in the post-vaccination period.

Shoukat et al. (24) reported a 30% decline in COVID-19 cases, a 51% decline in hospitalizations, and a 48% decline in deaths compared with the expected rates between pre-vaccination and post-vaccination periods, although single and double-dose vaccination rates among adults were 64% and 69%, respectively. In a cohort that comprised more than 90% fully vaccinated older adults, the vaccine effectiveness for vaccinated people with no known prior COVID-19 was 81.8% (25). Cavanaugh et al. (26) reported that in a nursing facility, approximately 90% of residents and 52% of HCWs were fully vaccinated and vaccine protection rates for COVID-19 development, hospitalization, and death were 66%, 94%, and 94%, respectively. Additionally, they revealed that the vaccination effectiveness for developing COVID-19 among HCWs was 76%. As a result, studies conducted with different types of vaccines, study protocols including study populations and time frame, viral dynamics including SARS-CoV-2 variants, and COVID-19 measures such as lockdown applications, have different results in preventing COVID-19 and related poor outcomes. However, most studies have confirmed either the efficacy, effectiveness, or positive impact of COVID-19 vaccines.

Study Limitations

Our study had some limitations. First, this study was conducted retrospectively in a single center. Second, given the study design, measuring the efficacy or effectiveness of COVID-19 vaccination could not be possible. We evaluated pre-vaccination and post-vaccination periods and could compare the two periods. Comparing two different periods does not reflect either vaccine efficacy nor vaccine effectiveness. However, this study allowed us to measure the impact of COVID-19 vaccination among HCWs in the real world setting. Third, different pandemic dynamics, such as viral mutations, lockdown applications, and community compliance with COVID-19 measures, may influence the impact of COVID-19 vaccination. However, this study had several strengths. First, we could closely evaluate the possible cases with active surveillance since the study population was comprised of HCWs in our pandemic hospital. Second, we could measure several possible confounding variables, including age, sex, and

comorbid conditions. These variables were not found as significant covariates for each outcome in our study setting comprising HCWs. Third, to mitigate the possible effect of the prior SARS-CoV-2 infection on cases, we performed subgroup analysis after excluding HCWs with a previous history of COVID-19 infection in the last 3 months.

Conclusion

This study demonstrates the real-life impact of vaccination against COVID-19 in both reducing disease development and preventing poor clinical outcomes in a setting where the vaccination rate among HCWs is fairly low. Additionally, previous history of COVID-19 and COVID-19 vaccination were detected as protective factors for the disease's development.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 96-2022, date: 11.05.2022)

Informed Consent: Written informed consent was waived because of the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.S., B.C., Design: S.S., B.C., O.F.B., Y.E.O. Data Collection or Processing: B.C., G.T., Analysis or Interpretation: S.S., B.C., O.F.B., G.T., Y.E.O., F.P., G.S., Literature Search: S.S., B.C., Y.E.O., Writing: S.S, B.C., O.F.B., G.T., Y.E.O.

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

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Original Article

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Relationship Between the Nasopharyngeal Swab Sampling Method, Nasal Obstruction, and SARS-Cov-2 Positivity

Dogan Cakan*, Zeliha Kubra Cakan**, Semih Usaklioglu***, Yetkin Zeki Yilmaz*, Omer Uysal****, Hasan Ahmet Ozdogan*

*Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Otorhinolaryngology, Istanbul, Turkey

**Eyupsultan State Hospital, Clinic of Internal Medicine Istanbul, Turkey

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

****Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Biostatistics, Istanbul, Turkey

Abstract

Aim: We think that the nasopharyngeal swab sample should be taken bilaterally to improve the sensitivity of the real-time-reverse transcriptase-polymerase chain reaction (RT-PCR) test since there may be pathologies that cause nasal obstruction, such as nasal septum deviation (NSD). In this context, we investigated the effect of the nasopharyngeal swab sampling method and the presence of nasal obstruction on the detection of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).

Methods: This prospective clinical study was conducted from March 2021 to January 2022. Forty-four hospitalized patients with NSD were included in the study group, and 44 hospitalized patients without NSD were included in the control group. The results of the RT-PCR test studied with a unilateral nasopharyngeal swab sample taken during hospitalization and the RT-PCR test studied with a bilateral nasopharyngeal swab sample taken on the 2nd day of hospitalization and the visual analog scale (VAS) scores showing the patients' pain during the first sampling were determined.

Results: In the first test, 23 (52.3%) patients in the study group and 32 (72.7%) patients in the control group were evaluated as SARS-CoV-2 positive. The first test sensitivity was significantly higher in the control group (p=0.048). The VAS score was significantly higher in the study group (p=0.00008). In the second test, 35 (79.5%) patients in the study group and 37 (84.1%) patients in the control group were evaluated as SARS-CoV-2 positive. The sensitivity increases in the study group and in the population were statistically significant (p=0.007 and p=0.004, respectively). The consistency of the first and second test results increased in patients without NSD and in patients with low VAS scores [odds ratio (OR)=3.779; p=0.001, OR=2.572; p=0.005, respectively].

Conclusion: Nasopharyngeal swab sampling may be affected by nasal congestion and the sampling method. To avoid this, it may be more appropriate to take a nasopharyngeal swab sample through the bilateral nasal cavity.

Keywords: COVID-19 testing, SARS-CoV-2, reverse transcriptase polymerase chain reaction, specimen handling/methods nasal obstruction

Introduction

The causative virus of coronavirus disease-2019 (COVID-19), the first pandemic since the 1918 influenza pandemic (1918-1920), is severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1,2). The most important step in the fight against this disease is to identify patients with SARS-CoV-2 quickly and accurately, especially asymptomatic patients, and to ensure their isolation (3). The reverse transcriptase-polymerase chain reaction (RT-PCR) is the most commonly used diagnostic method for detecting SARS-CoV-2 infection, which can be performed on different specimens (4). The samples can be obtained from the upper airways such as nasopharyngeal (NP) swabs, oropharyngeal (OP) swabs, and a combination

Address for Correspondence: Dogan Cakan, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Clinic of Otorhinolaryngology, Istanbul, Turkey
Phone: +90 554 963 91 29 E-mail: drdgnckn@gmail.com ORCID: orcid.org/0000-0002-6283-2916
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of OP and NP (naso/OP) swabs, the lower respiratory tract such as bronchoalveolar lavage, the gastrointestinal tract such as anal swabs, or directly from specimens such as tears, saliva, sputum, and feces (4). Despite all these methods, the naso/OP swab is used as the gold standard for detecting the virus (5). Although RT-PCR with a naso/OP swab sample is the most commonly used test for the identification of COVID-19, it has low sensitivity, ranging from 37% to 71% (6-8). This sensitivity, which decreases due to external factors such as improper sampling technique, the way the sample is transported and stored, and the characteristics of the kit used, is higher in chest computed tomography (CT), 70-93%, and artificial intelligence-supported programs, 80.5-98.7% (4,6,9). Additionally, different methods for collecting naso/OP swab samples have been described. For example, there are different recommendations regarding the use of the nasal cavity unilaterally or bilaterally for the NP swab sample (10-12). Nasal septum deviation (NSD) is a common reason for nasal obstruction. Although the prevalence of this pathology, which narrows the nasal passage and prevents access to the nasopharynx, depends on various factors such as gender and age, it was found to be 46.56% in Turkey (13). We think that the NP swab sample should be taken bilaterally to improve the sensitivity of the RT-PCR test since there may be pathologies that cause nasal obstruction, such as NSD. This study determines the relationship between RT-PCR test results of unilaterally or bilaterally taken naso/OP swab samples and the presence of NSD.

Materials and Methods

Ethical Standards

This clinical study was conducted on subjects who applied to Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine from March 2021 to January 2022 with the approval of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (decision date/number: 09.07.2020/604.01.02). All subjects signed an informed consent form.

Populations, Inclusion, and Exclusion Criteria

All subjects of this study applied to the Emergency (ER) of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine. The hospitalized patients, according to the criteria in the COVID-19 guideline of the Turkish Ministry of Health (TMH) (the patients with poor prognostic criteria (blood lymphocyte count <800/µl or C-reactive protein >10 mg/L x upper limit of normal value or ferritin >500 ng/mL or D-Dimer >1000 ng/mL) in blood tests, bilateral diffuse involvement (>50%) in lung imaging, respiratory rate >24/min, and/or SpO2 <93% in room air (12) were included in this study. The patients were on day 5 of COVID-19 symptoms and their clinic and chest CTs were compatible with COVID-19 (CO-RADS 4, high risk; 5, very high risk; 6, proven) (14). The naso/OP swab samples were taken through the right nasal cavity on the day of hospitalization. All patients signed an informed consent form. Group 1 consisted of subjects with a right deviated nasal septum and group 2 consisted of subjects without NSD.

The subjects under the age of 18 and over 80 years old, with a history of respiratory tract surgery or respiratory tract infection in the last 3 months, immunodeficiency, chronic lung disease, having a lack of mental capacity, having a prominent inferior turbinate (covering more than 2/3 of the nasal passage on anterior rhinoscopy), having a chest CT in COVID-19 Reporting and Data System (CO-RADS) category 0-3, smokers, and those who did not accept participating were excluded from the study. Additionally, patients with a deviated nasal septum to the left were excluded from the study (15).

Sample Size and Sampling Technique

The minimum subject number was estimated on the basis of the study by Yilmaz et al. (16). The minimum sample size with a 95% confidence interval and 5% tolerable error assumptions was 88. A stratified sampling method was used in this study. Patients admitted to the COVID-19 clinic were separated into subgroups according to the presence of NSD. The patients who had any exclusion criteria for the study were excluded from the subgroups. Among the patients in each stratum, 88 patients were randomly selected to be included in the study and control groups in equal numbers.

Procedures and Data Collection

Day 0: Detailed anamnesis of the patients who were transferred from the emergency room to the COVID-19 service was taken and the treatments (enoxaparin 1x4000 anti-Xa IU/0.4 mL, Favipiravir 2x1600 mg loading dose on the first day + 2x600 mg maintenance dose for four days) were arranged (13). It was determined how the swab sample was taken for the RT-PCR test. The patient's pain score during the swab test procedure was determined using the visual analog scale (VAS). The patients were asked to score their pain from 0 (no pain) to 10 (worst pain) (13). RT-PCR test results were recorded.

Day 2: The bilateral nasal cavity was evaluated with a nasal speculum by an expert otolaryngologist. Secondly, swab samples were taken from the patients. The second swab samplings of the patients were performed by another, same-expert, with 10 years of experience as an otolaryngologist, to ensure standardization and to avoid BIAS.

Methods

The naso/OP swab samples were taken in the ER by the same internal medicine specialist in accordance with the TMH guidelines (the sampling was performed first from the oropharynx and afterward from the nasopharynx with the same tool). Afterward, the swab samples were placed in a transfer container (Bio-Speedy-vNAT, Bioeksen, Turkey). The capped containers were transferred to the public health laboratory at temperatures ranging between 2 °C and 8 °C. Patients who were transferred to the COVID-19 service, whose NP swabs were taken unilaterally through the right nasal cavity and whose RT-PCR test did not result, were included in the study. Before the second swab sampling, nasal cavities were examined with a speculum (Hartmann nasal speculum; catalog number, 400500; Karl Storz SE & Co. KG, Germany). The inferior turbinates were evaluated and the patients whose inferior turbinate obstructed more than 2/3 of the nasal passage were excluded from the study. Nasal examinations were repeated 5 minutes after nasal administration of xylometazoline (Otrivine®; GlaxoSmithKline, UK). Patients whose nasal septum was deviated to the right and more than 1/3 of the right nasal passage was obstructed due to the septum deviation were included in group 1. The second swab samples were taken first from the oropharynx, afterward through the left nasal cavity, and then through the right nasal cavity by reaching the nasopharynx by the same person. The storage and transfer procedures were performed in the same manner as for the first swab applications.

Computed Tomography

Chest CT images were obtained using the same device (Siemens SOMATOM Scope 16, Siemens Healthineers, Erlangen, Germany). Parenchymal infiltrates were evaluated with high-resolution reconstruction images of 1-mm section thickness. Chest CT has a sensitivity of 70-93% and a specificity of 93-100% in distinguishing COVID-19 pneumonia (6). Although there are different classifications such as the British Society of Thoracic Imaging and the CO-RADS, CO-RADS is most commonly used for radiological evaluation of COVID-19 (6). There are 7 categories in CO-RADS. CO-RADS 0 technically indicates an inadequate review, while categories 1 to 6 describe an increased risk of COVID-19 (CO-RADS 1, very low risk; CO-RADS 6, definitive diagnosis) (7,14,15). High-resolution thin-section, non-contrast chest tomography was categorized according to the CO-RADS classification by the same expert, with 12 years of experience as a radiologist.

RT-PCR Test

The samples kept for at least 30 min were analyzed with the RT-PCR kit (Bio-Speedy DoubleGeneRT-qPCR, Bioeksen, Turkey). The presence of viruses in the samples passed through various stages was detected by the real-time PCR analyzer (Rotor-Gene Q, Qiagen, Germany). Samples with a cycle threshold value of less than 38 were considered positive for COVID-19.

Statistical Analysis

The minimal subject was estimated using the G*Power program (17). Statistical analysis was performed using the SPSS 21.0 program (IBM, USA). The normal distribution and homogeneity of data were analyzed with the Kolmogorov-Smirnov test and Levene's test, respectively. The Pearson chi-square test, the independent-samples t-test, and the Mann-Whitney U tests were used for statistical comparisons. A binary logistic regression analysis was performed to examine the association between the resulting variables. The level of significance was determined as a p-value<0.05.

Results

A total of 88 subjects, 53 (60.2%) males and 35 (39.8%) females, were included in this study. Group 1 consisted of 26 (59.1%) male and 18 (40.9%) female subjects. Group 2 consisted of 27 (61.4%) male and 17 (38.6%) female subjects. The groups were statistically similar in terms of the gender distribution (pearson chi-square test, the value=0.047 and p=0.828; p>0.05). The mean age of the subjects was 54.06+15.28 (minimum: 21-maximum: 80) years. The mean ages were 54.27±15.49 years in group 1 and 51.84±15.14 years in group 2. No significant difference was detected between the groups according to patient age (independent samples t-test, p=0.790; p>0.05). All subjects were discharged from the hospital after treatment.

The first RT-PCR test results are given in Table 1. In the comparison of the test results, the positivity rate (sensitivity) of the first RT-PCR test was significantly higher in group 2 (p=0.048; p<0.05) (Table 1).

The second RT-PCR test results are given in Table 2. In the comparison of the test results, no significant difference was found between the groups in terms of sensitivity of the second RT-PCR test (p=0.58; p>0.05) (Table 2). The mean VAS scores were 5.07±0.27 (median=5, minimum: 2 -maximum: 9) for group 1 and 3.66±0.18 (median=4, minimum: 2-maximum: 6) for group 2. The VAS score was significantly higher in group 1 (p=0.00008; p<0.05) (Figure 1). The comparison of RT-PCR test results with unilateral samples (first RT-PCR test) and RT-PCR test results with bilateral samples (second RT-PCR test), is given in Table 3. When all patients included in the study were examined as a single group (single group), the sensitivity of the first RT-PCR test was 63.5% and the sensitivity of the second RT-PCR test was 81.2%. The sensitivity

Table 1. Evaluation of RT-PCR results of unilateral swab samples			
Patient groups	**SARS-CoV-2 + n (%)**	**SARS-CoV-2- n (%)**	**p**
Group 1 (n=44)	23 (52.3%)	21 (47.7%)	**0.048***
Group 2 (n=44)	32 (72.7%)	12 (27.3%)	
*Pearson chi-square test, value: 3,927; df: 1, p<0.05. SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2			

Table 2. Evaluation of RT-PCR results of bilateral swab samples			
Patient groups	**SARS-CoV-2 + n (%)**	**SARS-CoV-2- n (%)**	**p**
Group 1 (n=44)	35 (79.5%)	9 (20.5%)	0.580*
Group 2 (n=44)	37 (84.1%)	7 (15.9%)	
*Pearson chi-square test, value: 0.306; df: 1, p>0.05. SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2			

Table 3. The comparison of test results					
Patients	**Swap sampling**	**SARS-CoV-2 + n (%)**	**SARS-CoV-2- n (%)**	**p**	**Kappa (κ) value**
Group 1 (n=44)	Unilateral	23 (52.3%)	21 (47.7%)	**0.007***	**0.439**
	Bilateral	35 (79.5%)	9 (20.5%)		
Group 2 (n=44)	Unilateral	32 (72.7%)	12 (27.3%)	0.195	**0.671**
	Bilateral	37 (84.1%)	7 (15.9%)		
All patients (n=88)	Unilateral	55 (63.5%)	33 (37.5%)	**0.004***	**0.541**
	Bilateral	72 (81.2%)	16 (18.2%)		
*Pearson chi-square test, p<0.05. SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2					

increases in group 1 and in the single group were statistically significant (the value=7,283; df: 1; p=0.007, and the value=8,173; df: 1; p=0.004, respectively). In the evaluation of test agreements, a moderate agreement was found in group 1 test results [kappa (κ) value=0.439], a substantial agreement was found in group 2 test results (κ value=0.671), and a moderate agreement was found in the single group results (κ value=0.541) (Cohen's kappa statistic, p<0.001) (Table 3). When the relationship between positive RT-PCR test results obtained using both methods and the patient's age, gender, presence of septum deviation, and VAS score was examined, it was found that the consistency of test results increased in patients without septum deviation and in patients with low VAS scores [Binary logistic regression, odd ratio (OR)=3,779; p=0.001, OR=2,572; p=0.005, respectively] (Table 4).

Discussion

Although several methods have been used in COVID-19 diagnosis, the RT-PCR test is used routinely (18). The sample required for this test is most often taken from both the oropharynx and nasopharynx with the swab technique (3-5). There are different techniques and recommendations for the naso/OP swab method, which is applied millions of times every day around the world (1-4,19). Due to the swab sampling technique and features of the RT-PCR test, different sensitivity and specificity rates for detecting SARS-CoV-2 have been reported in the literature (2,5,9,12,20,21). In this study, the sensitivity of the RT-PCR test, which was performed with a unilateral naso/OP swab sample, in subjects with NSD was significantly lower than in subjects without NSD, and the pain felt by the patients during the swab sampling was significantly higher in subjects with NSD (p<0.05). When the NP swab sample is taken through the bilateral nasal cavity, it increases the RT-PCR test sensitivity. Additionally, there was low agreement between the RT-PCR test sensitivity studied with a unilateral NP swab sample and the RT-PCR test sensitivity studied with a bilateral NP swab sample in the entire population, particularly in people with NSD. This agreement was higher in patients with low-pain VAS scores.

Table 4. The evaluation of study parameters with test result positivity		
Parameters	**p**	**OR**
Gender	0.078	0.472
Age	0.117	0.958
Nasal septum deviation	**0.001**	**3,779**
VAS score	**0.005**	**2,572**
Binary logistic regression, Constant significance of model p=0.005 correct classification 85%. VAS: Visual analog scale, OR: Odds ratio		

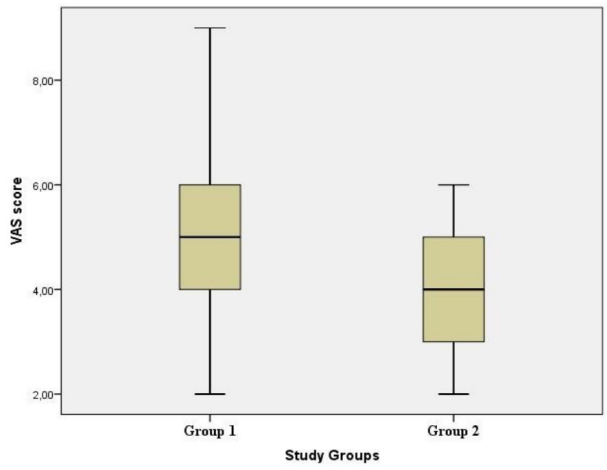

Figure 1. Evaluation of visual analogue scale (VAS) scores in the study groups with box plots (median, interquartile range, 5th and 95th percentiles)

There are different recommendations for taking a NP swab sample for the RT-PCR test, which is defined as the gold standard method in SARS-CoV-2 detection (5). Although there are opinions stating that it is sufficient to reach the nasopharynx from the unilateral nasal cavity and take a swab, some institutions recommend reaching the nasopharynx separately from the bilateral nasal cavity and taking a sample (10-12). In the COVID-19 guidelines of TMH, samples can be taken from both nostrils, but if the swab is saturated with enough liquid in the first application, it is not necessary to take a swab from both sides (12). Additionally, in the same guideline, it is requested to question whether there is any problem (deviation, polyp, bleeding tendency, etc.) related to the nasal passage. The Center for Disease Control and Preventions guidelines offer the same recommendations, but how to behave in such a situation is not specified in either of the guidelines (12,22). Although there are many reasons in the literature to reduce the sensitivity of the RT-PCR test, we did not encounter any study examining the relationship between NSD and SARS-CoV-2 RT-PCR test results in our literature review. Based on this information, we hypothesized that a unilateral NP swab sample for the RT-PCR test is not sufficient, especially in patients with NSD, and that swab samples should be taken from both nasal cavities separately by reaching the nasopharynx order to obtain higher test sensitivity. To ensure optimal standardization and avoid BIAS in our study, we determined the exclusion criteria and ensured that the samples were collected by the same specialists. Patients who were radiologically and clinically compatible with COVID-19 and had an indication for hospitalization were included in the study because they might have a higher viral load and the second RT-PCR test could be performed more easily (23). Because the SARS-CoV-2 viral load peaked on day 5 after that symptom onset, patients on day 5 of COVID-19 symptoms were included in our study (20). The second swab sampling was taken on the 7th day of the disease since the higher viral load persisted in the samples taken from the upper respiratory tract during the first 7 days of the disease (3). We performed a nasal examination with and without a decongestant to leave NSD as the only pathology causing nasal obstruction. In this study, the sensitivity of the RT-PCR test performed using a unilateral swab sample was significantly lower in subjects with NSD than in subjects without NSD. Additionally, this difference disappeared in the RT-PCR test performed using a bilateral swab sample. In group 1, the sensitivity of the RT-PCR test studied from a unilateral swab sample was 52.3%, while the sensitivity of the RT-PCR test studied from a bilateral swab sample increased to 79.5%. In group 2, the sensitivity increased from 79.5% to 84.1%. Additionally, the pain felt during swab sampling was significantly higher in patients with NSD. Discordance between the first (unilateral) and second (bilateral) RT-PCR test sensitivities exists in the entire population, particularly in patients with a septal deviation. Additionally, this inconsistency is also present in patients with high-pain-related VAS scores. Therefore, swab samples should be taken by entering the bilateral nasal cavity in the whole population, particularly in patients who feel excessive pain during NP swab sampling and have a history of NSD.

Study Limitations

There are some limitations to this study, which examines a subject that has not been addressed in the literature before. The first limitation is that we determined the subjects we defined as COVID-19 patients in our study according to their clinical symptoms and chest CT scans (24). Although the sensitivity and specificity of radiology are higher than RT-PCR, both the symptoms on the list of WHO for COVID-19 and the findings used for CO-RADS can also be observed in other viral types of pneumonia (6,12,25). The second limitation is that RT-PCR tests were performed in a different center, even though it was an approved center by the TMH. Accordingly, we cannot exclude human-induced errors during the transfer process or RT-PCR test run. Another limitation is that the first and second swab samples are taken by different doctors. If the first swab samples were also taken by the otorhinolaryngologist, they might have a higher sensitivity rate because of their better command of nasal anatomy. Another limitation is that we only perform nasal examinations with anterior rhinoscopic evaluation since the endoscopic examination is not recommended under pandemic conditions (26). Therefore, we may have miscalculated the amount of nasal obstruction and overlooked other pathologies that

may cause nasal obstruction (27). The final limitation is that we used a subjective test to assess the pain felt by patients during swab sampling. Despite all the limitations of the study, our study is the first study examining the relationship between RT-PCR test results, the way NP swab samples were obtained (unilateral or bilateral), and the presence of NSD in the patient.

Conclusion

Nasopharyngeal swab sampling used to obtain the sample required for RT-PCR testing may be affected by pathology that narrows the nasal passage. The NSD, which is one of the most common causes of nasal obstruction, may be one of these reasons. Patients with NSD experience more pain when taking a NP swab sample. To avoid the effects of nasal obstruction on the RT-PCR test, NP swab sampling should be performed by entering from both nasal cavities, particularly in patients who feel a lot pain during the swab sampling and have a history of NSD.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (decision date/number: 09.07.2020/604.01.02).

Informed Consent: All subjects signed an informed consent form.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.C., Z.K.C., H.A.O., Concept: S.U., Y.Z.Y., Design: D.C., S.U., Y.Z.Y., Data Collection and/or Processing: D.C., Z.K.C., H.A.O., Analysis and/or Interpretation: O.U., Literature Research: Z.K.C., S.U., Y.Z.Y., H.A.O., Writing: D.C., Z.K.C., O.U.

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Original Article

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Bell's Palsy and COVID-19 Infection: A Comparative Analysis with the Pre-pandemic Period

Gizem Gursoy, Ayla Culha Oktar, Ayse Ozlem Cokar

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

Abstract

Aim: Bell's palsy is an acute peripheral facial nerve paralysis affecting one side of the face and can be associated with various causes, such as infectious and autoimmune conditions. In line with this, an increase has been observed in the incidence of peripheral facial paralysis during the coronavirus disease-2019 (COVID-19) infection pandemic. We aimed to investigate whether the incidence of Bell's palsy increased before and after the COVID-19 in the pre-vaccine period.

Methods: All cases diagnosed with Bell's palsy in a tertiary hospital aged 18 and up in 2020 were analyzed, and to compare these numbers to pre-pandemic numbers, patients' data from 2019 was accessed. Excluding those who had recurrent facial palsy, those whose conditions were due to central causes, and those who were misdiagnosed, the frequency of the disease was calculated by proportioning it to the total number of patients presenting to Neurology, and Ear, Nose, and Throat Diseases Outpatient Clinics and the Green Zone of the Emergency Department at that time; and the Bell's palsy distribution within three-month periods and whether this distribution is correlated with the distribution of COVID-19 infection were examined.

Results: Three hundred twenty five cases from 2019 and 291 cases from 2020 were included in the study. No significant difference was detected between those years in terms of age and sex. The frequency of Bell's palsy in 2019 was 0.059% while it was 0.071% in 2020, which suggested a significant difference between the years. The significant difference could be clearly observed in the second and fourth quarters when the cases of COVID-19 infection were at their peak.

Conclusion: This study suggests that patients with complaints of peripheral facial paralysis should also be examined for COVID-19 infection.

Keywords: COVID-19, facial nerve, peripheral facial paralysis

Introduction

Bell's palsy is a lower motor neuron disorder that affects the muscles unnerved by the facial nerve and is characterized by acute and unilateral peripheral facial weakness. The literature shows that it is more common in men (1). The incidence has been calculated to be 20 to 30 in 100,000 individuals, and the most common cause is thought to be a herpes simplex infection. In Bell's palsy cases, which develop as secondary to infection, the facial nerve becomes swollen while coursing through the temporal bone, causing the nerve to get stuck in the bone (2). Apart from the direct infection, other factors that play a role in the etiology of the disease include immune reaction-stimulating viruses such as cytomegalovirus, Epstein-Barr virus, human herpesvirus 6 and 7, and adenovirus (3).

Although coronavirus, which was described as novel coronavirus pneumonia in Wuhan, China in December 2019 and caused a pandemic in a short time, manifests as the involvement of the respiratory tract, it also affects several other systems (4). Its neurological effects can include axonal peripheral neuropathy, myopathy, olfactory neuropathy, cerebral infarction, headache, impaired consciousness, seizure, ataxia, and Guillain-Barre syndrome (5).

Considering the facts that Bell's palsy is associated with viral infection etiology and that coronavirus may cause neuropathy, this study reveals the relationship between them by retrospectively scanning the data in

Address for Correspondence: Gizem Gursoy,
University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey
Phone: +90 537 302 49 07 E-mail: drgizemgursoy@gmail.com ORCID: orcid.org/0000-0003-4448-5962
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a single center, which has been serving as a pandemic hospital since March 2020, when the first cases were seen in our country.

Materials and Methods

Compliance with Ethical Standards

The study protocol was reviewed and approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Ethics Committee, with approval no: 2020/19. Because of the retrospective design of this study, no informed consent was obtained.

Study Design

The patients aged 18 and above who were first diagnosed with Bell's palsy in 2020, and cases aged 18 and above who were first diagnosed with Bell's palsy in 2019 were included the study to compare the incidence of Bell's palsy with the pre-pandemic period.

Patient Evaluation

The patients were documented using the codes in the ICD-10 diagnostic code list: G51.0-Bell's palsy, G51.8-Facial nerve paralysis disorders, and G51.9-Disorder of the facial nerve, unspecified. Facial cases of central nervous system (CNS) origin, recurrent Bell's palsy cases, cases aged under 18, cases identified to have facial paralysis according to ICD-10 codes but not diagnosed as such upon the examination, cases whose underlying cause was demyelinating polyneuropathy, cases that developed it secondarily to trauma, and cases diagnosed before 2019 were excluded from this study. Our study population was determined as the total number of patients who presented to the departments of Neurology, Ear-Nose and Throat, and the Green Zone of the Emergency Department where the diagnosis of Bell's palsy occurs. The total number of patients presenting to those departments was calculated as 545,657 for 2019 and 407,879 for 2020.

We examined the demographic characteristics of the patients, such as age and gender, from both years, and to detect if there was any correlation with coronavirus cases, we analyzed the incidence of Bell's palsy between those two years and compared the data belonging to the 4 quarters of 2020 with those of the previous year.

Statistical Analysis

Descriptive statistics regarding the age variable are presented as "average ± standard deviation" whereas descriptive statistics considering categorical variables are presented in numbers and percentages. Parametric independent t-test was used to compare the two independent year groups in terms of the age variable. For this analysis, variance homogeneity was checked by the Levene's test. Concerning the analysis of the relationship between categorical variables, Pearson's chi-squared test was used while the two-sample t-test was used for the groups that showed a difference. Statistical significance was set to be $p<0.05$.

Results

Three hundred twenty five cases from 2019 and 291 cases from 2020 meeting all the above-mentioned criteria were examined in the study. The average age of 325 patients from 2019 was calculated as 44.66±15.56 while it was 43.74±69 for 291 patients from 2020. The age distribution of patients was found to be homogeneous ($p=0.468$).

Regarding the gender distribution, the genders of the patients were reported as follows: 183 men and 142 women in 2019, and 159 men and 132 women in 2020. Similar to the age distribution, no statistically significant difference was found in terms of gender.

When the ratio of the patients diagnosed with Bell's palsy was compared to the total number of patients presenting to the hospital between the years of 2019 and 2020, the frequency of Bell's palsy in 2019 was 0.059% while it was 0.071% in 2020, which revealed a statistically significant difference ($p=0.025$). While the comparison of the total number of patients presenting to the hospital showed a difference of about one hundred and forty thousand between 2019 and 2020, the numbers of patients who were diagnosed with Bell's palsy in those years were found to be similar (Table 1).

To show the patient distribution throughout the year more clearly, both years (2019 and 2020) were divided into three-month periods as follows: January-February-March, April-May-June, July-August-September, and October-November-December. While there was no significant difference in the numbers of diagnosed patients in the first quarter between the two years, it was observed that this number significantly increased in the second quarter of 2020 ($p<0.01$). In the second quarter of 2020, even though the number of patients presenting to the hospital decreased by half compared to the second quarter of 2019, the number of patients diagnosed with Bell's palsy was found to be almost the

Table 1. Difference in the ratios of Bell's palsy cases between 2019 and 2020

Years	2019	2020	p-value
Diagnosis			
Diagnosed +	325 (0.06%)	291 (0.07%)	0.025
Diagnosed -	545,332 (99.9%)	407,588 (99.9%)	Chi-square=0.002

-Pearson's chi squared test was used.
-Frequency of Bell's palsy in 2019 was 0.06% while it was 0.07% in 2020, which revealed a statistically significant difference.

same. Furthermore, when the numbers collected from the third and fourth quarters were compared, it was found that while there was no significant difference in the third quarter between the years, the fourth quarter showed a significant difference (p=0.014) like the second quarter. These significant differences observed in the second and fourth quarters show us a connection between the times when coronavirus disease-2019 (COVID-19) infection made peaks during its spread throughout Turkey (Table 2), (Figure 1).

All patients diagnosed with Bell's palsy in 2020 were scanned in the registers of our hospital to check their COVID-19 polymerase chain reaction test results, and it was found that only 10 patients tested positive for COVID-19. Additionally, only 4 of them were found to have been infected with the coronavirus within the past month.

