ACTA MEDICA

Volume 55 • Issue 2 • 2024

formerly

Hacettepe Medical Journal

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ACTA MEDICA

formerly Hacettepe Medical Journal

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Vol 55 • Issue 2 • 2024

online ISSN: 2147-9488

ACTA MEDICA

online ISSN: 2147-9488

www.actamedica.org

Cilt 55, Sayı 2, 2024

Hacettepe Üniversitesi Tıp Fakültesi adına sahibi
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ACTA MEDICA

online ISSN: 2147-9488

www.actamedica.org

Vol 55, Issue 2, 2024

Owner on behalf of the Hacettepe Medical School
Deniz Demiryürek

Administrator
Gülen Eda Utine

Publication Type
Peer-reviewed journal

Publication Frequency and Language
Quarterly, English

Editor-in-Chief
Hakan Uzun

Editorial Office
Hacettepe University
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06100 Sıhhiye - Ankara
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Publisher
Hacettepe University
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06100 Sıhhiye - Ankara
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Publishing Services
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ACTA MEDICA

formerly Hacettepe Medical Journal

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online ISSN: 2147-9488

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REVIEW

Neoadjuvant endocrine treatment: Precious but insufficiently discovered issue

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ABSTRACT

We would like to emphazise the importance of neoadjuvant endocrine treatment which is overshadowed by neoadjuvant chemotherapy for breast cancer patients. Missing knowledge is evaluation in terms of conventional notion of neoadjuvant chemotherapy that is it better to complete before surgery at least for some selected patients? Another point is, since it is a long term treatment, may be it will be a way give patients the chance to follow up without surgery. So this correspondence tries to ask two questions; shall we think about lengthening the duration of neoadjuvant endocrine treatment in selected patients and who are these patients?

Keywords: breast cancer, neoadjuvant treatment, endocrine treatment.

Received: 17 November 2023, Accepted: 20 February 2024, Published online: 29 June 2024

INTRODUCTION

The goals of neoadjuvant systemic therapy in breast cancer are to increase local control and downstage tumor size to allow breast-conserving surgery (BCS) or mastectomy when the tumor is initially inoperable, to increase survival via pathologic complete responses (pCR) and also to tailor treatments through the oppurtunity that neoadjuvant setting provides by identifing predictive factors and biomarkers. Data has shown that chemotherapy that is suitable for the patient should be completed before surgery just the same as adjuvant period .

Neoadjuvant endocrine treatment (NAET) has been regarded as an option for elderly medically inoperabl and fragile patient group till 2000s but later on data has shown that it is as effective as neoadjuvant chemotherapy in regards of clinical response and pCR rates and somewhat more effective in regards of BCS rates whereas being less toxic [1,2].

Important question is when and how to use NAET and to whom. For premenopausal patients it was shown that when compared to NAET, a significant benefit of chemotherapy was seen with response rates of 75% and 44% respectively (p: 0.027) in GEICAM/2006-03 study [1]. If NAET is to be used in a selected premenapousal patient, then the choice should be aromatase inhibitors and goserelin combination since overall responses were shown to be higher compared to tamoxifen and goserelin [3].

In postmenapousal patients, although overall survival datas are still immature, NAET especially aromatase inhibitors rather than tamoxifen, is more effective than chemotherapy both about clinical responses and BCS rates and it wasshoen that all three aromatase inhibitors have similar activity [4,5]. In the ALTERNATE trial which randomizes patients with cT2–4 N0-3 M0 ER+/Her2– invasive breast cancer to either anastrozole, fulvestrant or its combination to assess a biomarker-driven treatment strategy, endocrine sensitive disease rate that was described as pCR or PEPI-0 residual disease (Ki67 ≤ 2.7%) difference between the fulvestrant containing arms and the anastrazole arm was not > 10%, so didn't reach the significance boundary

[6]. So fulvestrant seems not to be an option yet. However this strategy incorporates the findings that higher expression of Ki67 after 2 weeks of NAET is associated with poor recurrence-free survival for NAET.

CDK 4/6 inhibitors, that have been cornerstones in the treatment of metastatic ER+/ HER2 – group, were shown to molecularly downstage tumors similar to chemotherapy and cause statistically significant reductions in Ki67 levels and better complete cell cycle arrest rates. But still PEPI 0 rates in the CDK4/6 combination arm were not different from aromatase inhibitor only arm [7,8]. The same is true for PIK3CA inhibitors. Overall response rates have increased significantly both in the intend to treat population and PIK3CA mutant group, but pCR rates didn't differ in between combination or aromatase inhibitor only arm [9].

Up to date strong ER positivity, low Ki67 levels achieved after 2 to 4 weeks of NAET (cut off may be <10%) and being postmenapousal seem the most reliable predcitive markers for NAET. Neoadjuvant endocrine trials have shown that longer NAET periods resulted in higher response rates but missing area in these trials is the evaluation in terms of the conventional notion of neoadjuvant chemotherapy that it is better to complete before surgery, at least for some selected patients who will probably gain most benefit from this treatment. Another point is that since it is a long term treatment (suggested duration of adjuvant endocrine treatment is in between 5- 10 years) may be it will be a way give some patients the chance to follow up without surgery. So shall we think about lengthening the duration of neoadjuvant endocrine treatment in selected patients and who are these selected patients? May be for selected postmenapousal, strong ER+ HER2 – breast cancer patient whose tumor has shown decreased Ki67 levels after 2-4 weeks of treatment or for any other selected patient group? Can this be an ultimate way of breast conserving and to eliminate breast surgery in these selected cases? While combination strategy trials are in progress, detected predictive markers for long term responders will be very precious in this era.

CONCLUSION

In conclusion, we would like to emphazise the importance of NAET, a treatment that is overshadowed by neoadjuvant chemotherapy for breast cancer patients. It is obvious that ongoing trials will enlighten us more about the dark sides of neoadjuvant endocrine teatment.

Author contribution

Study conception and design: AO, ÖA; draft manuscript preparation: AO, ÖA. All authors reviewed the results and approved the final version of the manuscript.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

A conflict choice of treatment during defibrillation in cardiopulmonary resuscitation: Lidocaine, amiodarone or both? A retrospective study

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Received: 15 December 2023, Accepted: 20 March 2024, Published online: 29 June 2024

ABSTRACT

Objective: Cardiopulmonary arrest is considered to be an unpredicted event leading to sudden death. The primary purpose of the study is to investigate the effects of antiarrhythmic drugs during defibrillation within cardiopulmonary resuscitation (d-CPR) on survival outcomes.

Materials and Methods: The antiarrhythmic drug treatment during d-CPR management in our hospital from 2015 to 2022 were evaluated retrospectively. Demographic information, and details related to resuscitation were obtained from the "Cardiopulmonary Resuscitation and Code Blue Forms". According to inclusion criteria, from 898 patient data 135 were included. The treatment of anti-arrhythmic drugs administered during d-CPR management were lidocaine, amiodarone, or amiodarone&lidocaine together. Data recorded related to the present study were evaluated primarily according to the return of spontaneous circulation (ROSC) and survival outcomes.

Results: The mean cardiopulmonary resuscitation duration was 31.82±22.37 minutes in patients with ROSC and 42.40±9.28 minutes in non-ROSC, $p<0.01$. Amiodarone administration during d-CPR was the highest preffered treatment from 2015 to 2022, when compared with the usage of amiodarone&lidocaine together (14.1%), $p<0.01$. However the administration of lidocaine during d-CPR (39.3% of all) appered to be performed before 2020 in our hospital. Additionally amiodarone revealed a positive effect on systolic blood pressure and mean arterial pressure in ROSC patients ($p=0.02$, $p=0.04$ respectively), while the choice of antiarrhythmic drug treatment during d-CPR management showed no significant difference on survival status.

Conclusion: The observed ROSC was 42.2%. The choice of antiarrhythmic drug treatment during d-CPR management showed no significant difference on survival status, although amiodarone revealed a positive effect on systolic blood pressure and mean arterial pressure in the patients with ROSC.

Keywords: cardiopulmonary resuscitation, return of spontaneous circulation, lidocaine, amiodarone, defibrillation.

INTRODUCTION

Cardiac arrest (CA) is defined as an unexpected event that results in sudden death [1]. There are 17 million deaths per year in the world and sudden CA, approximately 25.0% [2]. There are around 200,000 in hospital CA each year in the United States with survival rates of 24% [3].

The most curable cause of CA is pulseless ventricular tachycardia or ventricular fibrillation which can be treated via defibrillation within cardiopulmonary resuscitation (d-CPR) [4]. The critical factors affecting survival in CA include early recognition, early cardiopulmonary resuscitation (CPR), and rapid defibrillation [5]. Defibrillation and external chest compression are critical procedures in the early resuscitation response, and each must come at the expense of the other [6].

Antiarrhythmic medications may play a role in ventricular fibrillation and pulseless ventricular tachycardia if defibrillators fail to achieve return of spontaneous circulation (ROSC) [7]. According to the American Heart Association guidelines published in 2015, amiodarone with lidocaine can be used, as an alternative to amiodarone alone, in adults unresponsive to CPR, defibrillation, or vasopressor therapy [8]. It was demonstrated in a recent review and meta-analysis that amiodarone and lidocaine showed increased survival to hospital admission compared to placebo [9]. Because CPR guidelines are periodically reviewed and revised based on the latest research evidence, it is crucial to practice the recent recommended information. In 2020 AHA published a new guideline for CPR, recommending the same practice, while the recommended drugs were either amiodarone or lidocaine [10].

The aim of this study was to assess the impact of administering amiodarone, lidocaine, or a combination of both antiarrhythmic drugs during d-CPR on survival and survival outcomes.

MATERIALS AND METHODS

Before initiating the study, the study protocol received approval from the ethics committee at Istinye University Hospital (Decision date: 01/02/2023; No: 2/2023.K-48). The conduct of this study adhered to the principles outlined in the Declaration of Helsinki.

We conducted a retrospective evaluation of adult patients from 01/01/2015 to 31/12/2022 who underwent d-CPR management, regardless of etiology. Demographic information of the patients: age, gender, diagnosis, possible causes, and details related to resuscitation: location [emencency room (ER), general intensive care unit (GICU), coronary intensive care unit (CICU), surgery intensive care unit (SICU) and ward], time of CPR duration, administered antiarrhythmic drugs, vital function outcomes (blood pressure, heart rate, SpO_2), and survival status (ROSC, non-ROSC) were obtained from the "Cardiopulmonary Resuscitation and Code Blue Forms". Patients with missing data and death on arrival (DOA) upon admission were excluded. Only 135 patients match the inclusion criteria of defibrillation management within CPR out of 898 Cardiopulmonary Resuscitation and Code Blue Forms analyzed. ROSC was defined as sustaining circulation for more than 24 hours and was determined by the ICU team members and noted on the form.

The primary aim of this study was to assess the impact of administering amiodarone, lidocaine, or a combination of both antiarrhythmic drugs during d-CPR on survival (ROCS or non-ROCS).

The seconder aims of this study were to assess the total CPR duration, the patients's diagnosis and possible causes, location of CPR management, the vital functions (systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, and SpO_2).

Statistical Analysis

Statistical analysis of this study was performed using the SPSS 26.0 (Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) statistical software. Categorical variables are given as frequencies (number, percentage), while numerical variables are expressed as descriptive statistics (mean, standard deviation). The normality of the numerical variables was examined the kurtosis and skewness. Differences between two independent groups were analyzed using the Independent Sample T-Test or Mann Whitney U test, and differences between more than two

independent groups were analyzed using One-Way Analysis of Variance (ANOVA) or Kruskal Wallis. The relationships between groups were interpreted using Chi-square analysis and Fisher's Exact test. The one sample outcome comparison related to groups was analyzed with one-sample chi-square test. $p<0.05$ values were considered statistically significant.

RESULTS

A total of 135 patients were enrolled in this study [57 (42.2%) ROSC, and 78 (57.8%) non-ROSC]. There was no statistical significance according to age between gender (66.41±12.8 male and 66.88±15.42 female) or between gender, and date related to survival status ($p>0.05$). However, the mean ages of the non-ROSC patients were significantly higher than the patients who had ROSC (68.65±12.58, and 63.75±14.96 years, respectively, $p=0.04$). The mean CPR duration of 135 patients was 37.93±16.91 minutes. The mean CPR duration of the ROSC patients was 31.83±22.37 minutes, while it was 42.40±9.28 minutes in the non-ROSC. Statistical evaluation showed that, the CPR duration of the non-ROSC patients was significantly higher than the ROSC patients (mean rank: 83.15 and 47.26, respectively) ($p<0.01$) (Table 1).