Discussion

In a study conducted in Wuhan, the first epicenter of the pandemic, 36.4% of the COVID-19-infected patients showed neurological symptoms (6). Observed neurological symptoms included CNS involvement such as headache, seizure, confusion, viral encephalitis, toxic encephalopathy, and cerebrovascular disease, along with peripheral nervous system involvement like anosmia, olfactory nerve involvement in the form of hyposmia, peripheral facial paralysis, and Guillain-Barre syndrome (6,7). Based on the data collected from those studies, COVID-19 has been thought to cause neurological symptoms by using direct and indirect mechanisms (8). There is evidence implying the direct involvement of the CNS in the pathological mechanism of the virus (9).

Respiratory tract viruses may invade the CNS by using blood circulation or neuronal retrograde routes. In terms of retrograde axonal transport, the virus is assumed to reach the CNS through some cranial nerves (such as the olfactory nerve, trigeminal nerve, glossopharyngeal nerve, and the vagus nerve) or peripheral nerves (10).

Even though cases are reported to have developed Bell's palsy following infection or vaccination, a relationship between them has not been clearly proven; the most commonly accepted hypothesis is the autoimmune mechanism through the mimicry of antigens of the vaccines (11-13). In contrast, the incidence of Bell's palsy during the third phase studies of BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines was reported to be no more common than the ordinary frequency observed in the general public (12). A small case-control study in Israel matched 37 patients with Bell's palsy to 74 controls and found no association with mRNA-based severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccination (14). Unfortunately, the inactivated vaccine started to be used in January 2021; thus, it is impossible to mention the effects of the vaccine in our study. A review study consisting of the studies conducted between March 2020 and December 2020, documented 20 cases of Bell's palsy and suggested that Bell's palsy could be an important clinical finding for COVID-19 infection. However, it reported that further studies were needed to demonstrate their possible relationship and to identify the underlying mechanism (15).

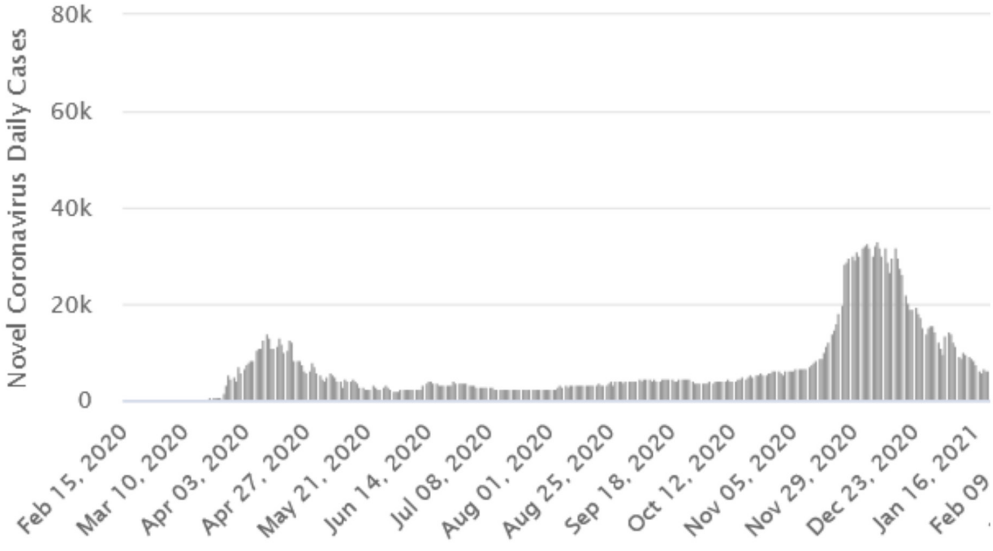

Figure 1. Distribution of novel coronavirus cases in Turkey over time

Table 2. Patient distribution in 2019 and 2020 (divided into 3-month periods)				
	Year	**2019**	**2020**	**p-value**
January February March	**Diagnosed +**	67 (0.1%)	96 (0.1%)	0.390 Chi-square=0.738
	Diagnosed -	95,917 (99.9%)	157,562 (99.9%)	
	Total	95,984	157,749	
April May June	**Diagnosed +**	78 (0.1%)	71 (0.1%)	<0.001 Chi-square=22,375
	Diagnosed -	142,594 (99.9%)	60,824 (99.9%)	
	Total	142,672	60,895	
July August September	**Diagnosed +**	75 (0.05%)	60 (0.05%)	0.716 Chi-square=0.133
	Diagnosed -	141,745 (99.95%)	120,786 (99.95%)	
	Total	141,820	120,846	
October November December	**Diagnosed +**	105 (0.1%)	64 (0.1%)	0.014 Chi-square=6,027
	Diagnosed -	165,076 (99.9%)	68,325 (99.9%)	
	Total	165,181	68,389	
- There were significant differences in the numbers of diagnosed patients in the second and fourth quarters between the years.				

In another publication retrospectively analyzing patient records from 41 different health institutions around the world, the incidence of Bell's palsy in patients with COVID-19 infection was calculated as 0.08%. This incidence has demonstrated that Bell's palsy was more common in COVID-19 patients and that it was also higher than the incidence of Bell's palsy reported in those vaccinated for COVID-19 (16). Similarly, our study has shown that the number of Bell's palsy cases in 2020, the year the pandemic began, was significantly higher than the number of cases reported in 2019. Moreover, the numbers of Bell's palsy cases reported during the second and fourth three-month periods of April-May-June and October-November-December, when COVID-19 cases reached their peaks, showed significant differences compared with the numbers of the previous year. However, another study found that the number of admissions for facial nerve palsy during the same period in the preceding years (2015-2020) and 2021 revealed a relatively stable trend (17).

Furthermore, in another study comparing the two-month records of 2020 with those of the previous year, it was detected that Bell's palsy cases were more common in 2020 and that 21% of the 22 Bell's palsy cases were already active COVID-19 patients or had recently had it. The patients were possibly thought to have postponed their hospital visit for fear of catching COVID-19 (18). However, this ratio was found to be much lower in our study: Thirty-one patients out of 291 were tested for COVID-19, and 10 of them were positive, with only 4 detected to have been infected within the past month. The reasons for lower patient numbers could be explained by the fact that the fear of catching COVID-19 deterred people from going to hospitals; that doctors may have refrained from further examinations to limit the time people spent in hospitals; and that not all doctors may have considered COVID-19 infection as the cause of Bell's palsy, which resulted in lower numbers of tests and, in turn, led to fewer positive cases.

In the only prospective study examining the relationship between Bell's palsy and COVID-19 infection, antibody levels for SARS-CoV-2 IgG + IgM of the 41 patients diagnosed with Bell's palsy were measured twice, and 24.3% of the patients were found to have tested positive for antibodies. The numbers were shown to be higher than those collected in seroprevalence studies conducted in asymptomatic patients (19).

Study Limitations

The limitations of our study were that it was a retrospective study and antibody tests for SARS-CoV-2 were not conducted as part of the clinical examinations.

Conclusion

Bell's palsy is a commonly observed condition in clinical practice and viral infections play an important role in its etiological factors. Even in cases presenting isolated neurological symptoms without respiratory tract symptoms, it should be considered that COVID-19 infection could be a cause of Bell's palsy.

Although our study supports the cause-effect relationship with the correlation between the change in the frequency of Bell's palsy and the course of the pandemic in our country, it could not reach a definite conclusion because the number of positive cases was much lower than expected. Larger-scale studies are needed to reveal the relationship and mechanism of action between them.

Acknowledgments: We thank Ceren Aktay Eryılmaz from Beykent University for translating this study from Turkish into English.

Ethics

Ethics Committee Approval: This study protocol was reviewed and approved by University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Ethics Committee in 28.04.2021, approval number 2020/19.

Informed Consent: Because of the retrospective design of this study, informed consent was not obtained.

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Authorship Contributions

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Original Article

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The Long-term Outcomes of Completion Pneumonectomy from a Tertiary Center

Yunus Aksoy[1], Ozkan Saydam[2], Necati Citak[4], Celal Bugra Sezen[2], Volkan Erdogu[2], Levent Cansever[2], Mehmet Ali Bedirhan[2], Muzaffer Metin[2], Ali Cevat Kutluk[2], Atilla Pekcolaklar[3]

[1]*Sakarya University Faculty of Medicine, Department of Thoracic Surgery, Sakarya, Turkey*

[2]*University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Health Application and Research Center, Department of Thoracic Surgery, Istanbul, Turkey*

[3]*Bursa City Hospital, Clinic of Thoracic Surgery, Bursa, Turkey*

[4]*University of Health Sciences Turkey, Dr. Suat Seren Chest Diseases and Thoracic Surgery Health Application and Research Center, Department of Thoracic Surgery, Istanbul, Turkey*

Abstract

Aim: Completion pneumonectomy is a compelling procedure that is associated with high rates of mortality and morbidity. The aim of the present study was to investigate long-term surgical and oncologic outcomes of completion pneumonectomy.

Methods: A retrospective review was conducted of 66 patients who underwent completion pneumonectomy in our clinic between 2006 and 2016. The patients were divided into two groups. The patients undergoing classical completion pneumonectomy (n=58), 56 had a malignant disease (non-small-cell lung carcinoma) and two patients had a benign disease. Eight patients had undergone rescue completion pneumonectomy; bronchopleural fistula in five patients, pulmonary venous occlusion in two patients, and upper lobe torsion in one patient.

Results: The median follow-up period was 37.6 months. The overall mortality rate was 7.6%. The amount of intraoperative bleeding and the percentage decrease in hemoglobin levels (p=0.003) were prognostic factors affecting mortality. The postoperative complication rate was 41.4% in classical completion pneumonectomy and 50% in rescue completion pneumonectomy (p=0.64), and it was significantly higher in patients older than 65 years (p=0.04). The 5-year survival rate was 58% in malignant disease.

Conclusion: Completion pneumonectomy procedure has satisfactory oncological and surgical results when performed in experienced centers on selected patients. The morbidity and mortality rates of classical completion pneumonectomy and rescue completion pneumonectomy are similar.

Keywords: Pneumonectomy, prognosis, postoperative complications, bronchopleural fistula, lung cancer

Introduction

Completion pneumonectomy (CP) refers to the surgical removal of the remaining lung after previous ipsilateral resections of the lung parenchyma. Indications for CP are extremely rare but involve both benign and malignant diseases (1). CP is often considered a risk factor for postoperative mortality among thoracic surgeons and in studies evaluating patients undergoing pneumonectomy (2). The advent of parenchyma-preserving surgical procedures for treating lung cancer, improvements in thoracic surgical techniques, longer patient follow-ups, increased frequency of lung cancer detection, and prolonged survival time after resection have increased the incidence of similar diseases (3). All of these secondary lesions and complications occurring after the initial operation increase the rate of CP procedures.

CP is a very complicated procedure and is associated with an increased perioperative risk. In the literature,

Address for Correspondence: Yunus Aksoy
Sakarya University Faculty of Medicine, Departmant of Thoracic Surgery, Sakarya, Turkey
Phone: +90 544 451 25 49 E-mail: dryunusaksoy@gmail.com ORCID: orcid.org/0000-0003-4966-2809
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there is a consensus on the application of CP surgery in experienced centers with a sufficient number of cases (2,4). CP is often performed for malignant disease, and studies on cases who underwent CP because of early complications of primary surgery, which we defined as rescue CP, are limited (1,5).

In this study, mortality, morbidity, indications, complications, results, and associated risk factors in patients undergoing classical CP (CCP) and rescue CP in our clinic were evaluated retrospectively.

Materials and Methods

Compliance with Ethical Standards

The University of Health Sciences Turkey, Istanbul Training and Research Hospital Clinical Research Ethics Committee approval of this study was acquired (decision no: 2018-KAEK-50/1259) and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

Study Design

The records of 75 patients who underwent CP between 2006 and 2016 were analyzed. Excluded from the study were six patients who discontinued follow-up and three patients who did not undergo an anatomical resection in their first surgery. The data of the remaining 66 patients were retrospectively evaluated. The patients were divided into two groups: those undergoing (CCP, n=58) and those undergoing rescue CP because of complications (RCP, n=8) (Graph 1).

Patients undergoing complete lung resection in the initial surgery due to primary NLCLC and patients undergoing completion CP due to complications such as bronchopleural fistula, pulmonary venous occlusion, and upper lobe torsion were included in the study. CP was defined as surgery performed to remove the remaining lung tissue after a previous anatomical lung resection. Recurrent lung cancer and a second primary lung cancer were defined according to the criteria proposed by Martini and Melamed (6). Rescue CP was defined as surgery performed on a patient undergoing completion CP due to complications.

Preoperative Assessment

The surgical notes related to the patients were retrieved and reviewed. All patients underwent re-staging, for which thoracic and upper-abdominal computed tomography scans were obtained. Positron emission tomography was requested to evaluate distant metastases and the mediastinum, and a pulmonary function test was requested to evaluate pulmonary reserves. All patients underwent bronchoscopy for diagnostic purposes before surgery. The mediastinal assessment of patients operated on for malignant disease has been made via video-assisted mediastinoscopy before the previous operations.

Surgical Approach

Endotracheal intubation with a double-lumen tube was performed in all patients following the induction of anesthesia. All patients underwent posterolateral thoracotomy in the lateral decubitus position via the previous thoracotomy incision site. The chest cavity was frequently entered from an upper intercostal area instead of the one used in the previous thoracotomy. Due to the rib separation could be difficult, subperiosteal resection of the fifth rib was performed carefully before the rib separation. With this maneuver, a wide exposure was provided for the removal of pleural adhesions. After the ribs were separated, the lung was mobilized intrapleurally or extrapleurally, depending on the pleural adhesion density. Manuel and/or sharp dissection with scissors and/or electro-cautery were performed to take care of the bleeding. Extrapleural dissection was confined to a limited area due to the risk of postoperative bleeding. However, it was performed if a risk of tearing the lung or leaving its fragments on the chest wall was seen. Moreover, when the pleural adhesion density was greater than expected, dissection was advanced toward the mediastinal surface, which has fewer dense adhesions, and this was followed by pneumolysis. Resection of the pulmonary vessels was usually (n=37) resected with an intrapericardial approach due to extensive inflammation around the hilum after previous surgery. However, if the pericardium was opened during the previous surgery, an intrapericardial approach for the control of the pulmonary vessels was avoided (n=2). Moreover, if the hilum adhesion was not dense, the pericardium was not opened (n=27). After this maneuver, the main pulmonary artery was encircled with a finger. Then, a blunt clamp held on the other side was encircled. Control over the vascular structures in the hilar region was achieved in the early periods of surgery (Figure 1). The pulmonary vessels were ligated first, and then the main bronchus was divided. A systematic lymph node dissection was routinely performed in cases with a tumor.

Postoperative Follow-up

The patients were awakened from anesthesia in the operating room, and were followed up in the surgical intensive care unit until their general conditions stabilized. The chest tube was withdrawn once the discharge dropped below 300 mL per day. The histopathologic evaluations of patients who were operated on due to primary NLCLC were performed according to the 8th edition of the TNM classification (7).

Mortality and morbidity were defined as incidences occurring during post-surgery hospitalization and within

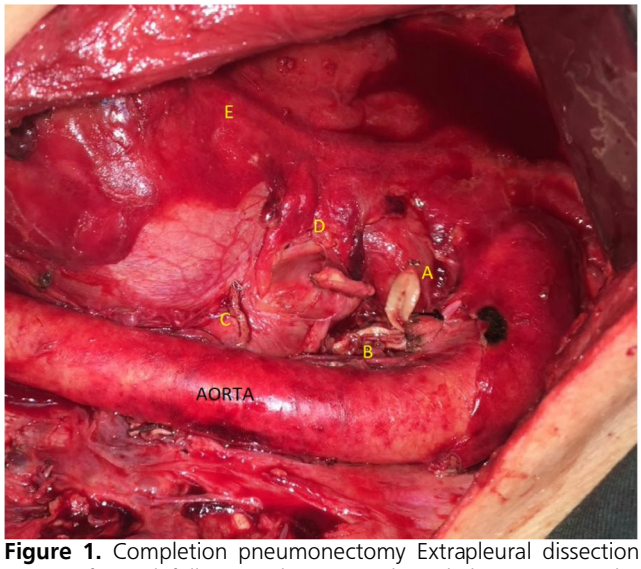
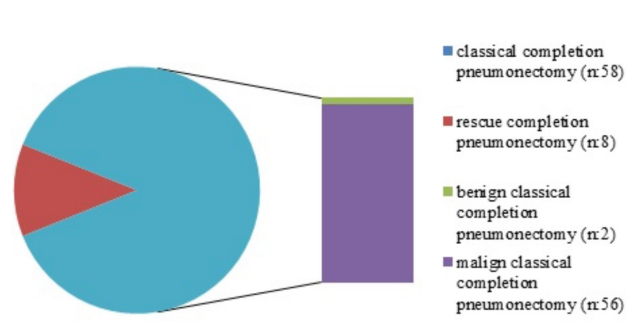


Figure 1. Completion pneumonectomy Extrapleural dissection was performed following the posterolateral thoracotomy. The pericardium was opened on the hilar side for the control of the pulmonary vessels. The pulmonary vessels were resected with intrapericardial approach
A: Left pulmonary artery, B: Left main bronchus, C: Left pulmonary vein inferior, D: pericardium



Graph 1. Subgroup description of completion pneumonectomy

the postoperative 30 days. Morbidities included respiratory failure, hemothorax, BPF, pyothorax, arrhythmia, and wound infections. Patients with a malignant disease were followed up in collaboration with the department of oncology during the postoperative period. Our postoperative treatment policy for patients with stage IIA.

IIIB NLCLC is to be administered only in adjuvant chemotherapy. In the presence of chest wall invasion and N2 disease, radiotherapy is also administered in addition to chemotherapy. Patients were followed up with thoracic CT scans and physical examinations every three months for the first two years, and every six months after that.

Statistical Analysis

Descriptive statistics were used for the demographic and clinical data. A chi-square test was used to evaluate the relationship between categorical variables, and a Student's t-test, Mann-Whitney U test, and Kruskal-Wallis test were used to evaluate continuous variables. A Kaplan-Meier test was used for the survival analysis, and a log-rank test was used to compare factors. A p-value below 0.05 was considered statistically significant in the study. The SPSS software package (version 22, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

Results

The mean age of the patients was 55.80±10.9 years. Among the patients undergoing CCP, 56 (83.3%) had a malignant disease non-small-cell lung carcinoma (NSCLC) and two patients (4.5%) had a benign disease. One of the benign diseases destroyed the lung with aspergilloma, and the other was bronchiectasis with hemoptysis. The reasons for undergoing RCP were BPF in five patients; pulmonary venous occlusion in two patients; and upper lobe torsion in one patient. The causes of primary surgery were NSCLC in the RCP group. Comorbidities were observed in 51 patients (77.3%), the most common of which were cardiac pathologies (42.2%) (Table 1a).

Initial Operation and Completion Pneumonectomy

The mean time between the initial surgery and the second surgery was 41.3 months (minimum: 1.3, maximum: 183 months) in the CCP group. The most frequent initial surgical procedure was right upper lobectomy (n=22, 33.4%), with one patient (1.5%) undergoing right middle lobectomy, one (1.5%) undergoing a sleeve right inferior bilobectomy, and nine (13.2%) undergoing a right inferior bilobectomy 10 (15.2%) were undergoing right inferior lobectomy, 13 (19.7%) were undergoing left upper lobectomy, and 10 (15.2%) were undergoing left lower lobectomy. When the histopathological diagnoses of patients undergoing CP due to malignant causes were evaluated, 20 (36.4%) had adenocarcinoma, 31 (56.4%) had squamous cell carcinoma, and five (7.3%) had other histopathological diagnoses. Among the patients undergoing CCP due to malignant causes, the N stage was reported as N0 in 39 patients (69.6%), N1 in 14 patients (25%), and N2 in three patients (5.4%). The most common tumor stage after CP in malignant CCP was stage 1 (n=26, 46.4%), whereas 20 patients (35.7%) had stage 2 and 10 (17.8%) had stage 3 disease (n=T4N0: 7, n=T3N2: 1, n=T1N2: 2).

Morbidity

While postoperative complications occurred in 28 patients (42.2%), with the most common complication being atrial fibrillation (19.7%), the postoperative complication rate was 41.4% in CCP and 50% in RCP (p=0.6). Aged >65 years was identified as a significant

prognostic factor affecting postoperative complications (p=0.04) (Table 1b).

A total of four patients underwent revision surgery due to bleeding. No bleeding focus was detected in two patients, whereas one patient suffered a leaking hemorrhage in which hemostasis was later achieved. In the one patient who experienced bleeding from the bronchial artery, bleeding was controlled through the ligation of the bronchial artery. Furthermore, two patients (3%) developed acute renal failure and two (3%) experienced postoperative hemoptysis. The patients underwent bronchoscopy, but no active bleeding focus was detected, and these patients subsequently recovered under medical therapy. Additionally, two patients (3%) developed wound site infections; and six patients (9.1%) developed pneumonia and were treated with non-invasive mechanical ventilation. Empyema was encountered in eight patients (12.1%) postoperatively. A chest tube was inserted in the patients who developed empyema and were treated with the appropriate antibiotherapies.

Following the completion of pneumonectomy, BPF was detected in 10 patients (15.2%). The BPF rate was 15.5% (n=9) in CCP and it was 12.5% (n=1) in RCP (p=0.8). Furthermore, three patients with BPF underwent fistula closure with omentoplasty, and two patients developed microfistulas and underwent chest tube insertion. The fistulae were observed to close because of closed drainage and antibiotherapy. Of the total, three patients underwent Eloesser flaps, and another patient underwent an Eloesser flap after developing recurrent BPF following omentoplasty. Additionally, one patient died of pneumonia after BPF. Supporting the bronchial stump with any tissue significantly reduced the risk of developing BPF (p=0.01), diabetes mellitus (p=0.03), and adjuvant therapy following initial surgery (p<0.001), and significantly increased the incidence of BPF. BPF was observed in 10 of 43 patients in whom the bronchial stump was not supported by tissue, and was detected in nine patients (36%) who received adjuvant therapy following initial surgery. The type of completion procedure (p=0.82), operation side (p=0.28), bronchial closure technique (p=0.13) and age (p=0.06) had no effect on the development of BPF.

Mortality and Follow-up

The median follow-up period was 37.6 months. Mortality occurred in five patients (7.6%). The rate of mortality was 6.9% among patients undergoing CCP and 12.5% among those undergoing RCP. There was no significant difference in mortality rates between CCP and RCP (p=0.57). The rate of mortality was 8.6% in patients undergoing CP due to NSCLC. Of the total, four patients died of respiratory failure and one died of pneumonia that developed after a bronchopleural fistula. The amount of intraoperative bleeding and the percentage decrease in Hb level were identified as prognostic factors affecting mortality (Table 2). The 5-year survival rate was 59.6% (81 months) in patients undergoing CCP. The mean survival was 70 months in patients undergoing CCP due to NSCLC. The 5-year and 10-year survival rates were 58.1% and 25.3%, respectively. Tumor diameter greater than 7 cm (p=0.05) and the stage of the second tumor

Table 1a. Demographic characteristics of the patients

Variables		CCP		RCP		p-value
		n	%	n	%	
Gender	Male	54	88.5	7	11.5	0.48
	Female	4	80	1	20	
The mean FEV1 of the patients		2.05±0.4 L				
Smoking history (packet/year)		30.6±22.9		21.2±24.8		
	No	13	72.2	5	27.8	0.017
	Yes	45	93.8	3	6.3	
Hospitalization (day) mean ± SD		10.6±6.6		12.5±8.7		0.50
Causes of CP	Benign	2	3.4	0	0	0.32
	Malign	56	96.6	8	100	
Comorbidities		44	75.9	7	87.5	0.46
	Cardiac disease	25	43.1	3	37.5	0.76
	Respiratory disease	12	20.7	4	50	0.70
	Serebrovascular disease	2	3.4	1	12.5	0.24
	Diabetes mellitus	14	24.1	2	25	0.95
	Peripheral vascular diseases	5	8.6	0	0	0.38

RCP: Rescue completion pneumonectomy, CCP: Classical completion pneumonectomy, SD: Standard deviation, FEV1: Forced expiratory volume in 1s s.
Smoking was significantly more common in patients undergoing CCP. No statistically significant difference was found in terms of any other demographic characteristics

Table 1b. Factors affecting complications						
Variables		**Complication (no)**		**Complication (yes)**		**p-value**
		n	**%**	**n**	**%**	
Age (years)	<65	36	62.1	22	37.9	**0.04**
	>65	2	25	6	75	
Gender	Male	35	57.4	26	42.6	0.90
	Female	3	60	2	40	
Comorbidity	No	7	46.7	8	53.3	0.33
	Yes	31	60.8	20	39.2	
Type of CP	CCP	34	58.6	24	41.4	0.64
	RCP	4	50	4	50	
Second operation resection type	Sleeve CP	3	37.5	5	62.5	0.22
	CP	35	60.3	23	39,7	
Operation side	Right	25	58.1	18	41.9	0.89
	Left	13	56.3	10	43.5	
Supporting the bronchial stump	No	23	53.5	20	46.5	0.43
	Yes	14	60.9	9	39.1	
Bronchial stump closure	Stapled	23	67.6	11	32.4	0.08
	Hand-sutured	15	46.9	17	53.1	
Operation time (minutes) mean ± SD		342.7±1190.3		372.5±142.0		0.49
Intraoperative bleeding (mL) Mean ± SD		353.8±158.4		434.6±222.6		0.09
Percentage decrease in Hb (%) Mean ± SD		10.3±10		13.8±12.1		0.13

Aged above 65 years was identified as a significant prognostic factor affecting postoperative complications (p=0.04).
RCP: Rescue completion pneumonectomy, CCP: Classical completion pneumonectomy, SD: Standard deviation, Hb: Hemoglobin

(p=0.01) were identified as prognostic factors affecting survival. The mean interval between the two operations was 37±34.6 months (p=0.42) (Table 3).

Discussion

High surgical mortality and postoperative complication rates have been reported in almost all series of patients undergoing CP due to benign or malignant lung disease (2,8). The overall mortality rate in the large series published in this field ranges between 3.4% and 21% (4,9-11) and reported intraoperative mortality rates range from 0% to 5.4% (9,12-14). There are different opinions on the factors affecting mortality. Chataigner et al. (15) reported obesity, coronary artery disease, right-sided surgery, and renal failure as factors affecting postoperative mortality. Some studies in the literature have found a link between mortality and postoperative complications, particularly bronchopleural fistula, and there are also studies that link increased mortality to advanced age and the use of adjuvant therapy after initial surgery (11,16). No intraoperative mortality occurred in this study, and the overall mortality rate was found to be 7.6%.

The mortality rate in patients undergoing CP to treat complications after an initial surgery was reported to be as high as 37.5% by Muysoms et al. (17), 27% by Pan et al. (5) and 33% by Jungraithmayr et al. (12). This rate was only 12.5% among the patients undergoing RCP in our series, which can be attributed to both the small patient sample and the strict inclusion criteria applied in the selection of patients.

There was no significant difference in mortality rates between CCP and RCP. The operation site, age, development of BPF and administration of adjuvant therapy following initial surgery had no effect on mortality in this study. The amount of intraoperative bleeding and the percentage decrease in Hb levels were identified as prognostic factors affecting mortality. Bleeding exceeding 720 mL and a more than 25% decrease in hemoglobin levels increased mortality. Significant pleural and sometimes pericardial adhesions associated with previous surgeries may complicate hilar exposure during CP. In other words, catastrophic hemorrhage and significant vessel injuries are possible. Extrapleural dissection may be required to achieve intraoperative pneumolysis. For the above reasons, intraoperative blood loss is significantly higher in patients undergoing CP than in those undergoing standard pneumonectomy (5,13,14). The primary goal in our center is to gain access to and start pneumolusys from the mediastinum, due to there being fewer dense adhesions on the mediastinal surface in such patients.

Table 2. Prognostic factors affecting mortality						
Variables		**Mortality (No)**		**Mortality (Yes)**		**p-value**
		n	**%**	**n**	**%**	
Age (years)	<65	53	91.4	5	8.6	0.38
	>65	8	100	0	0	
Comorbidity	No	13	86.7	2	13.3	0.33
	Yes	48	94.1	3	5.9	
Gender	Male	56	91.8	5	8.2	0.50
	Female	5	100	0	0	
Type of CP	CCP	54	93.1	4	6.9	0.57
	RCP	7	87.5	1	12.5	
Operation side	Right	40	93	3	7	0.80
	Left	21	91.3	2	8.7	
Supporting the bronchial stump	No	39	90.7	4	9.3	0.65
	Yes	21	91.4	2	8.6	
Bronchial stump closure	Stapled	32	94.1	2	5.9	0.59
	Hand-sutured	29	90.6	3	9.4	
Tumor diameter (cm)	<7 cm	44	89.8	5	10.2	0.60
	>7 cm	6	85.7	1	14.3	
Operation time (minutes)		351.9±83.7		370.7±38.7		0.42
Intraoperative bleeding (mL) mean ± SD		360±157.9		720±297		**0.003**
Percentage decrease in Hb (%) mean ± SD)		10.6±10.2		25.9±11.6		**0.003**
The time interval (between primary surgery and occurrence of lesion) month		38.2±35.6		29.7±16.5		0.80

The amount of intraoperative bleeding and the percentage decrease in Hb levels were prognostic factors affecting mortality.
RCP: Rescue completion pneumonectomy, CCP: Classical completion pneumonectomy, SD: Standard deviation

There is no widely accepted factor for complications, despite the many large surgical series subjected to study (1,18). Complication rates following CP have been reported to range between 24% and 62% in the literature (10,14-16), with the most common being empyema and cardiopulmonary complications (8,14). The rate of complications in our series was 42.2%, and the most common complication was atrial fibrillation (19%). There was no significant difference in complication rates between CCP and RCP. It can be seen that the rate of postoperative complications is significantly higher in those aged above 65 years. Although common and serious complications are seen after completion of pneumonectomy, better results can be obtained with proper management of complications.

A bronchopleural fistula is a significant complication after CP. The rates of BPF in CP have been reported to be between 10% and 24% (15,19). A higher rate of BPF has been reported in RCP patients by Pan et al. (5) (36%) and Yazgan et al. (19) (40%). There is strong consensus regarding the preservation of the bronchial stump as a means of preventing the development of a bronchopleural fistula after pneumonectomy. These series recommend supporting the bronchial stump as much as possible with pericardial fat tissue, azygos, parietal pleura, and omental flaps (20,21). Despite this information, supporting the bronchial stump with the surrounding tissue is not routinely applied by every surgeon. Chataigner et al. (15) identified a relationship between the development of BPF and right-sided surgery and no support of the bronchial stump with any tissue. Another study found a relationship between the administration of adjuvant therapy following initial surgery and the high incidence of bronchopleural fistula (22). In this study, the incidence of BPF was 15.5% in CCP while it was 12.5% in RCP, and it was shown that the support of the bronchial stump with any tissue significantly reduced the risk of developing BPF. Furthermore, diabetes mellitus and adjuvant therapy following initial surgery significantly increased the incidence of BPF. The type of completion procedure, operation site, and the bronchial closure technique had no effect on the development of BPF. The authors consider that, apart from supporting the bronchial stump with any tissue, avoiding excessive dissection and strict control of diabetes may be effective in preventing BPF. Bronchial stump coverage with any tissue was not practiced as a standard in this study, as ours is an

Table 3. Prognostic factors affecting survival						
Variables		**5-year survival (%)**	**10-year survival (%)**	**Mean survival (month)**	**95% CI**	**p-value**
Age (years)	<65	66.9	22.9	81	54-107	0.25
	>65	31.3	15.6	17	0-40	
Tumor diameter (cm)	<7 cm	62.9	29.1	81	48-113	**0.05**
	>7 cm	50	0	11	0-49	
Operation side	Right	62.8	19.2	70	55-84	0.34
	Left	58.1	46.5	111	47-174	
The time interval (between primary surgery and occurrence of lesion) years	<2	50.4	36	111	0-222	0.42
	2-4	62.7	0	67	40-93	
	>4	84.6	21.2	81	7-154	
N Stage	N0	63.4	32.9	117	32-201	0.38
	N1–N2	57.8	16.8	70	25-114	
Histopathology	Squamous cell carcinoma	70.5	34.2	92	47-136	0.10
	Adenocarcinoma	46.5	11.6	49	24-73	
Second op. stage	1	51.1	34	74	48-100	**0.01**
	2	73.3	37.9	97	74-121	
	3	50	0	43	19-66	
Adjuvant therapy (after second operation)	No	53.8	0	67	14-119	0.08
	Yes	66	27.4	92	29-154	

A tumor diameter greater than 7 cm (p=0.05) and the stage of the second tumor (p=0.01) were prognostic factors affecting survival.
CI: Confidence interval, Op: Operation

education hospital, and the surgeons adopted different approaches.

Five-year survival rates were reported to be between 18% and 57% in patients undergoing CP due to a malignant disease (13,23). Pan et al. (5) reported a five-year survival rate of 30% in patients undergoing CP due to a malignant disease and showed better survival in patients with stage I and II disease than in patients with stage III disease. In a multicenter study, five-year survival rates of 49% and 24% were reported in patients with squamous cell cancer and adenocarcinoma, respectively (p=0.04) (8). In a recent study published in 2022 (2), the five-year survival rate was reported as 51% in patients who underwent CP for malignant disease, and prolongation of resection, pathological stage, T, and N factors were associated with survival. In this interesting study examining the effects of induction therapy on postoperative outcomes in patients undergoing CP, better survival outcomes were reported in the group that received induction therapy before resection (2).

In our current study, the five-year survival for CP was 59.6% in patients undergoing CCP while it was 87.5% in RCP, and there was no significant difference between the two groups in terms of survival. The mean survival was 70 months in patients undergoing CCP due to a malignant disease in this study, and the five-year survival rate was 58%. Contrary to other studies (2,8), in our series, there was no difference in survival rates between patients with squamous cell carcinoma and those with adenocarcinoma. A tumor diameter greater than 7 cm and the stage of the second tumor were identified as prognostic factors affecting survival. Receiving adjuvant therapy recorded better survival, but the difference was not significant. Although the interval between the two operations affects survival, this study found no significant difference.

Study Limitations

The limitations of the study include its retrospective study design; it is difficult to have reliable statistical conclusions with a small and heterogeneous cohort within a retrospective study. Despite these limitations, our study has several strengths. Our study included data from a center that was experienced in lung resection. Although the number of patients in studies on complementary pneumonectomy is quite limited, the number of patients in our study was sufficient for a valid evaluation.

Conclusion

For the reasons mentioned earlier, the list of indications for CP has expanded, and this has increased our experience of CP, which is gaining in popularity owing to its low mortality rate and long-term survival. RCP and CCP have a similar risk ratio in terms of mortality and morbidity. Bronchopleural fistula is the most significant complication

after completion of pneumonectomy. The CP procedure has achieved satisfactory oncological and surgical results. To obtain satisfactory results from CP, it is necessary to minimize the risk factors as much as possible. The prevention of intraoperative hemorrhage, strict glycemic control, and coverage of the bronchial stump with tissue will further improve the outcomes of complementary pneumonectomy.

Ethics

Ethics Committee Approval: The University of Health Sciences Turkey, Istanbul Training and Research Hospital Clinical Research Ethics Committee approval of this study was acquired (decision no: 2018-KAEK-50/1259).

Informed Consent: Informed consent was obtained from all patients.

Peer-reviewed: Internally and externally peer-reviewed.

Authorship Contributions

Concept: Y.A., N.C., M.A.B., M.M., Design: O.S., V.E., L.C., Data Collection and/or Processing: Y.A., V.E., A.C.K., A.P., Analysis and/or Interpretation: N.C., C.B.S., A.C.K., Literature Research: O.S., M.M., A.P., Writing: Y.A.

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Original Article

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The Relationship Between Bacterial Pathogen Presence Detected by Bronchial Lavage and Acute Rejection: 1-Year Follow-up Results Following Lung Transplantation

Pinar Atagun Guney, Ayse Nigar Halis, Ertan Saribas, Sevinc Citak, Mustafa Vayvada, Murat Ersin Cardak, Yesim Uygun Kizmaz, Ahmet Erdal Tasci

University of Health Sciences Turkey, Istanbul Kartal Kosuyolu Yuksek Ihtisas Training and Research Hospital, Clinic of Lung Transplantation, Istanbul, Turkey

Abstract

Aim: Lung transplant recipients are the highest risk group in terms of infective complications among solid organ transplants. It has improved the management of the most common infectious complications with the aid of advances in diagnostic methods, prophylaxis, and therapeutic strategies. In the present study, we evaluated the results of microbiological culture samples by the bronchoscopic method.

Methods: This retrospective cohort study included patients who were admitted between November 2016 and May 2019 in a Lung Transplantation Department. We evaluated the results of bacteria detected in the lavage fluid obtained by serial bronchoscopy in the first year after lung transplantation in lung transplant patients. We divided the patients into two groups: those with acute rejection and those without. The two groups were compared according to their culture of growth and analyzed.

Results: Of the 77 patients included in the study, 77.2% were male. In the first year after transplantation, 79 bronchoscopic lavage cultures were positive in the follow-up. While bacterial culture positivity by post-transplant bronchial lavage was found to be 62% in the first 3 months, it decreased to 43.6% between the third month and the first year. There was no significant difference between the groups with and without acute rejection of lavage culture growth.

Conclusion: This study revealed the importance of the bronchoscopic method in terms of the detection of microbiological findings and the prempitic antibiotic therapy approach in the evaluation of lung infections in lung transplant patients.

Keywords: Lung transplantation, bronchoscopy, bronchoalveolar lavage fluid

Introduction

Lung transplantation has become a curative treatment option for patients with end-stage lung diseases who have tried all treatment regimens (1). In a randomized controlled study on flexible bronchoscopy, which is a necessary procedure to ensure success after lung transplantation, they emphasized that they can make it comfortable for patients thanks to the explanation given to the recipients using a graphical expression before the procedure (2). As immunosuppressive and antibiotic therapy treatment strategies have evolved, the early signs of infections in the post-transplant period have changed. Susceptibility to infections in lung transplantation has been defined by various factors such as airway anatomy, ischemic complications, and the absence of tracheobronchial reflexes (3,4). The main causes of mortality after lung transplantation are graft failure and infectious complications (1). These should be identified to be the main causes of both the early and late post-transplant period (5,6). In the study by Büyükkale et al. (7), in which

Address for Correspondence: Pinar Atagun Guney,
University of Health Sciences Turkey, Istanbul Kartal Kosuyolu Yuksek Ihtisas Training and Research Hospital, Clinic of Lung Transplantation, Istanbul, Turkey
Phone: +90 535 967 44 90 E-mail: atagunpnar@yahoo.com ORCID: orcid.org/0000-0003-1277-513X
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they presented their 3-year experience in 29 patients who underwent lung transplantation, they concluded that in selected recipients, appropriate donor and post-transplant patient management significantly improved survival.

They emphasized that, thanks to the completion of the learning process by the entire transplant team over time, it is possible to obtain satisfactory results by being organized on the basis of serious teamwork (7). It is important to know the epidemiology of post-lung transplant infections to prevent and treat infections. Although the predictive value of bronchoscopy in the detection of chronic rejection is weak, it was emphasized that it should be performed to exclude lower respiratory tract infections and acute rejection (AR) in the review of Bağ and Kıyan (8).

This study aimed to evaluate the patient population who underwent lung transplantation, the identification of the bacterial cultures, the time of infection, and the emergence of infection diagnosed using the bronchial lavage method in the 1-year period after the transplantation.

Materials and Methods

Compliance with Ethical Standards

This retrospective study was conducted in the lung transplantation department of a tertiary teaching hospital for chest diseases from November 2016, to May 2019. The study was conducted in full accordance while patients' signed informed consent was not obtained because of the retrospective nature of the study, and permission was obtained from the University of Health Sciences Turkey, Istanbul Kartal Kosuyolu Yuksek Ihtisas Training and Research Hospital Local Ethics Committee (date: 08.05.2020, decision no: 2020.4/30-335) who waived the need for patient consent to review their medical files. As informed consent from patients to review their medical records was not obtained, all patients' ID information was kept confidential.

Study Design

This study enrolled consecutive patients aged over 18 years, who underwent lung transplantation according to underlying diseases: obstructive lung disease, interstitial lung disease, end-stage infectious lung disease, lung cancer, and idiopathic pulmonary arterial hypertension (IPAH) at our institution. Cases could complete all of their routine visits planned as the clinical protocol established in our institution in the first year after transplantation were included. Patients who could not be sampled by death or bronchoscopic method for 1 year after transplantation were excluded from the study (n=8).

Bronchoscopic lavage samples were purchased from 77 lung transplant recipients. The stratification of patients was summarized in a flowchart in Figure 1. Lavage specimens by bronchoscopy are obtained routinely at 1 week, 1 month, 3 months, 6 months 9 months (as need) and 1 year post-transplant and as clinically indicated for suspected infection or rejection at this center. Whenever lavage by bronchoscopy is performed on a lung transplant recipient at this center, a bacterial specimen is performed routinely as part of a panel of microbiologic tests for immunocompromised patients, and transbronchial biopsy is also performed.

Bacterial Culture Assessment

Bronchial lavage samples taken from the patients were cultivated on solid medium (5% sheep blood agar, MacConkey agar) by a quantitative method. After incubation at 37 °C 24-48 hours, identification and antibiotic susceptibility testings were performed using VITEK® 2 Compact (bioMérieux, France) according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) (9).

Acute Rejection

AR was diagnosed and graded by the biopsies from each bronchoscopy procedure were interpreted collectively. An overall AR grade of A0 (none), A1 (minimal), A2 (mild), A3 (moderate), or A4 (severe) was assigned for the biopsies from each procedure (10,11).

Treatment of Acute Rejection

When A1 rejection accompanying clinical symptoms was detected, the typical treatment procedure was applied, while the symptomless A1 rejection episodes were not treated. A2 and higher rejection degrees are treated. 10-15 mg/kg of methylprednisolone was used for 3 days and then reduced to one mg/kg (12).

Statistical Analysis

The data were collected from patient files and hospital operating systems and analyzed with IBM SPSS Statistics for Windows v.23.0. Descriptive statistics were used to show the demographic and clinical characteristics of the patients. According to the distribution of values; median and interquartile range were used for non-parametric variables, while mean±standard deviation was used for parametric variables. Culture and biopsy samples were taken from the patient's post-transplantation routinely at the 1st week, 1st month, 3rd month, 6th month, and 1st year by the bronchoscopy method in our clinic. Discrete data is shown as percentages and absolute numbers. The results were compared using chi-square for categorical variables. Statistical significance-level p-value was taken as <0.05.

Results

In the study group of 77 patients, 77.2% were males, and the median age was 48 (34-56). The median waiting-list time was 3 (1-5) months, the median best FEV1 by

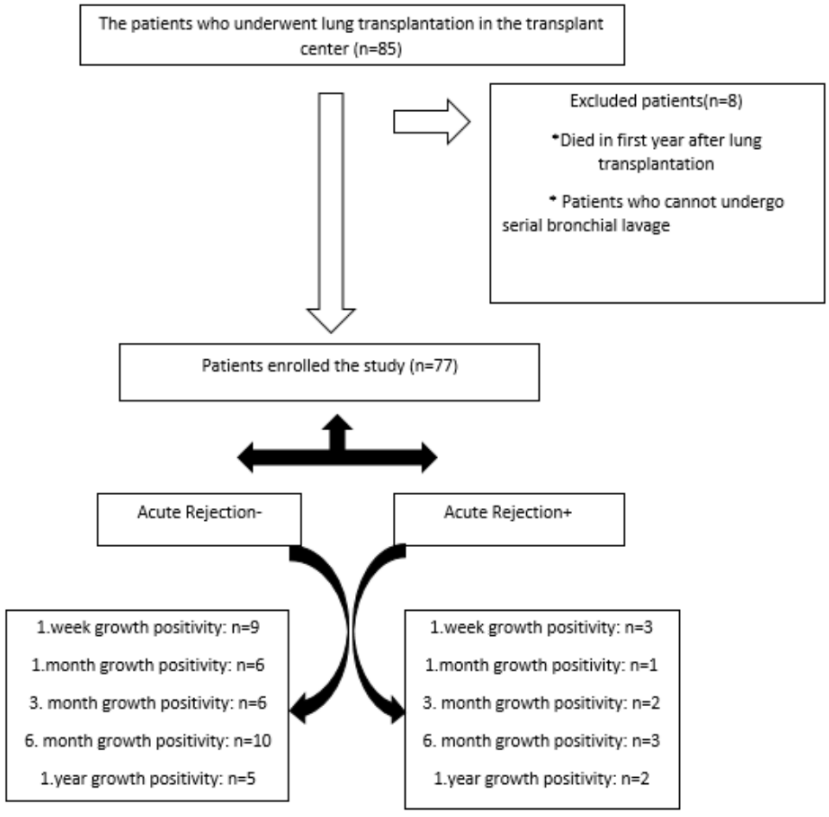

Figure 1. Flow chart of patients distribution

pulmonary function test was 2.52 (1.69-2.71) lt, the median duration of mechanical ventilation was 2 (1-8.5) days, the median length of ICU stay was 5 (3-13) days, and the median length of hospital day was 19 (16.4-19) days (Table 1).

According to the Charlson comorbidity index, 31.2% of the study population (n=24) was calculated as having 1 score, 46.8% (n=36) had 2 scores, and 22.1% (n=17) had 3 scores.

Fifty-nine (73.7%) bacterial isolates were in the first 3 months, 13 (16.2%) bacterial growth in the sixth month, and 8 (10%) in the first year (Table 2). The culture positivities of serial bronchial lavage samples are shown in Figure 2. Between the third month and the first year, the incidence of bacterial growth decreased drastically to 86.4%. Eighty isolates were recovered: *Methicillin-sensitive staphylococcus aureus* (n=11), *Streptococcus pneumonia* (n=2), *Klebsiella pneumoniae* (n=21), *Enterobacter cloacae* (n=2), *Acinetobacter baumannii* (n=9), *Extended spectrum beta-lactamase escherichia coli* (n=2), *Pseudomonas aeruginosa* (n=28), *Stenotrophomonas maltophilia* (n=2), *Staphylococcus haemolyticus* (n=1), *Escherichia coli* (n=2), *Proteus miriabilis* (n=2).

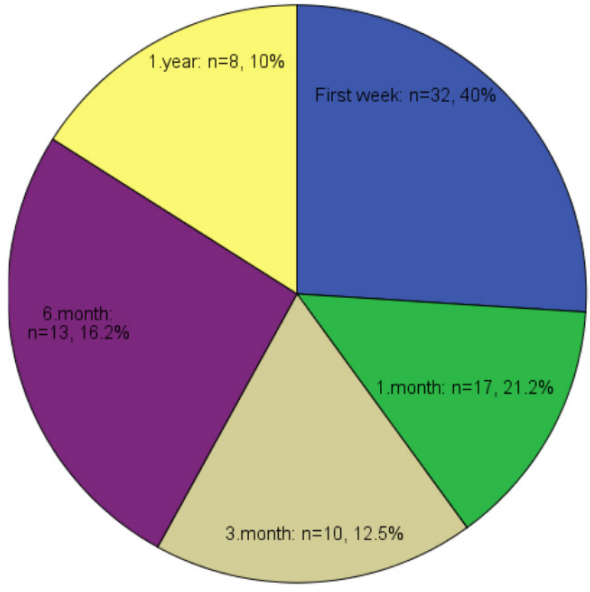

Figure 2. Culture positivities of serial bronchial lavage samples were showed

Table 1. Demografic and clinical parameters of the study

Variables	Total Patients (n=77)	OLD	ILD	EILD	Lung cancer	IPAH
Gender, male, n (%)	61 (77.2%)	15 (24.6%)	25 (41%)	21 (34.4%)	1 (1.6%)	1 (1.6%)
Age, median, IQR	48 (34-56)	55 (50-57)	51 (44-58)	33 (24-55)	43 (43-43)	25 (25-25)
Waiting list time, month, median, IQR	3 (1-5)	2 (1-6)	2 (1-5)	4 (2-6)	1 (1-1)	2 (2-2)
CRP (1st-3rd day), median, IQR	8.7 (2.8-19.6)	9.57 (1.67-21.15)	9.57 (3.02-19.60)	6.95 (3.13-15.10)	15 (15-15)	124 (124-124)
WBC (1st-3rd day), median, IQR	12200 (8550-18550)	9100 (7700-16805)	11850 (7650-16650)	14900 (9200-19000)	19100 (19100-19100)	29300 (29300-29300)
FEV_1 (lt) values						
Post-transplant best FEV_1 (lt), median, IQR	2.52 (1.69-2.71)	2.51 (1.88-3.08)	2.32 (1.76-2.78)	2.04 (1.61-2.38)	2.00 (2.00-2.00)	1.88 (1.88-1.88)
1. visit FEV_1 (lt), median, IQR	2.03 (1.58-2.52)	1.87 (1.76-2.67)	2.06 (1.64-2.55)	1.60 (1.33-2.15)	1.76 (1.76-1.76)	1.85 (1.85-1.85)
2. visit FEV_1 (lt), median, IQR	2.05 (1.46-2.44)	2.18 (1.78-2.61)	2.04 (1.49-2.54)	1.55 (1.26-2.26)	2.44 (2.44-2.44)	1.78 (1.78-1.78)
3. visit FEV_1(lt), median, IQR	2.14 (1.56-2.57)	2.40 (1.98-2.57)	2.28 (1.56-2.57)	1.73 (1.30-2.31)	2.01 (2.01-2.01)	1.98 (1.98-1.98)
4. visit FEV_1(lt), median, IQR	2.10 (1.54-2.75)	2.46 (2.16-2.68)	2.01 (1.61-2.76)	1.74 (1.38-2.50)	2.16 (2.16-2.16)	-
Duration of mechanical ventilation, day, median, IQR	2 (1-8.5)	2 (1-5)	4 (1-9)	2 (1-9)	14 (14-14)	2 (2-2)
Length of ICU stay, day, median, IQR	5 (3-13)	5 (3-13)	5 (3-16)	4 (3-11)	14 (14-14)	9 (9-9)
Length of hospital stay, day, median, IQR	19 (16.4-19)	14 (11-21)	17 (9-35)	22 (16-36)	24 (24-24)	30 (30-30)
Acute rejection, n (%)	8 (10.1%)	1 (16.7%)	4 (28.6%)	3 (23.1%)	0 (0%)	0 (0%)
BOS, n (%)	3 (3.8%)	1 (16.7%)	1 (7.7%)	1 (7.7%)	0 (0%)	0 (0%)

OLD: Obstructive Lung Disease, ILD: Interstitial Lung Disease, EILD: End-Stage Infectious Lung Disease, IPAH: Idiopathic Pulmonary Arterial Hypertension, CRP: C-reactive protein, WBC: White blood cell, FEV_1: Forced expiratory volume in 1 second, ICU: Intensive Care Unit, BOS: Bronchiolitis obliterans syndrome, IQR: Interquartile Ratio

Table 2. Bacterial growths obtained with serial bronchial lavage samples in the post-transplant period

Etiology	1st week	1st month	3st month	6st month	1st year	Total (n)
Acinetonobacter baumanii, n (%)	6 (7.6%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	-	9
Enterobacter clocacae, n (%)	2 (2.5%)	-	-	-	-	2
ESBL + *E. coli*, n (%)	1 (1.3%)	-	-	-	-	1
Klebsiella pneumonia, n (%)	5 (6.3%)	6 (7.6%)	4 (5.1%)	5 (6.3%)	1 (1.3%)	21
Pseudomonas aeroginosa, n (%)	7 (8.9%)	7 (8.9%)	3 (3.8%)	5 (6.3%)	6 (7.6%)	28
Staf. aureus, n (%)	8 (10.1%)	2 (2.5%)	-	1 (1.3%)	-	11
Stenotrophomonas maltophilia, n (%)	2 (2.5%)	-	-	-	-	2
Streptococcus pneumonia, n (%)	1 (1.3%)	-	-	-	1 (1.3%)	2
Staphylococcus haemolyticus, n (%)	-	1 (1.3%)	-	-	-	1
E. coli, n (%)	-	-	1 (1.3%)	1 (1.3%)	-	2
Proteus miriabilis, n (%)	-	-	1 (1.3%)	-	-	1
Total	32	17	10	13	8	80

Data are presented as percentages and absolute numbers n (%).
ESBL: Extended spectrum beta-lactamase, *E. coli*: *Escherichia coli*

There was no difference in bronchoscopic lavage cultures on the first-third day after lung transplantation between with/without AR. The first month of culture positivity was higher in the AR-negative group than in the AR-positive group, but it was not statistically significant (n=6, 85.7%, n=1, 14.3%). In the six-month period, culture positivity was found to be lower in the group with AR, but it was not significant (n=5, 25%, n=15, 75%). Summarily, serial bronchoscopic lavage culture positivity during post-transplantation was not found to be significant when patients with and without AR were compared (Table 3).

Discussion

The primary finding of this article was that the bacterial growth numbers obtained from post-transplant periodic bronchoscopic lavage were not predictive of AR in lung transplant patients. AR remains a significant cause of morbidity after lung transplantation and can range from mild to severe. Even a single episode of AR is a risk factor for developing bronchiolitis obliterans syndrome, which is the cause of a progressive decline in lung function and the cause of death in most patients. Despite the critically important importance of AR, the risk factors have not been fully defined. To date, adequate data on the role of lung bacterial load in post-transplant AR has not been presented. Culture-dependent studies have shown that colonization with pseudomonas aeruginosa is a risk factor for chronic lung allograft dysfunction (CLAD) development (13). However, recent studies have suggested that lung bacteria are a key factor in post-transplant pulmonary inflammation and allograft dysfunction, independent of acute infections. Based on post-lung transplant BAL growth results in 134 healthy lung transplant recipients, Combs et al. (14) demonstrated that the lung microbiome was a new risk factor for the development of CLAD. However, in the same study, they found that bacteria isolated with BAL were not associated with host dysfunctions such as AR, consistent with the primary findings of our study. Furthermore, they proposed that the bacteria isolated from the lung reflect the underlying host detoriation (14).

In the early days of post-transplant, lower airway growth with bacteria is recognized as one of the major causes of recipient mortality, but with the use of aggressive antibiotic therapy for recipients, the incidence of recipient pneumonia has recently decreased significantly (15). In this study, it has been shown that the bacterial growth detected in the early period according to the serial bronchoscopic control culture results from the first week of lung transplantation gradually decreases in long-term follow-ups after appropriate antibiotic therapy modalities targeting pathogens.

In 1998, Fishman and Rubin (16), two of the first clinicians to deal with the infection status of transplant patients, drew attention to 3 periods of infection after solid organ transplantation: These are nosocomial infections up to 1 month after transplantation; opportunistic infections in the 1-to 6-month period; and community-acquired or persistent infections 6 months later. This important timeline has guided the appropriate design of empirical treatments. Six months after transplantation, community-acquired pathogens were found to be a major problem (16).

It was shown that infection rates were highest in the first month post-transplant and decreased after 6-12 months. The cumulative incidence of infection reached 62% at 12 months post-transplant. Bacterial infections caused 63% of all infections. Of the bacterial infections identified, 54% belonged to Enterobacteriaceae infections, with *Escherichia coli* and *Klebsiella* spp. (47%) predominant. Bacterial infections predominated during the first year post-transplant. Infections with Enterobacteriaceae were common, especially in the first 180 days after transplantation, and non-fermenting gram-negative bacteria appeared frequently in the first 150 days after transplantation. After that, it decreased but still continued at a regular rate. Pseudomonas aeruginosa and enterobacteriaceae occurred throughout the post-transplant first year. The most frequent pathogens infecting lung transplant recipients include gram-negative rods such as pseudomonas aeruginosa and enterobacteriaceae (17).

Table 3. Comparison of bacterial growth numbers in post-transplantation periods between presence of acute rejection and absence

	Acute rejection (+)	Acute rejection (-)	p-value
FOB 1st-3rd day culture, n (%)	3 (25%)	9 (75%)	0.827
FOB 1st month culture, n (%)	1 (14.3%)	6 (85.7%)	0.546
FOB 3rd month culture, n (%)	2 (25%)	6 (75%)	0.869
FOB 6th month culture, n (%)	3(23.1%)	10 (76.9%)	0.961
Culture positivity in the six-month period, n (%)	5 (25%)	15 (75%)	0.809
FOB 12th month culture, n(%)	2 (28.6%)	5 (71.4%)	0.724

Data are presented as descriptive analyze (percentages and absolute numbers) n (%) and chi-square test.
FOB: Fiberoptic bronchoscopy

Infections are most common in the first year after lung transplantation. Predominantly, bacterial infections occur in the first 3 months post-transplant (18). The most common bacterial infection in the first six months after lung transplantation was pseudomonas aeruginosa (19). Stjärne Aspelund et al. (20) found that bronchoalveolar lavages have a high bacterial load. The most commonly detected bacterial infection was pseudomonas aeruginosa. In the same study, the incidence of lung infections decreased over time (20). In addition, we also found pseudomonas aeruginosa (35.4%) as the vast majority of pathogens in findings similar to the studies mentioned in the 6-month period following transplantation. Among solid organ transplants, the lung is the only organ with direct external exposure. Additionally, the lower respiratory tract is susceptible to pathogens in the first months due to impaired mucociliary clearance and denervation that inhibit the cough reflex in the early post-transplantation period (18).

In this study, 91.1% of bacterial growth was detected in the first 6 months, and 10.1% of growth was detected after 6 months, and we found a gradual decrease within a year. We also reported similar results in other studies where the first three months after surgery were defined as the critical period for infections, especially for bacterial etiology (20,21).

It was thought that although survival increased thanks to the development of the immunosuppressive protocol and the increased bacterial load, the middle-low income of the country where the study was conducted contributed to the risk of pulmonary infection in the study in which pulmonary infections were investigated in the kidney transplant patient group.

Infections occurred in the early months after transplantation, whereas in this study the timeline had shifted to later months. We believe that this may be even stronger in geography, where the general exposure to infections in the population is high and population density increases the risk even in the late post-transplant period (22).

Potent immunosuppressive strategies have been developed to reduce the post-transplant rejection rate, however, alter the recipients' susceptibility to infections. Additionally, with the contribution of effective and modern antibiotics, the frequency and schedule of post-transplant infections may have changed (23). Additionally, rapid and effective diagnostic detection of potential pathogens, keeping in mind geographical conditions and epidemiological exposures, is vital in establishing prevention strategies to further reduce the morbidity and mortality associated with post-transplant infections. For this reason, we believe that each center must have its own unique aspects in the treatment schemes. The common goal of pulmonologists and doctors treating infections specializing in lung transplantation is to determine patient-specific prophylactic and empirical antibiotic therapies. Thus, it minimizes the possibility of AR or chronic rejection, which shortens post-transplant survival. In this study, we attributed the absence of AR in the group with more bacterial growth to the development of appropriate strategies against pathogens detected early with close follow-up of the patients.

Study Limitations

One of the most important limitations of our study was that the underlying patient group was not homogeneous: there was a large group of patients with suppurative pulmonary diseases and IPAH patients. Secondly, we excluded comorbidities of the patient population due to a lack of data. Thirdly, we included all of the bronchoscopic lavage growth results without distinguishing between colonization and infection, especially in the patient groups such as bronchiectasis or cystic fibrosis. We can explain this situation. We also designed the current study to present a timeline of the main bacterial infections after transplantation in this specific population.

Conclusion

Microbiological culture samples obtained using bronchoscopy after serial lung transplantation are an important method that helps predict the patient's preemptive antibiotic treatment. Although we could not find a significant relationship between AR and microbiological culture growth, we believe that more prospective studies are needed to clarify this ambiguous situation.

Ethics

Ethics Committee Approval: The ethical approval was obtained from the University of Health Sciences Turkey, Istanbul Kartal Kosuyolu Yuksek Ihtisas Training and Research Hospital Local Ethics Committee (date: 08.05.2020, decision no: 2020.4/30-335).

Informed Consent: Informed consent was not obtained because of the retrospective nature of the study.

Peer-reviewed: Internally and externally peer-reviewed.

Authorship Contributions

Concept: M.E.C., E.S., Design: P.A.G., Data Collection and/or Processing: M.V., S.C., Analysis and/or Interpretation: P.A.G., A.E.T., Literature Research: Y.U.K., A.N.H., Writing: P.A.G.

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

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Original Article

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Can We Use Inflammation Biomarkers Based on Complete Blood Cell Count in the Follow-up of COVID-19 in Hemodialysis Patients?

Kubra Aydin Bahat, Tugba Tahtali

Kartal Dr. Lutfi Kirdar City Hospital, Clinic of Nephrology, Istanbul, Turkey

Abstract

Aim: Coronavirus disease-2019 (COVID-19) is more severe in hemodialysis patients than in the average population and causes much higher mortality. This study investigated the effect of inflammation parameters obtained from complete blood count on the prognosis of COVID-19 in hemodialysis patients with COVID-19.

Methods: Hemodialysis patients admitted to our hospital between 11.03.2020 and 01.12.2020 with the diagnosis of COVID-19 were included in this study. The relationship between the oxygen requirement, intensive care requirements, and mortality development of the patients and the parameters obtained from the complete blood count, C-reactive protein (CRP), secondary infection, and demographic characteristics of the patients were investigated.

Results: A total of 94 hemodialysis patients were included in the study. There was a correlation between secondary infections and the need for oxygen and intensive care (p=0.001 and p<0.001, respectively). CRP levels were associated with mortality, need for intensive care and oxygen demand (p=0.031, p=0.019 and p=0.014, respectively). Systemic inflammation index, derived neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio were associated with oxygen demand (p=0.002, p=0.009 and p=0.044, respectively). The systemic inflammation index, platelet-lymphocyte ratio, and derived neutrophil-lymphocyte ratio exhibited the highest specificity (19.4% vs 26.9% vs 16.4%) and sensitivity (96.7% vs 92.6% vs 96.7%) and the largest areas under the curve of 0.672 vs 0.652 vs 0.666, respectively.

Conclusion: Systemic inflammation index, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio obtained from complete blood count parameters in hemodialysis patients are functional parameters that can be used to predict the course of COVID-19.

Keywords: COVID-19, hemodialysis, systemic inflammation index, complete blood cell count

Introduction

Coronavirus disease-2019 (COVID-19) is important because of its rapid spread, incurability, and fatal course. It can cause various signs of infection, from asymptomatic to severe pneumonia. Although studies show that the disease is milder in severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) variants that emerged in the last months of 2021, the disease is especially severe in the elderly and patients with comorbidities. The most common symptoms of COVID-19 are cough, fever, shortness of breath, and fatigue. There is data that COVID-19 is severe in patients undergoing hemodialysis (HD) treatment (1-3). Chronic uremia may cause inflammation at the molecular level in patients with HD, suppressing immunity and altering the immune response to viral diseases (4). Acute respiratory distress associated with the rapid onset of the systemic proinflammatory process is the leading cause of death in COVID-19 patients. According to clinical symptoms and laboratory test results, patients are classified as mild, moderate, severe, and critical (5). Patients with severe symptoms may develop severe pneumonia, acute respiratory distress syndrome (ARDS), or death (6).

In revealing the severity of COVID-19, it is essential to determine the biomarkers with fast results that are easily accessible. These tests can help provide early and aggressive treatment, reduce mortality, and reduce hospital stays and costs. In the early diagnosis of most diseases, routine

Address for Correspondence: Kubra Aydin Bahat
Kartal Dr. Lutfi Kirdar City Hospital, Clinic of Nephrology, Istanbul, Turkey
Phone: +90 532 270 70 60 E-mail: asbkubra@gmail.com ORCID: orcid.org/0000-0002-2620-9991
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blood tests used to evaluate inflammatory processes are often helpful and necessary (7). Complete blood count (CBC), an easy, accessible, and inexpensive test, is frequently used to evaluate inflammatory processes. CBC provides information about the number and morphological appearance of various cell types [white blood count (WBC), neutrophils, lymphocyte monocytes, mean platelet volume (MPV)], platelet, etc (8,9).

Recent studies show that the following factors help predict the severity of COVID-19: platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), derived NLR (dNLR), MPV-platelet ratio (MPR), monocyte-lymphocyte ratio (MLR), neutrophil ratio, lymphocyte x platelet ratio (NLPR), systemic inflammation response index (SIRI), and systemic inflammation index (SII) (7-11).

In this study, we aimed to investigate whether readily available and low-cost CBC parameters-WBC, lymphocyte, platelet, MPV, MPR, NLR, dNRL, PLR, SII, and NLPR-help predict disease severity.

Materials and Methods

Compliance with Ethical Standards

The research protocol was approved by the Kartal Dr. Lutfi Kirdar City Hospital Clinical Research Ethics Committee (approval number: 2020/514/187/13). Our study was retrospective and was waived under the patient consent form.

Study Design

Hemodialysis patients admitted to our hospital between 11.03.2020 and 01.12.2020 with the diagnosis of COVID-19 were included in this study. A real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) test was performed for SARS-CoV-2 with nasopharyngeal and oropharyngeal samples in all patients who applied to our hospital, with findings suggestive of COVID-19. Additionally, chest-computed tomography was performed on all of these patients. The presence of crazy-paving patterns, ground-glass opacities, and consolidation in chest tomography was defined as tomography findings compatible with COVID-19. Patients with HD who had a positive rRT-PCR test for SARS-CoV-2 and/or had typical findings for COVID-19 on lung tomography were included in the study. CBC and CRP tests were performed at the time of admission to the hospital.

The relationship between the oxygen requirement, intensive care requirements, and mortality development of the patients included in the study and the parameters obtained from the CBC, CRP, secondary infection, and demographic characteristics of the patients were investigated.