The patients's diagnosis at the time of CPR, and possible causes of arrest were shown briefly in Table 1. Patients' diagnoses and possible causes of arrest were evaluated statistically after eliminating the unknown ones (14 of 135) as cardiac or respiratory arrest, and cardiac or non-cardiac possible causes. 30.6% of the 121 patients had ROSC diagnosed as cardiac arrest (100 / 82.6%) and 9.9% of them had ROSC diagnosed as respiratory arrest (21 / 17.4%).

In total, 95 patients were diagnosed with possible cardiac causes and 26 patients were diagnosed as possible non-cardiac causes. There was no statistical significance found related to survival according to diagnosis and possible causes ($p>0.05$) as shown in Table 1.

However, the survival status evaluation related to the location of CPR management was statistically significant ($p<0.01$), with the highest ROSC rate of CICU with 12 patients out of 12, and the lowest ROSC rates were in the GICU, SICU, and ward with 0 out of 5, 0 out of 4, and 0 out of 3. Since the highest and the lowest ROSC rates in those locations to the total of 135 evaluated patients in the study was 8.9% in CICU, and 8.9% in GICU, SICU, and ward total, we decided to evaluate the location of the patients as ER and non-ER according to survival status. There were no significant differences found statistically ($p>0.05$) (Table 1).

Drug utilization choice during d-CPR management is evaluated in 135 patients according to the location of CPR management, survival status, the year of the CPR management that was done (before 2020, and from 2020 to 2022), and in 121 patients according to the diagnosis, possible causes are briefly shown in Table 2. Evaluation related to the drug utilization choice in d-CPR management showed statistical significance ($p<0.01$), since the lowest choice of the drug administration was the usage of the drugs together (amiodarone & lidocaine) with 14.1%, while amiodarone alone was the most chosen drug with 63 (46.7%) followed by lidocaine alone with 53 (39.3%). The evaluation of the location of CPR management related to the drugs' choice during d-CPR was not statistically significant neither directly to the location nor ER vs non-ER comparison as shown in Table 2. However, there was a statistical significance according to the drugs' utilization in ER ($p>0.01$, one-sample Chi-Square test). In ER, utilization of amiodarone alone was the highest choice with 48.6% followed by lidocaine alone at 37.8%, and both drugs in the same patient with 13.5% (Table 2).

Although the rates of drug administration choice according to years "before 2020" to "from 2020 to 2022" presented differences as 25.9% to 20.7% in amiodarone alone, 17.8% to 21.5% in lidocaine alone, and 5.2% to 8.9% in amiodarone&lidocaine usage together, according to statistical evaluation, there was no statistical difference ($p>0.05$). However the evaluation of drug choice related to years separately before 2020, and from 2020 to 2022 showed statistical significance, $p<0.01$ and $p=0.02$ respectively. The evaluation revealed that the usage of both amiodarone and lidocaine together in d-CPR management was the least chosen one from 2015 to 2022.

The statistical evaluation of drug utilization choice in d-CPR management evaluated in 121 patients according to the diagnosis (cardiac arrest & respiratory arrest), and possible causes (cardiac causes & non-cardiac causes) revealed

Table 1. Demographic and clinical data of the patients according to survival status

		ROSC	Non-ROSC	Total	p
Patients (n / %)		57 / 42.2%	78 / 57.8%	135 / 100%	>0.05^{os-c}
Date (n / %)					
< 2020		30 / 22.2%	36 / 26.7%	66 / 48.9%	> 0.05^{c}
≥2020		27 / 20%	42 / 31.1%	69 / 51.1%	
Age (mean±SD)		63.8 ± 15.0	68.7 ± 12.8	66.6 ± 13.8	**0.04^{t}**
Gender (n / %)					
Female		21 / 15.6%	30 / 22.2%	51 / 37.8%	> 0.05^{c}
Male		36 / 26.6%	48 / 35.6%	84 / 62.2%	
Diagnosis (n / %)					
Cardiac Arrest		37 / 30.6%	63 / 52.1%	100 / 82.6%	>0.05^{c}
Respiratory Arrest		12 / 9.9%	9 / 7.4%	21 / 17.4%	
Unknown*		8	6	14	
Possible causes (n / %)					
Cardiac causes (95 / 78.5%)	MI	29 / 24%	31 / 25.6%	60 / 49.6%	>0.05^{c}
	Cardiac def	7 / 5.8%	26 / 21.5%	33 / 27.3%	
	Hypotension	1 / 0.8%	0	1 / 0.8%	
	Aort anev	0	1 / 0.8%	1 / 0.8%	
Non-cardiac causes (26 / 21.5%)	Respiratory failure	11 / 9.2%	5 / 4.1%	16 / 13.3%	
	Suicide	0	1 / 0.8%	1 / 0.8%	
	Tbc- pneumonia	0	1 / 0.8%	1 / 0.8%	
	Cancer	1 / 0.8%	3 / 2.5%	4 / 3.3%	
	Metabolic causes	0	4 / 3.3%	4 / 3.3%	
Unknown*		8	6	14	
CPR Location (n / %)					
ER (111 / 82.2%)	ER	45 / 33.3%	66 / 48.9%	111 / 82.2%	>0,05^{c}
Non-ER (24 / 17.8%)	GICU	0	5 / 3.7%	5 / 3.7%	
	CICU	12 / 8.9%	0	12 / 8.9%	
	Ward	0	3 / 2.2%	3 / 2.2%	
	SICU	0	4 / 3%	4 / 3%	
CPR duration (min) (mean rank)		47.26	83.15		**<0.01^{m}**
Antiarrhythmic drugs (n / %)					
Amiodarone		28 / 20.8%	35 / 25.9%	63 / 46.7%	>0.05^{c}
Lidocaine		20 / 14.8%	33 / 24.5%	53 / 39.3%	
Amiodarone &Lidocaine		9 / 6.7%	10 / 7.4%	19 / 14.1%	

n:number, ROSC: return of spontaneous circulation, MI: myocardial infarctus, def: deficiency, anev: anevrism, Tbc: tuberculosis, CPR: cardiopulmonary ressusitation, ER: emencency room, GICU: general intensive care unit, CICU: coronary intensive care unit, SICU: surgery intensive care unit min: minute, c: chi-square, t: independent t test, m: mann whitney u test, os-c: one sample chi-square test

*Unknown causes and diagnosis are eliminated.

no significant difference. However, the higher choice of amiodarone alone utilization in cardiac arrest diagnosis (45%) and cardiac possible causes (45.3%) revealed significant differences when compared with lidocaine alone (38% and 36.8% respectively) or usage of both which was the least chosen administration (17% and 17.9% respectively), as shown in Table 2.

The drug administration choice during d-CPR comparison on survival status showed no significant difference as informed before in Table 1, additionally, amiodarone alone, lidocaine alone, or the usage of both drugs during d-CPR presented no statistical difference according to survival status separately (p>0.05 at all) as shown in Table 2.

Table 2. Evaluation of drug utilization during defibrillation in CPR related to CPR location, date, possible causes, diagnosis, and survival status

		Amiodarone	Lidocaine	Amiodarone & Lidocaine	p
Patient (n / %)		63 / 46.7%	53 / 39.3%	19 / 14.1%	**<0.01** os-c
CPR Location (n / %)					
ER (111)		54 / 48.6%	42 / 37.8%	15 / 13.5%	**<0.01** os-c
ER (111 / 82.2%)		54 / 40.0%	42 / 31.1%	15 / 11.1%	
Non-ER (24 / 17.8%)	GICU	1 / 0.7%	4 / 3%	0	
	CICU	6 / 4.4%	2 / 1.5%	4 / 3%	>0.05c
	Ward	2 / 1.5%	1 / 0.7%	0	
	SICU	0	4 / 3%	0	
Date (n / %)					
< 2020 (66)		35 / 53%	24 / 36.4%	7 / 10.6%	**<0.01** os-c
≥2020 (69)		28 / 40.6%	29 / 42%	12 / 17.4%	**0.02** os-c
p		>0.05 os-c	>0.05 os-c	>0.05 os-c	
< 2020 (66/ 48.9%)		35 / 25.9%	24 / 17.8%	7 / 5.2%	>0.05c
≥2020 (69 / 51.1%)		28 / 20.7%	29 / 21.5%	12 / 8.9%	
Possible causes (n / %)					
Cardiac causes (95)		43 / 45.3%	35 / 36.8%	17 / 17.9%	**0.04** os-c
Non-cardiac causes (26)		16 / 61.5%	8 / 30.8%	2 / 7.7%	**0.03** os-c
Cardiac causes (95 / 78.5%)		43 / 35.5%	35 / 28.9%	17 / 14.1%	>0.05c
Non-cardiac causes (26 / 21.5%)		16 / 13.2%	8 / 6.6%	2 / 1.7%	
Unknown*		4	10	0	
Diagnosis (n / %)					
Cardiac Arrest (100)		45 / 45%	38 / 38%	17 / 17%	**0.002** os-c
Respiratory Arrest (21)		14 / 66.7%	5 / 23.8%	2 / 9.5%	**0.004** os-c
Cardiac Arrest (100 / 82.6%)		45 / 37.2%	38 / 31.4%	17 / 14.0%	>0.05c
Respiratory Arrest (21 /17.4%)		14 / 11.6%	5 / 4.1%	2 / 1.7%	
Unknown*		4	10	0	
Survival status (n / %)					
ROSC		28 / 20.7%	20 / 14.8%	9 / 6.7%	>0.05c
Non-ROSC		35 / 25.9%	33 /24.4%	10 / 7.4 %	
p		>0.05 os-c	>0.05 os-c	>0.05 os-c	

n:number, ROSC: return of spontaneous circulation, CPR: cardiopulmonary ressusitation, ER: emencency room, GICU: general intensive care unit, CICU: coronary intensive care unit, SICU: surgery intensive care unit min: minute,

c: chi-square test, os-c: one sample chi-square test

*Unknown causes and diagnosis are eliminated.

Afterward, the vital functions (systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, and SpO_2) of the 57 patients who had ROSC were evaluated according to the drugs administrated during d-CPR management. Firstly, to make sure if atropin utilization affected the overall heart rate or not in ROSC patients, we evaluated heart rate data under atropin usage. There were no significant difference was found (p>0.05). Additionally, adrenalin effect to the blood pressure of the ROSC patients was not evaluated since it was given to all of the patients in the study. Therefore, evaluation of the vital functions related to drug utilization in ROSC patients revealed that there were no significant differences according to heath rate, SpO_2, and diastolic blood pressure (p>0,05) (Table 3). However, we found that the patients' systolic blood pressure and mean arterial blood pressure (MAP) related to drug utilization during d-CPR management were significantly different when compared with drug utilization. Systolic blood pressure and MAP were found to be higher depending on the usage of amiodarone alone (Systolic blood pressure mean±SD:

Table 3. Evaluation of vital functions in ROSC patients according to drug utilization during defibrillation in CPR including age, gender, date, CPR duration

	Amiodarone	Lidocaine	Amiodarone & Lidocaine	p
Patient (n / %)	28 / 49.1%	20 / 35.1%	9 / 15.8%	**0.08^{os-c}**
Age (mean±SD)	61.6±13.8	63.8±17.2	70.3±12.5	>0.05^{owa}
Gender (n / %)				
Female (21 / 36.8%)	14 / 24.6%	4 / 7%	3 / 5.3%	>0.05^{c}
Male (36 / 63.2%)	14 / 24.6%	16 / 28.1%	6 / 10.5%	
Date (n / %)				
< 2020 (30 / 52.6%)	16 / 28.1%	9 / 15.8%	5 / 8.8%	>0.05c
≥2020 (27 / 47.4)	12 / 21.1%	11 / 19.3%	4 / 7%	
p	>0.05 $^{os-c}$	>0.05 $^{os-c}$	>0.05 $^{os-c}$	
CPR duration (min) (mean±SD)	34.61±29.66	28.65±11.81	30.22±12.36	>0.05^{kw}
Heart rate after ROSC (mean±SD)	100.93±21.53	106.20±28.67	105.0±39.07	>0.05^{owa}
SpO_2 after ROSC (mean±SD)	93.9±2.04	93.4±3.98	94.3±2.3	>0.05^{kw}
Systolic BP	113.71±32.73	109.70±27.20	85.00±13.27	**0.02^{kw}**
Diastolic BP	66.79±20.10	64.80±18.16	50.78±9.08	>0.05^{kw}
Map	82,43±23,46	79.77±20.07	62.19±10.07	**0.04^{kw}**

n:number, SD: standard derivation, ROSC: return of spontaneous circulation, CPR: cardiopulmonary ressusitation, min: minute, SpO_2: saturation, BP: blood pressure, Map: mean arterial pressure, c: chi-square, os-c: one sample chi-square test, owa: one way anova test, kw: kruskal wallis test

113.71±32.73, MAP mean±SD: 82,43±23,46) when compared with the lidocaine alone usage, and both amiodarone&lidocaine usage (Systolic blood pressure mean±SD: 109.70±27.20 and 85.00±13.27, MAP mean±SD: 79.77±20.07 and 62.19±10.07, respectively)(p=0.02, and p=0.04, respectively), as shown in Table 3. Additionally, we revealed that in the patients who had ROSC amiodarone alone administration (48.1%) was significantly higher when compared to lidocaine alone (35.1%) or both amiodarone&lidocaine (15.8%) utilization, p=0.008.

DISCUSSION

The most important finding of this study is that the choice of amiodarone administration during d-CPR was the highest one when compared with lidocaine alone or amiodarone & lidocaine together in the patients who had ROSC, and in the total of the patients who had included the study. Additionally, amiodarone usage had a significant positive effect on systolic blood pressure and mean arterial pressure in the patients who had ROSC. However, this study revealed that the rate of drug utilization choice during d-CPR showed no significant difference, and amiodarone alone, lidocaine alone, or the usage of both drugs during d-CPR presented no positive effect on survival separately.

In this study, we examined the demographic and clinical features of patients receiving d-CPR. In addition, we compared the same parameters according to the antiarrhythmic drugs administered during d-CPR management. The age of non-ROSC patients who had CPR due to cardiac arrest was reported as 68 years in the literature [11]. In a study performed by Arac et al., the mean age was statistically significantly greater among nonsurvivors [12]. In our study, the mean age of non-ROSC patients was 68.7±12.8 which was significantly higher than patients who had ROSC. Additionally, in the same study by Arac et al., 64.0% of the non-survivors were male and 36.0% were female [12]. In our study, 62.2% of all patients were male and 37.8% were female. In the comparison of age with survival status from 78 non-ROSC patients 61.5% of them were male and 38.5% were female. Our results were consistent with the literature.

The duration of CPR is an important factor associated with outcomes. In a study by Esen et al., the mean CPR duration was reported as 32.3±13.5 minutes, additionally, Acar et al. showed that the rate of CPR duration of more than 21 minutes was 60% in both survivors and non-survivors [13,14]. The ROSC comparison is also an important factor in the studies to assess the success of CPR management. In a study by Arac et al., the survival rate was 31.82% [12]. Kashiura indicated that the

rate of ROSC was 50.5%, and in another study, the rate of ROSC was reported as 51% by Rohlin et al., [15,16]. In the present study, the rate of ROSC was 42.2%, while the mean CPR duration was found as 31.8±22.4 minutes in the patients who had ROSC, and 42.4±9.3 minutes in the non-survivors. In this respect, our outcomes were close to the literature reported above.

Assessment of diagnosis of CPR as respiratory or cardiac arrest, and possible causes of arrest is essential. In the study of Esen et al., the most commonly encountered cause of CPR application was found as cardiopulmonary arrest at 79.6% [13]. In our study, the most common diagnosis of the patients who had CPR was cardiac arrest (82.6%) followed by respiratory arrest (17.4%). The highest possible cause was myocardial infarction with a rate of 49.6% of all possible causes within the cardiac possible causes (78.5%). The highest rate of patients with respiratory arrest was respiratory failure with 13.3% within non-cardiac possible causes. Our different results could be attributed to our limited study population.

It has been reported that the patients could have benefited from the d-CPR management when the anti-arrhythmic drugs were given initially [17]. In a study by Arac et al., amiodaron was given in 12.7% of the CPR patients, while lidocaine was not used [12]. Amiodarone was the only drug which was recommended in the pre-2020 AHA CPR guidelines for administration during defibrillations in CPR, while in 2020 AHA decided to widen the recommendation of antiarrhythmic drug administration during d-CPR management, and added lidocaine as another antiarrhythmic drug which has already been utilized in d-CPR managements in our hospital since 2015 [8,10]. Therefore we were able to compare the outcomes of the patients to whom d-CPR was performed, and to whom different antiarrhythmic drugs were administered. In our study, amiodarone alone was the most chosen drug in d-CPR with statistical significance. In this respect, our outcomes were close to the trial reported above. In addition, according to our vital outcome data evaluations, systolic blood pressure and mean arterial pressure were significantly higher in the amiodarone-administrated ROSC patients. Though there were no studies published in the literature about vital outcomes like our study according to the best of our knowledge, there was a study published related to amiodarone, and lidocaine therapy among adult patients with in-hospital cardiac arrest comparing the rates of ROSC, reporting that lidocaine has a positive significant effect on ROSC [18]. Our study results showed no significant difference according to ROSC in comparison with amiodarone, lidocaine, or amiodarone&lidocaine treatment during d-CPR management. However, we also revealed that the highest ROSC score was in the CICU with %100(12/12) where the choice of lidocaine administration was nearly the lowest (%1.5) of all the locations in which d-CPR was managed. Our different results could be attributed to our limited study population. In this respect, we think that there is still a need for more trials in this field of medicine about the success of CPR management.

Study Limitations

The major limitations of this study include its retrospective design and the relatively small sample size. In addition, the lack of recordings in the Cardiopulmonary Resuscitation and Code Blue Forms that the data of the trials collected lessen the quality of the evaluation of CPR success, like as the drugs' administration doses, the drugs' administration time, the etCO2 outcome, or the arterial blood gas sample outcomes. Since similar studies were limited in the literature, we could not effectively compare our findings. Nevertheless, we think that our trial will lead to further comprehensive studies with a larger patient population.

CONCLUSION

The mean age of the non-survivors was significantly higher than survivors receiving d-CRP. The rate of ROSC was 42.22%. However only amiodarone usage was recommended in the pre-2020 AHA CPR guidelines, and lidocaine had been utilized in our hospital. Lidocaine was administered in 53 (39.26%) patients during d-CPR management. Although systolic blood pressure and mean arterial pressure were significantly higher statistically in the amiodarone than the both drugs' (amiodarone & lidocaine) administration, there were no significant differences between ROSC. Further studies are warranted to investigate CPR parameters in detail.

Author contribution

Study conception and design: EB; data collection: EB; analysis and interpretation of results: EB; draft manuscript preparation: EB. The author reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Istinye University (Decision date: 01/02/2023; No: 2/2023.K-48).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Evaluation of pediatric patients with palpitations via cardiac event recorder, Holter monitoring and transesophageal electrophysiologic study in detecting arrhythmia*

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* The study had been presented as a poster in the 13th National Pediatric Cardiology and Cardiovascular Surgery Congress, 16-19 April 2014, Diyarbakir, Türkiye

ABSTRACT

Objective: Palpitations are a common reason for referral to pediatric cardiologists, the diagnostic workup involves ambulatory, non-invasive recording devices and invasive procedures. We aimed to evaluate arrhythmic symptoms of pediatric patients with a cardiac event recorder, Holter monitoring and transesophageal electrophysiologic study (TEEPS) results.

Materials and Methods: Retrospective evaluation of pediatric patients who fitted an event recorder at tertiary University Hospital between January 2002 and August 2012. The data obtained from the same patients' as cardiac event recorder, Holter monitoring and TEEPS results were studied for comparison.

Results: During the study period, 40 patients who had all data of cardiac event recorder, Holter monitoring and TEEPS were included. The median age of the patients included in the study was 12 [interquartile range, 7-15] years. Using the Holter monitoring, supraventricular extrasystoles (SVEs) were detected in six (15%) patients and ventricular extrasystoles (VESs) in three (7.5%). According to the event recorder data of the 40 patients, there was sinus tachycardia in 20 (50%), supraventricular tachycardia (SVT) in three (7.5%), and SVEs in two (5%) patients. The event recorder data of the remaining 15 patients were assessed as normal. The analysis of the TEEPS results revealed atrioventricular nodal reentrant tachycardia in four (10%), atrioventricular reentry tachycardia in three (7.5%), and normal results in the remaining 33 (82.5%) patients.

Conclusions: This study demonstrated that a cardiac event recorder may also be considered as an important diagnostic tool in the diagnosis and ruling out of SVT in pediatric patients for whom the cause of arrhythmia cannot be identified with the Holter monitor, in patients who do not accept the use of TEEPS method following the use of Holter monitor, and in patients in whom SVT cannot be stimulated by TEEPS yet complaints persist.

Keywords: arrhythmia, cardiac event recorder, children, palpitation, supraventricular tachycardia.

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Received: 25 January 2024, Accepted: 13 June 2024,
Published online: 29 June 2024

INTRODUCTION

Palpitation is one of the major reasons for pediatric cardiology admissions [1,2]. Differentiation of sinus tachycardia from the pathologic subtypes is one of the major challenges. Detection of tachycardia is also difficult in patients with short-term complaints. Recording systems such as 24-hour Holter monitoring, event recorders or provocation tests such as electrophysiologic studies (transesophageal or intracardiac) are some of the methods for diagnosis and differentiation [1,3]. Supraventricular tachycardia (SVT) is the most common symptomatic arrhythmia in childhood [4]. The diagnosis of SVT and the frequency of recurrence are not easy to determine due to the difficulties experienced with children in describing their complaints, short duration of SVT attacks, and the fact that these attacks end before an electrocardiogram (ECG) recording can be taken [5]. Various non-invasive (ECG, 24-hour Holter monitoring, event recorder, and exercise stress ECG test), semi-invasive [transesophageal electrophysiologic study (TEEPS)], and interventional (implantable loop recorder, intracardiac electrophysiologic study/intracardiac electrophysiologic study (IEPS)] methods are currently utilized to detect SVT [5].

In the event of symptoms that suggest the presence of SVT in children, the first choice is ECG recording, which is known as the gold standard method for diagnosing arrhythmia given its practical nature and easy accessibility. However, it may be difficult to diagnose short-term transient tachycardia using ECG. Therefore, 24-hour Holter monitoring is widely used in patients that cannot be diagnosed by surface ECG [6]. In cases where the symptom frequency is low, and due to the fact that symptoms may not occur during 24-hour Holter monitoring, the symptom moment can be captured with an event recorder, which is designed to record such data over a longer time [1,3,7,8]. However, there are only a limited number of publications providing event recorder data in pediatric age group.

TEEPS is a semi-invasive, easy-to-use, low-risk, reliable, and inexpensive diagnosis and treatment method with no major complications [9,10]. The TEEPS method has been shown to be effective in stimulating tachycardia and determining its mechanisms, assisting in the differential diagnosis of SVT, and guiding medical or ablative treatment decisions [10,11].

In this study, we aimed to report our experience using cardiac event recorder in pediatric patients since studies in the pediatric population are limited. Also, we aimed to assess arrhythmic symptoms in these pediatric patients using a cardiac event recorder, Holter monitoring, and findings from TEEPS.

MATERIALS and METHODS

Pediatric patients aged between 0-18 years, who fitted an event recorder at the Department of Pediatric Cardiology of Hacettepe University Faculty of Medicine between January 2002 and August 2012 were retrospectively evaluated. 24-hour Holter monitoring (Rozinn® Digital Holter Recorder Model No. RZ153PM) and TEEPS results of the event recorder patients were also included.

The patients' age, gender, reasons for admission, diagnoses, 12-lead ECG data, echocardiographic examinations were also recorded. The records were evaluated by the pediatric cardiologists of our department. Approval for the study was obtained from the Non-interventional Clinical Research Ethics Committee of University Faculty of Medicine (approval date/number: 19.10.2012/LUT 12/112).

An event recorder device which has a small phone size (Rozinn® "King of Hearts") was used for recording data for a predetermined time (looping memory) starting from the moment that the patient feels symptoms and presses the record button and ending with a warning sound. Two electrodes are attached to the chest wall, and the patient carries the monitor constantly, but the patient's rhythm is only recorded when the patient or his/her caregiver presses the record button. The recording system is equipped with a receiver/transmitter device that converts the patient's ECG to sound waves, a standard telephone line, and a central computer unit. After the patient's ECG is converted to sound waves, they are sent to the center via the telephone line and converted back into ECG waves and recorded there.