Clinical Data Collection

The demographic characteristics of all patients (age, gender), chronic diseases [hypertension (HT), diabetes mellitus, congestive heart failure (CHF), asthma, chronic obstructive pulmonary disease], coronary artery diseases (angina pectoris, myocardial infarction, documented coronary heart disease) were recorded. Admission symptoms (fever, cough, shortness of breath, nausea, vomiting, diarrhea, abdominal pain, myalgia, conjunctivitis, loss of smell or taste) were questioned. The need for oxygen support was determined as <93% oxygen saturation in room air, and the patients in need of oxygen were recorded. The diagnosis of secondary infection was made by infectious disease specialists (findings of the presence of additional infection focus; pyuria, abscess, catheter infection, etc. and culture growths were evaluated), and the patients with secondary infection were recorded. The patients needing intensive care were recorded as per the COVID-19 Guidelines of the Ministry of Health (12). Additionally, laboratory values [WBC, neutrophils, platelets, lymphocytes, C-reactive protein (CRP)], and clinical results (cure, in-hospital follow-up, death, and treatments) were evaluated. Leukocytosis, lymphopenia, neutrophilia, and increased CRP were defined as follows, according to the hospital laboratory's given normal ranges: WBC: >10800 u/L leukocytosis, lymphocyte count: ≤1300 u/L lymphopenia, neutrophil count: >7700 u/L neutrophilia, platelet count: <130000 u/L thrombocytopenia and CRP: >3 mg/L CRP increase. MPV value normal range: 9.2-11.2 μm^3.

Complete blood count indices predicting systemic inflammation were calculated using the following formulas: PLR; platelet/lymphocyte, NLR; neutrophil/lymphocyte, dNLR; neutrophils/(WBC-neutrophils), MPR; MPV/platelet, NLPR; neutrophil/(lymphocyte X platelet), SII (neutrophil X platelet/lymphocyte].

Statistical Analysis

Statistical analysis was performed with the software SPSS Statistics for Windows, version 21 (IBM Corporation, Armonk, NY, USA). The statistical significance limit of the p-value was accepted as 0.05. Numerical variables were given as mean + standard deviation if normally distributed and mean + standard deviation (median) if skewed continuous were distributed. Categorical variables are shown as frequencies. Chi-square. A test was used to evaluate the categorical data. In the analysis of continuous variables, the independent samples t-test and Mann-Whitney U were used under the data distribution. Receiver operating characteristic (ROC) analysis was performed with calculations of area under the curve, sensitivity, and specificity to evaluate the predictive value of parameters with significant p-values.

Results

Our study was completed with 94 patients diagnosed with HD and COVID-19. The most common symptom in the patients was dyspnea, and the most common accompanying disease was HT.

At follow-up, oxygen support was required in 72% of the patients (68 patients). Secondary infection was detected in 35% of these 68 patients (24 patients). Secondary infection was observed in 4% (1 patient) of 26 patients who did not need oxygen support (p=0.001). Secondary infection was detected in 53% (16/30 patients) of those who needed intensive care. Secondary infection was observed in 14% (9/64 patients) patients not requiring intensive care (p<0.001).

The mean CRP value of the patients who needed oxygen was 110.2 mg/L, and the mean CRP value of the patients who did not need oxygen was 70.3 mg/L (p=0.014). The mean CRP value of patients requiring intensive care was 128 mg/L, and the mean CRP value of patients not requiring intensive care was 85.5 mg/L (p=0.019). The mean CRP value of seventy-one surviving patients was 88.7 mg/L, while the mean CRP value of the deceased patients was 131.6 mg/L (p=0.031).

The mean PLR value of the patients who needed oxygen was 307.9, the mean dNLR value was 5.41, and the mean SII value was 2025. The mean PLR value of the patients who did not need oxygen was 202, the mean dNLR value was 3.42, and the mean SII value was 1061 (p=0.009, p=0.044, p=0.002, respectively).

These parameters' ROC curves were found to correlate significantly with the oxygen demand (Figure 1) (13,14). SII exhibited the most significant specificity (19.4%) and sensitivity (96.7%) and the largest area under the curve at 0.672. PLR exhibited the highest specificity (26.9%) and sensitivity (92.6%) and the largest area under the curve at 0.652. dNLR exhibited the most significant specificity (16.4%) and sensitivity (96.7%), with the largest area under the curve at 0.666. The optimal threshold values for SII, PLR, and d-NLR were 3184.4, 408.5, and 10.9, respectively.

No significant correlation was found between age, gender, WBC, neutrophil, lymphocyte, platelet, NLR, dNLR, PLR, MPR, NLPR, and SII values of 30 (32%) patients who needed intensive care and 23 (24%) patients who died. There was no significant relationship between oxygen demand and age, gender, WBC, neutrophil, lymphocyte, platelet, CRP, NLR, MPR, or NLPR values. The oxygen demand characteristics of the study population are detailed in Table 1. ROC analysis results for dNLR, SII, and PLR values in the estimation of oxygen demand are detailed in Table 2.

Discussion

COVID-19 is a fatal disease that affects the entire world. It forces the health system to handle a high number

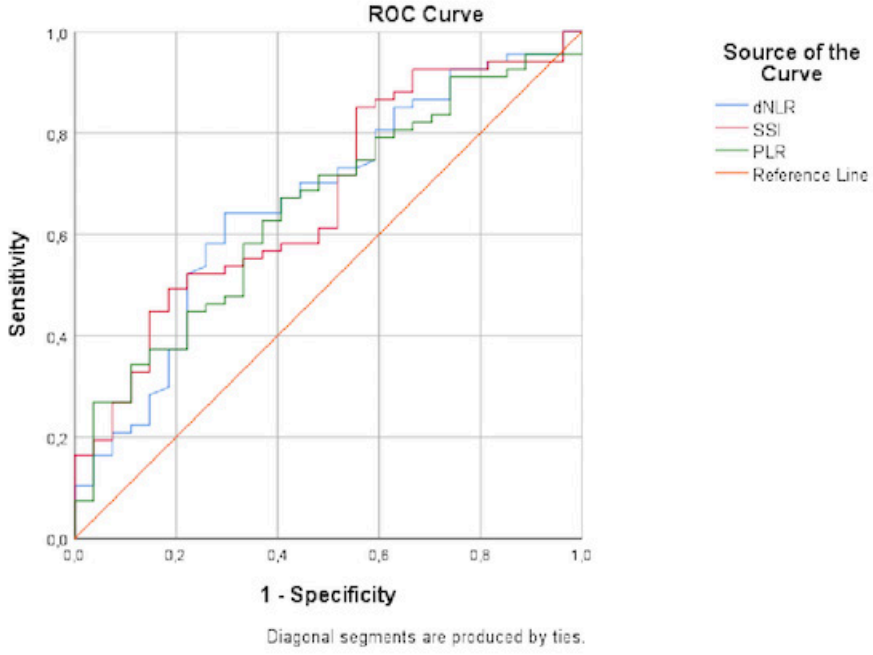

Figure 1. SII, PLR, and dNLR ROC curves in COVID-19 patients developing oxygen demand
ROC: Receiver operating characteristic, SII: Systemic inflammation index, PLR: Platelet-lymphocyte ratio, dNLR: Derived neutrophil-lymphocyte ratio

Table 1. The features of the patients stratified by oxgen support need in the follow-up				
Parameters	**Oxgen support (-)**	**Oxgen support (+)**	**Total**	**p-value**
Demographic features				
Age	60.3±12.6 (67)	63.2±15.8 (66.5)	62.5±15 (65)	0.287
Sex				1
Female, n	11 (42%)	38 (56%)	49 (52%)	
Male, n	15 (58%)	30 (44%)	54 (48%)	
Hypertension, n	16 (57%)	55 (81%)	71 (76%)	0.063
Diabetes mellitus, n	9 (32%)	41 (60%)	50 (54%)	0.417
CHF, n	4 (15%)	11 (16%)	15 (16%)	1
CVD, n	7 (27%)	20 (29%)	27 (29%)	1
COLD, n	3 (12%)	3 (4%)	6 (6%)	0.208
Dispne, n	9 (35%)	39 (57%)	48 (51%)	0.065
Fever, n	8 (31%)	21 (31%)	29 (31%)	1
Cough, n	12 (46%)	21 (31%)	43 (46%)	0.126
Secondary infection, n	1 (4%)	24 (35%)	25 (27%)	0.001
Mortality, n	0 (0%)	23 (34%)	23 (24%)	0.000
Laboratory findings				
WBC, u/L	7192±4483	8217±4483	7821±4438	0.312
Neutrophils, u/L	5388±4074	6522±4252	6208±4213	0.245
Lymphocytes, u/L	1176±557	1004±701	1052±666	0.264
Platelets, u/L	198730±79830 (197000)	213397±97531 (205555)	209340±92788 (204000)	0.704
CRP, mg/dL	70.3±59	110±88.9	99±83.4	0.577
Data calculated from CBC parameters				
NLR,	5.85±3.8	9.8±10.2	8.7±9.3	0.064
dNLR,	3.4±2.9	5.4±4.8	4.9±4.4	0.044
PLR,	202±126	308±251	278±228	0.009
MPR,	0.055±0.039	0.051±0.027	0.052±0.038	0.623
NLPR,	0.046±0.096	0.058±0.086	0.055±0.089	0.559
SII,	1.06±0.91	2.02±1.9	1.75±1.80	0.002

CHF: Congestive heart failure, CVD: Coronary vascular diseases, COLD: Chronic obstructive lung disease, WBC: White blood cell, CRP: C- reactive protein, CBC: Complete blood count, NLR: Neutrophil-to-lymphocyte ratio, dNLR: Derived NLR, PLR: Platelet-lymphocyte ratio, MPR: Mean platelet volume to platelet ratio, NLPR: Neutrophil to lymphocyte x platelet ratio, SII: Systemic inflammation index
Data are given as (mean ± standard deviation) (median)

Table 2. ROC analysis results for dNLR, SII, PLR values in estimating the oxygen demand requirement					
Parameters	**AUC**	**Optimal cut-off**	**p-value**		
				Specificity, %	**Sensitivity, %**
dNLR	0.666	10.9	0.012	16.4	96.7
SII	0.672	3184.4	0.009	19.4	96.7
PLR	0.652	408.5	0.021	26.9	92.6

AUC: Area under the curve**,** dNLR: Derived neutrophil-lymphocyte ratio, SII: Systemic inflammation index, PLR: Platelet-lymphocyte ratio, ROC:

of patients and increases costs. For this reason, there is a need for fast, easy-to-access and low-cost monitoring parameters.

WBC, lymphocyte, platelet, MPV, MPR, NLR, NLPR, dNRL, PLR, SII, MLR, and SIRI parameters were examined in the general patient population with COVID-19 (7). A limited number of studies show the effect of parameters obtained from CBC count on prognosis in patients with HD. These studies investigated the relationships of WBC, lymphocytes, platelets, NLR, and PLR with disease severity (15,16).

We revealed the relationship between the clinical course of inflammation parameters arising from the whole blood cell count of 94 patients with HD infected with COVID-19 during the 10 months of the pandemic.

The mean age of the patients included in the study was 62.4±15 (median: 65). Similar to other studies (between 57-66) in patients with HD infected with COVID-19, it showed that the patients in our study were generally older (1-3). Most of our patients (72%) were women. The distribution of gender varies according to research (1,17,18).

Cough and shortness of breath were the most common symptoms in our study, similar to the patient groups diagnosed with COVID-19 who received HD treatment and those who did not receive HD treatment (1,3,19,20). Similarly, the most common comorbid disease was HT (21,22).

We examined inflammatory tests related to ICU requirement, oxygen requirement, mortality, and CBC count. The most common abnormal laboratory parameters were lymphopenia and increased CRP.

The severity of COVID-19, mortality rates, need for intensive care, leukocytosis, lymphopenia, high neutrophils, thrombocytopenia, NLR, dNLR, PLR, SII, and high CRP were associated in general population studies (10,17,20,23).

In COVID-19 studies specific to patients with HD, severe COVID-19 was associated with mortality and the need for intensive care, leukocytosis, lymphopenia, neutrophil elevation, thrombocytopenia, NLR, PLR, and CRP (15,16,21). Consistent with the literature data, our study found a statistically significant relationship between the need for intensive care, mortality, and CRP. Additionally, significant relationships were found between oxygen demand and CRP, systemic inflammation index, PLR, and dNLR. In several studies in patients with HD and some normal population studies, SII, PLR, and dNLR parameters have been associated with severe COVID-19 infection (10,24-26). The lack of statistical significance with other parameters may have resulted from the small number of patients limiting the statistical analysis results.

When the data was examined, it was discovered that there was a significant relationship between secondary infection and oxygen demand, as well as between secondary infection and intensive care, which was consistent with the literature (1,17,23). The mortality rate in our patient group was 24% and was similar to other studies in patients with HD (1,3).

Study Limitations

Our study's small number of patients should be noted as a limitation. However, patients with HD are a small group when considering all COVID-19 patients. Additionally, examinations to exclude different atypical pneumonia pathogens may not be performed due to the high patient load, particularly in the first period of the pandemic. Another limitation is the absence of positive rRT-PCR testing for SARS-CoV-2 in all of our study patients.

Due to insufficient laboratories in the first period of the pandemic, PCR tests gave results in 48-72 hours. All patients underwent lung CT scans for a rapid diagnosis of COVID-19. In our study, all patients with negative rRT-PCR tests had typical CT lesions suggestive of COVID-19. In some studies, it was observed that the PCR tests of patients with tomography findings were positive in repeated PCR tests but negative in the first PCR test (19,27). Despite these limitations of our study, it was one of the first studies to investigate the subject of the HD patient group, and it was one of the first to deal with dialysis patients.

Conclusions

It has been revealed that secondary infections adversely affect the prognosis of patients with HD with COVID-19. Furthermore, dNLR, PLR, and SII parameters from CBC count were determined as low specificity but high sensitivity parameters for disease severity and hospital stay in patients with HD with COVID-19. Studies with more patients are needed to reveal the place of dNLR, PLR, and SII parameters in the follow-up of COVID-19 in patients with HD with the available data.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Kartal Dr. Lutfi Kirdar City Hospital (decision number: 2020/54/187/13).

Informed Consent: Informed consent was waived.

Peer-reviewed: Internally peer-reviewed.

Authorship Contributions

Concept: K.A.B., Design: K.A.B., T.T., Data Collection and/or Processing: K.A.B., T.T., Analysis and/or Interpretation: K.A.B., Literature Research: K.A.B., T.T., Writing: K.A.B., T.T.

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

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Health Literacy and Cyberchondria Levels in Healthcare Workers and Their Relationship with Body Awareness and Physical Activity

Raziye Savkin, Izgi Guven, Nihal Buker

Pamukkale University Faculty of Physiotherapy and Rehabilitation, Denizli, Turkey

Abstract

Aim: The level of health literacy and cyberchondria of healthcare providers can affect service beneficiaries, and the influence of health literacy and cyberchondria on physical activity and body awareness remains unclear. The aim of this study was to determine the health literacy and cyberchondria levels of healthcare workers and examine their relationship with physical activity level and body awareness.

Methods: This cross-sectional study was conducted between August and November 2021 on 168 healthcare professionals working at the university hospital. The Turkish Health Literacy scale (TSOY-32), Cyberchondria scale, Body Awareness Questionnaire (BAQ), and International Physical Activity Questionnaire-Short Form (IPAQ-SF) were used for outcome measurements.

Results: The TSOY-32 and Cyberchondria scale total scores were 37.76±7.98 and 63.83±19.45, respectively. There were low positive and significant correlations with TSOY-32, BAQ (r=0.213, p=0.006) and IPAQ-SF (r=0.162, p=0.036), while a low negative correlation was found between cyberchondria level and BAQ (r=-0.179, p=0.022) and IPAQ-SF (r=-0.193, p=0.013).

Conclusion: This study shows that, unlike predicted, health professionals did not have perfect health literacy and were found to have moderate cyberchondria. Physical activity and body awareness may affect increasing health literacy and reducing cyberchondria, which will empower individuals to make beneficial health decisions.

Keywords: Exercise, health literacy, health professional, internet usage

Introduction

Modern healthcare systems are complex and often confusing for healthcare consumers because of technological advances and changes in healthcare policies. In this modern system, individuals should take on new roles, such as seeking health information, understanding rights and responsibilities, and making health decisions for themselves and others on an individual, regional, and global scale (1). The definition of personal health literacy has been updated in the Healthy People 2030 report as "the degree to which individuals can find, understand, and use information and services to inform health-related decisions and actions for themselves and others" (2). However, there is a clear difference between the demands of health systems and the health literacy level of people who will benefit from health services (3).

The use of the Internet is large and growing due to changing healthcare models, an increase in health-related information, health cost limitations, health promotion, and disease prevention strategies. It is also attractive to users because it allows anonymous access to a wide variety of health-related information and opinions from anywhere, at any time, and at relatively low costs (4). According to Turkish Statistical Institute (TurkStat) 2021 data, 69.6% of individuals use the internet to search for health-related information (e.g. injury, disease, nutrition, improving health, etc.) (5). But, repetitive health-related information-seeking behavior on the Internet to benefit himself or his loved ones may increase health-related anxiety due to an abundance of unreliable, uncertain, and confusing health-related information (6,7). Although there is no consensus on its definition and conceptualization, cyberchondria emphasizes excessive or repeated online health research that is associated with increased health anxiety (8).

Address for Correspondence: Izgi Guven,
Pamukkale University, Faculty of Physiotherapy and Rehabilitation, Denizli, Turkey
Phone: +90 0258 296 42 84 E-mail: guvenizgi@gmail.com ORCID: orcid.org/0000-0003-1284-8431
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The health literacy level of healthcare providers can affect everyone who receives health care (9). However, it has been reported that despite having the opportunity to obtain information directly from physicians, healthcare professional seek health-related information through different channels, such as the Internet (10). It has been reported that people with high health literacy have higher skills and abilities to acquire health-enhancing behaviors, and therefore, a higher level of health literacy is associated with higher levels of physical activity (11,12). An increase in health literacy may also be effective in reducing cyberchondria (13). Body awareness, known as the attentional focus on and awareness of bodily states, processes, and actions, provides information about body parts and senses, creating an emotional memory for physical capacity (14). Misinterpretations of body sensations and symptoms, health anxiety, and various psychological processes, such as catastrophizing pain, can increase cyberchondria (15). Physical activity level and body awareness can be affected by health literacy and cyberchondria level, but this relationship has not yet been fully explained. The aim of this study was to determine the health literacy and cyberchondria levels of allied health professionals and health officials working in a university hospital. A secondary aim was to examine the relationship between health literacy and cyberchondria with physical activity level and body awareness.

Materials and Methods

Compliance with Ethical Standards

This cross-sectional study was conducted on allied health professionals and healthcare assistants at Pamukkale University Hospitals between August 2021 and November 2021. The study was approved by the Pamukkale University Clinical Research and Ethics Committee of the authors' affiliated institution (approval date: 13.07.2021 and approval number: 13). All study participants provided written informed consent, and the study was carried out according to the Helsinki Declaration's criteria.

Participants

The inclusion criteria were as follows: being allied health professionals and healthcare assistants at Pamukkale University Hospitals, and volunteering to participate in the study. Participants with missing data were excluded from the study.

Assessments

The demographic data of the participants (age, gender, body mass index, occupation, education level) were recorded. The Turkey Health Literacy scale-32 (TSOY-32) scale was used to determine the health literacy level of the participants. The scale is based on the conceptual framework of the European Health Literacy Survey Questionnaire. The scale consists of 32 questions and includes two main dimensions related to health (treatment and service; disease prevention/health promotion) and four factors, including the process of making decisions about health and obtaining information about practices (reaching-, understanding-, evaluating-, and using/implementing health-related information). The total score ranges from 0 to 50, with a score of 0-25 indicating insufficient health literacy; >25-33 problematic-limited health literacy; >33-42 sufficient health literacy; and >42-50 excellent health literacy. Okyay and Abacigi (16) developed the scale and investigated its reliability and validity.

The Cyberchondria scale was used to assess the participants' emotional, cognitive, and behavioral tendencies toward cyberchondria. The scale consists of 27 items with a 1-5 Likert type scoring and includes five subdimensions: Anxiety-Increasing Factors, Compulsion/Hypochondria, Anxiety-Reducing Factors, Physician-Patient Interaction, Non-functional Internet Use. Higher scores reflected higher levels of cyberchondria. A Turkish version of the validity and reliability study was conducted by Durak Batigun et al. (17).

The Body Awareness Questionnaire was used to assess body awareness. The questionnaire consists of 18 items covering four subdimensions: prediction of body responses, sleep-wake cycle, prediction at the onset of disease, and pay attention to changes and reactions in the body process. The total score ranges from 18 to 126, with a higher score indicating a better body awareness level. The Turkish validity and reliability of the questionnaire were carried out by Karaca and Bayar (18).

The International Physical Activity Questionnaire-Short Form (IPAQ-SF) was used to determine the physical activity levels of the participants. The scale consists of seven items requiring physical activity estimates during the previous week. A key purpose of the IPAQ instruments is to combine the many markers into an overall indicator of PA-related EE (Metabolic equivalent, MET min-1). The IPAQ's MET estimates were used as follows: Walking on average=3.3 METs, vigorous PA=8 METs, moderate PA=4 METs. Each category was multiplied by its unique MET estimate value to calculate the overall MET PA (we call it IPAQ METs). If someone stated that they "never" walked or walked "0" days per week, they labeled their hours and minutes as "0". A Turkish validity and reliability study was performed by Saglam et al. (19).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used to analyze the data. Continuous variables are represented by mean, standard deviation, median,

and interquartile range percentiles ranging from 25 to 75; categorical variables are represented by absolute numbers (n), and percentages (%).The conformity of continuous variables with a normal distribution was evaluated using the Kolmogorov-Smirnov test. The Spearman's correlation coefficient was used to assess the correlation between TSOY-32 and the Cyberchondria scale, the International Physical Activity Questionnaire-Short Form, and the Body Awareness Questionnaire. Statistical significance was set at p≤0.05.

Results

A total of 168 allied health professionals and healthcare assistants (130 female, 38 male) with a mean age of 33.69±8.57 years and a mean body mass index of 24.22 kg/m^2 participated in the study. The occupation and education of the participants are provided in Figure 1-2.

Health literacy, cyberchondria, body awareness, and physical activity outcomes are presented in Table 1. The TSOY-32 and Cyberchondria scale total scores were 37.76±7.98 and 63.83±19.45, respectively. The Body Awareness Questionnaire and IPAQ-SF scores of the participants were 96.84±13.47 and 2367.93±4701.60, respectively.

The relationship between TSOY-32 and the Body Awareness Questionnaire and IPAQ-SF is shown in Table 2. A significant low positive correlation was found between health literacy and body awareness (r=0.213, p=0.006) and physical activity scores (r=0.162, p=0.036). The main dimensions of TSOY-32-treatment and service and disease prevention/health promotion-are also significantly positively correlated with body awareness and physical activity (p≤0.005).

The relationship between the Cyberchondria scale with Body Awareness Questionnaire and IPAQ-SF is provided in Table 3. A significant low negative correlation was found between cyberchondria with body awareness (r=-0.179, p=0.022) and physical activity scores (r=-0.193, p=0.013). Anxiety-Increasing Factors and Compulsion/Hypochondria subdimensions of the Cyberchondria scale were also significantly negatively correlated with body awareness and physical activity (p≤0.005).

Discussion

This study aimed to assess the level of health literacy and cyberchondria among university hospital health professionals, as well as to investigate their relationship

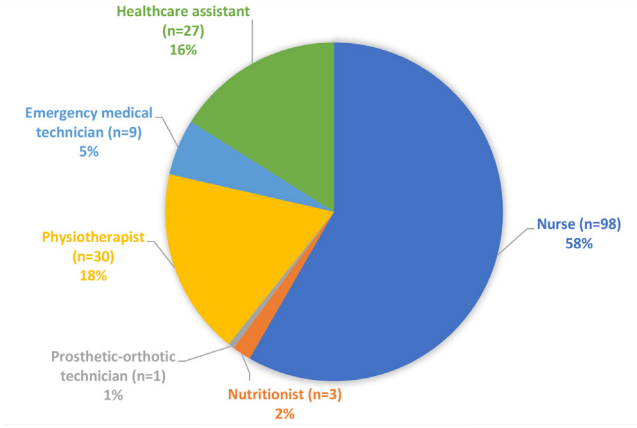

Figure 1. Occupation distribution of the participants

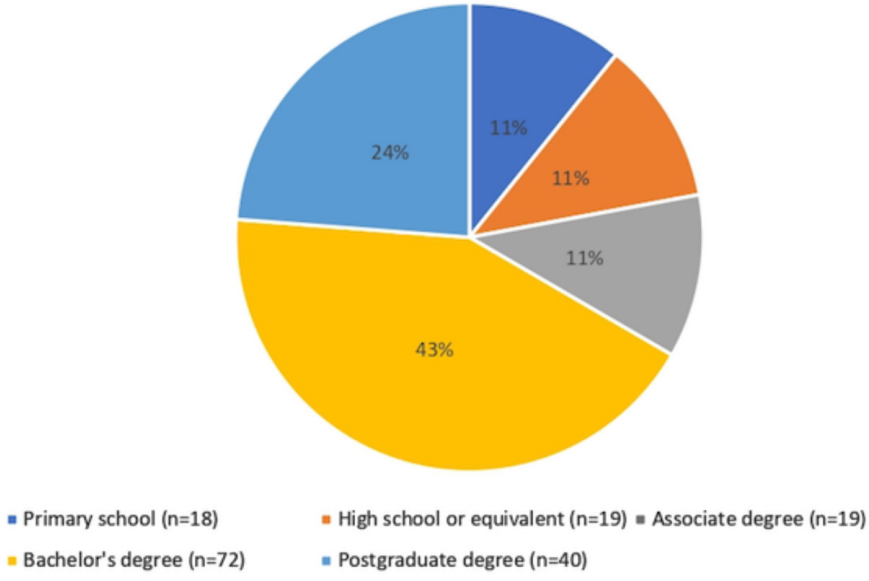

Figure 2. Education data of the participants

Table 1. Health literacy, cyberchondria, body awareness and physical activity-level scores		
	Participants (n=168)	
Turkey Health Literacy scale-32		
Total score	37.14±7.76	36.46 (31.77-43.23)
Treatment and services	37.76±7.98	36.46 (32.29-44.79)
Reaching health-related information	38.10±8.61	37.50 (33.33-45.83)
Understanding health-related information	38.23±9.10	37.50 (33.33-45.83)
Evaluating health-related information	35.69±9.17	33.33 (29.17-41.67)
Using/implementing health-related information	38.85±8.79	37.50 (33.33-45.83)
Disease prevention/Health promotion	36.50±8.46	36.01 (30.90-42.71)
Reaching health-related information	37.76±9.21	37.50 (33.33-45.83)
Understanding health-related information	38.06±9.50	37.50 (33.33-45.83)
Evaluating health-related information	38.63±9.80	37.50 (33.33-45.83)
Using/implementing health-related information	33.58±10.43	33.33 (27.78-41.67)
Reaching health-related information	37.92±8.15	37.50 (31.25-45.83)
Understanding health-related information	38.13±8.63	37.50 (33.33-45.83)
Evaluating health-related information	36.17±8.62	35.91 (31.32-43.75)
Using/implementing health-related information	36.24±8.27	35.42 (31.25-41.67)
Cyberchondria scale		
Anxiety-increasing factors	14.05±5.48	14 (10-18)
Compulsion/Hypochondria	11.98±4.97	11 (8-15)
Anxiety-reducing factors	12.69±4.31	13 (10-15.50)
Physician-patient interaction	9.17±3.40	9 (7-11.50)
Non-functional internet use	16.07±5.09	16 (13-19)
Total score	63.83±19.45	62 (51-76)
Body Awareness Questionnaire	96.84±13.47	98 (88-106)
International Physical Activity Questionnaire	2367.93±4701.60	1095 (69.20-1899)
Data are expressed as mean with standard deviation, median with interquartile range 25-75 as appropriate		

with physical activity level and body awareness. Allied health professionals and healthcare assistants had sufficient health literacy and moderate cyberchondria. Both health literacy and cyberchondria levels were poorly associated with physical activity levels and body awareness.

Health professionals play an important role in increasing individuals' health literacy, communicating effectively with patients, and providing them with reliable information, thereby increasing treatment effectiveness.Therefore, they are expected to have high levels of health literacy (20). In our study, health literacy was found to be sufficient, and our results were similar to previous studies on healthcare workers (21,22).

When the dimension and factor scores were examined, the highest dimension score was obtained from understanding health-related information, and the lowest factor score was the using/implementing health-related information factor of the dimension of disease prevention and health promotion. Although healthcare professionals are expected to have excellent health literacy levels, this result could not be reached in any dimension or factor score. Additionally, it is very close to the problematic-limited level of health literacy in terms of health promotion and protection. Attempts to increase health literacy are mostly aimed at patients and their relatives (23-26). According to our study results, studies for health professionals can also be considered.

Increased accessibility to health-related information on the Internet and ease of access to the Internet provide advantages such as a huge amount of information, tailoring of information, facilitating interpersonal interaction and social support, and being anonymous (27-29). Internet use also has disadvantages such as roadblocks to access, information overload and disorganization, inaccessible or overly technical language, lack of user-friendliness designs, lack of permanence, hazardous conditions, lack of peer review or regulation, creating the potential for inaccurate, misleading, and dangerous information, online pathologies, and maladaptive behavior (29-31). One of the most important disadvantages in terms of health is that it increases people's health anxiety (28,30,32,33). In our study, it was determined that the cyberchondria score

Table 2. Correlations between Turkey Health Literacy scale-32 with body awareness questionnaire and international physical activity questionnaire

	Body Awareness Questionnaire	International Physical Activity Questionnaire
Turkey Health Literacy scale-32		
Total score	0.213/0.006*	0.162/0.036*
Treatment and services	0.186/0.016*	0.169/0.029*
Reaching health-related information	0.101/0.194	0.170/0.027*
Understanding health-related information	0.211/0.006*	0.085/0.271
Evaluating health-related information	0.206/0.007*	0.116/0.133
Using/implementing health-related information	0.172/0.026*	0.184/0.017*
Disease prevention/Health promotion	0.224/0.003*	0.152/0.050*
Reaching health-related information	0.138/0.075	0.147/0.057
Understanding health-related information	0.200/0.009*	0.114/0.141
Evaluating health-related information	0.243/0.001*	0.128/0.097
Using/implementing health-related information	0.203/0.008*	0.134/0.082
Reaching health-related information	0,130/0.093	0.181/0.019*
Understanding health-related information	0.222/0.004*	0.098/0.204
Evaluating health-related information	0.235/0.002*	0.146/0.058
Using/implementing health-related information	0.218/0.005*	0.194/0.012*

Data are expressed as correlation coefficient with p-value.
*Significant p-values
Spearman's correlation coefficient used for determining the relationship between health literacy, body awareness level and physical activity level

Table 3. Correlations between cyberchondria scale with body awareness questionnaire and international physical activity questionnaire

	Body Awareness Questionnaire	International Physical Activity Questionnaire
Cyberchondria scale		
Anxiety-Increasing Factors	-0.217/0.005*	-0.212/0.006*
Compulsion/Hypochondria	-0.246/0.001*	-0.162/0.038*
Anxiety-Reducing Factors	-0.146/0.062	-0.138/0.077
Physician-Patient Interaction	-0.092/0.242	-0.095/0.225
Non-functional Internet Use	-0.047/0.545	-0.142/0.068*
Total score	-0.179/0.022*	-0.193/0.013*

Data are expressed as correlation coefficient with p-value.
*Significant p-values
Spearman's correlation coefficient used for determining the relationship between cyberchondria, body awareness level and physical activity level

of allied health professionals and healthcare assistants was at a moderate level. Our study results revealed that although they can easily access the most accurate information about health due to their occupation and working environment, healthcare professionals search for health information on the Internet. To ensure access to reliable health information, there is a need to create websites based on evidence-based filtered sources.

Body awareness and health literacy may be related, and individuals with low health literacy may also have low body awareness (34,35). This may have an impact on healthy lifestyle behaviors such as physical activity (36,37). The results showed that allied health professionals and healthcare assistants with high health literacy and low cyberchondria were physically active and had high body awareness. Awareness is closely related to health knowledge. Healthcare professionals are aware of the changes in their bodies, and because they have information about symptoms, they can predict when and where to seek professional help (34).

Study Limitations

Several limitations might be considered when interpreting the findings of this study. The study sample consisted of allied health professionals and healthcare assistants in a single hospital in a single province. The overall length of service could also be evaluated as it affects health literacy. Additionally, the duration of internet use and the determination of whether the information obtained from the internet is evidence-based

could be questioned in terms of the interpretation of the cyberchondria score.

Conclusion

Physical activity and body awareness may contribute to increasing health literacy and reducing cyberchondria, which will empower individuals to make beneficial health decisions. However, it is unclear how more diverse variables may influence health literacy and cyberchondria. Healthcare professionals need to be able to comprehend health information, decide on the accuracy of the information, conduct accurate and timely consultations, and provide counseling to patients in rapidly changing health conditions, such as pandemic conditions. This requires evidence-based filtered online resources that contain reliable and up-to-date health information. Unlike predicted, health professionals did not have perfect health literacy and were found to have moderate cyberchondria. In this context, awareness can be created about the concepts of health literacy and cyberchondria.