The patients were instructed how to use the event recorder by their doctors, and the first ECG recordings were created together. In addition, the patients and/or their parents were asked to record

data during symptoms, take at least one recording every day even if they had no symptoms, and send these records from a corded landline telephone to the corded landline telephone of the cardiology department. For the patients aged below three years, the parents were asked to take at least one recording every day (in the event of asymptomatic attacks) and record the times when they thought their children had symptoms (restlessness, constant crying, etc.). The ECG recordings received by the telephone were transferred to the computer. All the ECG recordings were evaluated by a pediatric cardiologist. An event recorder was applied to the patients that rarely had symptoms, couldn't be diagnosed with ECG or Holter monitoring and didn't prefer to undergo TEEPS as the first method or had persistent complaints after TEEPS.

TEEPS indications were defined as the presence of symptoms suggestive of arrhythmia, such as tachycardia and syncope, determination of SVT mechanisms, and evaluation of treatment after ablation. Consent was obtained from the parents of the patients in terms of TEEPS indications. IEPS was performed before ablation in the patients with recurrent arrhythmias who did not respond to anti-arrhythmic therapy.

Statistical analysis

Measurable variables were expressed as medians with interquartile ranges (IQR) and the percentages of all values relative to the total were given. Statistical Package for the Social Sciences (SPSS) v.18.0 for Windows XP software package was used to analyze the data.

RESULTS

During the study period, 40 patients who had all data of cardiac event recorder, Holter and TEEPS were included. Females consist the majority of patients (n=26 females; 65%). Median age was 12 [7-15] years. Three (7.5%) patients were under three and 37 (92.5%) were between 4-18 years old. Complaints of the patients during admission were palpitation in 37 (92.5%), chest pain in 12 (30%), syncope in 10 (25%), fatigue in 4 (10%). Three of the remaining patients, who did not encounter palpitations, disclosed incidents of syncope. Also, some patients had more than one complaint. The diagnoses made as a result of the examinations performed based on the patient complaints are shown in Table 1.

Transthoracic echocardiography, 12-lead ECG, Holter monitoring, event recorder, and TEEPS methods were applied to all the patients. The data obtained by the surface ECG, echocardiography, Holter monitoring, exercise ECG stress test, event recorder, and TEEPS methods are summarized in Table 2. Surface ECGs were taken during pediatric cardiology outpatient clinic admissions and found normal in 95% of the patients. However, one patient was diagnosed with sick sinus syndrome and needed a permanent pacemaker. The ECG showed a first-degree AV block. SVE was also found in Holter, but the event recorder and TEEPS results were normal. Additionally, left ventricular hypertrophy was detected in one patient's ECG. Although SVE was found in Holter and sinus tachycardia in the event recorder, TEEPS result was normal for this patient.

Table 1. Tests performed and diagnoses according to the presentation complaints

Complaints*	Holter monitoring		Event recorder		TEEPS	
	SVE (n = 6)	VES (n = 3)	SVT (n = 3)	ST (n = 20)	AVRT (n = 3)	AVNRT (n = 4)
Palpitation (n = 37)	5	3	3	16	3	4
Chest pain (n = 12)	3	1	3	6	1	1
Syncope (n = 10)	2	1	-	4	-	-
Fatigue (n = 4)	2	-	1	2	-	-

TEEPS: Transesophageal electrophysiologic study, SVE: Supraventricular extrasystole, VES: Ventricular extrasystole, SVT: Supraventricular tachycardia, ST: Sinus tachycardia, AVRT: Atrioventricular reentry tachycardia, AVNRT: Atrioventricular nodal reentrant tachycardia
*Some patients had more than one complaint.

Table 2. Surface ECG, echocardiography, Holter, event recorder and TEEPS results

n (%)	Surface ECG	Echocardiography	Holter monitoring	Event Recorder	TEEPS
Normal	38 (95.0)	31 (77.5)	31 (77.5)	15 (37.5)	33 (82.5)
1' A.V block	1 (2.5)	-	-	-	-
SVH	1 (2.5)	-	-	-	-
MVP	-	6 (15.0)	-	-	-
MVI	-	3 (7.5)	-	-	-
SVE	-	-	6 (15.0)	2 (5.0)	-
VES	-	-	3 (7.5)	-	-
ST	-	-	-	20 (50.0)	-
SVT	-	-	-	3 (7.5)	-
AVRT	-	-	-	-	3 (7.5)
AVNRT	-	-	-	-	4 (10.0)

TEEPS: Transesophageal electrophysiologic study, A.V: Atrioventricular, SVH: Left ventricular hypertrophy, MVP: Mitral valve prolapse, MVI: Mitral valve insufficiency, SVE: Supraventricular extrasystole, VES: Ventricular extrasystole, ST: Sinus tachycardia, SVT: Supraventricular tachycardia, AVRT: Atrioventricular reentry tachycardia, AVNRT: Atrioventricular nodal reentrant tachycardia

Twenty patients whose Holter results did not show palpitation and who did not want to undergo TEEPS fitted an event recorder device. Additionally, for the patients whose tachycardia could not be stimulated by TEEPS, they fitted an event recorder due to persisting complaints. Accordingly, 20 patients first wore the event recorder and then underwent TEEPS, whereas the remaining 20 patients first underwent TEEPS and then wore the event recorder.

1)*The patients who fitted an event recorder before TEEPS* (n=20)

Analysis of the data obtained by Holter monitoring revealed supraventricular extrasystoles (SVEs) in five and ventricular extrasystoles (VESs) in three patients. Event recorder revealed sinus tachycardia (ST) in ten, SVT in one, SVEs in two, and normal results in the remaining seven patients. The etiological examinations (anemia, hyperthyroidism, and fever) of the patients with ST were normal. For successful identification and discrimination of tachycardia, TEEPS was used following the event recorder and tachycardia was induced in six patients [atrioventricular reentry tachycardia (AVRT) in three and atrioventricular nodal reentrant tachycardia (AVNRT) in three]. Two of these patients were found to have SVT and SVE patterns based on the event recorder data (Figure 1). Radiofrequency ablation was successfully applied to these patients after IEPS, and their complaints did not recur during the follow-up.

2) *The patients who fitted an event recorder following TEEPS* (n=20)

SVEs was detected based on the Holter monitoring results in one patient. Additionally, among the 19 cases who were performed TEEPS due to the persistence of symptoms however in whom SVT could not be detected, ST was detected in 10 patients and SVT was detected in one (5.2%) patient based on the event recorder data. A patient with AVNRT detected by TEEPS had recurrent symptoms after RF ablation. SVT was detected in this patient based on the event recorder data, and therefore ablation was performed again (Figure 2).

DISCUSSION

This research highlighted the significance of a cardiac event recorder as a valuable diagnostic instrument for identifying SVT in pediatric patients when the cause of arrhythmia remains elusive through Holter monitoring analysis. This is particularly relevant when comparing it to the TEEPS method, where SVT cannot be induced despite persistent complaints.

Palpitation complaints in childhood may be ambiguous, and diagnosis may be challenging in this patient population due to difficulties in documentation [2]. Hence, non-invasive methods are preferred for diagnosis in the pediatric patient group in particular. Nevertheless, palpitations

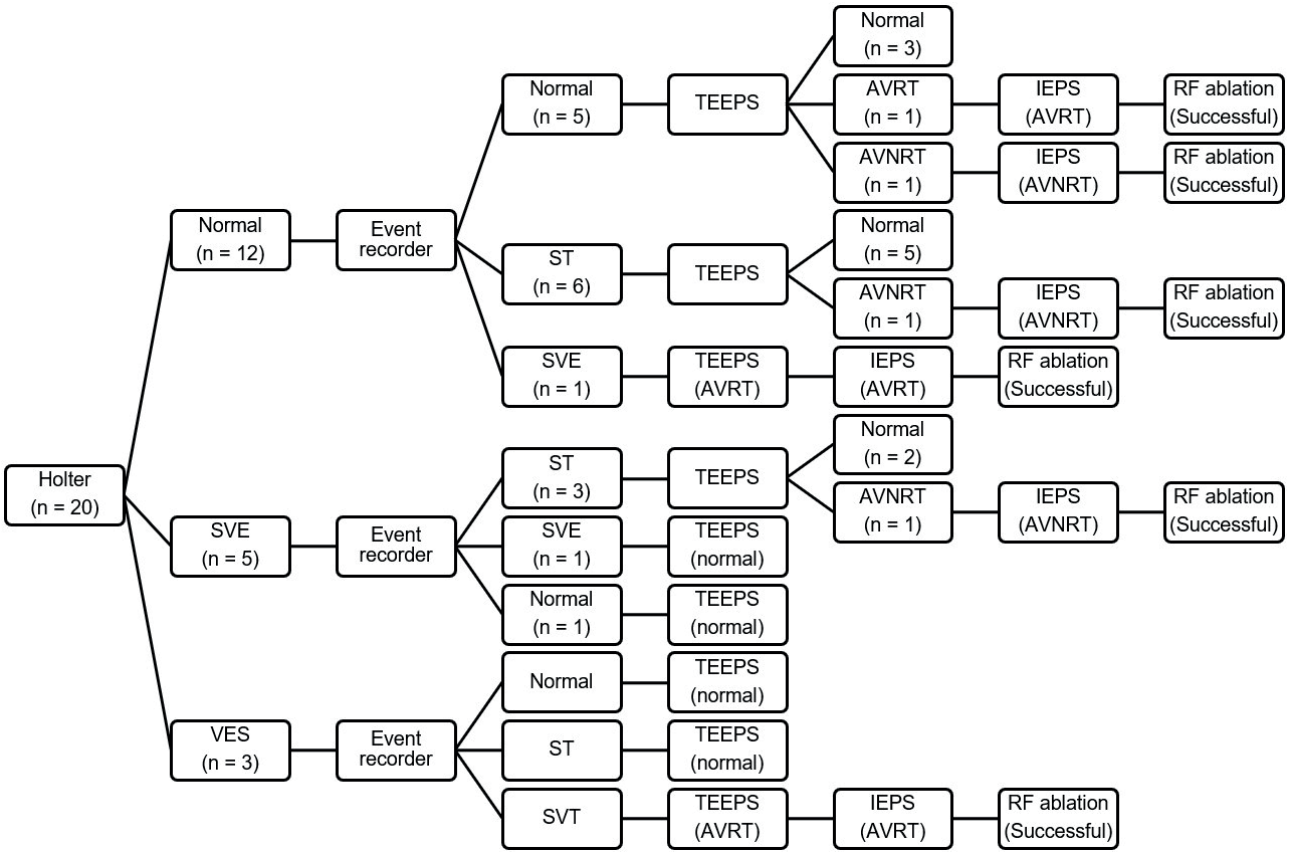

Figure 1. Data of the patients who fitted event recorder after Holter monitoring

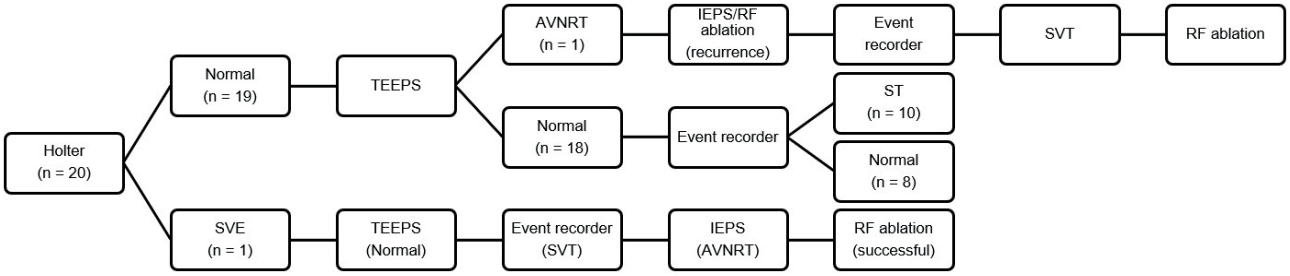

Figure 2. Data of the patients who fitted an event recorder after TEEPS

may not be detected using short-term recordings, such as ECG and Holter monitoring. In such cases, methods that allow long-term recordings, such as an event recorder or semi-invasive methods are used [1,3]. Since the event recorder device produce long-term recordings and the record button can be pressed whenever the patient begins to feel symptoms, it can detect SVT more accurately than a Holter monitoring.