Ethics

Ethics Committee Approval: The study was approved by the Pamukkale University Clinical Research and Ethics Committee of the authors' affiliated institution (approval date: 13.07.2021 and approval number: 13).

Informed Consent: All study participants provided written informed consent.

Peer-reviewed: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.S., I.G., N.B., Concept: R.S., I.G., N.B., Design: R.S., I.G., N.B., Data Collection, or Processing: R.S., I.G., Analysis, or Interpretation: R.S., N.B., Literature Research: R.S., I.G., Writing: R.S., I.G., N.B.

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Original Article

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Coexistence of Fibromyalgia, Myofascial Pain Syndrome and Depression Among Patients with Lumbar Disc Herniation

Gonca Saglam*, Serdar Karakullukcu**, Hanife Baykal Sahin*, Demet Saglam Aykut***

*Karadeniz Technical University Faculty of Medicine, Physical Medicine and Rehabilitation, Trabzon, Turkey

**Bayburt Community Health Center, Public Health, Bayburt, Turkey

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

Abstract

Aim: Pain in lumbar disc herniation (LDH) may originate from a multisource other than the intervertebral disc, and magnetic resonance imaging (MRI) findings are not always correlated with clinical symptoms in LDH patients. This study aimed to determine the prevalence of fibromyalgia (FM), myofascial pain syndrome (MPS), and depression in patients with LDH and to evaluate the clinical variations caused by these comorbidities.

Methods: One hundred and fifty-four patients with a diagnosis of LDH confirmed by MRI and admitted to a physical medicine and rehabilitation outpatient clinic between July 2021 and January 2022 were enrolled in this cross-sectional study. Pain intensity was recorded according to the visual analog scale (VAS). The presence of FM and MPS was examined. The Beck Depression Inventory (BDI) was used to research the presence of depression. Patients were divided into three groups: LDH without FM or MPS, LDH+FM, LDH+MPS.

Results: Of the 154 LDH patients, 60 of them had LDH without FM or MPS (38.9%), 52 of them had LDH+FM (33.8%), and 42 of them had LDH+MPS (27.3%). Forty-eight LDH patients (31.2%) had depression. The mean VAS of the FM+LDH group was higher than that of the other two groups ($p<0.001$). Depression was more common in the LDH+FM and LDH+MPS groups than in the LDH without the FM or MPS group ($p<0.001$).

Conclusion: These results indicate that the coexistence of FM, MPS, and depression in LDH patients is frequent, and a multidimensional approach is required for LDH treatment.

Keywords: Low back pain, intervertebral disc herniation, fibromyalgia, myofascial pain syndrome, trigger point, depression

Introduction

Low back pain is a frequent and challenging worldwide health problem and remains the leading global cause of years lived with disability worldwide (1). Emerging data reveals that, although low back pain is often self-limited, some patients experience recurrences and may go on a chronic course (2). Chronic low back pain (CLBP) impacts the daily activities of patients, decreases their quality of life, and results in an important socio-economic problem. 39% of CLBP's pain etiology has been attributed to intervertebral disc diseases (3). Moreover, all degenerated or herniated disks are not associated with pain, and disc degeneration is moderately associated with radiating pain (4). Therefore, it is important to assess the coexistence of other potential pain etiologies in patients with discogenic lower back pain.

Fibromyalgia (FM) is a widespread muscular tenderness illness characterized by tiredness, psychosomatic symptoms, sleep difficulties, headaches, and visceral pain syndromes such as interstitial cystitis and irritable bowel syndrome. Musculoskeletal pain arises in the neck, interscapular area, and low back in

Address for Correspondence: Gonca Saglam,
Karadeniz Technical University Faculty of Medicine, Physical Medicine and Rehabilitation, Trabzon, Turkey
Phone: +90 505 452 56 88 E-mail: goncasaglam@hotmail.com ORCID: orcid.org/0000-0001-7713-4435
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most FM patients (5). Myofascial trigger points (MTrPs) are hyperirritable, palpable nodules in the skeletal muscle fibers that cause muscular discomfort and stiffness in one or more muscles (6). MTrPs are the cardinal symptoms of myofascial pain syndrome (MPS). The neck, shoulders, and back are the predominant areas for MPS, while there are no standardized diagnostic criteria for MPS, which makes it easy to confuse with other painful conditions (7). Although some studies believe MPS can occur in FM, there is still controversy over whether MPS is a unique clinical entity in FM. The American Pain Society considers MPS a unique clinical entity from FM (8-10).

Pain is a symptom with cognitive, behavioral, emotional, and physical manifestations (11). Psychological symptoms such as sadness, exhaustion, and overload have been related to the existence of low back pain, and these emotions may be linked to the progression of pain chronicity. The combination of lumbar disc herniation (LDH) and depression constitutes a significant health issue that is linked to higher rates of disability, socioeconomic disadvantage, and increased use of healthcare resources (12,13). The presence of FM or MPS in patients with LDH is probably related to increased depression rates. However, the definitiveness of this link has not been well established in the literature.

FM and MPS occur as the primary sources of low back pain and comorbid pain with other conditions. While FM and MPS are commonly observed as painful syndromes in patients with chronic LDH in daily clinical practice, there are a limited number of studies investigating the presence of FM and MPS in patients with CLBP (14,15). Failure to recognize FM or MPS in these patients may lead to over-investigation and unnecessary medical intervention. Thus, this study investigated the presence of concomitant FM and MPS in patients diagnosed with LDH using magnetic resonance imaging (MRI) and to identify the influence of these comorbidities on clinical variables.

Materials and Methods

Compliance with Ethical Standards

Before participating in the study, the evaluations were explained to the patients in detail, and the informed consent form was signed by all participants. This study was approved by Karadeniz Technical University Faculty of Medicine, Scientific Research Ethics Committee (dated: 2021/05/31, and numbered: 2021-133).

Study Design

This cross-sectional study assessed 200 patients with low back pain lasting more than 3 months and diagnosed with LDH confirmed by MRI in the last year. Patient enrollment was performed at the physical medicine and rehabilitation outpatient clinic. The exclusion criteria included patients with features of inflammatory spinal pain or rheumatic disease diagnosis, scoliosis or other structural vertebral deformities, spinal fracture or spinal surgery history, neurological deficit, history of severe psychiatric disease, uncontrolled diabetes mellitus, neurologic disorders such as multiple sclerosis, spinal infectious diseases, malignancy, pregnancy or women who had recent delivery, patients who had previous exercise therapy for their low back pain, use of antidepressant or analgesic drugs (except non-steroidal anti-inflammatory drugs or acetaminophen taken two weeks before the patient evaluation).

The physical examination included a routine neurological examination. Patients with extremity motor dysfunctions, sensory deficits, absent or asymmetrical deep tendon reflexes, or sphincter dysfunctions were excluded from the study. All MRIs were reviewed and patients with bulging disks on MRI were deemed radiologically normal. Consequently, 154 LDH patients were available for the evaluation.

Patient Evaluation

Anamnesis, demographic and clinical properties, and physical examination results were recorded on a case report form. Demographic characteristics involved age, body mass index (BMI), and comorbid diseases.

All patients underwent assessments for pain level, the presence of FM, MPS, and depression. First, pain intensity measurements were performed using a visual analog scale (VAS). Accordingly, in a line of 100 mm, a 0 point was accepted as the absence of pain and a 100 point as the maximum pain. The point between the marked point and point 0 was measured with the help of a ruler (16).

Then, patients were screened to determine the potential diagnosis of FM in accordance with 2016 American College of Rheumatology (ACR) criteria. FM was diagnosed in a patient when all of the following criteria were met: 1) Widespread pain index (WPI) ≥7 and symptom severity scale (SSS) score ≥5 or WPI 4-6 and SSS score ≥9. 2) Pain in at least four of the five body areas is referred to as generalized pain. The WPI uses a 0-19 scale to assess the severity of pain by asking patients if they have experienced pain or tenderness in 19 different body areas (shoulder girdle, hip, jaw, upper arm, upper leg, lower arm, lower leg, upper back, lower back, chest, neck, and abdomen) over the past week, with each painful or tender region scoring 1 point. The 2016 ACR criteria modified SSS as a checklist of 41 symptoms with a somatic symptom score (score range: 0-3) expressing the sum score for three items: the presence or absence of (1) headaches, (2) pain or cramps in the lower abdomen, or (3) depressive symptoms (17).

Patients who did not meet 2016 ACR FM criteria were evaluated for the diagnosis of MPS. The physical examination of MPS was based on muscle palpation. The regional muscles were palpated to reveal the MTrPs. The posterior cervical (splenius capitis and cervicis, semispinalis, and oblique capitis inferior), sternocleidomastoid, levator scapulae, psoas, quadratus lumborum, paraspinal muscles (iliocostalis, longimus thoracis, multifidi), abdominal oblique, and rectus femoris) were defined muscles with trigger points that may reproduce regional pain in the lower back region, which were examined in this study (18).

The most commonly applied criteria for the definition of MPS were used. Simons (19) proposed major and minor criteria for diagnosing MPS, which were later amended by Long and Kephart (20). These four criteria involved the following: (1) tender spot in a taut band of skeletal muscle, (2) patient pain recognition, (3) pain referral pattern prediction, and (4) local twitch response. Active and latent MTrPs were also noted.

The Beck depression inventory (BDI) was used to evaluate the psychological status of the patient population. The BDI consists of a 21-self-reported item scale to assess the current severity of depression symptoms. Each item is evaluated on a four-point scale (0-3) with a total score range of 0 to 63. Depression is indicated by a cut score of 17 or above (21). The Turkish validity and reliability analysis of this scale was performed by Hisli (22).

Additionally, the presence of radicular pain, fatigue, waking unrefreshed, cognitive symptoms, headache, pain, or cramps in the lower abdomen has been recorded. All were examined by the same experienced physician and patients were divided into three groups: patients with only LDH, with LDH and FM, with LDH+MPS, then compared accordingly.

Statistical Analysis

The Statistical Package for the Social Sciences software (23.0 version) (SPSS Inc., Chicago, IL, USA, 2008) was used for the statistical analysis. Qualitative data were represented as number and percentage for categorical variables and were calculated by computing the mean and standard deviation of each variable. The one sample Kolmogorov-Smirnov test was used to determine the normality. Comparisons of numerical variables between two independent groups were evaluated with the Mann-Whitney U test. The Kruskal-Wallis test was used to evaluate non-normal data in the comparison of three dependent groups. The post hoc comparisons were assessed with the Bonferroni test. Pearson's chi-square test was used to compare qualitative data. Differences were considered statistically significant when the p-value<0.05.

Results

In total, 154 LDH patients were included in the analysis. Sixty of them had LDH without FM or MPS (38.9%), 52 of them had LDH+FM (33.8%), and 42 of them had LDH+MPS (27.3%). The mean patient age was 46.0±10.8 with no statistical difference between groups. The mean BMI of all LDH patients was 27.6±4.9, while there was no significant between-group difference in BMI. The comparison of demographic data between the groups is summarized in Table 1.

Sixty-three LDH patients (40.9%) had at least one active trigger point and 43 LDH patients (27.9%) had at least one latent trigger point. The mean VAS in the LDH+FM group was 76.4±15.4 and significantly greater than that of the other groups (p<0.001). The mean WPI score was the highest in the LDH+FM group. The mean BDI scores of the LDH+FM group and LDH+MPS group were statistically

Table 1. Comparison of demographic data between groups

*		LDH without FM or MPS (n=60)	LDH + FM (n=52)	LDH + MPS (n=42)	p	Total (n=154)
Age (years) (mean ± SD)		44.5±10.7	46.3±10.6	47.7±11.0	0.324**	46.0±10.8
Gender (%)	**Female**	31 (51.7)[a]	41 (78.8)[b]	29 (69.0)[a,b]	**0.009*** **	101 (65.6)
	Male	29 (48.3)[a]	11 (21.2)[b]	13 (31.0)[a,b]		53 (34.4)
BMI (kg/m²) (mean ± SD)		27.4±6.2	28.2±3.9	27.0±3.8	0.262**	27.6±4.9
Comorbid diseases n (%)	**Comorbidity**	22 (36.7)[a]	30 (57.7)[a]	15 (35.7)[a]	**0.040*** **	67 (43.5)
	Diabetes	3 (5.0)	7 (13.5)	5 (11.9)	-	15 (9.7)
	Hypertension	13 (21.7)	17 (32.7)	10 (23.8)	-	40 (26.0)
	Thyroid disease	2 (3.3)	4 (7.7)	1 (2.4)	-	7 (4.5)
	Renal disease	4 (6.7)	3 (5.8)	-	-	7 (4.5)
	Cardiac disease	2 (3.3)	6 (11.5)	3 (7.1)	-	11 (7.1)
	Other	3 (5.0)	6 (11.5)	2 (4.8)	-	11 (7.1)

*Different letters **(a,b,c)** within the same row represent significant differences,**One way ANOVA, ***Chi-Square test,****Kruskal Wallis test
SD: Standard deviation, BMI: Body mass index, LDH: Lumbar disc herniation, FM: Fibromyalgia, MPS: Myofascial pain syndrome

similar. However, the mean BDI score of the LDH without the FM or MPS group was the lowest compared to the other two groups (p<0.001). A comparison of clinical features is presented in Table 2.

Cognitive symptoms, pain or cramps in the lower abdomen and depression were more common in the LDH+FM and LDH+MPS groups than in the LDH without the FM or MPS group. Forty-eight of 154 LDH patients (31.2%) had depression according to BDI scores. A comparison of other clinical variables between the groups is shown in Table 3 and Figure 1.

Discussion

The bone-disc complex anatomy and spinal nerves are usually the focus of clinical evaluations of low back pain. Although earlier research has shown that these diagnostic imaging modalities are not necessarily connected with symptom severity, computed tomography or MRI are often used to evaluate patients with low back pain. They may provide erroneous positive or negative results as well as provide relevant information (23).

This study suggests that MTrP is a common clinical entity observed in the LDH patient population. Of all

Table 2. Comparison of back pain duration, VAS, WPI, BDI and number of trigger points between groups

*		LDH without FM or MPS (n=60)	LDH + FM (n=52)	LDH + MPS (n=42)	p**	Total (n=154)
Duration of back pain (months)	mean ± SD	14.4±15.0	16.5±17.4	15.3±16.5	0.882	15.4±16.5
VAS		63.6±14.4[a]	76.4±15.4[b]	64.6±11.5[a]	**<0.001**	68.2±15.1
WPI		4.0±1.9[a]	8.9±2.9[b]	5.0±2.7[a]	**<0.001**	5.9±3.3
BDI		5.5±9.1[a]	17.0±16.7[b]	11.9±9.3[b]	**<0.001**	11.1±13.2
Number of active trigger points		0.2±0.9[a]	2.9±4.4[b]	3.9±3.4[c]	**<0.001**	2.1±3.5
Number of latent trigger points		0.3±0.7[a]	0.9±1.5[b]	1.1±2.0[b]	**0.009**	0.7±1.4

*Different letters (a,b,c) within the same row represent significant differences,**Kruskal-Wallis test
VAS: Visual analog scale, WPI: Widespread pain index, BDI: Beck depression inventory LDH: Lumbar disc herniation, FM: Fibromyalgia, MPS: Myofascial pain syndrome, SD: Standard deviation

Table 3. Comparison of clinical features between groups

*		LDH without FM or MPS (n=60)	LDH + FM (n=52)	LDH + MPS (n=42)	p**	Total (n=154)
		n (%)	n (%)	n (%)		n (%)
Level of LDH	**L1-L2**	4 (6.7)	6 (11.5)	-	-	10 (6.5)
	L2-L3	12 (20.0)[a]	5 (9.6)[a,b]	1 (2.4)[b]	0.021	18 (11.7)
	L3-L4	19 (31.7)	20 (38.5)	8 (19.0)	0.123	47 (30.5)
	L4-L5	32 (53.3)	24 (46.2)	29 (69.0)	0.080	85 (55.2)
	L5-S1	28 (46.7)	18 (34.6)	16 (38.1)	0.408	62 (40.3)
Radicular pain		16 (26.7)	13 (25.0)	12 (28.6)	0.927	41 (26.6)
Presence of active trigger points		3 (5.0)[a]	21 (40.4)[b]	39 (92.9)[c]	<0.001	63 (40.9)
Presence of latent trigger points		9 (15.0)[a]	19 (36.5)[b]	15 (35.7)[b]	0.017	43 (27.9)
Fatigue		34 (56.7)	34 (65.4)	29 (69.0)	0.403	97 (63.0)
Waking unfreshed		30 (50.0)	32 (61.5)	30 (71.4)	0.090	92 (59.7)
Cognitive symptoms		8 (13.3)[a]	24 (46.2)[b]	20 (47.6)[b]	<0.001	52 (33.8)
Headache		17 (28.3)[a]	31 (59.6)[b]	18 (42.9)[a,b]	0.004	66 (42.9)
Pain or cramps in lower abdomen		8 (13.3)[a]	18 (34.6)[b]	15 (35.7)[b]	0.012	41 (26.6)
Depression (BDI ≥17)		6 (10.0)[a]	22 (42.3)[b]	20 (47.6)[b]	<0.001	48 (31.2)
FM		-	-	-	-	52 (33.8)
MPS		-	-	-	-	42 (27.3)

*Different letters **(a,b,c)** within the same row represent significant differences, **Chi-square test
LDH: Lumbar disc herniation, FM: Fibromyalgia, MPS: Myofascial pain syndrome, BDI: Beck depression inventory

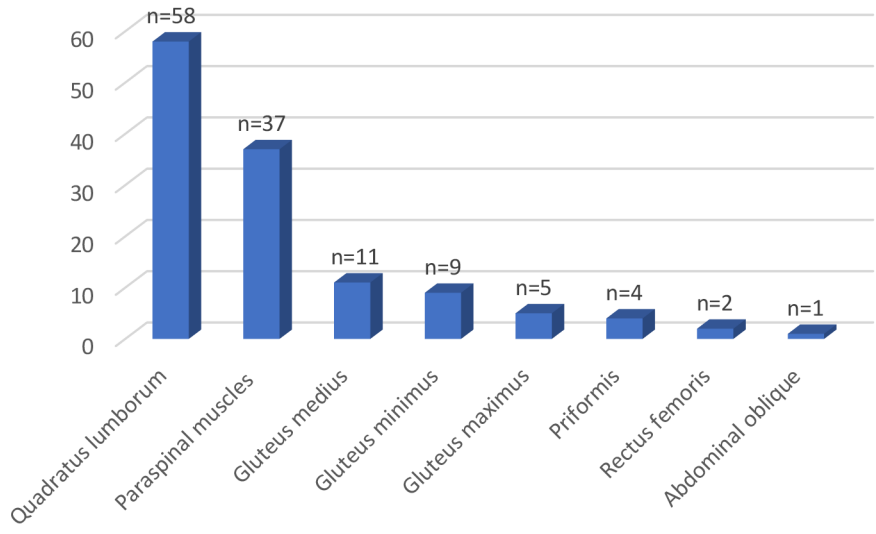

Figure 1. Distrubution of trigger point muscles in lumbar disc herniation patients

LDH patients, 68.8% presented with MTrP, and the most frequent MTrPs were determined in the quadratus lumborum and paraspinal muscles. According to an earlier study, more than 90% of low back pain patients with no objective abnormalities had MTrPs, and nearly 60% of CLBP patients were identified as having regional pain syndromes (24). Rozhkov et al. (25) determined a 52% rate of MPS in female patients with CLBP, while 27.3% of our patient population had concomitant LDH and MPS. Hoeritzauer et al. (26) stated that over half of the patients with low back pain had nerve root compression, which may have contributed but did not explain their clinical presentation.

FM and MPS have been suggested as probable overlapping problems in lumbar disc illnesses as well as alternate origins of low back pain (27,28). Many individuals with concurrent or isolated FM or MPS are diagnosed with only LDH based on MRI results. However, FM and MPS have comparable clinical symptoms with LDH and one condition may hide the other. In line with previous studies, we observed a high incidence of FM and MPS in patients with LDH. Although the diagnosis of these two soft tissue pain syndromes is generally straightforward, because of a lack of knowledge, an appropriate diagnosis may be ignored. In this context, it has been reported that some patients with FM or MPS have had unnecessary LDH surgery (29,30). During an 18-year period study, it was discovered that 25% of the CLBP patients acquired symptoms of FM (14). We determined a 33.8% indicence of FM in the LDH patient population.

According to our results, both the LDH + FM group and the LDH + MPS groups consistently expressed a higher number of MTrPs, higher pain scores, more cognitive symptoms, depression, and pain or cramps in the lower abdomen. These results conform to another study, which found enhanced pain facilitation in FM and MPS patients compared with CLBP patients (31). FM patients seem to have localized pain before the development of widespread pain, and a link between MTrPs and FM is more than plausible. Previous studies reported that MTrPs were found in 18-70% of the immediate vicinity of a designated tender-point site in FM patients (32,33). This wide incidence rate of MTrPs in FM patients may be explained by the differences in sample sizes and diagnostic criteria used. We observed that most of the FM patients had at least one trigger point. 40.4% of LDH+FM patients had active trigger points and 36.5% had latent trigger points. This result proved the fact that a patient with FM may have latent MTrPs, which may be activated if central sensitization progresses. Alonso-Blanco et al. (34) investigated individuals with FM and found that each woman with FM had an average of 11 MTrPs, with 10 of them being active. They reported a substantial positive association between the number of activated MTrPs and pain severity among FM patients. Additionally, widespread mechanical pain hypersensitivity was associated with a greater number of active MTrPs (34). MTrPs may play a role in the generation of pain, and proper manual examination can detect MTrPs in FM patients. Treatment of active MTrPs alters the central nervous system excitability and alleviates pain in FM (35-37).

Psychopathological changes related to low back pain are highly relevant and they affect pain perception, expression, and persistence (38-40). This study revealed that depressive symptoms may be linked to increased pain severity in LDH patients, similar to previous studies (41-43). 31.2% of all LDH patients experienced depression, whereas patients with FM or MPS exhibited higher depressive symptoms. This association between LDH,

FM, MPS, and depressive symptoms highlights somatic perception as a risk factor for low back pain. In contrast, no difference in depression levels was identified between patients with low back pain and healthy controls in a study (44). Another cross-sectional study of 137 CLBP patients established that none of the patients exhibited signs of clinical anxiety or depression (45). Despite this, the body of knowledge in this field clearly suggests that low back pain and depression are linked in both emerging and general adult populations.

The results of this study support the evidence that FM, MPS, and depression are prevalent in the LDH patient population. Our results follow previous literature demonstrating that low back pain is associated with several comorbid factors (46-48). Although there are significant differences that substantially impact the diagnosis and treatment of FM and MPS, there are no reliable laboratory tests. The potential co-occurrence of FM and MPS raises awareness of the need to examine individuals with LDH. A comprehensive evaluation is necessary to determine a diagnosis and develop a successful comprehensive treatment plan.

Study Limitations

The results of the current study should be seen while considering some limitations. First, other risk factors identified to influence back pain, including inactivity and education level, were not collected as part of this study. As well, the patient population was limited to a single hospital, which may not be representative of the diversity of the adult population. Another limitation was that we did not enroll a healthy control group without LDH in this study. That may be valuable for the determination of depression rates and somatic symptoms of the patient groups.

A study similar to ours was not detected according to literature research related to this topic. This study design and patient examination by experienced physicians may be counted as study strengths. We compared patient groups according to age, gender, and BMI, and all the patients were of the same race.

Conclusion

The prime defining characteristic of LDH is low back pain. However, it's critical to recognize potential sources of pain other than those related to disc herniation. Considering that the diagnostic accuracy and reliability of FM and MPS are inadequate, while they are common sources of low back pain, the coexistence of these clinical syndromes requires attention among LDH patients. In patients with LDH, FM, MPS, and depression seem to impact pain severity and cause additional symptoms. Accurate and reliable examination is essential to ensure optimal management and outcomes for these patients.

Ethics

Ethics Committee Approval: Approval was obtained from Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (dated 2021/05/31, numbered 2021-133).

Informed Consent: Informed consent was taken from all patients.

Peer-reviewed: Internally peer-reviewed.

Authorship Contributions

Concept: G.S., Design: G.S., Data Collection, or Processing: G.S., H.B.S., Analysis, or Interpretation: S.K., Literature Research: G.S., Writing: G.S., D.S.A.

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Original Article

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The Effects of Different Doses of Tranexamic Acid Infusions on the Postoperative Outcomes of Pediatric Cardiovascular Surgery

Hatice Dilek Ozcanoglu*, Serife Ozalp*, Incila Ali Kahraman*, Selin Saglam*, Behzat Tuzun*, Okan Yildiz**, Erkut Ozturk***, Funda Gumus Ozcan*, Alican Hatemi**

*University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinic of Anaesthesiology and Reanimation, Istanbul, Turkey

**University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinic of Pediatric Cardiovascular Surgery, Istanbul, Turkey

***University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinic of Pediatric Cardiology, Istanbul, Turkey

Abstract

Aim: There are still concerns about its benefits and possible risks in pediatric patients, as well as the dosage regimen, frequency, and form of tranexamic acid. In this study, the effects of different doses of tranexamic acid used in pediatric congenital heart surgery were investigated.

Methods: The study was conducted between August 1, 2020 and April 30, 2021, by screening patient files and hospital data systems. Accordingly, patients in Group TXA-10 and Group TXA-25 were continuously administered 10 mg/kg/hour and 25 mg/kg/hour tranexamic acid infusions, respectively, from the induction of anesthesia until their transfer to the intensive care unit. The groups were compared in terms of the amount of bleeding, blood products used, and postoperative complications.

Results: Thirty-five patients were included in Group TXA-10, and 36 patients were included in Group TXA-25. There was no statistical difference between the groups in terms of gender, weight, height, or presence of cyanotic heart disease. The median post-pump activated clotting time in Group TXA-10 was significantly longer than in Group TXA-25 (153 vs. 141.5 seconds, p=0.003). There was no significant difference between the groups also in terms of the amount of bleeding; the median erythrocyte transfusion amount was 50 ml in both groups. The amount of fresh frozen plasma and platelets that needed to be transfused in Group TXA-10 was higher than in Group TXA-25, albeit not significantly. There was no difference between the groups in terms of postoperative complication rates.

Conclusion: Tranexamic acid can be safely and effectively used in pediatric heart surgery cases with an infusion rate of 10 mg/kg/hour.

Keywords: Child, heart defects, congenital

Introduction

The use of excessive and different types of blood products due to increased bleeding during cardiac surgery has been associated with increased morbidity and mortality in patients diagnosed with congenital heart disease (1,2). Traditionally, the use of antifibrinolytic drugs has been one of the most effective strategies employed in reducing blood loss, particularly during and after cardiopulmonary bypass (CPB). Tranexamic acid is a synthetic lysine derivative that binds to lysine-binding sites in plasminogen and inhibits plasmin activation (3,4). Its effectiveness has been demonstrated in studies conducted with large samples of adult cardiac surgery patients. Furthermore, its use in pediatric cardiac surgery featuring different doses and applications has also become widespread in recent years (3,4).

Address for Correspondence: Hatice Dilek Ozcanoglu,
University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinic of Anaesthesiology and Reanimation, Istanbul, Turkey
Phone: +90 212 909 60 00 E-mail: dilekmersin@hotmail.com ORCID: orcid.org/0000-0001-8091-9997
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However, still concerns about its benefits and possible risks in pediatric patients, as well as about the dosage regimen, frequency, and method of use (5). In clinical practice, tranexamic acid is administered by either bolus or infusion or by bolus and infusion combined, and at various doses that vary from clinic to clinic. Only a few studies are available in the literature on the effects of these different dosage regimens and different frequencies and ways of use. The results of these limited studies revealed that the administration of tranexamic acid by infusion is more effective and safe compared with other ways of use (5-7).

In view of the foregoing, the objective of this study was to evaluate the effects of different tranexamic acid infusion doses on the amount of postoperative bleeding, blood/blood product use, and postoperative intensive care outcomes in patients younger than six months who underwent cardiovascular surgery with a diagnosis of congenital heart disease.

Materials and Methods

Compliance with Ethical Standards

The study was planned in accordance with the Declaration of Helsinki after obtaining the required approval from the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital local ethics committee (number: 2020-21-14 and dated: 19.10.2020). Written and verbal consent were obtained from all participants.

Study Design

This study was conducted retrospectively with patients younger than six months old who underwent congenital heart surgery between August 1st, 2020, and April 30th, 2021, in the hospital where this study was conducted. The patients were divided into two groups according to the tranexamic acid infusion dosage, that is, 10 mg/kg/h (TXA-10) or 25 mg/kg/h (TXA-25), used from the beginning of the surgical procedure until the patients were transferred to the intensive care unit. The patients' age, gender, height and weight information, the name of the surgery they underwent, the presence of any syndrome, whether their heart disease was cyanotic or not, their hemoglobin, hematocrit, thrombocyte, activated partial thromboplastin time, prothrombin time, international normalized ratio values measured both during the preoperative and postoperative periods, duration of surgery, cross-clamp and pump times, use of blood and blood products during the surgery and in the first 24 hours after the surgery, amount of drainage in the first 24 hours after the surgery, the need for revision and peritoneal dialysis, and whether there was a seizure were recorded in the study form. The patients who were older than six months, did not undergo CPB, did not receive a tranexamic acid infusion, had previous renal failure, and whose records could not be reached were excluded from the study.

Surgical Procedure

Infants whose oral intake was discontinued in accordance with the guidelines (solid foods: 6 h, breast milk: 4 h, and clear liquids: 2 h) were monitored by electrocardiography, pulse oximetry, non-invasive blood pressure measurement, and near-infrared spectrometry in the operating room. No premedication was administered to the patient. Mask ventilation and orotracheal intubation were performed after the administration of 0.05 mg/kg midazolam, 1 mg/kg ketamine, 1 microgram/kg fentanyl, and 0.1 mg/kg rocuronium in anesthesia induction.

Tranexamic Acid Infusion

A bolus dose of 25 mg/kg tranexamic acid was administered to all patients after anesthesia induction and after the conclusion of CPB. Also, 25 mg/kg of tranexamic acid was added to the CPB prime solution as well. Patients in group TXA-10 and Group TXA-25 were continuously administered 10 mg/kg/hour and 25 mg/kg/hour tranexamic acid infusions, respectively, from the induction of anesthesia until their transfer to the intensive care unit.

Erythrocyte transfusion was performed if the hemoglobin level was <10 g/dL after the conclusion of CPB, fresh frozen plasma transfusion was performed based on the coagulation test results, and platelet transfusion was performed after the surgery at the surgeon's discretion. Mortality was defined as death that occurred in the first 30 days following the completion of the surgery in the hospital. However, morbidity was defined as having at least one of the following conditions: stroke, seizure, renal failure, development of deep venous thrombosis, use of extracorporeal membrane oxygenation, reoperation for bleeding, and dependence on long-term mechanical ventilation.

Stroke was defined as a new ongoing focal neurologic deficit and infarction or hemorrhage demonstrated by brain tomography or magnetic resonance imaging. The seizure was defined as an incipient neuropsychiatric disorder with increased motor activity or in an agitated or hyperactive state. Renal failure was defined as the need for peritoneal dialysis in the postoperative period. On the basis of the venous Doppler ultrasonography findings and clinical symptoms, deep venous thrombosis was diagnosed. Reoperation for bleeding was performed if tamponade developed due to bleeding or in the event of a drainage rate of more than 10% of the total blood volume per hour. Prolonged mechanical ventilation was defined as greater than or equal to 72 hours of mechanical ventilation (8). The results were analyzed statistically.

Statistical Analysis

Descriptive statistics were given as mean ± standard deviation and median, with minimum-maximum values for continuous variables depending on their distribution. Numbers and percentages were used as categorical variables. The normal distribution of the numerical variables was analyzed using the Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests. The Independent Samples t-test was used to compare two independent groups where numerical variables had a normal distribution. The Mann-Whitney U test was used on variables that did not have a normal distribution. The Pearson chi-square and Fisher's exact tests were used to compare the differences between categorical variables. For statistical analysis, "Jamovi" project (2021), Jamovi (Version 2.2.2.0) (Computer Software) (Retrieved from https://www.jamovi.org) and JASP (version 0.16) (Retrieved from https://jasp-stats.org) were used. In all statistical analyses, the significance level (p-value) was set at 0.05.

Results

The demographic and clinical characteristics of the study groups are given in Table 1 and Figure 1. There were 35 and 36 patients in groups TXA-10 and TXA-25. The groups were similar in sex distribution, height and weight measurements, and the frequency of cyanotic congenital heart disease (Table 1).

The groups were similar considering the intraoperative features except for the post-pumping ACT value and the requirement for additional heparin use (Table 2).