The comparison of Holter recordings with TEEPS results in this study indicated that arrhythmia recordings could not be obtained with Holter monitoring in most patients. TEEPS provided more accurate results than Holter monitoring and the event recorder in diagnosing SVT and determining the type of tachycardia. Similarly, in a study, it was stated that Holter monitoring was insufficient in showing the tachycardia mechanism in 140 patients with SVT detected by surface ECG [10]. In that study, it was reported that SVT and ST were definitively demonstrated only in 9.3% and 15.7% of the patients, respectively, with using Holter monitoring. Tachycardia was detected in the remaining 33 (23.5%) patients, but the onset and end times of tachycardia could not be recorded, and thus ST and SVT could not be differentiated. Since Holter recordings could not distinguish between ST and SVT in a significant number of patients, the authors of the study emphasized the effectiveness of the TEEPS method in elucidating the mechanisms of SVT that develop without pre-excitation in children. In another study, it was reported that the positive predictive value of TEEPS

in detecting SVT mechanisms was 91%, and stated that transesophageal atrial stimulation was effective in the evaluation of patients with arrhythmia [11]. A study reported that surface ECG, Holter monitoring, and exercise stress ECG methods frequently yielded negative results in patients with suspected SVT and suggested the use of TEEPS in these patients [12]. In the same study, AVNRT was induced in 45.1% of the 82 patients included in the study, AVRT in 23.1%, Wolff-Parkinson-White syndrome in 6%, and ventricular tachycardia (VT) in 1.2%, while the remaining 30.4% had normal findings. The tachycardia was induced at a rate of 69.5% based on TEEPS. The authors emphasized that TEEPS was a fast and low-cost method that could be used to detect SVT as an alternative method.

In comparison, in a study conducted with an event recorder, it was stated that ST was recorded in 87% of the patients and SVT in 13%, and invasive diagnostic methods could be avoided in patients with ST detected at the time of symptoms [8]. The authors also noted that the event recorder provided more information compared to 24-hour Holter monitoring, given its longer recording duration and the fact that it can be activated by the patient in the event of symptoms. In a study conducted with 495 patients, they have obtained the event recorder data for a mean duration of 103 ± 97 days and reported that the event recorder detected SVT in 15% of the patients with a sensitivity of 83% and negative predictive value of 99% [13]. Due to our small sample size and retrospective study design, we were unable to provide results for the event recorder sensitivity and specificity. They also stated that the event recorder detected SVT especially in children with palpitation complaints, and no SVT was detected in the presence of chest pain, syncope, and pre-syncope. Furthermore, the authors reported in the light of other studies that the event recorder recording durations longer than 16 weeks did not increase its sensitivity, and the most cost-effective recording duration for SVT detection was four weeks.

In a study conducted with 460 patients, ectopic beats were detected only in 5% of the patients in whom Holter monitoring was used, whereas the event recorder recorded ST in 25%, SVT in 8%, 198 VES in 4%, SVEs in 2%, and VT in 0.04% of the patients, indicating a diagnostic success rate of 40% [7]. Based on these results, the efficacy of stand-alone use of the event recorder in detecting SVT remains uncertain, but it may be useful in the non-invasive evaluation of patients with intermittent symptoms before or after TEEPS. Although SVT was not detected with the event recorder in most of our cases when SVT was not stimulated by TEEPS, we think that it can be applied to selected patients with persisting symptoms before repeated use of invasive methods. In patients presenting with palpitations or syncope, an event recorder can provide data which can be useful in differentiating between benign and malignant arrhythmias.

In our study, it was observed that SVT could be induced when TEEPS was applied to the patients whose tachycardia could not be detected with the event recorder or who had ST. Therefore, we concluded that further measurements are needed in patients where no tachycardia is detected with the event recorder, and that the data obtained from the event recorder alone would not be sufficient for the follow up of such patients. In addition, patients diagnosed with SVT with the event recorder may need to undergo TEEPS, which is a semi invasive and reliable method, in order to detect the mechanism of SVT. The fact that chest pain was a frequent symptom in our patients with ST might be associated with the anxiety levels of the patients at the time of recording. Although ST is usually a benign arrhythmia, it may be associated with conditions such as hyperthyroidism, fever, anemia, drugs, and hypoxia. No etiological cause was determined in our patients.

The main limitations of our study were its retrospective nature and the relatively small size of the study sample. Hence, further prospective randomized studies with larger series are needed to corroborate the findings of this study.

Therefore, we suggest that in cases where no tachycardia is detected with the event recorder, it is not appropriate to only follow up patients considering that this result would be sufficient. In addition, patients diagnosed with SVT with the event recorder may need to undergo TEEPS, which is a semi-invasive and reliable method, to detect the mechanism of SVT.

CONCLUSION

This study revealed that cardiac event recorder can be used as an important diagnostic tool for the follow-up of patients with intermittent symptoms, those who do not accept the TEEPS procedure, and cases in which SVT cannot be stimulated by TEEPS but complaints persist. However, the use of an event recorder may be limited in patients who cannot activate the monitor during recording, who are asymptomatic, or who have arrhythmias accompanied by loss of consciousness. Furthermore, ensuring patient compliance may be difficult since the event recorder needs to be left attached for a long time.

Author contribution

Study conception and design: SÖ, NE, and İE; data collection: NE and İE; analysis and interpretation of results: NE, SÖ and İE; draft manuscript preparation: NE, SÖ and İE. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Non-interventional Clinical Research Ethics Committee of Hacettepe University Faculty of Medicine (Approval No: 12/112; 19.10.2012).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

The level of implementation of COVID-19 measures in workplaces: Ideas for the future

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Received: 16 February 2024, Accepted: 11 June 2024, Published online: 29 June 2024

ABSTRACT

Objective: The initial phases of Coronavirus Disease 2019 (COVID-19) pandemic required a wide range of preventive measures for various settings, including workplaces. The evaluation of workplace applications may guide all stakeholders for future similar outbreaks. This study aimed to evaluate the practice of Turkish occupational safety and health (OSH) professionals regarding COVID-19.

Materials and Methods: The study included responses of OSH professionals who were members of three national organizations. Data were collected during the third peak of COVID-19 cases in Turkey.

Results: Of 457 respondents, 92.6% reported at least one infected worker, and 12.7% reported mortality among workers due to COVID-19. Multiple regression analyses revealed an association with workplace size ≥250 for any COVID-19 infection among workers (OR=6.70, 95% CI:2.64–16.98, p<0.001) and for COVID-19 related mortality (OR=3.37, 95% CI:1.59–7.13, p=0.002). Moreover, working in governmental business enterprises was related to COVID-19 related mortality (OR=4.83, 95% CI:2.33–10.01, p<0.001). The mean number of available measures was significantly lower (p<0.001) in governmental business enterprises, the service sector, and workplaces with less than 250 workers.

Conclusion: The results indicate a need for improvement in small- and large-sized workplaces, governmental business enterprises, and service sector workplaces.

Keywords: COVID-19, occupational medicine, workplace measure, occupational diseases, occupational safety and health professionals.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a pandemic on March 11, 2020, by the World Health Organization [1]. The rapid global spread has led to significant morbidity and mortality and influenced nearly all aspects of life, with varying national measures to control the outbreak [2]. The measures primarily aimed to decrease human contact and prevent transmission, mainly through the respiratory route [3]. The national measures were guided by international organizations, which have also published their suggestions for safe work as the knowledge has gradually increased [4,5].

The first case of COVID-19 in Turkey was diagnosed on March 10, 2020 [6]. Soon after, national-level preventive measures were announced [7]. At the initial phase of the outbreak, less was known about the disease. Thus, measures included large-scale lockdowns for non-essential public workplaces and all educational institutions. Afterward, re-opening strategies have gained importance to provide a safe return to work, and several guidelines were published for various workplaces and other settings [8-10]. According to international and national guidelines, the risk of COVID-19 at workplaces should be evaluated with the participation of all parties, particularly workers or their representatives, under the supervision of occupational safety and health (OSH) professionals [11,12].

Studies show a variation in the availability of COVID-19 measures. For example, a Chinese investigation demonstrated relatively lower frequencies of hand sanitizing and avoidance of social gatherings for meals or crowded places in factory workers, compared to the percentage of 96.8 for workers wearing a face mask in the workplace [13]. In a study conducted with healthcare workers in Turkey, employees attached less importance to protective measures such as social distance and wearing masks in areas where they considered the risk of contamination was low [14]. A survey conducted in December 2020–January 2021 by the G20 OSH Experts Network evaluated the country-level OSH responses in 12 countries and found the most frequent administrative and non-administrative measures were remote work and use of personal protective equipment (PPE), respectively [15].

The evaluation of the practice in the workplace may guide workers, employers, and the government for future similar outbreaks. Despite a wide range of national guidelines for COVID-19 protection measures in Turkey, studies on the level of practice in the workplace are scarce [8-10]. Therefore, this study aimed to evaluate the practice of Turkish OSH professionals regarding COVID-19.

MATERIALS and METHODS

Study design, participants, and the survey

This nation-level descriptive study included Turkish OSH professionals, namely occupational physicians, occupational safety experts, and other occupational health personnel. The participants were approached via the Occupational Physicians Society, the Risk Management Society and the Society for Other Occupational Health Personnel. Each society delivered the electronic survey link to its members' communication platform (e.g., Whatsapp messaging group, Google group, members' messaging group, etc.), and participants were obtained via snowball sampling. The web link to the survey was sent on April 9, 2021, and three reminders on the 5th, 10th, and 14th days. The survey was closed on May 9, 2021. The study period corresponds to Turkey's third peak of COVID-19, with a daily number of new cases exceeding 60,000 [16].

A 43-item electronic survey was used to collect the data via Google Forms. The survey questions were prepared by researchers following the Guidelines of the Ministry of Health, Ministry of Industry and Technology and Ministry of Family, Labor, and Social Services [8-10]. The survey included sub-headings as follows: workplace features, the practice of job organization, social distancing and PPE use, sanitization, and OSH training on COVID-19. Additional questions were also asked regarding measures for workers' transportation services, social distancing at the entry and exit areas, cafeterias, break areas, and dressing rooms, short employment allowance, and a history of dismissal with Code-29 (i.e., a dismissal by the employer due to the worker's violation of code of ethics and

goodwill) between March 2020 and April 7, 2020, during the termination ban. The participants were asked to answer considering their practices from the beginning of the pandemic to the period when the survey was administered. The participants were asked to choose among four set answers (i.e., always, partially, no idea, and no) for items under each subheading. Moreover, questions were also asked about the history of any COVID-19 infection and mortality due to COVID-19 in workers. A pre-test was performed on sixteen OSH professionals, and adjustments in the items to provide maximum clarity were made accordingly. The pre-test data were not included in the results.

Statistical analysis

The analyses were based on workplace characteristics, including workplace ownership type, size, type of OSH services, and sector groups. Participants were accepted from different workplaces. The continuous variables are presented as mean ± standard deviation (SD) or median and quartiles, and categorical variables as numbers and percentages. The answer of "always" was accepted as the availability of the measure. This answer was compared with any other answers. The mean numbers of available measures under each sub-heading were compared according to workplace characteristics using Student's t-test. The frequencies of COVID-19 disease and mortality were compared according to workplace characteristics using the chi-square test. Univariate and multiple logistic regression tests were performed to evaluate the relationship between workplace characteristics and history of any COVID-19 infection and mortality due to COVID-19 in workers. For all comparisons, type 1 error (alpha) was accepted as 0.05. The statistical analyses were performed using IBM SPSS for Windows v.25.0 (IBM Corp., Armonk, NY).

Ethics

The study was performed following the principles of the Declaration of Helsinki. The study protocol was approved by the Ministry of Health General Directorate of Health Services and Non-interventional Clinical Researches Ethics Board of Hacettepe University (Board Decision Number: 2021/06-47). The administrative board of each society granted permission for the study, and informed consent was obtained from participants.

RESULTS

The study included responses from 457 OSH professionals (174 occupational physicians, 128 occupational safety experts, and 155 other occupational health personnel). The mean and median of the total numbers of workers in the participants' workplaces were 942.7 ± 2057.5 and 350 (first quartile: 92, third quartile: 1,000). The characteristics of OSH professionals' workplaces are presented in Table 1. Most of the workplaces were private enterprises (65.4%). Most workplaces were from either the service (45.1%) or the industry (43.5%) sectors. The percentage of workplaces with internal OSH units was 39.4%. More than forty percent of workplaces (41.8%) employed 500 or more workers.

The majority of OSH professionals (92.6%) reported any positive history of at least one worker contracting COVID-19. Moreover, 12.7% reported mortality among workers due to COVID-19. There was no significant relationship between any positive history of COVID-19 infection or any COVID-19-related mortality among workers and mean numbers of measures on job organization, social distancing and PPE, sanitization, and OSH training. The relationship between any history of COVID-19 infection and mortality among workers and workplace characteristics is shown in Table 2. A multiple regression model for any COVID-19 infection among workers revealed a statistically significant association with workplace size ≥250 (OR=6.70, 95% CI: 2.64–16.98, p<0.001) compared to workplace size <250. The model for any history of mortality among workers due to COVID-19 revealed a significant relationship with governmental business enterprise (OR=4.83, 95% CI: 2.33–10.01, p<0.001) compared to other workplace types and workplaces with 250 or more workers compared to workplaces with less than 250 workers (OR=3.37, 95% CI: 1.59–7.13, p=0.002).

The frequencies of availability for each measure are shown in Table 3. The most frequently available measure was the education for hand hygiene (90.8%). The majority of the measures were available in more than half of the workplaces, but some measures, which included suspending the production or work (16.8%), avoiding face-to-face meetings (24.9%), and providing a time shift between entry and exit to avoid face-to-face contact

Table 1. The distrubition according to the workplace characteristics

Characteristic		n	%
Workplace status	Private enterprise	299	65.4
	Government business enterprise	99	21.7
	Foreign capital enterprise	43	9.4
	Enterprises with public-private partnership	16	3.5
Sector	Service	206	45.1
	Industry	199	43.5
	Construction	42	9.2
	Agriculture	10	2.2
OSH services	Internal OSH unit	180	39.4
	External OSH service	178	38.9
	Any combination of OSH service types	78	17.1
	An authorized unit of the Ministry of Health	21	4.6
Size	≥500	191	41.8
	250-499	74	16.2
	50-249	106	23.2
	10-49	70	15.3
	<10	16	3.5
Total		457	100.0

OSH= Occupational safety and health

Table 2. Univariate and multiple logistic regression analysis of the relationship between workplace features and workers' history of COVID-19 diagnosis and mortality

COVID-19 diagnosis							
Workplace characteristics		n	%	Univariate		Multiple	
				OR (95% CI)	p*	OR (95% CI)	p*
Workplace status	Other†	358	90.5	Reference		-	-
	Governmental	99	100.0	-	**0.001**	-	-
Sector	Service	206	91.3	Reference		Reference	
	Other‡	251	93.6	1.41 (0.70-2.83)	0.338	1.10 (0.53-2.28)	0.789
OSH services	Other§	277	90.6	Reference		Reference	
	Internal	180	95.6	2.23 (0.99-5.04)	**0.049**	1.40 (0.60-3.29)	0.438
Size	<250	192	85.4	Reference		Reference	
	≥250	265	97.7	7.35 (2.99-18.18)	**<0.001**	6.70 (2.64-16.98)	**<0.001**
COVID-19 mortality							
Workplace characteristics		n	%	Univariate		Multiple	
				OR (95% CI)	p*	OR (95% CI)	p*
Workplace status	Other†	358	7.3	Reference		Reference	
	Governmental	99	32.3	6.10 (3.41-10.90)	**<0.001**	4.83 (2.33-10.01)	**<0.001**
Sector	Other‡	251	9.2	Reference		Reference	
	Service	206	17.0	2.03 (1.16-3.56)	**0.012**	1.12 (0.54-2.29)	0.766
OSH services	Other§	277	8.3	Reference		Reference	
	Internal	180	19.4	2.67 (1.52-4.69)	**<0.001**	1.42 (0.76-2.66)	0.270
Size	<250	192	5.2	Reference		Reference	
	≥250	265	18.1	4.03 (1.98-8.18)	**<0.001**	3.37 (1.59-7.13)	**0.002**

*Bold values indicate statistical significance.
†Private enterprise, foreign capital enterprise, and enterprises with public-private partnership
‡Industry, construction, agriculture
§External, an authorized unit of the Ministry of Health, any combination of OSH service types
COVID-19, coronavirus disease 2019; PPE, personal protective equipment; SD, standart deviation

Table 3. The frequencies of avaliable measures in the workplaces (n=457)

Measure	n	%
Job organization		
Applying flexible working models, including distant working or working from home, for the workers suggested a transition to flexible working by related guideline	329	72.0
Applying flexible working models, including distant working or working from home, for the workers other than those suggested a transition to flexible working by related guideline	260	56.9
Applying alternate working	261	57.1
Suspending the production or work	77	16.8
Changing work or shift hours to decrease the number of the workers in the workplace at a particular time	251	54.9
Providing a time shift between entry and exit to avoid face-to-face contact	197	43.1
Encouraging workers for the vacation leave, paid leave, or unpaid leave	230	50.3
Decreasing work activites with distant assignment	315	68.9
Limiting the entry of providers or visitiors to the workplace	328	71.8
Updating the risk evaluation in line with the COVID-19 measures	412	90.2
Updating the emergency plans in line with the COVID-19 measures	410	89.7
Measuring the body temperature of workers in the workplace	364	79.6
Checking the workers' COVID-19 status using HES-codes	176	38.5
Checking the visitors' COVID-19 status using HES-codes	297	65.0
Evaluating workers with COVID-19 risky contact according to the guidelines	406	88,8
Isolating any COVID-19 case from other workers in a designated room	280	61.3
Social distancing and PPE use		
Avoiding face-to-face meetings	114	24.9
Adapting online methods for the meetings, conferences, or congresses	267	58.4
Providing adequate and appropriate PPEs to workers for protection against COVID-19	353	77.2
Sanitization		
Cleaning and disinfecting the surfaces, equipment and workplace media regularly	322	70.5
Providing adequate amount of hand sanitizers in easy-access areas	384	84.0
Providing adequate toilet and lavatory according to the number of workers	305	66.7
Placing adequate waste bins for paper towels, wet towels, gloves, and face masks in appropriate areas	332	72.6
Applying appropriate ventilation using external air ventilation or natural air circulation for the central ventilation systems	235	51.4
OSH training on COVID-19		
Training the workers on what to do in case of COVID-19 symptoms	406	88.8
Training the workers on what to do in case of a history of risky contact	412	90.2
Training the workers on hand hygiene	415	90.8
Placing visual and auditory warnings on COVID-19 measures	406	88.8
Total	-	100.0

COVID-19= Coronavirus disease 2019; HES-code= The code provided by the Ministry of Health to allow sharing COVID-19 status with third parties; PPE= Personal protective equipment; OSH= Occupational safety and health

(43.1%), were available in less than half of the workplaces. The responses for short employment allowance and history of dismissal with Code-29 were 40.0% and 6.1%, respectively. The most frequent measures for workers' transportation services, social distancing at the entry and exit areas, cafeterias, break areas, and dressing rooms are presented in Supplementary Table 1.

The overall mean number of the available measures in workplaces was 18.70 ± 5.90. According to sub-headings, the mean numbers of measures were 10.05 ± 3.69 for job organization, 1.61 ± 0.90 for social distancing and PPE, 3.45 ± 1.63 for sanitization, and 3.58 ± 0.94 for OSH training. The mean numbers of measures were significantly lower in governmental business enterprises ($p<0.001$), workplaces in the

service sector (p<0.001), and workplaces with less than 250 workers (p<0.001) (Table 4). This pattern was similar for job organization, sanitation and disinfection, and education. For the sub-heading of physical distance and PPE, lower mean numbers of measures were observed in workplaces in the service sector (p=0.018), workplaces without internal OSH department (p=0.008), and workplaces with less than 250 workers (p<0.001).

DISCUSSION

The present study was conducted during the third peak of COVID-19 in Turkey to evaluate workplace practice according to OSH professionals' responses. In the literature, there are several alternatives for data source regarding similar studies. Garzillo et al. surveyed 41 workplaces located in the province of L'Aquila, Abruzzo, Italy [17]. An Algerian study evaluated 115 workplaces by visiting and asking one of the workplace officials about workplace measures [18]. In contrast, both Sasaki et al.'s and Ishimaru et al.'s studies evaluated the level of workplace measures through workers' responses [19,20]. The advantage of surveying OSH professionals includes their active role in determining and enforcing the measures, although this role might influence the accuracy of their responses. Future studies evaluating the views of both OSH professionals and workers may overcome this issue.

The measures were suggested in the very early stage of the pandemic by the authorities, including the Ministry of Health, enabling workplaces to adapt rapidly [21]. In contrast to most of the measures, some measures, such as suspending production or work, avoiding face-to-face meetings, and providing a time shift between entry and exit to avoid face-to-face contact, were available in less than half of the workplaces. In Turkey, curfews and restrictions were enacted during surges in COVID-19 case numbers, with sectoral and activity-based exemptions [22]. Thus, the low frequency of the relevant measure may be a result of these exemptions.

The present study's results demonstrated lower mean numbers of available measures in workplaces in the service sector and workplaces with less than 250 workers. A Turkish study compared transportation and metal sectors and showed differences in job characteristics, physical distance, PPE use, and workplace size [23]. The sector-based differences were similar to other international studies [17,19]. Moreover, two studies from Japan similarly showed better implementation and announcement of measures in large enterprises [19,20]. Garzillo et al. showed a higher level of measures in larger companies [17]. This finding could also be related to additional factors depending on workplace size (e.g., the OSH culture and level of the OSH services), infection rates in the general population, and the level of community transmission.

There was a significant difference between governmental business enterprises and other workplace types in terms of mean numbers of available measures. Furthermore, the multiple regression model revealed a significant relationship

Table 4. The distrubition of mean numbers of measures according to workplace characteristics (n=457)

Workplace characteristics		n	Job organization		Social distancing and PPE		Sanitization		OSH training		Total	
			Mean±SD	p*	Mean±SD	p*	Mean±SD	p*	Mean±SD	p*	Mean±SD	p*
Workplace status	Other†	358	10.56±3.55	**<0.001**	1.65±0.89	0.076	3.65±1.55	**<0.001**	3.69±0.82	**0.001**	19.54±5.58	**<0.001**
	Governmental	99	8.22±3.64		1.46±0.90		2.73±1.74		3.22±1.25		15.64±6.05	
Sector	Other‡	251	10.81±3.50	**<0.001**	1.70±0.85	**0.018**	3.67±1.48	**0.002**	3.72±0.79	**0.001**	19.90±5.49	**<0.001**
	Service	206	9.12±3.72		1.50±0.94		3.19±1.78		3.42±1.09		17.23±6.07	
OSH services	Internal	180	10.37±3.41	0.133	1.74±0.86	**0.008**	3.57±1.54	0.232	3.63±0.84	0.435	19.31±5.37	0.072
	Other§	277	9.84±3.86		1.52±0.91		3.38±1.70		3.56±1.01		18.30±6.20	
Size	<250	192	9.09±3.66	**<0.001**	1.39±0.90	**<0.001**	3.18±1.76	**0.003**	3.51±1.03	0.120	17.16±5.92	**<0.001**
	≥250	265	10.74±3.57		1.77±0.86		3.65±1.52		3.65±0.88		19.81±5.65	

*Student's t-test. Bold values indicate statistical significance.
†Private enterprise, foreign capital enterprise, and enterprises with public-private partnership
‡Industry, construction, agriculture
§External, an authorized unit of the Ministry of Health, any combination of OSH service types
PPE, personal protective equipment; SD, standart deviation

between being a governmental business enterprise and any history of mortality among workers due to COVID-19. Those results indicate a requirement for improving those workplaces, which may also serve as an example for private companies.

To the best of our knowledge, this is the first study evaluating the workplace practice regarding COVID-19 by surveying OSH professionals in a large number of Turkish workplaces. Moreover, the current study evaluates a substantial number of workplaces compared to other studies regarding COVID-19 measures. The study's strengths also include the diversity of workplaces, obtaining data from the OSH professionals who are directly responsible for the OSH services, and a wide range of measures evaluated. However, there are some limitations to the current study. Firstly, the level of participation might be lower than expected due to workplace conditions resulting from an ongoing pandemic and the study's method of electronic surveying. Although the survey was kept open for one month to overcome this issue, the results may not represent all workplaces. The analyses did not include the quality of the application and the effectiveness of preventive measures. Although not aimed at this study, the infection and mortality rates might be related to parameters other than the availability of workplace measures, such as local infection rates. As mentioned above, the responses of the participants might be influenced by their role in planning the measures and applying them in the workplace, in addition to intrinsic limitations of similar epidemiologic studies using the survey method.

To conclude, the current study's results reveal a need for improvement in small-sized workplaces, governmental business enterprises, and workplaces of the service sector, and on certain workplace measures, including prevention of the workers' face-to-face contact. Future studies may provide a comprehensive assessment by evaluating the measures from both the workers' and OSH professionals' perspectives and the effectiveness of measures applied in, which may contribute to adjusting the deficiencies. These investigations within the context of workplace biological risk factors can contribute to the understanding of workplace safety and guide efforts to enhance preventive measures for future similar outbreaks.