The median post-pumping ACT values were significantly higher in Group TXA-10 than in Group TXA-25 (153 sec vs. 141.5 sec, p=0.003). Although there were no newborns with additional intraoperative heparin use in Group TXA-10, most of the newborns (91.7%) in Group TXA-25 required an additional heparin dose during the surgery (p<0.001). Other intraoperative features were similar between the groups (Table 2).

Table 3 presents the laboratory investigations during the preoperative, intraoperative, and postoperative periods. We detected no significant differences in the laboratory investigations between the groups.

In Group TXA-10, the amount of bleeding in the postoperative period was similar. The median amount of erythrocyte transfusion was 50 mL in both groups. Although more fresh frozen plasma and platelets were transfused to the newborns in Group TXA-10, the differences between the groups were insignificant (Table 4).

The postoperative outcomes in Group TXA-10 and Group TXA-25 are given in Table 5. The median lengths of hospital stay and intensive care unit were 18 and 14.5 days in Group TXA-10. These lengths were 18.5 and 12.5 days in Group TXA-25. The differences were insignificant. The mortality rates were 25.7% and 22.2% in Group TXA-10 and Group TXA-25 (Table 5).

Discussion

In this study, the effects of tranexamic acid infusion administered using different dose protocols, that is, 10 mg/kg/hour or 25 mg/kg/hour, on the amount of

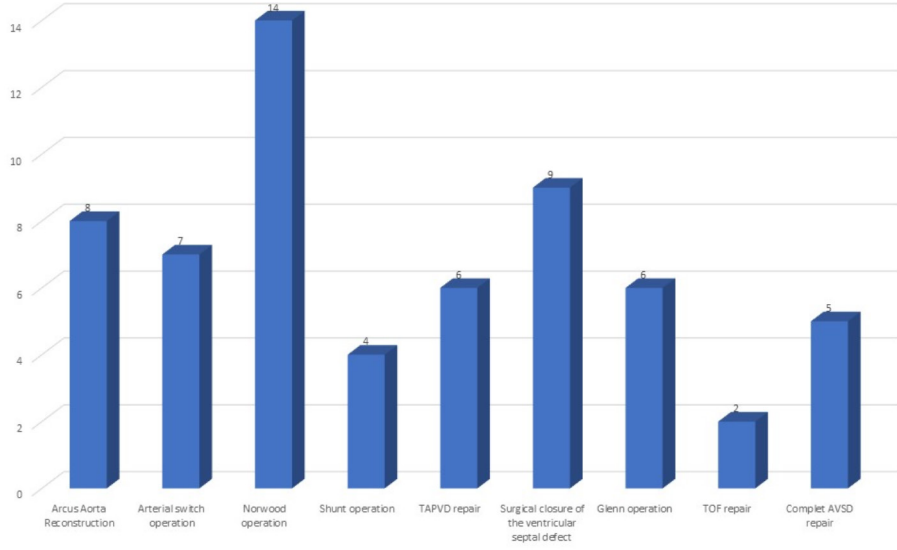

Figure 1. Types of operations performed in the cases atrioventricular septal defect (AVSD)

TAPVD: Total anomalous pulmonary venous drainage, TOF: Tetralogy of Fallot

postoperative bleeding, blood and blood product use, and postoperative intensive care outcomes were investigated. The study results revealed that both infusion strategies had similar effects on the amount of bleeding, blood product use, and complications observed while in the intensive care unit. To the best of the authors' knowledge, this study is one of the few conducted on the subject matter.

The development of coagulopathy following CPB may adversely affect the surgical results due to increased bleeding risk and hemodynamic instability. Different factors such as the prime solution used in CPB, the cardioplegic solution applied, the hemodilution, contact activation, thrombin and plasmin created by the fluids given in the perioperative period, and the consumption triggered by inflammation are effective in the development of coagulopathy. Anticoagulation agents such as unfractionated heparin, which are used in addition to coagulation, patient-specific conditions such as hypothermia, acidosis, and hypocalcemia may further increase the risk of bleeding (1-3). To prevent this situation,

Table 1. Demographic and clinical characteristics of the study groups

	Group TXA-10 (n=35)	Group TXA-25 (n=36)	p-value
Age (day)†	13.0 (3.0-70.0)	9.0 (3.0-66.0)	0.164*
Sex‡			
Female	14 (40.0)	15 (41.7)	0.999***
Male	21 (60.0)	21 (58.3)	
Height (cm)ɣ	50.7±3.6	50.1±3.3	0.443**
Weight (kg)ɣ	3.2±0.7	3.3±0.7	0.510**
Type of congenital heart disease‡			
Acyanotic	20 (57.1)	16 (44.4)	0.405***
Cyanotic	15 (42.9)	20 (55.6)	

†: Median (min-max), ‡: n (%), ɣ: mean ± standard deviation
*: Mann-Whitney U test
**: Independent samples t-test
***: Pearson chi-square or Fisher's exact test

Table 2. Comparison of the operative findings between the groups

	Group TXA-10 (n=35)	Group TXA-25 (n=36)	p-value
Time for surgery (min)†	250.0 (170.0-500.07	280.0 (150.0-420.0)	0.197*
Time for anesthesia (min)†	330.0 (240.0-600.0)	332.5 (190.0-480.0)	0.647*
Time for cardiopulmonary bypass (min)†	116.0 (59.0-300.0)	132.5 (34.0-259.0)	0.633*
Time for cross-clamping (min)†	71.0 (31.0-199.0)	80.0 (12.0-188.0)	0.618*
Activated coagulation time (sec)†			
Baseline	163.0 (102.0-600.0)	151.5 (93.0-248.0)	0.061*
Pre-pumping	600.0 (404.0-698.0)	600.0 (417.0-1000.0)	0.399*
Post-pumping	153.0 (119.0-261.0)	141.5 (50.0-185.0)	**0.003***
Total heparin dose (units)ɣ	1098.6±259.1	1144.4±238.1	0.440**
Additional heparin use‡	0 (0.0)	33 (91.7)	**<0.001*****
Additional heparin dose (units)†	-	1000.0 (750.0-1250.0)	-
Protamine dose†	1650.0 (900.0-3200.0)	1500.0 (200.0-2400.0)	0.713*
Intraoperative transfusions†			
Erythrocyte (mL)	40.0 (10.0-170.0)	50.0 (20.0-130.0)	0.339*
Fresh frosen plasma (mL)	10.0 (10.0-20.0)	10.0 (5.0-20.0)	0.617*
Platelet (mL)	20.0 (10.0-50.0)	30.0 (10.0-60.0)	0.217*
Cryoprecipitate (mL)	25.0 (17.0-50.0)	23.0 (17.0-32.0)	0.473*

†: Median (min-max), ‡: n (%), ɣ: mean ± standard deviation
*: Mann-Whitney U test
**: Independent samples t-test
***: Pearson chi-square or Fisher's exact test

Table 3. Laboratory investigations during the preoperative, intraoperative, and postoperative periods between the groups			
	Group TXA-10 (n=35)	**Group TXA-25 (n=36)**	**p-value**
Preoperative			
Hemoglobin (gr/dL)[ɣ]	12.7±1.7	13.1±2.2	0.440**
Hematocrit (%)[ɣ]	37.8±4.8	39.0±6.9	0.401**
Platelet count (10^9/L)[ɣ]	240.4±112.0	275.5±137.7	0.245**
aPTT (sec)[ɣ]	43.2±10.8	44.2±9.0	0.706**
INR[†]	1.3 (0.9-5.0)	1.3 (1.0-2.2)	0.913**
Post-pumping (in arterial blood gas sampling)			
Hemoglobin (gr/dL)[ɣ]	11.0±1.7	10.9±1.6	0.824**
Hematocrit (%)[ɣ]	33.8±5.5	33.5±4.9	0.788**
Postoperative (in the first arterial blood gas sampling)			
Hemoglobin (gr/dL)[ɣ]	11.9±1.7	12.2±1.9	0.477**
Hematocrit (%)[ɣ]	36.5±5.3	37.4±6.1	0.523**
Postoperative 12th hour			
Hemoglobin (gr/dL)[ɣ]	12.7±2.3	13.4±1.7	0.192**
Hematocrit (%)[ɣ]	37.2±6.7	38.7±4.6	0.269**
Platelet count (10^9/L)[†]	146.5 (29.0-421.0)	146.0 (40.0-808.0)	0.819*
INR[†]	1.4 (1.0-2.2)	1.3 (1.0-2.2)	0.124*

[†]: Median (min-max), [ɣ]: mean ± standard deviation
*: Mann-Whitney U test
**: Independent samples t-test

Table 4. Comparison of the postoperative bleeding and transfusion between the groups			
	Group TXA-10 (n=35)	**Group TXA-25 (n=36)**	**p*-value**
Postoperative bleeding (mL)[†]			
6th hour	40.0 [5.0. 175.0]	30.0 [5.0. 100.0]	0.623
12th hour	50.0 [5.0. 240.0]	50.0 [10.0. 130.0]	0.630
24th hour	70.0 [10.0. 325.0]	75.0 [25.0. 170.0]	0.986
Postoperative transfusions during the first 24 hour			
Erythrocyte (mL)[†]	50.0 [20.0. 285.0]	50.0 [10.0. 130.0]	0.810
Fresh frozen plasma (mL)[†]	75.0 [25.0. 160.0]	40.0 [10.0. 110.0]	0.286
Platelet (mL)[†]	210.0 [210.0. 210.0]	120.0 [120.0. 120.0]	0.317

[†]: median (min-max)
*: Mann-Whitney U test

the fibrinolytic system needs to be stabilized using aprotinin and lysine analogs such as epsilon-aminocaproic acid (EACA) and antifibrinolytic agents such as tranexamic acid (TXA). Today, the use of TXA has come to the fore as the use of aprotinin has been abolished due to marketing and safety concerns (9-14). However, although sufficient studies have been conducted on the use of TXA in adults, the studies on the use of TXA during pediatric cardiac surgery are limited.

There are controlled studies in which tranexamic acid was compared with placebo and other antifibrinolytic agents. The results of two different studies conducted with small samples with different cardiac pathologies indicated that the use of TXA reduces the use of blood products and is safe (13,14).

The data available in the literature on the effect of tranexamic acid on postoperative outcomes is contradictory. For instance, in a study involving children, Hasegawa et al. (7) reported that the inotrope usage and the peak lactate level in patients on TXA were lower than those of the control group, and they concluded that TXA improved clinical stability. They also reported that the TXA use shortened the extubation time and significantly reduced the length of stay in both the intensive care unit

Table 5. Postoperative outcomes in the study groups			
	Group TX-10 (n=35)	**Group TX-25 (n=36)**	**p-value**
Sternal closure‡			
No	29 (82.9)	25 (69.4)	0.296***
Yes	6 (17.1)	11 (30.6)	
Revisional surgery‡	29 (82.9)	25 (69.4)	0.296***
Reoperation for bleeding	1 (2.9)	1 (2.9)	0.999***
Length of hospital stay (day)†	18.0 (6.0-64.0)	18.5 (6.0-71.0)	0.734*
Length of intensive care unit (day)†	14.5 (4.0-64.0)	12.5 (4.0-66.0)	0.560*
Stroke	0	0	0.999***
Deep venous trombozis	0	0	0.999***
ECMO	2 (5.7)	1 (2.9)	0.620***
Peritoneal dialysis‡	1 (2.9)	1 (2.9)	0.999***
Postoperative urea (mg/dL)ɣ	20.5±8.4	20.9±8.0	0.819**
Postoperative creatinine (mgdL)ɣ	0.5±0.2	0.5±0.2	0.358**
Seiuzeres	1 (2.9)	1 (2.9)	0.999***
Outcome‡			
Survived	26 (74.3)	28 (77.8)	0.947***
Non-survived	9 (25.7)	8 (22.2)	

†: Median (min-max), ‡: n (%), ɣ: mean ± standard deviation
*: Mann-Whitney U test
**: Independent samples t-test
***: Pearson chi-square or Fisher's exact test

and hospital. In contrast, Zhang et al. (8) reported that TXA use neither affected the clinical situation significantly nor reduced the length of stay in the intensive care unit or hospital. A recently published meta-analysis including 15 randomized controlled trials including 1641 patients revealed that tranexamic acid is very effective for reducing blood loss in Chinese patients who have undergone pediatric heart surgery but is less effective for reducing the need for blood transfusions (9).

In comparison, in this study, TXA, an antifibrinolytic agent, was used in cardiovascular surgeries, in line with the standard clinical practice in the clinic where this study was conducted. The results of this study, taken together with the respective data reported in the literature, suggest that the use of TXA reduces the use of blood and blood products.

A wide range of TXA dosage regimens has been reported in the literature, from 10 to 100 mg/kg/hour administered by bolus and/or infusion (12). One reason for such a wide range is the lack of data on the effective dose in plasma caused by the fact that only a limited number of pharmacokinetic studies have been carried out on the subject matter (13,14). Zhang et al. (8) reported that they could use 15 mg/kg/hour TXA effectively and safely by infusion in pediatric cases. However, Grassin-Delyle et al. (14) stated that they obtained effective results when they used 10 mg/kg/hour TXA by infusion. In another study, TXA was administered at a dose of 25 mg/kg in a triple dose regime and compared with a lower dose of 10 mg/kg in cyanotic patients who underwent pediatric cardiac surgery; 25 mg/kg in a triple dose regime was associated with lower post-op blood loss without having major side effects (10). In comparison, in this study, both 10 mg/kg/hour and 25 mg/kg/hour doses of TXA were used safely.

Several side effects of tranexamic acid, including an increased risk of seizures in particular, have been mentioned in several studies. In one of these studies, Maeda et al. (15) stated that the frequency of seizures in patients who were administered TXA was eight times higher than that of other patients (1.6% vs. 0.2%). In another study conducted with 2026 cases, which also included the pediatric population, it was stated that the use of TXA caused no seizures (8). In comparison, in this study, seizures were observed in one patient in each group.

Another important side effect reported with the use of TXA is the risk of developing acute renal failure. Accordingly, in one study, it was reported that peritoneal dialysis was needed in only one case out of the 970 cases that were administered TXA (10). In comparison, in this study, peritoneal dialysis was needed in one patient in each

group, which refers to a higher incidence of renal failure compared to the abovementioned study. The fact that the age group covered in this study was younger and that the surgical complexity of the cases included in this study was higher might be the reason for the said discrepancy.

Other reported side effects were deep vein thrombosis and stroke (3-7), which were not observed in this study in any group.

Study limitations

The primary limitation of this study is that it was conducted as a single-center retrospective study with a limited number of cases. Secondly, there was no control group. However, it was possible to deduce an idea about efficacy and safety by comparing the study data with the relevant data in the literature. Thirdly, the plasma tranexamic acid levels of the cases were not studied. The strength of this study is that it was performed in neonatal and infant patients, and a similar CPB protocol was used in all patients.

Conclusion

Tranexamic acid can be used safely and effectively in cases of pediatric cardiac surgery. There was no significant difference between the study groups created on the basis of the doses of tranexamic acid administered by infusion in the amount and rate of bleeding, the number and number of blood products used, or the frequency of complications observed while in the intensive care unit. Multicenter studies to be conducted with larger samples are needed to verify the findings of this study.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital local ethics committee (number: 2020-21-14 and dated: 19.10.2020).

Informed Consent: Written and verbal consent were obtained from all participants.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: H.D.O., S.O., I.A.K., S.S., B.T., O.Y., E.O., F.G.O., A.H., Design: H.D.O., S.O., I.A.K., S.S., B.T., O.Y., E.O., F.G.O., A.H., Data Collection and/or Processing: H.D.O., S.O., I.A.K., S.S., B.T., O.Y., E.O., F.G.O., A.H., Analysis and/or Interpretation: H.D.O., S.O., I.A.K., S.S., B.T., O.Y., E.O., F.G.O., A.H., Literature Research: H.D.O., S.O., I.A.K., S.S., B.T., O.Y., E.O., F.G.O., A.H., Writing: H.D.O., S.O., I.A.K., S.S., B.T., O.Y., E.O., F.G.O., A.H.

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Original Article

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A Comparative Analysis of Posterior and Lateral Approaches in Hip Hemiarthroplasty of Patients Older than 65 Years Regarding Dislocation and Periprosthetic Fracture Rates

Serkan Onder Sirma, Mehmet Ekinci, Murat Yilmaz, Mehmet Mesut Sonmez

University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Orthopedics and Traumatology, Istanbul, Turkey

Abstract

Aim: The two most commonly used approaches for hip hemiarthroplasty operations are the lateral and posterior approaches (PAs). The PA is claimed to have a higher risk of dislocation. In this context, we aimed to investigate if there is a difference between posterior and lateral approaches (LAs) in terms of postoperative dislocation rates. Mortality rates and the risk of operative periprosthetic fracture were also analyzed.

Methods: A retrospective investigation was conducted of patients who underwent hip hemiarthroplasty for a femur neck fracture at our hospital between 2010 and 2020. The operation notes, medical records in the hospital electronic records system, and the Turkish national health record system (E-nabız personal health system) were reviewed. Patients with additional severe diseases or trauma that may affect the risk of dislocation were excluded from the study. Patients were grouped into the PA group and the LA group. PAs were performed using the Moore technique, and LAs were performed using the modified Hardinge technique. Dislocation, periprosthetic fractures, and mortality rates were noted.

Results: There were 321 females and 147 male patients in the study. The PA group included 262 patients, and the LA group, 206. There were 6 dislocations and 5 periprosthetic fractures in the PA group and 2 dislocations and 1 periprosthetic fracture in the LA group, with a minimum of 1-year follow-up. The difference was not statistically significant. The mortality rates in postoperative years 1 and 10 were 26.4% and 82.1%, respectively. The lateral versus PA had no statistically significant effect on these rates.

Conclusion: Since there was no significant difference between these approaches in terms of dislocation, periprosthetic fracture, and mortality rates; it was concluded that the choice of approach should depend on surgeon preference and experience.

Keywords: Hip dislocation, hemiarthroplasty, postoperative complications, femoral neck fractures, periprosthetic fractures

Introduction

Hip fractures occur most commonly in patients older than 70 years due to decreased bone mass and are more common in females. Femoral neck fractures are slightly less common compared with intertrochanteric fractures and account for approximately 40% of proximal femur fractures (1). These fractures are associated with high mortality rates, and the 1-year mortality rate for operated patients can range from 4% to as high as 48% (2,3). For treating displaced femoral neck fractures in elderly and low demand patients, the literature supports cemented hemiarthroplasty, because of the lower risk of complications, less blood loss, and shorter operating time, compared to total and cementless arthroplasty (4).

Different surgical approaches can be used for hip hemiarthroplasty, including the anterior, antero-lateral, lateral, and posterior approaches. Although the two most commonly used are the lateral and posterior approaches, the best approach remains controversial (5,6). The

Address for Correspondence: Serkan Onder Sirma
University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Orthopedics and Traumatology, Istanbul, Turkey
Phone: +90 533 224 38 07 E-mail: serkansirma@gmail.com ORCID: orcid.org/0000-0003-3073-1342
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posterior approach (PA) is claimed to have a higher risk of dislocation (7), while it has been suggested that the lateral approach (LA) leads to worse functional outcomes depending on gluteus medius muscle damage and hip abductor dysfunction (6,8).

This study aimed to investigate any difference between the posterior and LAs in terms of postoperative dislocation rates. During this investigation, the mortality rates and risk of operative periprosthetic fracture were also analyzed.

Methods

Study Design

Ethical approval for this study was obtained from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (150-2022; 10.08.2022). The study was retrospective, so no informed consent form was applicable.

From the hospital database, patients older than 65 years who underwent hip hemiarthroplasty operations for displaced femoral neck fractures between 2010 and 2020 were identified. The operation notes and medical records in the hospital electronic records system of all patients were reviewed. It was also noted from the records whether any procedures such as reduction of dislocation, revision, or debridement had been performed after the initial surgery.

The study exclusion criteria were defined as revision operations of previous osteosynthesis, cementless prosthesis operations, patients with iatrogenic fracture, Alzheimer's disease, Parkinson's disease, epilepsy, hemiplegia, stroke, malignant oncological disease, lytic or blastic bone lesion involving the fracture site, concomitant trochanter major fracture, contralateral hip prosthesis, knee prosthesis before or after the surgery, other concomitant fractures (distal radius, proximal humerus etc.), the development of postoperative deep surgical site infection or those who were immobile or bedbound before the hip fracture.

After the exclusion of these patients from the 684, the study sample comprised 468 patients. A record was made of age, surgery date, surgery side, approach type, prosthesis type, dislocations, and periprosthetic fractures.

The Turkish National Health Record System (e-nabız personal health system) was checked for the records of the deaths of these patients and to check if the patients had undergone any intervention at another hospital for complications.

Surgical Technique

The operations were performed by different experienced surgeons or by registers under the supervision of experienced surgeons. The surgeon who performed the surgery had decided which approach to use according to his own experience. In the PA group, repair of the capsule and external rotators was always performed; in the LA group, repair of the capsule and gluteus medius tendon was always performed. A single cemented monobloc stem design with a high-offset and a 135° neck-shaft angle was used. The head was bipolar or unipolar depending on the surgeon's preference. Three hundred and ninety-four were bipolar and 74 were unipolar. Unipolar heads are generally used in older patients.

LA (modified Hardinge): In the lateral decubitus position, a curved incision was made centered over the greater trochanter. After retracting the tensor fasciae latae anteriorly and the gluteus maximus posteriorly, the gluteus medius was split longitudinally at its anterior third and the tendinous insertions of the anterior portion were elevated to expose the joint capsule (Figure 1). At the end of the procedure, the capsule and the split flap were repaired (Figure 2).

PA (Moore): In the lateral decubitus position, a curved incision was made over the posterior margin of the greater trochanter. After dividing the deep fascia, the gluteus maximus muscle was split in line with its fibers and retracted to expose short external rotator muscles

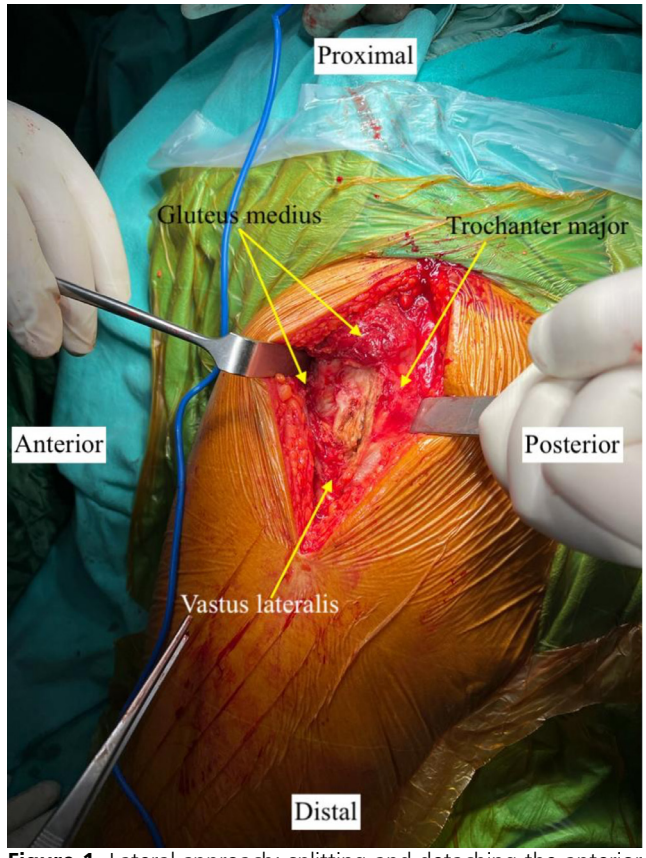

Figure 1. Lateral approach; splitting and detaching the anterior part of the gluteus medius muscle

(Figure 3). These external rotator muscles were, then freed from femur insertion and the capsule incised. After the implantation, detached posterior structures were repaired (Figure 4).

Statistical Analysis

Data obtained in the study was statistically analyzed using computer software. Categorical variables were expressed as numbers and percentages, and continuous variables as average, standard deviation, minimum, maximum, and median values. Continuous outcomes for the two independent groups were analyzed using the Student t-test and binary outcomes with the chi-square test. A value of $p<0.05$ was considered statistically significant.

Results

An evaluation was made of 468 patients, comprising 321 (69%) females and 147 (31%) males, with a median age of 80.3 years (range, 65-94 years). All the patients underwent surgery in the lateral decubitus position with cemented hemiarthroplasty implants. The operated hips were right-side in 215 (46%) cases and left-side in 253 (54%). The PA was applied to 262 (56%) patients and the LA to 206 (44%) (Table 1).

The PA group comprised 174 (66%) females and 88 (34%) males with a mean age of 80.6 years. The LA group comprised 147 (71%) females and 59 (29%) males with a mean age of 79.9 years. No significant difference was determined between the groups with respect to gender or age ($p=0.252$, $p=0.572$, respectively) (Table 1).

Dislocation Rates

Postoperative hip dislocation occurred in 8 patients, 6 (2.3%) in the PA group and 2 (1%) in the LA group (Figure 1). The difference was not statistically significant ($p=0.475$) (Table 2). The mean time from surgery to the first dislocation was 58.5 days (2-166 days). Six of those eight dislocations occurred within the first seven weeks of surgery (days 2, 22, 33, 35, 42, and 46), and two late dislocations occurred on days 122 and 166 (Table 3).

The reported results were from a mix of operations performed with unipolar and bipolar designs, but mostly bipolar (394/468), and all the patients who experienced complications (8 dislocations and 6 periprosthetic fractures) had bipolar implants.

In the PA group, 2 patients' hips were reduced under sedation, and the other 4 patients underwent open surgery for the reduction. In 2 of these open reduction cases, the anteversion of the femoral stem was normal and the repair of the short external rotator muscles and the capsule were done properly. In 1 patient, the anteversion was normal but the external rotator muscles were necrotic and non-functional. In the other patient, the anteversion of the femoral stem was less than the normal range.

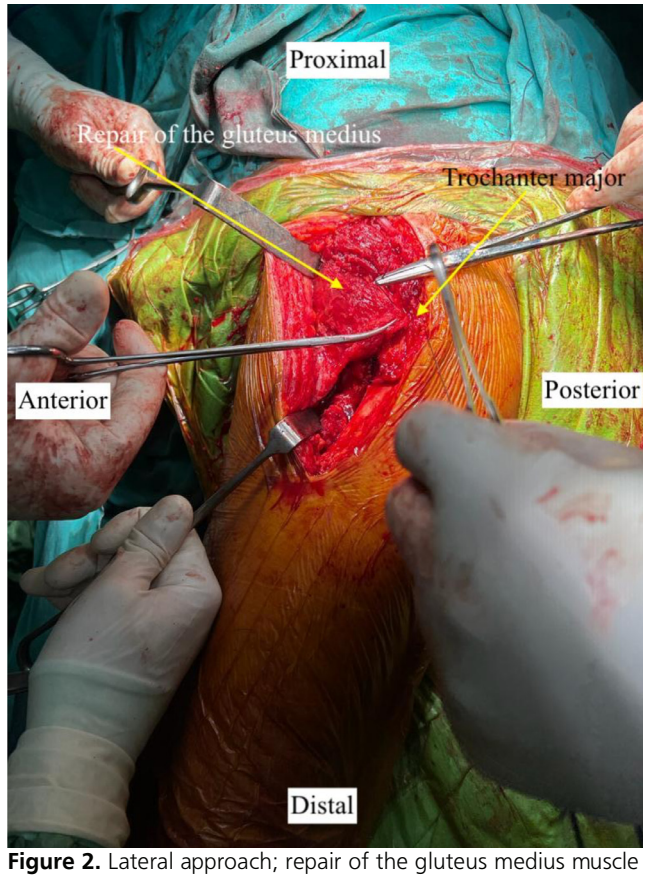

Figure 2. Lateral approach; repair of the gluteus medius muscle

In the LA group, both patients underwent open reduction. In 1 patient, the capsule and the gluteus medius muscle repair and the anteversion of the femoral component were normal. In the other patient, the capsule had been repaired but was loose and some capsule tissue was absent.

Postoperative Periprosthetic Fracture Rates

Periprosthetic fractures in the postoperative period occurred in 5 patients (2%) in the PA group and in 1 patient (0.5%) in the LA group (Figure 5). The difference was not statistically significant ($p=0.236$) (Table 2).

This complication occurred 524 days postoperatively in the LA group patients, and on days 92, 112, 224, 274, and 350, respectively, in the 5 cases in the PA group. All these patients were treated with open reduction and internal fixation using plates and cables.

Mortality Rates

The mortality rates in postoperative years 1 and 10 were 26.4% and 82.1%, respectively, and the lateral versus PA had no statistically significant effect on these rates (Table 2 and Figure 6).

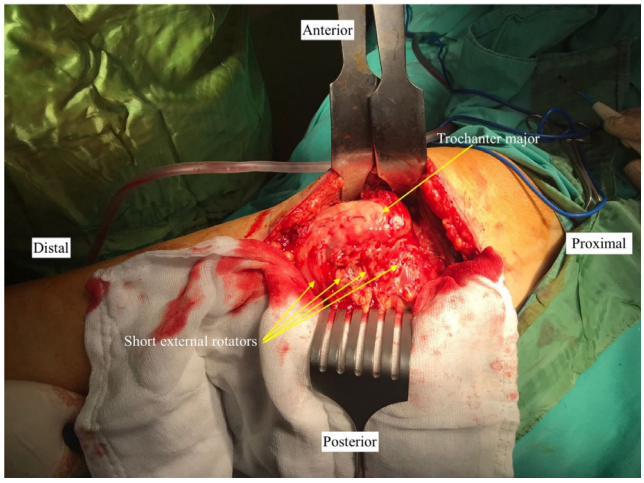

Figure 3. Posterior approach; exposure of the short external rotator muscles

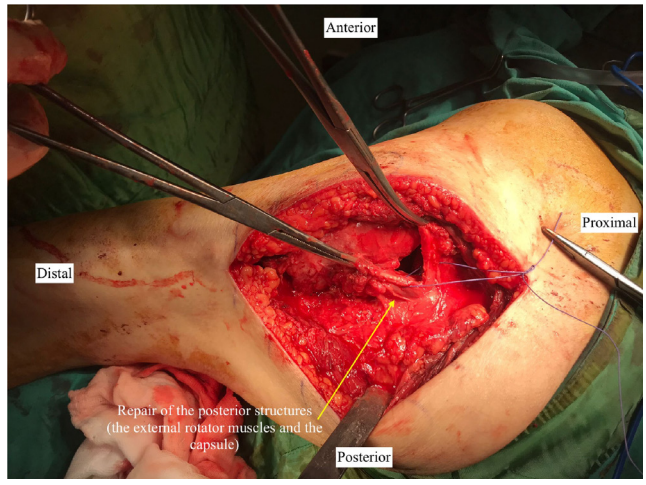

Figure 4. Posterior approach; repair of the posterior structures (the external rotator muscles and the capsule)

Discussion

Many complications can be seen after hip arthroplasty operations, such as dislocation, infection, and periprosthetic fracture, which are devastating for these elderly and vulnerable patients, and have high mortality rates (9-11).

Gill et al. (12) stated that an increased dislocation risk was associated with a posterior approach; with the use of bipolar prosthesis, and with the use of cement. Hongisto et al. (8) and Parker (13) reported that there was no significant difference in mobility level or pain between the LA and PA groups, despite an increased need for mobilization assistance in patients operated on using the LA.

There are also studies reported that the risk of dislocation after the PA is significantly decreased as there is minimal dissection, repair of the capsule and anatomical reattachment of the short external rotators and that there is no statistically significant difference between the PA and LA (13-18).

In a recent study by de Vries et al. (14), 1009 hemiarthroplasty cases were evaluated retrospectively. Five hundred sixteen patients were operated on via a PA and 493 were via a LA. There were 15 (2.9%) dislocations in the PA group and 7 (1.4%) in the lateral group. The authors stated that this difference was not statistically significant.