Acknowledgements

The authors thank the members of the administrative boards of the Occupational Physicians Society, the Risk Management Society, and the Society for Other Occupational Health Personnel for their collaboration and support.

Author contribution

Study conception and design: MY, AS, DK and ANY.; data collection: MY, AS, DK and ANY; analysis and interpretation of results: MY, AS, DK and ANY; draft manuscript preparation: MY, AS, DK and ANY. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study protocol was approved by the Ministry of Health General Directorate of Health Services and Non-interventional Clinical Researches Ethics Board of Hacettepe University (Board Decision Number: 2021/06-47).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Supplementary Table 1. The distribution of most frequent measures for workers' transportation services, social distancing at the entry and exit areas, cafeterias, break areas, and dressing rooms

	n	%
Workers' transportation services (n=237)		
Arranging single-seat, decreasing the workers per vehicle at least half, increasing the number of vehicles, and/or making a cross seating arrangement	202	85.2
Disinfecting the surfaces and/or providing hand sanitizers	87	36.7
Mandatory facial mask usage	63	26.6
Social distancing at the entry and exit areas (n=196)		
Placing signs at the ground or sight-level	57	29.1
Providing single-way entry and exit areas to prevent face-to-face contact	37	18.9
Adjusting the time of entries and exits as different hours and/or preventing the crowd by determining an order for worker groups	20	10.2
Social distancing at the cafeterias (n=336)		
Decreasing the capacity, decreasing the worker per table, and/or making a cross seating arrangement	269	80.1
Preventing the crowd by determining an order for worker groups or increasing the duration of meal break	121	36.0
Separating the tables or cafeteria personnel with plexiglass sheets	105	31.3
Social distancing at the break areas (n=226)		
Placing signs at the ground or sight-level, and/or providing physical distance between seats	142	62.8
Limiting the number of workers in the area	45	19.9
Preventing the crowd by determining an order for worker groups	38	16.8
Social distancing at the dressing rooms (n=177)		
Limiting the number of the workers in the rooms	83	46.9
Preventing the crowd by determining an order for workers	46	26.0
Increasing the distance between lockers, placing the lockers of workers of another shift or empty lockers between the lockers of workers of the same shift	28	15.8

acta medica

ORIGINAL ARTICLE

Haglund's deformity: Clinical outcomes of endoscopic calcaneoplasty

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Received: 18 February 2024, Accepted: 28 June 2024, Published online: 29 June 2024

ABSTRACT

Objective: Haglund's deformity is characterized by a bony prominence of the calcaneus, leads to posterior heel pain, swelling, and morning stiffness. Endoscopic calcaneoplasty is becoming increasingly popular due to its numerous advantages over conventional surgical methods. This study aims to evaluate the clinical and radiological results of patients who underwent endoscopic calcaneoplasty.

Materials and Methods: A total of 17 patients were diagnosed with Haglund's deformity and underwent endoscopic calcaneoplasty surgery in our clinic between June 2019 and January 2023 were included in this retrospective study. Pre-operative and post-operative parameters of patients with 6 months or more of follow-up were compared. The VAS was used for pain assessment, the AOFAS score for functional outcomes, and the length of bone deformity for radiological assessment.

Results: Significant pain resolution was observed at the final follow-up compared to the preoperative period. The mean VAS score decreased from 6.77±1.3 pre-operatively to 1.62±1.12 post-operatively ($p<0.001$). The AOFAS score showed a significant increase from 61.23±7.7 preoperatively to 92.46±6.04 postoperatively ($p<0.001$). Bony hump length decreased significantly from 4.12±1.14 preoperatively to -2.29±1.56 postoperatively ($p<0.001$).

Conclusion: Endoscopic calcaneoplasty is a reliable method in Haglund's deformity, that provides rapid recovery, early return to daily activities and sports, and a low complication rate.

Keywords: AOFAS score, endoscopic calcaneoplasty, Haglund's Deformity.

INTRODUCTION

Haglund's deformity, first described by Haglund in 1928. It is characterized by a bony prominence of the calcaneus, specifically at the posterosuperior aspect, which leads to posterior heel pain, swelling, and morning stiffness. Especially in progressed cases, the condition can reduce an individual's quality of life [1]. Haglund's deformity can frequently occur alongside retrocalcaneal bursitis or insertional Achilles tendinitis [2].

Conservative therapies are the primary choice of treatment, however, several studies reported that conservative treatment could fail and surgery may be necessary, especially in patients with symptoms lasting more than 6 months [3-6]. The surgery aims to remove the posterosuperior bony hump and remove the inflamed tendon and retrocalcaneal bursa [7]. Currently, there are many surgical approaches used for open surgery, including lateral paratendinous, medial paratendinous, central tendon splitting (with or without Achilles tendon detachment), and transverse Cincinnati incision [8-10,7,11-13]. Regrettably, present surgical methods may yield complications and adverse consequences, including wound dehiscence, Achilles tendon rupture, scar tenderness, prolonged posterior heel pain, altered sensation, nerve injury (sural nerve), incisional neuroma, and prolonged immobilisation and convalescence [14-17]. Hence, there is no consensus on the optimal surgical approach, and research on this subject is still ongoing.

Van Dijk's initial description of an endoscopic approach is perceived to alleviate the limitations of traditional approaches [18]. Endoscopic calcaneoplasty has become increasingly popular for its numerous benefits including reduced post-operative pain, lower incidences of post-operative complications, early mobilisation and rapid recovery when compared to open surgery [19-21]. In our study, we aimed to evaluate the clinical and radiological results of patients who underwent endoscopic calcaneoplasty.

MATERIALS and METHODS

We retrospectively reviewed the data of 17 patients who were diagnosed with Haglund's deformity (Figure 1-A) and underwent endoscopic calcaneoplasty surgery in our clinic between June 2019 and January 2023. We included patients who had symptoms for at least 6 months and whose complaints did not improve with conservative treatment. Patients with a previous fracture or surgery of the foot or ankle (one patient in our study), patients with rheumatological diseases (one patient in our study), and patients with a follow-up of less than 6 months, were excluded from the study. Moreover, we could not complete the surgery endoscopically in two patients, due to technical reasons, these patients' surgery was completed as open calcaneoplasty and they were excluded from the study.

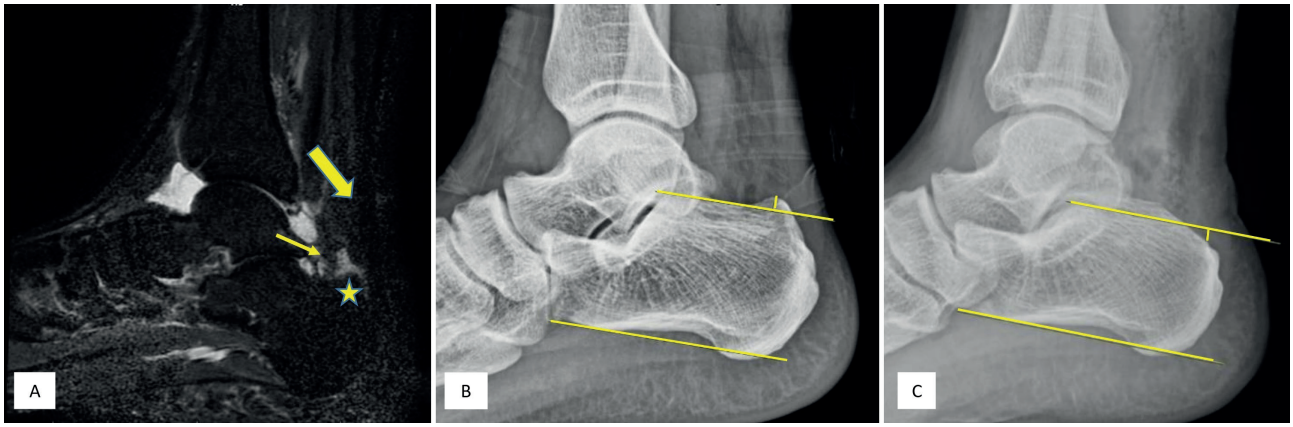

Figure 1. (A) MRI image of a Haglund deformity. The star indicates a bony prominence, the thin arrow indicates retrocalcaneal bursitis, and the thick arrow indicates the Achilles tendon. (B) and (C) The parallel pitch line consists of two parallel lines (yellow lines), the lower line running from the inferior calcaneal tuberosity to the anterior calcaneal tubercle and the upper line running parallel to the lower line from the posterior lip of the talocalcaneal articular facet. The length of the perpendicular line drawn from the highest point of the bony prominence to the upper line was measured as the "length of the bony prominence". The measurements are shown in (B) pre-operatively and (C) post-operative.

Pre-operative and post-operative parameters of patients with 6 months or more of follow-up were compared. The VAS was used for pain assessment, the AOFAS score for functional outcomes, and the length of bone deformity for radiological assessment. A lateral ankle radiograph was used to measure the height of the bone deformity. First, parallel pitch lines were determined; the inferior line from the inferior margin of the calcaneocuboid joint to the plantar tuberosity of the calcaneus was drawn parallel to the inferior line, starting from the posterior margin of the subtalar joint. Then a line perpendicular to the superior pitch line was drawn from the point where the bone deformity was greatest. The amount remaining above the superior line was measured in mm and recorded as the height of the bony deformity (Figure 1-B, 1-C). All patients were assessed by an experienced orthopedic surgeon with a specialist interest in ankle surgery, and the outcomes were recorded by the same person. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Surgical procedure and post-operative care

The entire surgical procedure was performed under pneumatic tourniquet control and regional anesthesia and sedation with the patient in the prone position. Firstly, 50 cc of physiological saline was injected into the posterior ankle (Figure 2-A), deep into the Achilles tendon, and a space was formed to assist portal entrance. Two portals are approximately 2.5 cm proximal to the calcaneal tuberosity medial and lateral adjacent to the Achilles tendon (Figure 2-B). The 4.5 mm 30° arthroscope and a 4 mm motorized shaver were introduced from lateral and medial portals, respectively. Portal change was performed frequently to expand the viewing and working areas (Figure 2-C). The motorized shaver was used to remove the retrocalcaneal bursa and degenerated parts of the tendon. A radiofrequency ablation device was used to remove the soft tissue on the bony deformity and expose the bone (Figure 2-D). A 4.5 mm motorized burr was used for resection of the bony deformity (Figure 2-E). Intra-operative C-arm fluoroscopy control was performed to ensure adequate and