Graulich et al. (17) retrospectively analyzed patients who had dislocated bipolar hemiarthroplasty, which was performed after a femur neck fracture. A total of nine met the inclusion criteria. These patients were matched to 30 femoral neck fracture patients who had undergone hip hemiarthroplasty but didn't experience a dislocation. Seven (78%) patients out of 9 with a dislocated hip were

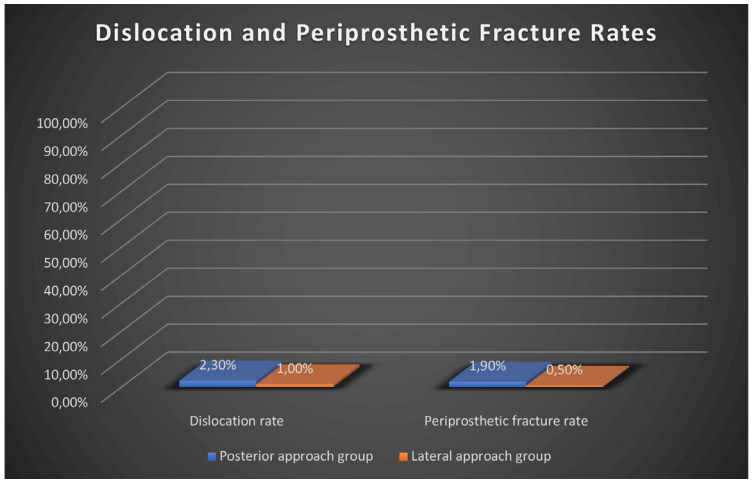

Figure 5. Dislocation and periprosthetic fracture rates in the PA and LA groups

PA: Posterior approach, LA: Lateral approach

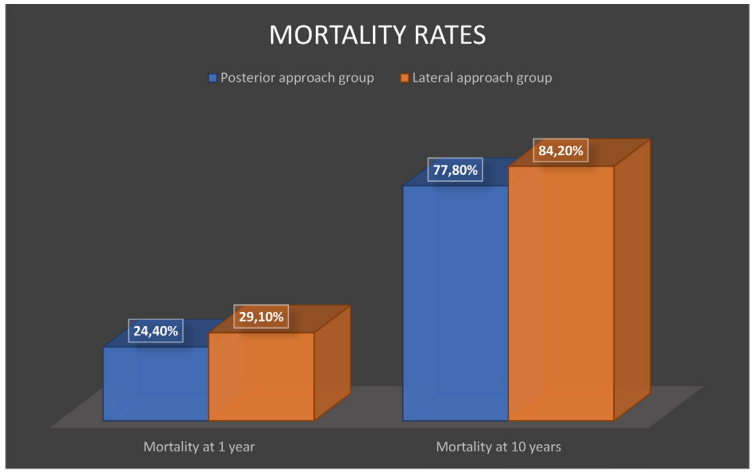

Figure 6. Mortality rates in the PA and LA groups

PA: Posterior approach, LA: Lateral approach

operated via a LA, while 2 (22%) were operated via a posterior approach. In the non-dislocated control group, there were 19 (63%) lateral versus 11 (37%) PA patients. According to these results, the authors concluded that the rates of lateral and posterior approaches were not statistically different in both groups and that surgical approaches were not associated with a higher risk of dislocation in bipolar hemiarthroplasty.

In contrast, a meta-analysis by van der Sijp et al. (19), which was published in 2018, concluded that the risk of dislocation after a hip hemiarthroplasty is significantly higher with a posterior approach. In this meta-analysis, 2646 cases from 9 studies were collected as the PA group and 3394 cases as the LA group. There were 133 dislocations in the PA group (5%) and 61 dislocations in the LA group (1.8%). The difference was statistically significant, and the authors reported that the PA should not be used. Similar results were reported by Jobory et al. (20) including 25678 hemiarthroplasty patients in 2021. They concluded that a PA and dementia were linked to an increased risk of dislocation (20).

In this study also, the percentage of dislocated hips was slightly higher in the PA group (2.3% vs 1%); but this difference did not reach statistical significance. Although dislocation rates as high as 13-16% with PA have been reported (9,10), we do not see such high rates in our hospital. It may be because the lifestyles of the elderly people in our service area are more sedentary than in the region in which these studies were conducted. Besides, studies reported similar dislocation rates to our study. For example, Parker (13) reported the dislocation rate of the PA group in his study as 0.9% (1/108) and Sierra et al. (16) reported it as 2% (5/245). Therefore, in our opinion, it is not necessary to completely abandon the posterior approach, but in patients with high dislocation risk, such as hip flexion contracture or acetabular dysplasia, a LA may be more appropriate. In contrast, if limping is an important concern for an individual, a PA may be more appropriate

Table 1. Patient characteristics

	Posterior approach group	Lateral approach group	p-value
Number of patients	262	206	
Mean age	80.6 (65-94)	79.9 (65-93)	0.572
Male	88 (33.6%)	59 (28.6%)	0.252
Female	174 (66.4%)	147 (71.4%)	0.252
Right/Left	Right: 119 (45.4%)/Left: 143 (54.6%)	Right: 96 (46.6%)/Left: 110 (53.4%)	0.799

Table 2. Dislocation, fracture and mortality rates

	Posterior approach group	Lateral approach group	p-value
Mortality at 1 year	64/262 (24.4%)	60/206 (29.1%)	0.253
Mortality at 10 years	14/18 (77.8%)	32/38 (84.2%)	0.711
Dislocations	6 (2.3%)	2 (1%)	0.475
Periprosthetic fractures	5 (1.9%)	1 (0.5%)	0.236

Table 3. Details of the patients with dislocated hips

	Age	Gender	First dislocation day	Intervention	Note	Second dislocation day	Second intervention
Posterior approach group							
Patient 1	85	Male	42	Femoral length was increased	The short rotators were necrotic and non-functional	_____	_____
Patient 2	87	Female	22	Closed reduction	There was an adductor stiffness	54	Anteversion was normal but femoral stem was changed and placed in a more anteverted position
Patient 3	79	Female	46	Open reduction	Anteversion and capsule-muscle repair were normal	_____	_____
Patient 4	94	Male	33	Femoral length was increased	Anteversion and capsule-muscle repair were normal	_____	_____
Patient 5	92	Female	122	The femoral stem was changed and placed in a more anteverted position	Anteversion was less than normal	_____	_____
Patient 6	87	Male	35	Closed reduction	_____	_____	_____
Lateral approach group							
Patient 1	88	Female	2	Open reduction	Anteversion was normal but the capsule was partially repaired	26	Femoral length was increased but a third dislocation occurred on day 38 and a girdlestone procedure was performed
Patient 2	90	Female	166	Open reduction	Anteversion and capsule-muscle repair were normal	_____	_____

for this patient; the LA is associated with problems related to hip abductor dysfunction, altered gait, limping, and a positive Trendelenburg sign due to gluteal muscle damage, avulsion of the gluteal flap after the operation, the failure of the reattachment of the aponeurosis, or damage to the superior gluteal nerve (6,21,22). Ramesh et al. (22) reported 11% persisting damage to the superior gluteal nerve after this approach.

Like postoperative prosthetic hip dislocation, periprosthetic fracture is also a devastating complication after hip hemiarthroplasty operations and is associated with increased morbidity and mortality (23). The literature correlates the periprosthetic fractures mostly with the fixation methods (cemented versus uncemented) (9,14,23,24), but there are also several studies that have investigated the correlation between periprosthetic fractures and the types of approach (11,13,14). de Vries et al. (14) reported no difference in periprosthetic fracture rates between the PA and the LA. Parker (13) noted a tendency for periprosthetic fractures to occur more with the posterior approach, but it was not significant. Keene and Parker (11) reported significantly higher rates of periprosthetic fracture with the posterior approach. In this study, there were more periprosthetic fractures in the PA group (5 vs 1), but not to a statistically significant level.

The 1-year mortality rate in this study was a little high at 26.4%, even though patients with other injuries or fatal diseases were excluded. In the literature, it ranges from 4% to 48% (2,3).

The long-term (>10 years) mortality rates for these patients have been reported to be very high. There are few studies on this point, most probably because it is

thought that most of the long-term deaths of this elderly population are natural and there would be little value in studying the long-term mortality rates. Ravikumar and Marsh (25) reported a mortality rate of 86% for hemiarthroplasty patients at 13 years, while Parker et al. (26) found the rate to be 93% at 11 years. In this study, the 10-year mortality rate was 82.1%, which was similar to the data in those studies.

Study Limitations

The limitations of this study were the small number of patients, the lack of analysis of surgeon grade, the lack of a radiographic assessment, and the lack of evaluation of functional outcomes. The retrospective design of the study prevented the evaluation of functional outcomes to determine whether the LA leads to an increased need for mobilization assistance or any other functional disadvantages. The operations were performed by experienced surgeons or by registers under the supervision of experienced surgeons, and previous studies have demonstrated that there is no correlation between the grade of the surgeon and dislocation rates (27).

The study's strength is the exclusion of patients with additional disease, trauma, or any other condition that could have affected the risk of dislocation. Therefore, a more homogenous population was obtained.

Conclusion

The results of this study showed no significant differences in the rates of postoperative dislocations, periprosthetic fractures, and mortality between the lateral and posterior surgical approaches for hip hemiarthroplasty surgery. Therefore, it can be concluded that the choice of the approach should depend on surgeon preference and experience.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (150-2022; 10.08.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: S.O.S., Design: S.O.S., Data Collection and/or Processing: M.E., Analysis and/or Interpretation: M.Y., Literature Research: M.M.S., Writing: S.O.S.

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

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Original Article

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The Relationship Between Dietary Intakes and Total Kidney Volume in Patients with Autosomal Dominant Polycystic Kidney Disease Dietary Intake and Polycystic Kidney Volume

Yonca Sevim*, Egemen Cebeci**, Ozlem Persil Ozkan***, Yildiray Savas****, Savas Ozturk**, Gul Kiziltan*****

*Bahcesehir University Faculty of Health Science, Department of Nutrition and Dietetics, Istanbul, Turkey

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

***Istanbul Arel University Faculty of Health Sciences, Department of Nutrition and Dietetics, Istanbul, Turkey

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

*****Baskent University Faculty of Health Sciences, Department of Nutrition and Dietetics, Ankara, Turkey

Abstract

Aim: There is a need to understand autosomal dominant polycystic kidney disease (ADPKD) patients' dietary habits since dietary interventions may have potential effects on ADPKD. In this study, we aimed to analyze the relationship between dietary nutrient intake and total kidney volume (TKV).

Methods: This cross-sectional study was conducted on 54 ADPKD patients recruited from the Nephrology outpatient clinic between June and July 2014. TKV was determined by magnetic-resonance imaging and general characteristics, biochemical and urinary parameters were determined. The nutrient intakes of patients were calculated using the three-day dietary records obtained on three consecutive days.

Results: The total kidney-volume median was found to be 1407 mL. Patients' total dietary energy and protein intakes were 25.8±9.4 kcal/kg, 0.9±0.3 g/kg, respectively. The percentage of carbohydrates, protein, and fat in energy was 49±7%, 14±3%, 37±7%, respectively. The mean intakes of thiamin, riboflavin, B6, calcium, magnesium, and zinc were sufficient, the mean dietary potassium intake was insufficient; and sodium intake was excessive in both sexes. In females, there was a negative but weak correlation between dietary vitamin C intake and TKV. In males, a negative but weak correlation was found between TKV and dietary intake of fiber, water, vitamin B6, vitamin K, magnesium, and iron.

Conclusions: Dietary micronutrient intake may affect TKV according to sex.

Keywords: Autosomal dominant polycystic kidney, ADPKD, kidney, nutrition, diet therapy, dietary intakes

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary kidney disorder characterized by renal and extrarenal involvement with cystic and non-cystic manifestations. ADPKD accounts for approximately 5% of total end-stage renal disease (1). Pharmaceutical therapies (i.e., tolvaptan and octreotide) with supportive measures such as blood pressure control, increased fluid intake, decreased salt intake, and smoking cessation are the basis of the current management of AKPD (2).

Data on dietary interventions in patients with ADPKD is still limited. The role of medical nutrition therapy hasn't been fully investigated in ADPKD (3). The lack of specific, based on strong evidence, dietary recommendations for

Address for Correspondence: Yonca Sevim
Bahcesehir University Faculty of Health Science, Department of Nutrition and Dietetics, Istanbul, Turkey
Phone: +90 212 381 00 20 E-mail: yonca.sevim@hes.bau.edu.tr ORCID: orcid.org/0000-0003-2793-1318
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ADPKD patients and the general recommendations for chronic kidney disease (CKD) patients remains important. Blood pressure control, dietary modification toward a low-protein diet, the use of antioxidants and lipid lowering agents have been investigated in PKD to reduce renal progression (4). While low protein diets are generally recommended for PKD patients, the type rather than the amount of protein may be considered more important, and omega-3 polyunsaturated fatty acids, phytochemicals, and phytoestrogens may affect PKD and cyst pathogenesis (5). Recent research with murine models of PKD showed that PKD cyst lining cells are glucose-dependent as an energy source (the Warburg effect), pointing out that defects in energy metabolism underlie the pathogenesis of PKD (6,7). Because of these findings, dietary management of ADPKD has become a focus of interest again. It's been shown that non-caloric reduction with time-restricted feeding strongly inhibits the mammalian target of rapamycin signaling, fibrosis, and proliferation in a PKD rat model (8). Conflicting results of pharmacologic and dietary strategies have been used so far to preserve renal function and slow renal damage in humans with PKD.

Data on ADPKD is mostly based on animal or human cell studies, and there is insufficient data about ADPKD patients' actual dietary consumption. This study improved the understanding of ADPKD patients' dietary behaviors and the relationship between total kidney volume (TKV) and diet, and provided evidence to support improvements in dietary recommendations and dietary interventions to reduce renal damage.

Materials and Methods

Compliance with Ethical Standards

This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Non-Pharmaceutical Clinical Research Ethics Committee (date: 18.06.2014, protocol no: 122). Written informed consent was obtained from the patients. The privacy of the study participants was protected.

Study Population

Patients who were diagnosed with ADPKD confirmed by family history, clinical findings, and determinate kidney volume by magnetic resonance imaging (MRI) were enrolled, recruited from the Nephrology outpatient clinic during routine visits between June and July 2014, and were informed about the study. Patients who accepted to voluntarily participate in this study were screened. Patients were excluded if they used drugs affecting the cyst volume (tolvaptan, rapamycin, lithium, etc.), received renal replacement therapy, were on diet therapy for preexisting or comorbid medical conditions not related to the ADPKD standard care, those with creatinine clearance ≤15 mL/min, chronic liver or lung disease, hyperthyroidism, pregnancy, active infection, malignancy, and malnutrition (albumin less than 4 g/dL). The final number of patients was 54 (20 male and 34 female). This study is derived from Sevim's (9) doctoral thesis.

Study Design

In this study, the general characteristics, biochemical parameters, TKV, and dietary intake of patients were examined. Patients' data on general characteristics such as age, gender, height, weight, duration of illness diagnosis, chronic disease presence, and smoking status were collected through face-to-face interviews with the patients.

Height and weight are measured using a stadiometer and an electronic scale, respectively, as light as possible and without shoes. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared (kg/m^2) (10). Biochemical parameters such as glucose, total protein, albumin, prealbumin, total cholesterol, very low-density lipoprotein cholesterol, low-density lipoprotein cholesterol, high density cholesterol, trigliserid, uric sit, urea, creatinine, sodium, potassium, phosphorus, calcium, iron, total iron-binding capacity, unsaturated iron-binding capacity, hemoglobin, ferritin, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, urine protein level, and systolic-diastolic blood pressure, and pulse were obtained from the patient's files related visit. The estimated glomerular filtration rate (eGFR) was calculated using the creatinine equation published by The Chronic Kidney Disease Epidemiology Collaboration (11). Staging CKD was classified based on eGFR as 1, 2, 3, and 4 (12).

Total Kidney Volume with Magnetic Resonance

The MRIs of the patients were taken with a gradient-strength 48 mT ACHIEVA NOVA MRI system (Philips Koninklijke Netherlands) device with 1.5-T magnet power. The volumes of bilateral polycystic kidneys were calculated in cm^3 (mL).

Three-day Dietary Records

Patients were trained how to take three-day diet records by a dietitian using supporting materials such as photographs and replicas of various foods on the first visit. After training, dietary intakes were recorded for three consecutive days that were two weekdays and one weekend day, and the dietary records were collected and controlled by a dietitian with a face-to-face interview on the second visit. Dietary records included detailed information about all foods and beverages consumed in terms of type, amount, preparation, recipes, and ingredients. To determine the amount of food consumed, patients used an electronic food scale and/or typical volumetric

household measures. When these measurement methods were unavailable, patients were asked to estimate the portion sizes with food portion size picture books provided by a dietitian.

Evaluation of Dietary Intakes

Daily energy and nutrient intakes were calculated using the nutrition information system Ebispro for Windows, Turkish Version 2010 (BeBiS 7.2) (13). Fluid intake (water) patients was calculated as the sum of drinking water, water in beverages and food. Salt intake was also calculated as the sum of table salt (additional), the natural content of foods and beverages, and recipes.

Since there is a lack of dietary recommendations for ADPKD, the calculated energy and nutrient intakes of patients were evaluated according to the recommended dietary allowances (RDA), and adequate intakes with respect to age and gender (14). The recommendations for micronutrients, macronutrient intakes and their ratios of energy concentration are based on the acceptable macronutrient distribution range (AMDR) (15), estimated energy requirements (EER), Kidney Disease Improving Global Outcomes 2020 (16), and Turkey Nutrition Guide 2015 (TUBER) (17). The AMDR is a range of intake for macronutrient carbohydrates, protein, or fat, expressed as a percentage of total energy (kcal). To evaluate the percentage of meeting the RDA recommendations (RDA% met), a percentage of 66 or less was considered insufficient intake, and a percentage of 132 and above was considered excessive intake.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) Version 15.0 software (18) was used for the data analysis. The normality of the distribution was determined using the Kolmogorov-Simirnov test. Normally distributed continuous variables (quantitative variables) obtained by measurement are presented with mean, standard deviation (X± SD). Non-normally distributed variables were expressed as medians and interquartile ranges (M, IQR1-IQR3) and categorical data were reported as n (%). The correlations between TKV and energy, dietary nutrient intakes, salt, and caffeine were determined using the bivariate Pearson correlation coefficient for normally distributed variables and the Spearman correlation coefficient for non-normally distributed variables. The statistical significance level was 0.05 in all tests.

Results

This study was conducted on 34 female (63%) and 20 male (37%) patients with ADPKD. The general characteristics, biochemical findings, and kidney function of the patients are shown in Table 1. The eGFR median value of the patients was calculated as 53.3 mL/min/1.73 m^2 and the TKV median value was found to be 1306 mL in females and 1953 ml in males. A total of 94.4% (n=51) n of the patients had a family history of ADPKD. A total of 70.4% (n=38) n of the patients have hypertension. Most of the patients were on stage 2 and 3 CKD (Figure 1).

Dietary Intakes

Table 2 shows the daily energy, nutrient, and other intakes of the patients. Patients' mean daily energy intake was found 26.7±7.0 kcal/kg in men and 25.3±10.6 kcal/kg in women, and the results were on the lowest edge of KDIGO recommendations for energy. Simultaneously, patients' energy intakes were under the EER in both

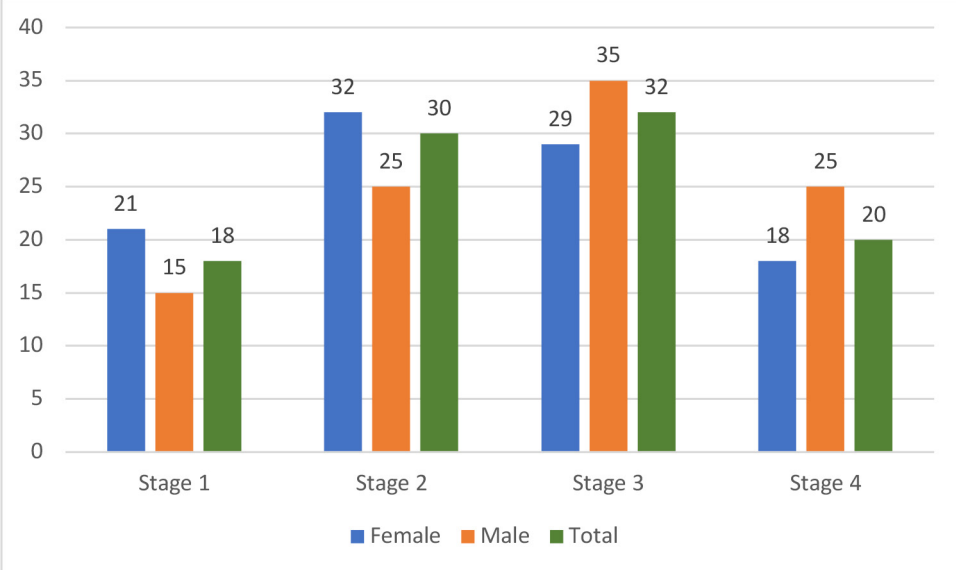

Figure 1: The percentages of patients according to chronic kidney disease stages and sex

Table 1. General characteristics of the patients according to sex									
General characteristics	Female n=34			Male n=20			Total n=54		
	$\bar{X}$±SD (M, Q1-Q3)	Min.	Max.	$\bar{X}$±SD (M, Q1-Q3)	Min.	Max.	$\bar{X}$±SD (M, Q1-Q3)	Min.	Max.
Age (year)	46±10	23	67	50±10	33	69	47±10	23	69
Duration of diagnosis (month)	122±8	4	300	86±71	4	240	108±78	4	300
BMI, kg/m^2	29.5±6.1	15.6	43.9	26.1±4.3	17.0	31.7	28.2±5.7	15.6	43.9
SBP, mmHg	133±15	100	170	148±20	115	200	138±18	100	200
DBP, mmHg	86±11	70	120	90±13	70	130	87±12	70	130
Pulse, min.	80±9	58	100	74±10	55	100	78±10	55	100
Biochemical findings									
Glucose, mg/dL	94±8	78	109	96±16	78	145	95±12	78	145
Urea, mg/dL	44±23	17	110	60±22	31	108	50±24	17	110
Uric acid, mg/dL	5.6±1.6	3.1	8.4	6.5±1.4	3.3	10.0	5.9±1.6	3.1	10.0
Creatinine, mg/dL	1.3±0.8	0.5	3.3	1.9±1.0	0.8	4.4	1.5±0.9	0.5	4.4
CRP, mg/dL	2.9 (1.3-9.0)			2.3 (1.0-6.2)			2.5 (1.2-6.6)		
Sodium, mEq/L	139±2	135	143	140±3	136	147	140±2	135	147
Potassium, mmol/L	4.6±0.5	3.6	5.8	4.6±0.5	3.7	5.5	4.6±0.5	3.6	5.8
Phosphorus, mg/dL	3.4 (3.0-3.9)			3.5 (3.0-3.6)			3.5 (3.0-3.8)		
Calcium, mg/dL	9.5±0.4	8.5	10.2	9.3±0.5	8.2	10.4	9.4±0.4	8.2	10.4
Iron, wg/dL	68±34	22	156	79±29	14	149	72±32	14	156
UIBC, wg/dL	280±55	141	407	249±59	133	390	269±58	133	407
TDBK, wg/dL	350±39	286	437	329±53	233	450	341±45	233	450
Hemoglobin, g/dL	12.5±1.3	9.5	15.1	14.2±1.5	10.7	16.8	13.1±1.5	9.5	16.8
Ferritin, ng/mL	22.8 (15.0-47.7)			66.1 (35.0-81.2)			35.3 (18.4-64.0)		
Pre-albumin, mg/dL	24.2±4.5	16.5	38.0	26.2±4.6	17.1	33.7	24.9±4.6	16.5	38.0
Albumin, g/dL	4.1±0.2	3.7	4.5	4.3±0.3	3.7	4.8	4.2±0.2	3.7	4.8
Total protein, g/dL	7.4±0.4	6.5	8.5	7.2±0.6	6.4	8.3	7.3±0.5	6.4	8.5
Total cholesterol, mg/dL	205±51	81	339	196±33	155	275	201±45	81	339
VLDL-cholesterol, mg/dL	28±14	7	65	28±13	13	57	28±13	7	65
LDL-cholesterol, mg/dL	126±41	34	232	124±28	77	170	126±36	34	232
HDL-cholesterol, mg/dL	50±12	25	78	44±6	36	62	48±11	25	78
Trigliserid, mg/dL	142±73	33	325	139±64	64	285	141±69	33	325
AST, U/L	20±6	11	45	20±5	12	32	20±5	11	45
ALT, U/L	14±4	8	25	15±4	6	25	15±4	6	25
eGFR, mL/dk/1.73 m^2	60.9 (36.9-87.1)			42.1 (25.8-74.8)			53.3 (31.8-79.5)		
Proteinuria, g/day	0.19 (0.12-0.31)			0.24 (0.14-0.98)			0.21 (0.13-0.36)		
The total kidney volume, cm^3	1306 (798-1947)			1953 (1238-3439)			1407 (939-2908)		

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BMI: Body mass index, CRP: C-reactive protein, DBP: Diastolic blood pressure, eGFR: Estimated glomerular filtration rate, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SBP: Systolic blood pressure, TIBC: Total iron-binding capacity, UIBC: Unsaturated iron-binding capacity, VLDL: Very low-density lipoprotein, Min.: Minimum, Max.: Maximum, SD: Standard deviation

sexes, 1176±533 kcal in females and 2058±473 kcal in male patients. The mean daily protein intake was lower than the recommendation in patients with CKD stage 2 without PKD and was higher in patients with CKD stage 3-4 without PKD. Animal and plant-based protein intakes were similar. The mean carbohydrate and protein intake contributions to the total energy according to AMDR were within the recommended range, while fat was slightly higher. An excessive fat and saturated fatty acid (SFA) intake was seen in female patients as their intakes exceeded the AMDR and TUBER. While male patients consumed lower monounsaturated FA (MUFA) than

Table 2. Daily dietary macro nutrient, caffeine and salt intake of the patients according to the sex										
	Female (n=34)			Male (n=20)			Total (n=54)			Recommendation
	$\bar{X}$±SD (M, IQR1-IQR3)	Min.	Max.	$\bar{X}$±SD (M, IQR1-IQR3)	Min.	Max.	$\bar{X}$±SD (M, IQR1-IQR3)	Min.	Max.	KDIGO[a] RDA[b], AMDR[c], TUBER[d], Other[e] (Female/Male)
Energy/Protein needs										
Energy kcal/kg	25.3±10.6	9.1	54.5	26.7±7.0	12.8	37.9	25.8±9.4	9.1	54.5	25-35[a]
Protein g/kg	0.8±0.3	0.3	1.8	0.9±0.3	0.5	0.3	0.9±0.3	0.3	1.8	Stage 1-2 0.8[a,b] 0.55-0.60 without DM Stage 3-4[a] 0.6-0.8 with DM Stage 3-4[a] Individual dietary plans[a]
CKD Stage 1	1.1±0.5	0.6	1.8	1.4±2	1.2	1.6	1.2±0.4	0.6	1.7	
CKD Stage 2	0.7±0.3	0.3	1.1	0.8±0.2	0.5	1	0.7±0.3	0.3	1.1	
CKD Stage 3	0.8±0.3	0.4	1.3	0.9±0.3	0.5	1.3	0.9±0.3	0.4	1.3	
CKD Stage 4	0.8±0.3	0.6	1.3	0.9±0.2	0.6	1	0.8±0.2	0.6	1.3	
Energy and Nutrients										
Energy, kcal	1176±533	943	2903	2058±473	1178	3147	1880±525	943	3147	2403 (EER) 3067 (EER)
Carbohydrate, g	211±79	87	465	259±69	105	418	229±79	87	465	130[b]
Carbohydrate, percentage of energy	48±7	35	67	51±7	36	65	49±7	35	67	45-65[c] 45-60[d]
Fructose, percentage of energy	3.1±1.5	0.5	6.9	2.7±2.0	0.3	7.5	2.9±1.7	0.3	7.5	
Fructose, g	13.6±8.6	3.6	36.1	14.4±12.1	1.8	49.1	13.9±9.9	1.8	49.1	
Fiber, g	21.4±8.9	5.5	41.4	26.5±9.8	15.3	44.5	23.3±9.5	5.5	44.5	25[b] 38[b]
Soluble	7.0±2.8	1.7	14.3	8.3±3	4.3	13.3	7.5±2.9	1.7	14.3	
Insoluble	13.2±5.7	3.0	24.5	16.2±5.9	9.7	28.7	14.3±5.9	3.0	28.7	
Protein, g	59±19	19	96	72±18	47	118	64±19	19	118	46[b] 56[b] 10-35[c]
Protein, percentage of energy	14±2	8	18	15±3	9	21	14±3	8	21	10-20[d]
Animal protein, percentage of protein	52±14	21	79	50±14	26	67	51±13	21	79	IE[a]
Fat, g	75±24	36	139	79±26	41	152	76±25	36	152	ND[b]
Fat, percentage of energy	38±6	20	50	34±7	21	43	37±7	20	50	20-35[c,d]
PUFA, g	0.13±0.11	0	0.50	0.25±0.20	0	0.71	0.17±0.16	0	0.71	
PUFA, percentage of energy	10±3	3	16	10±3	5	17	10±3	3	17	7-10%[d]
MUFA, g	25±9	12	46	26±8	14	41	26±9	12	46	
MUFA, percentage of energy	13±3	5	18	12±3	7	12	12±3	5	18	12-15%[d]
SFA, g	25±11	12	64	23±9	10	42	24±10	10	24	
SFA, percentage of energy	13±4	5	20	10±3	6	15	12±4	5	20	<10%[d]
Cholesterol, mg	252±101	21	498	216±87	74	426	239±97	21	498	
Omega 6 FA, g	18±7	5	36	21±11	11	53	19±9	5	53	12[b] 17[b]
Omega 3 FA, g	1.4 (1.0-1.9)			1.8 (1.3-2.9)			1.5 (1.1-2.3)			1.1[b] 1.6[b] ~2, Stage 3-4[a]

Table 2. Continued

	Female (n=34)			Male (n=20)			Total (n=54)			Recommendation
	$\bar{X}$±SD (M, IQR1-IQR3)	Min.	Max.	$\bar{X}$±SD (M, IQR1-IQR3)	Min.	Max.	$\bar{X}$±SD (M, IQR1-IQR3)	Min.	Max.	KDIGO[a] RDA[b], AMDR[c], TUBER[d], Other[e] (Female/Male)
Water, (mL)	2904±948	1439	5536	3119±987	1568	5043	2984±960	1439	5536	2700[a] 3700[a] 2000-2500[d]
Others										
Caffeine, mg	61 (39-103)			120 (65-188)			87 (50-128)			<200[e]
Salt, g	8.6±3.6	2.7	17.5	9.3±2.5	5.4	15.2	8.8±3.2	2.7	17.5	<5[d]

[a]: 16th reference.
[b,c]: Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (2002/2005).
[d]: 17th reference.
[e]: 23rd reference.
AMDR: Acceptable macronutrient distribution range, DM: Diabetes mellitus, EER: Estimated energy requirements, FA: Fatty acids, MUFA: Monounsaturated fatty acids, PUFA: Polyunsaturated fatty acids, SFA: Saturated fatty acids, vit.: Vitamin, s IE: Insufficient evidence to recommend, ND: Not determined, TUBER: Turkiye Beslenme Rehberi 2015

recommended according to TUBER, their SFA ratio was higher. Patients had a higher consumption of Omega 6 FAs than recommendations for healthy people, according to TUBER. Additionally, the mean Omega 3 FA intake was found to be 1.5 g, which is lower than the 2 gram recommendation suggested by KDIGO 2020 to lower serum triglyceride levels. Patients also did not reach the fiber RDA recommendations.

According to the KDIGO-2020 guideline, a male patient's mean water intake of 3119 mL, was insufficient, which was still below the recommended intake for healthy people. However, according to the recommendation for healthy people in the TUBER, patients meet the water needs. Patients' daily salt intake was above 5 grams.

Vitamin and mineral intake and the percentage of RDA mets are shown in Table 3. The mean intakes of thiamin, riboflavin, B6, calcium, magnesium, and zinc were sufficient in both male and female patients since the percentage of RDAs was between 66 and 132 for these nutrients. Dietary vitamin D and folate intake in female patients and only dietary vitamin D intake in male patients met the RDA insufficiently. Patients' mean dietary vitamin A and K intakes were excessive, the percentage of RDAs was above 132. In all patients, the mean dietary potassium intake was insufficient and the sodium intake was excessive.

Kidney Volume and Dietary İntake

The correlations between TKV and energy, dietary nutrient intake, salt and caffeine are shown in Table 4. In female patients there were negative but a weak correlation between dietary vitamin C intake and TKV (r=0.372, p=0.030). There were negative correlations, but not statistically significant, between energy (kcal/kg), omega 6 FA, B12, vitamin E intakes, carbohydrate /protein/ animal protein/PUFA percentage of energy and TKV in female patient. In male patients, the negative but weak correlation was found between TKV and intake of fiber (r=-0.493, p=0.027) and similar to soluble and insoluble fiber, water (r=-0.462, p=0.040), vitamin B6 (r=-0.444, p=0.050), vitamin K (r=-0.522, p=0.018), magnesium (r=-0.449, p=0.047), iron (r=-0.508, p=0.022). In male patients, there were more negative but weak correlations between TKV and dietary intake. Generally, any statistically significant correlations could not be found in all patients.

Discussion

In this cross-sectional study in patients with ADPKD, patients' total dietary energy intake was on the lowest edge of recommendations for CKD on energy need, and was under the EER value. The mean daily protein intake was lower than the recommendation for patients with CKD stage 2 without PKD and was higher for patients with CKD stage 3-4 without PKD. The mean intake of micronutrients such as thiamin, riboflavin, B6, calcium, magnesium, and zinc was sufficient, the mean dietary potassium intake was insufficient; and the sodium intake was excessive. In females, there was a negative but weak correlation between dietary vitamin C intake and TKV. In males, a negative but weak correlation was found between TKV and dietary intake of fiber, water, vitamin B6, vitamin K, magnesium, and iron.

Generally, ADPKD guidelines contain several specific dietary recommendations beyond the general CKD guidelines, or advice that is not based on strong data (19). Recent studies on protein, water, caffeine and alcohol intake, salt, BMI, and caloric restriction show that recommendations would be the same as those in CKD (4). A low protein diet (≤0.6 g/kg/day) has not been shown to delay ADPKD progression and may increase the risk of

Table 3. Daily dietary micro nutrient intake of the patients according to the sex

	Female (n=34)			Male (n=20)			Total (n:54)			Recommendation
Vitamins and Minerals	**X̄±SD (M, IQR1-IQR3)**	**Min.-Max.**	**RDA-AI % met (X̄- M)**	**X̄±SD (M, IQR1-IQR3)**	**Min.-Max.**	**RDA-AI % met (X̄- M)**	**X̄±SD (M, IQR1-IQR3)**	**Min.-Max.**	**RDA-AI % met (X̄- M)**	**RDA[a]/AI[b]/KDIGO[c] (Female/Male)**
Thiamin, mg[a]	0.7±0.2	0.2-1.6	70	0.9±0.2	0.5-1.4	73	0.8±0.2	0.2-1.6	71	1.1 1.2
Riboflavin, mg[a]	1.2±0.4	0.4-2.7	112	1.3±0.3	0.9-2.0	100	1.3±0.4	0.4-2.7	107	1.1 1.3
Vit. B12, µg[a]	2.9±1.6	0.5-6.6	122	3.3±2.0	0.9-8.2	137	3.0±1.7	0.5-8.2	128	2.4
Vit. B6, mg[a]	1.1±0.4	0.2-2.0	85	1.2±0.3	0.8-2.1	85	1.2±0.4	0.2-2.1	85	1.5 1.3-1.7
Folate, µg[a]	275±95	84-583	69	326±80	206-521	82	293±92	84-583	74	400
Vit. A, µg[a]	1160±730	263-3401	165	1019±532	325-2443	117	1108±662	263-3401	147	700 900
Vit. D, µg[b]	0.8 (0.6-1.3)		13.8	0.97 (0.5-6.6)		12.9	0.8 (0.6-1.5)		13.3	5-10
Vit. E, mg[a]	19±8	6-38	135	19.7±7.7	10.7-38.4	147	19.2±7.8	6.4-38.4	140	15
Vit. K, mg[b]	346±158	68-688	384	341±161	135-852	295	344±157	68-852	352	90 120
Vit. C, mg[a]	102±63	12-263	136	102±64	22-254	115	102±63	12-263	128	75 90
Calcium, mg[b]	759±272	275-1725	71	775±230	498-1283	71	765±255	275-1725	71	1000-1200 (800-1000 Stage 3-4)[c]
Magnesium, mg[a]	260±83	114-398	81	310±85	189-494	75	279±87	114-494	79	310-320 400-420
Potassium, mg[b]	2128±771	639-4045	46	2335±684	1437-3588	50	2205±740	639-4045	47	4700 (Individual adjust Stage 3-4)[c]
Phosphorus, mg[a]	976±313	420-1728	139	1195±283	836-1890	170	1057±318	420-1890	151	700 (Individual adjust Stage 3-4)[c]
Sodium, mg[b]	3539±1458	1192-7406	250	3821±1015	2500-6165	273	3643±1308	1192-7406	260	1500-1300 (<2300 g Stage 3-4)[c]
Zinc, mg[a]	9.9±2.9	4.7-16.3	125	12.4±3.5	8.1-21.4	114	10.9±3.3	4.7-21.4	121	8 11
Iron, mg[a]	10.8±3.6	4.3-19.3	87	12.9±3.2	8.1-18.7	161	11.6±3.6	4.3-19.3	114	18-8 8

[a,b]: Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001); Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate (2005); Dietary Reference Intakes for Calcium and Vitamin D (2011); and Dietary Reference Intakes for Sodium and Potassium (2019).
[c]: 16th reference.
AI: Adequate intakes, KDIGO: Kidney disease improving global outcomes, RDA: Recommended dietary allowances, Vit.: Vitamin, SD: Standard deviation, Min.: Minimum, Max.: Maximum

malnutrition, and is only recommended when it's suitable (20). The general recommendation is to apply a moderate protein diet (0.75-1.0 g/kg/day) (16,21,22), and diet therapy should be planned individually for these patients. In the current study, patients' mean dietary protein intake was above 0.8 g/kg, except for those in CKD stage 2. There were several patients who had a low protein diet, which should be considered to evaluate malnutrition risk. Energy intake of 30-35 kcal/kg/day is important to maintain neutral nitrogen balance and nutritional status (16). In both sexes, patients' mean daily energy intake was under 30-35 kcal/kg/day. To achieve energy and protein intake goals for patients, it's been recommended to have counseling with a renal dietitian who will provide medical nutrition therapy (16,22).

A sodium restricted diet, ≤2.4 g/day is recommended for patients who undergo tolvaptan treatment (23), and for blood pressure and volume control improvement (16). In this study, mean salt and sodium intakes were 8.8 g and 3643 mg, respectively. The excessive intake of dietary sodium has been defined as a key modifiable factor for the enlargement of kidney cysts (24,25). Each decrease of one

Table 4. The correlation between daily dietary macronutrient, micronutrient, caffeine, salt intakes and total kidney volume of the patients according to the sex

Energy, Macro/Micronutrients, and Others	Female n=34		Male n=20		Total n=54	
	r	p	r	p	r	P
Energy, kcal	0.189	0.285	-0.156	0.511	0.124	0.371
Energy, kcal/kg	-0.001	0.997	-0.209	0.376	-0.038	0.784
Carbohydrate, g	0.143	0.420	-0.126	0.597	0.109	0.434
Carbohydrate, percentage of energy	-0.031	0.863	0.045	0.850	0.031	0.825
Fructose, percentage of energy	0.080	0.652	-0.120	0.857	-0.012	0.933
Fructose, g	0.090	0.612	-0.139	0.559	0.003	0.983
Fiber, g	0.194	0.273	-0.493	**0.027***	0.000	0.999
Soluble	0.098	0.581	-0.495	**0.027***	-0.070	0.616
Insoluble	0.240	0.172	-0.457	**0.043***	0.047	0.734
Protein, g	0.157	0.375	-0.321	0.167	0.059	0.671
Protein, percentage of energy	-0.050	0.777	-0.226	0.338	-0.088	0.527
Plant protein, percentage of protein	0.063	0.724	-0.043	0.857	0.041	0.769
Animal protein, percentage of protein	-0.063	0.724	0.043	0.857	-0.041	0.769
Protein, g/kg	-0.013	0.914	-0.326	0.160	-0.077	0.581
Fat, g	0.189	0.283	-0.073	0.759	0.107	0.440
Fat, percentage of energy	0.028	0.877	0.050	0.834	-0.018	0.895
PUFA, g	0.016	0.928	-0.135	0.569	0.011	0.939
PUFA, percentage of energy	-0.223	0.206	-0.217	0.358	-0.212	0.124
MUFA, g	0.240	0.206	-0.007	0.978	0.174	0.208
MUFA, percentage of energy	0.122	0.492	0.103	0.664	0.080	0.567
SFA, g	0.260	0.137	0.103	0.667	0.201	0.144
SFA, percentage of energy	0.154	0.386	0.262	0.265	0.113	0.939
Cholesterol, mg	0.089	0.619	-0.010	0.966	0.027	0.847
Omega 6 FA, g	-0.047	0.652	-0.197	0.406	-0.074	0.596
Omega 3 FA, g**	0.068	0.704	-0.320	0.169	-0.004	0.974
Water, (mL)	0.174	0.325	-0.462	**0.040***	-0.020	0.883
Caffeine, mg**	0.068	0.704	-0.318	0.172	-0.024	0.863
Salt, g	0.160	0.365	-0.128	0.590	0.102	0.464
Thiamin, mg	0.198	0.262	-0.267	0.255	0.090	0.515
Riboflavin, mg	0.200	0.256	-0.275	0.240	0.089	0.521
Vit. B12, µg	-0.202	0.252	-0.199	0.399	-0.177	0.201
Vit. B6, mg	0.099	0.577	-0.444	**0.050***	-0.043	0.758
Folate, µg	0.273	0.118	-0.436	0.055	0.108	0.437
Vit. A, µg	0.009	0.958	-0.287	0.220	-0.041	0.766
Vit. E, mg	-0.080	0.655	-0.114	0.631	-0.081	0.559
Vit. K, mg	0.090	0.614	-0.522	**0.018***	-0.113	0.414
Vit C, mg	0.372	**0.030***	-0.237	0.315	0.168	0.225
Calcium, mg	0.194	0.272	-0.387	0.092	0.029	0.835
Magnesium, mg	0.116	0.513	-0.449	**0.047***	-0.021	0.881
Potassium, mg	0.170	0.336	-0.430	0.058	0.012	0.929
Phosphorus, mg	0.171	0.335	-0.441	0.051	0.041	0.767
Sodium, mg	0.160	0.365	-0.143	0.546	0.099	0.475
Zinc, mg	0.034	0.848	-0.422	0.064	-0.063	0.650
Iron, mg	0.042	0.814	-0.508	**0.022***	-0.071	0.611

*p<0.05, Pearson correlation, ** Spearman correlation
FA: Fatty acids, MUFA: Monounsaturated fatty acids, PUFA: Polyunsaturated fatty acids, SFA: saturated fatty acids, vit. : Vitamin

gram of salt resulted in less kidney enlargement of 0.43% per year (24). Meijer and Gansevoort (4) advise less than 5 g/day salt intake for ADPKD (4).

A review by Picard et al. (26) stated that high potassium intake was related to lower risk, while low intake showed higher progression, and in some studies there was no relationship. Dietary potassium intake at the highest level was around >2500 mg/day, whereas the lowest was of ~1500 mg/day in studies with participants age ≥40 with CKD stage 2 and CKD patients (without CKD stage informing) (27). Unfortunately, there is no data about ADPKD patients' actual dietary mineral and vitamin intakes. In our study, patients' dietary potassium intake was found to be 2205±740 mg, which means 47% of the recommendation. dietary potassium intake levels are related to the number of fruits, vegetables, and fiber consumed in the diet. Taylor et al. (28) found that ADPKD patients' (n=11) vegetable and fruit consumption was 441 g/day, and they showed that increasing fruit and vegetable consumption from 400 g to about 1200 g daily intake was possible and well tolerated by ADPKD patients. Fruits and vegetables are rich in potassium and poor in sodium. Fruits, vegetables, nuts, and legumes, dairy, and meat products are potassium-rich foods that are also high in minerals, vitamins, and dietary fiber; it is critical to tailor dietary potassium restrictions to the nutritional status of the individual patient (16).

In this study, a negative but weak correlation between dietary vitamin C intake and TKV was seen in only female patients. The RDA percentage of vitamin C intake was found to be 136 and 115 for females and males, respectively. Since vegetables and fruits are rich in vitamin C, we may assume that female patients consumed more vegetables and fruits than males. Simultaneously, both female and male patients' dietary fiber intakes were under recommendation. A negative but weak correlation was found between TKV and fiber intake only in male patients. Fiber was discovered in legumes and grains, as well as vegetables and fruits. It can be concluded that consumption of grains and legumes is low due to patients' high intake of vitamin C but low intake of fiber. Further studies are needed to understand the possible effects of vitamin C and fiber on TKV.

In this study, patients met water intake recommendations, and only in male patients was a negative but weak correlation found between TKV and water intake. Water loading is a proposed therapy for ADPKD as it slows cyst and kidney enlargement (29). Several interventions studied increased water intake in ADPKD patients (30,31). But inconsistent results highlight the fact that randomized controlled trials are needed for ADPKD. There is no conclusion yet on how much water should be received. Individually prescribing the amount of water is a potential and viable therapeutic option. Torres et al. (32) recommended that APKD patients whose eGFR is above 30 mL/min/1.73 m^2 should have a water intake of usually 2.5-4 L per day, and for patients with an eGFR less than 30 mL/min 1.73 m^2, additional water intake should be limited to prevent hyponatremia. Patients on tolvaptan should be under dietitian supervision in terms of decreasing osmolality and sodium intake (24).

In this study, male and female patients consumed 120 and 61 mg of caffeine, respectively. Caffeine is considered to increase cAMP and contribute to disease progression by increasing renal volume in cultured cell and ADPKD mice studies. But this relationship has not been observed in human studies (4). A limit of ≤200 mg/day of caffeine, which is ≤2 cups of coffee or ≤4 cups of tea per day, is recommended to control or avoid caffeine intake (23).

Study Limitations

This study's limitations include a cross-sectional study, one center, a small sample size, and the skewness of sex. Patients had some knowledge or thoughts about nutrition, and this may have affected their dietary intake, particularly in terms of water consumption. Their dietary records may not completely reflect patients' usual dietary habits. Diet records were based on the patient's statement, and food amounts that were consumed were subjective. Therefore, the results of this study should not be generalized to the entire ADPKD population.

The most important missing part in the literature is the insufficient data about ADPKD patients' actual dietary consumption. The current study makes an important contribution to the literature, as studies examining the effect of nutrition on TKV in ADPKD patients are limited. Another strength of this study was to evaluate TKV via MRI.

Conclusion

In female patients with ADPKD, there was a negative but a weak correlation between dietary vitamin C intake and TKV. In males, a negative but weak correlation was found between TKV and dietary intake of fiber, water, vitamin B6, vitamin K, magnesium, and iron.

Ethics

Ethics Committee Approval: Ethics committee approval dated 18.06.2014 and numbered 122 was obtained from the Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Non-Drug Clinical Research.

Informed Consent: Informed consent was obtained.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: Y.S., E.C., Design: Y.S., E.C., O.P.O., G.K., Data Collection, or Processing: Y.S., O.P.O., Yi.S., Analysis, or Interpretation: Y.S., E.C., S.O., G.K., Literature Research: Y.S., O.P.O., E.C., Writing: Y.S., O.P.O., S.O., G.K.

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The Protective Effect of Resveratrol on Cisplatin Induced Damage in Rat Liver

Ozlem Kara*, Asuman Kilitci**

*Kirsehir Ahi Evran University Faculty of Medicine, Department of Histology and Embryology, Kirsehir, Turkey

**Duzce University Faculty of Medicine, Department of Pathology, Duzce, Turkey

Abstract

Aim: One of the underlying causes of cisplatin-induced hepatotoxicity is oxidative stress. We assessed the effect of an antioxidant, resveratrol, on cisplatin-induced damage in the rat liver.

Methods: The project-starting date was designed as 01.10.2020 and the project-ending date was planned as 01.04.2021. Three groups were created with 30 female Wistar-Albino rats: In group 1 (control group), 1 mL of 0.9% NaCl (saline) was administered intraperitoneally for 3 days. In group 2 (cisplatin group), 7.5 mg/kg intraperitoneal cisplatin was given for 3 days. In group 3 (cisplatin + resveratrol group), 7.5 mg/kg cisplatin and 10 mg/kg resveratrol were given via the intraperitoneal route. The livers were surgically extirpated in all the groups. In both blood and tissues, malondialdehyde (MDA) levels and activities of catalase (CAT) and superoxide dismutase (SOD) were measured. Also, toxicity markers such as hepatocyte damage (cellular changes), inflammation, hemorrhage, congestion, fibrosis, disorganization of the hepatic cords, and necrosis were assessed by examining the preparations prepared from hepatic tissue with light microscopy and immunohistochemistry.

Results: Histopathological tissue damage was significantly higher in group 2 than in other groups (p 0.03). MDA levels were significantly higher and the activities of SOD and CAT were lower in group 2 than in the other groups (p=0.04 and p=0.01, respectively).

Conclusion: According to our short-term findings, resveratrol might be an effective molecule for preventing the harmful effects of cisplatin in the rat liver.

Keywords: Cisplatin, resveratrol, rat, liver, toxicity

Introduction

Cisplatin is a potent chemotherapeutic drug and has been used for malignancies. However, cisplatin can have toxic effects on the kidney and liver even at normal therapeutic doses. Cisplatin constitutes a compound that binds covalently to the DNA bases (1). These crosslinks in the DNA lead to cytotoxic damage in cancer cells. If cisplatin levels rise above the toxic dose, normal cells are affected as well as cancer cells (2). It has been shown that cisplatin toxicity tends to increase in hypochloremic status. At these low chlorine levels, especially harmful compounds such as reactive oxygen species (ROS) and free radicals are released more frequently. The final result of this situation is cell and tissue damage (3). Also, cisplatin causes oxidative stress on cellular organelles, especially mitochondrion. Calcium uptake into the cell is reduced, mitochondrial protein-SH level decreases, and as a result, the function of the mitochondrial membrane deteriorates (4). Numerous protective mechanisms were developed by the cells to prevent oxidative damage due to cisplatin. Antioxidant effects are increased due to protective enzymatic activities (5,6). Gupta et al. (7) indicated that administration of antioxidants could diminish the extent of the injury.

Resveratrol is a natural antioxidant compound, detected in red wine, grapes, mulberries, and peanuts. It has been shown that resveratrol could be useful for the prevention of vascular diseases, metabolic syndrome, coronary heart diseases, and stress (8). Den Hartogh and Tsiani (9) reported that usage of resveratrol enhanced the injury of renal injury by diminishing oxidative stress,

Address for Correspondence: Ozlem Kara
Kirsehir Ahi Evran University Faculty of Medicine, Department of Histology and Embryology, Kirsehir, Turkey
Phone: +90 532 343 06 50 E-mail: ozlemozturk34@hotmail.com ORCID: orcid.org/0000-0002-2084-8290
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decreasing inflammation, and increasing antioxidant activity.

Therefore, it was hypothesized that the addition of an antioxidant such as resveratrol would be useful to prevent the ovarian damage due to cisplatin. There are no studies demonstrating the preservative effect of resveratrol on hepatic injury. In this study, we assessed the protective effect of resveratrol on cisplatin-induced hepatic damage in rats.

Materials and Methods

Compliance with Ethical Standards

This study was approved by the Kirikkale University Animal Experiments Local Ethics Committee (date: 18.06.2020, approval no: 2020/03-16). Cisplatin and resveratrol were obtained from a pharmacy (Kirsehir, Turkey). Cisplatin and resveratrol were given in relation to the treatment protocols reported in previous studies (10,11).

Study Design

A total of 30 female adult Wistar-Albino rats weighing 150-220 g were included in the study. All animals were housed for one week at 24±2 °C. The ad libitum method was performed using a laboratory diet. The ages of the rats were between 8 and 12 weeks. The rats were randomly allocated into three groups (10 rats per group): control (1 mL of 0.9% NaCl), cisplatin (7.5 mg/kg cisplatin), cisplatin + resveratrol (7.5 mg/kg cisplatin+10 mg/kg resveratrol).

Ketamine hydrochloride (45 mg/kg, Ketalar, Eczacibasi, Istanbul, Turkey) and xylazin hydrochloride (5 mg/kg, Rompun, Bayer, Leverkusen, Germany) were used for anesthesia. Cervical dislocation was performed as a sacrifice procedure. Then, the liver was extirpated.

Histopathology

The samples of liver tissue were fixed in a 10% formalin solution and were dehydrated with alcohol. Then the embedding process is completed using paraffin. The tissues were cut at a thickness of 4 µ¼m and the sections were stained with hematoxylin and eosin dye (H&E). Additionally, immunohistochemically, bcl-2 and Masson trichrome staining were performed to evaluate fibrosis. Histopathological findings were examined using a microscope (Olympus CX41 microscope, Olympus Corp., Tokyo, Japan) by a pathologist who did not know the experimental groups. A minimum of 10 fields for each kidney slide were analyzed and evaluated for the severity of changes. Histopathological scoring was performed by determining the highest area. The four categories (0: None, 1: Minimal, 2: Mild, 3: Moderate, 4: Severe) were determined by making a semi-quantitative analysis and the parameters were scored accordingly. We used the parameters of "hepatocyte damage (cellular changes), inflammation, hemorrhage, congestion, fibrosis, disorganization of the hepatic cords, necrosis" to determine the degree of damage.

Immunohistochemistry

The Bcl-2 expression levels were graded using the 0-3+ range (Bcl-2; 0 indicates no staining, 1: hepatocytes with less than 10% cytoplasmic or membranous staining, 2: hepatocytes with 10-30% cytoplasmic or membranous staining, 3: hepatocytes with more than 30% cytoplasmic or membranous staining). A Masson trichrome dye was used to assess fibrosis.

Biochemistry

Both tissue and blood samples were analyzed for MDA levels and SOD and CAT activities using a spectrophotometer (Shimadzu UV 1800, Kyoto, Japan). A thiobarbituric acid test was used to calculate the MDA levels (12). SOD enzyme activity was calculated in relation to the method reported by Marklund and Marklund (13). The activity of CAT was assessed in relation to a prior study (14).

Statistical Analysis

The Statistical Package for the Social Sciences (22.0 SPSS Inc., Chicago, IL) was used for statistical analyses. A One-Way ANOVA test was used for levels of tissue and blood MDA and activities of SOD and CAT. Tissue damage scores were compared using the non-parametric chi-square test. A p-value <0.05 was set as statistically significant.

Results

SOD and CAT activities were lower in the cisplatin group than in the cisplatin + resveratrol group, and the difference was found to be statistically significant (p=0.01). The level of MDA was significantly lower in the cisplatin + resveratrol group than in the cisplatin group (p=0.04) (Table 1).

There was no difference between the groups in terms of the macroscopic appearance of the tissues. Scores indicating histopathological damage were lower in the cisplatin + resveratrol group than in the cisplatin group (p=0.03) (Table 2).

Groups were demonstrated as pie chart (Figure 1). The morphology and structural characteristics of the liver tissue were close to normal in the control group. Hepatic damage parameters such as hepatocyte damage, inflammation, hemorrhage, congestion, fibrosis, disorganization of the hepatic cords, and necrosis, were more prominent in the cisplatin group than in the cisplatin + resveratrol group (Figure 2). Immunohistochemical staining of rats using Masson trichrome dye showed that the hepatic damage was more in the cisplatin group (Figure 3).

Table 1. Distribution of malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT) in experimental groups			
Groups (n=10)	**MDA (nmol/mg)**	**SOD (U/mg)**	**CAT (U/mg)**
Control	5.91±0.12	40±3.2	88±6.0
Cisplatin (7.5 mg/kg)	10.33±0.34*	18±1.9*	27±2.8*
Cisplatin + resveratrol (7.5 mg/kg+10 mg/kg)	7.61±0.21*	29±2.5*	58±4.6*

Data are presented as mean ± SD.
*Significant difference ($p<0.05$) between cisplatin group and cisplatin + resveratrol group
SD: Standard deviation

Table 2. Distribution of histopathologic findings								
Groups (n=10)	**Hepatocyte damage**	**Disorganization of the hepatic cords**	**Inflammation**	**Congestion**	**Hemorrhage**	**Necrosis**	**Fibrosis**	**Bcl-2 expression**
Control	0	0	0	0	0	0	0	0
Cisplatin (7.5 mg/kg)	1	1	2*	2*	2*	1*	1	1
Cisplatin + resveratrol (7.5 mg/kg+10 mg/kg)	1	1	0*	1*	0*	0*	1	1

*: Significant difference ($p<0.05$) between cisplatin group and cisplatin+resveratrol group.
Histopathological scoring was done by determining the highest area. Four categories (0: None 1: Minimal 2: Mild 3: Moderate 4: Severe) were determined by making semi-quantitative analysis and the parameters were scored accordingly

Although the parameters-indicating injury were more prominent, the fibrosis was similar in the cisplatin group and the cisplatin + resveratrol group. Likewise, more damage was observed in the cisplatin group than in the cisplatin + resveratrol group, with bcl-2 staining (Figure 4).

Discussion

Although cisplatin has been widely used for treating cancers, it has severe toxicities such as hepatotoxicity, nephrotoxicity, and ototoxicity. Hepatotoxicity is uncommon, as is nephrotoxicity. However, Zicca et al. (15) demonstrated that when cisplatin was used in high doses, it could have a toxic effect on the liver. There are a few studies on the toxicity of cisplatin in the liver. Therefore, we assessed the preservative effect of resveratrol on cisplatin-induced hepatic damage. To the best of our knowledge, this is the first trial indicating the protective effect of resveratrol on cisplatin-induced hepatotoxicity. Our study has demonstrated that MDA levels tend to increase because of cisplatin. Also, SOD and CAT activities decreased. Additionally, the histopathology of the liver was adversely affected by cisplatin. Resveratrol reduced cisplatin-induced biochemical and histological changes in the rat liver.

Cisplatin could deteriorate liver function by disrupting the balance of oxidants and antioxidants. ROS, hydroxyl radicals, and free radicals formed after oxidative stress might disrupt cellular integrity (16). Koc et al. (17) reported that erdostein reduced cisplatin-induced liver damage by scavenging free radicals and ROS. Cisplatin exhibits toxic effects by binding DNA. Xanthorrhizol could reverse these harmful environments via regulation of DNA-binding activities of transcription factors (18).

SOD and CAT are powerful endogenous enzymatic antioxidants. They reverse oxidative stress by converting H_2O_2 into water and oxygen. Several molecules are used to prevent oxidative stress, such as quercetin, selenium, and curcumin, which were used to decrease the toxicity of cisplatin (19-21). Resveratrol is a natural derivative of phenol. Several theories have been suggested about resveratrol's mechanisms of action. These are antioxidant features, antiinflammatory activities, and related to its

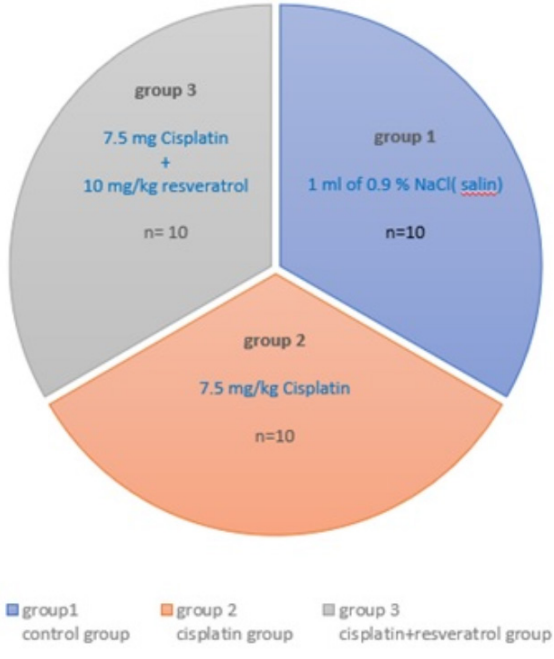

Figure 1. Demonstration of the groups as pie chart

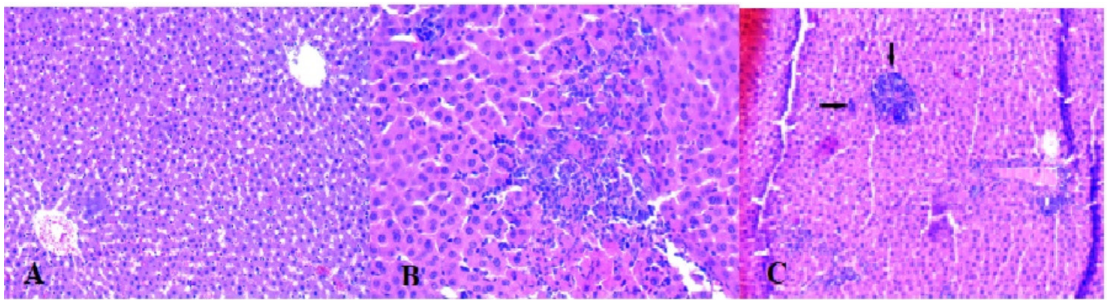

Figure 2. Light microscopic appearance of liver. (A) In the control group, erythrocytes in the sinusoids and the contents of the veins (H&E, X100). (B) In the cisplatin group, focal area of inflammation within the liver parenchyma) (H&E, x100). (C) In the cisplatin + resveratrol group, mild mononuclear inflammatory cell infiltration in the central vein and parenchyma (black arrow) (H&E, x100)

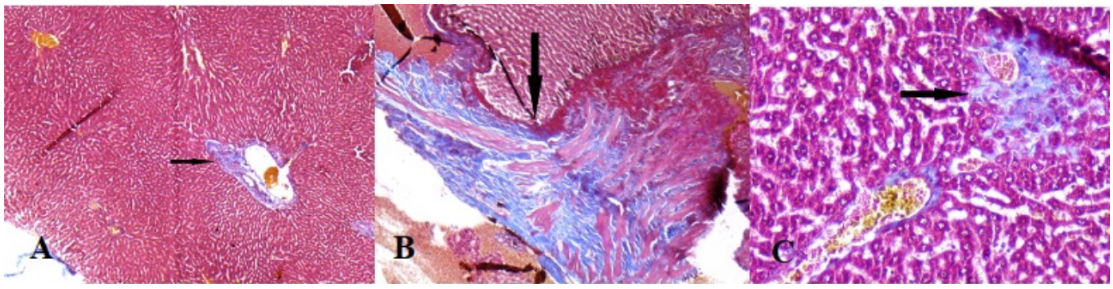

Figure 3. Immunohistochemical staining with Masson trichrome dye. (A) In the control group, a minimal to near-normal increase in connective tissue around the portal area (Masson trichrome, X50). (B) In the cisplatin group, connective tissue increase in the portal area (Masson trichrome, X50). In the cisplatin + resveratrol group, mild fibrosis around the central veins (Masson trichrome, X50)

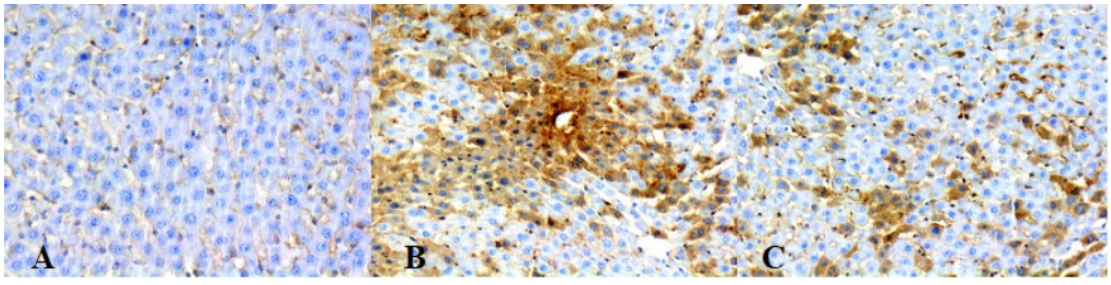

Figure 4. Immunohistochemical staining with bcl-2 dye. (A) In the liver of a rat from the control group, negative immunoexpression by bcl-2 (x200). (B) In the cisplatin group, cytoplasmic immunoexpression (x200). (C) In the cisplatin + resveratrol group, more focal cytoplasmic immunoexpression than cisplatin group (x200)

ability to modulate many molecules such as vascular endothelial growth factor, cytokines, and caspases (22).

Mansour et al. (23) reported that silymarin, an antioxidant flavonoid, ameliorates the hepatotoxicity of cisplatin. They hypothesized that silymarin reversed the oxidative stress by inhibiting lipid peroxidation and enhancing SOD and CAT activities (23). In another study, silymarin and gallic acid were used against cisplatin-induced nephrotoxicity and hepatotoxicity (24). The researchers reported that these molecules reverse the harmful effects of cisplatin. Thus, we thought that a substance with strong antioxidant properties, such as resveratrol, could be useful to prevent the toxic hepatic injury due to cisplatin.

Study Limitations

The small number of subjects and the possibility of variation when the study was adapted to humans are the limitations of our study. The advantage of this study was the widespread use of resveratrol as an antioxidant and the availability of tablets used in many conditions, especially ischemic events.

Conclusion

Decreased MDA levels and increased the activities of SOD and CAT enzymes. Furthermore, an improvement was observed histopathologically too. The parameters demonstrating damage, such as inflammation, congestion,

hemorrhage, and necrosis, were significantly lower in the cisplatin + resveratrol group than in the cisplatin group. In conclusion, resveratrol could be a useful agent in the short-term treatment and prevention of hepatic damage due to cisplatin.

Ethics

Ethics Committee Approval: Approval was obtained from Kirikkale University Animal Experiments Local Ethics Committee (18.06.2020 2020/03, approval no: 16).

Informed Consent: Our study is prospective randomized controlled study.

Peer-reviewed: Externally and internally peer-reviewed.

Authorship Contributions

Concept: O.K., Design: O.K., A.K., Data Collection, or Processing: O.K., Analysis, or Interpretation: A.K., Literature Research: O.K., Writing: O.K.

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

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Cansu Elmas Tunc, M. Duran Bayar, Ezgi Bakircioglu Duman, Birgul Bastan, Belgin Petek Balci
University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey

Reported Correction;

Cansu Elmas Tunc, M. Duran Bayar, Ezgi Bakircioglu Duman, Belgin Petek Balci
University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey

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