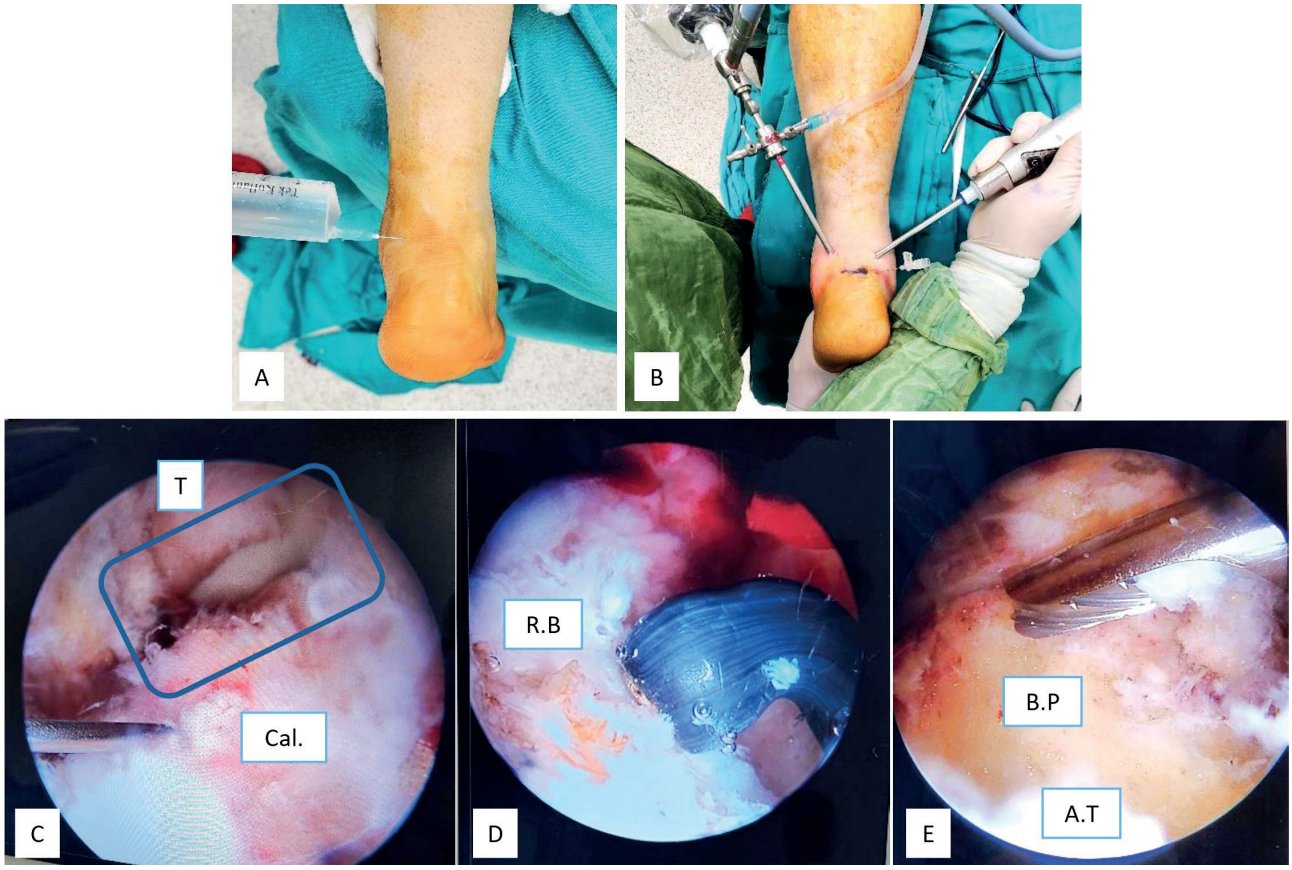

Figure 2. (A) Saline was administered to the posterior ankle, deep to the Achilles tendon to facilitate portal access. (B) The procedure was performed using postero-medial and postero-lateral portals with the patient in the prone position. (C) Endoscopic view of the surgical field, with the talus (T) and calcaneus (Cal) bones visible and the subtalar joint highlighted in the rectangle. (D) Retrocalcaneal bursa (R.B) was debrided with a radiofrequency ablation device. (E) The bony prominence (B.P) was resected using a motorised burr, taking care to protect the Achilles tendon (A.T).

appropriate bone resection was performed. Finally the portals were sutured and the operation was terminated.

All patients were discharged the day after operation. The patients were allowed perform partial weight bearing during the first 2 weeks and then full weight-bearing was allowed at the 3. post-operative week. Patients were encouraged for all active and passive ankle movements on the first post-operative day and returned to daily activities 4-6 weeks after the surgery. VAS and AOFAS scores and the length of bone deformity were recorded at the final follow-up.

Statistical analysis

Statistical analyses were performed using SPSS for Windows 25.0 software. For descriptive statistics, quantitative continuous variables were expressed as mean and standard deviation, and qualitative variables were expressed as frequencies and percentages. The normality of the distribution of continuous variables was tested by Kolmogorov-Smirnov / Shapiro-Wilk tests. In the Kolmogorov-Smirnov test, the distribution was considered normal if the p-value was greater than 0.05. Student t test was used to compare the means of two normally distributed dependent samples, $p<0.05$ indicates statistical significance.

RESULTS

A total of 13 patients met the inclusion criteria and were included in the study. Eight of the patients were male and 5 were female, with a mean age of 47.46 ± 6.63 (range, 38-60 years). The mean follow-up time was 15.92 ± 4.73 (range, 8-24 months) (Table 1). No patients were missed during the follow-up. The mean duration of the surgical procedure was 58.08 ± 9.1 (range, 45-75) minutes (Table 1).

Notable pain relief was observed in the final control of the patients compared to the pre-operative period. The mean VAS score decreased significantly from 6.77 ± 1.3 pre-operatively to 1.62 ± 1.12 post-operatively ($p<0.001$), (Figure 3-A). The mean AOFAS score increased significantly from 61.23 ± 7.7 pre-operatively to 92.46 ± 6.04 post-operatively ($p<0.001$), (Figure 3-B). According to post-operative AOFAS score, 9 patients had excellent (90–100 points), 3 good (80–89 points), and 1 fair (70–79 points) clinical results, respectively (Table 1). There was also significant post-operative radiological improvement. The mean length of bony hump decreased significantly from 4.12 ± 1.14 pre-operatively to -2.29 ± 1.56 post-operatively ($p<0.001$), (Table 1), (Figure 3-C). No complication was noted such as infection, irritating scars or neurovascular complication.

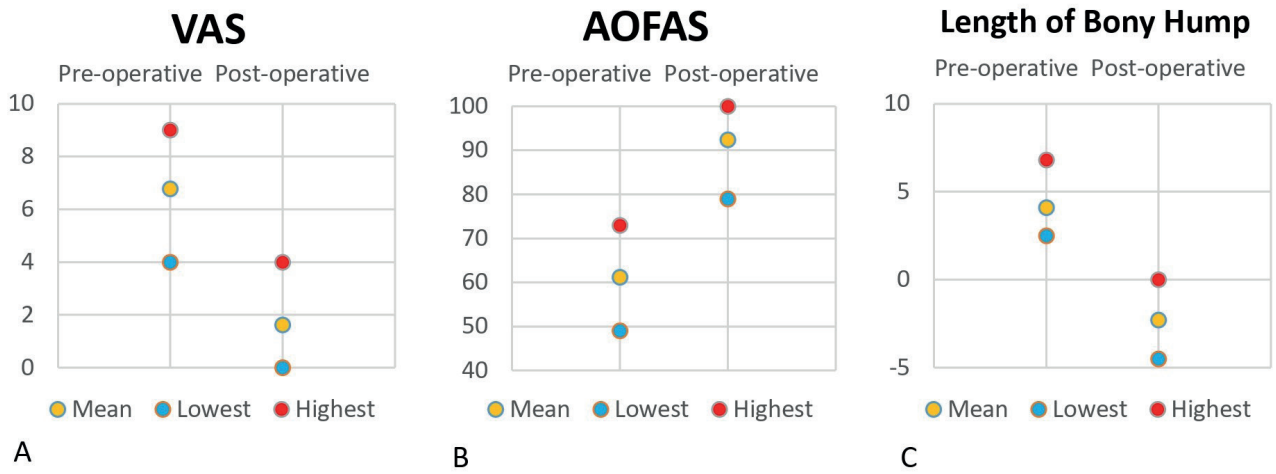

Figure 3. Comparison of pre- and post-operative results for (A) VAS, (B) AOFAS and (C) length of bone prominence.

Table 1. Demographic characteristics, pre-operative and post-operative clinical and radiological findings

Variable	Pre-operative Value	Post-operative Value	P
Sex: M (%) / F (%)	8 (61.5 %) / 5 (38.5 %)		
Age (Years)			
Mean ± SD (Range)	47.46 ± 6.63 (38-60)		
Operated Side			
Right: n (%)	7 (53.8 %)		
Left: n (%)	6 (46.2 %)		
Follow-up time (Months)			
Mean ± SD	15.92 ± 4.73		
(Range)	(8-24)		
Duration of Surgery (Minutes)			
Mean ± SD	58.08 ± 9.1		
(Range)	(45-75)		
VAS			
Mean ± SD	6.77 ± 1.3		<0.001
(Range)	(5-9)		
AOFAS Score			
Mean ± SD	61.23 ± 7.7		<0.001
(Range)	(49-73)		
AOFAS Class: n (%)			
Excellent	-	9 (69 %)	
Good	-	3 (23 %)	<0.001
Fair	3 (23 %)	1 (8 %)	
Poor	10 (77 %)	-	
Length of Bony Hump (mm)			
Mean ± SD	4.12 ± 1.14	-2.29 ± 1.56	<0.001
(Range)	(2.5-6.8)	(-4.5-0)	

M: Male, F: Female, SD: Standard Deviation, VAS: Visual Analogue Scale, AOFAS: American Orthopedic Foot and Ankle Society.

DISCUSSION

The main finding of the present study was that post-operative functional scores were improved and pain was relieved significantly, compared to the pre-operative period. According to the AOFAS scoring, 92.3% (12/13) of the patients had excellent and good results. Although our series had a small number of patients, we did not observe any post-operative complications, which is a promising aspect of this surgical method.

However, endoscopic heel surgery is gaining ground, many centers still perform open surgery. Whether it is conventional or endoscopic calcaneoplasty, complete removal of the bony prominence and debridement of the retrocalcaneal bursa without damage to the Achilles tendon insertion site is critical to surgical success [22]. Endoscopic calcaneoplasty enables excellent medial and lateral visualization, direct examination of the Achilles tendon, adequate removal removal of bone, and the inflamed bursa. It also offers smaller incisions, less morbidity and post-operative pain, earlier functional rehabilitation, and a quicker return to normal daily and sports activities [23,24]. The return to sports time is crucial for especially professional athletes. Open procedures can take up to 9 months, while endoscopic surgeries have an average recovery time of 12 weeks (range: 6 to 24) [25]. In a study by Kaynak et al. endoscopic calcaneoplasty was performed on 5 professional athletes. The athletes were allowed to return to training with the team in the 6th post-operative week and to full sports activities without restrictions in the 12th post-operative week [26].

Jerosch reported a review in 2015, including the results of 164 patients (average follow-up 46.3 months) who underwent endoscopic calcaneoplasty. Good and excellent results were achieved in more than 90% of patients [19]. In our series, although the number of cases was lower (13 cases) and the average follow-up period was shorter (15.9 months), we obtained a similar result (92.3%) in terms of good and excellent outcomes. In 2022, Mahmoud et al published the results of 17 patients on whom they performed endoscopic calcaneopalsty. They reported an increase in AOFAS scores from 55.7 pre-operatively to 94.3 post-operatively, a decrease in VAS scores from 8.1 to 0.7, and excellent and good results in 94% (16/17) of patients [27]. In the study, bony hump length was also measured and recorded for radiological evaluation, and mean bony hump length decreased from 4.7 pre-operatively to -0.2 post-operatively. Similarly, in our study, we observed a decrease in the mean length of bone prominence from 4.1 to -2.2. Although the pre-operative bone protrusions in the study by Mahmoud et al. and our study were similar (4.7/4.1), more bone resections were performed in our series (-0.2/-2.2). In our cases, we aimed to perform extensive bone resection, with the hypothesis that would result in greater post-operative relief. On comparison of the mean post-operative AOFAS scores in the two studies, results were similar (94.3/92.5). It can be concluded that post-operative relief is not directly proportional to radiological parameters. Lu et al. reported that there is not a direct correlation between radiological parameters and complaints of the patients in their publication [1], as we noted in the current study. Therefore, when deciding on surgery for Haglund's deformity, radiological measurements alone should not be considered. These measurements should only be used as ancillary information.

Comparing the clinical outcomes of endoscopic and open calcaneoplasty have been the subject of comparisons by researchers. Lietze et al. conducted a study including 50 cases, with 33 cases in the endoscopic group and 17 cases in the open calcaneoplasty group. The post-operative outcomes in both groups were significantly better than the pre-operative outcomes, but there was no difference in the post-operative outcomes between the groups. However the endoscopic group had a lower rate of complications, including altered sensation, infection, and scar tenderness, compared to the open calcaneoplasty group (20% vs. 48%) [28]. Pi et al conducted a study comparing the clinical outcomes of endoscopic (27 patients) and open (20 patients) calcaneoplasty. There was no significant difference between the two groups in post-operative AOFAS scores, VAS and radiological parameters. No complications were observed in the endoscopic calcaneoplasty group, but two patients in the open group experienced local neurological complications, which were reported to have fully recovered spontaneously within six months [29]. It should be noted that some studies are reporting superior results for endoscopic calcaneoplasty compared to open surgeries. Bohu et al. Chimenti et al. and Cusumano et al. declared that the endoscopic technique was superior to open techniques in their studies in 2009, 2017, and 2021, respectively [30,15,7]. Although the number of centers performing endoscopic calcaneoplasty is increasing, the gold standard surgical procedure for Haglund's deformity has not yet been clarified.

The study has limitations such as the retrospective nature of the research, the small number of cases, the short follow-up period, and the lack of a comparison group.

CONCLUSION

Endoscopic calcaneoplasty is a reliable treatment method in patients with Haglund's deformity, that provides rapid recovery, early return to daily activities and sports, and a low complication rate. Trials with larger patient populations, longer follow-ups, and comparison groups may shed more light on this procedure.

Author contribution

Study conception and design: İHR, EÇ, and NG; data collection: İHR and NG; analysis and interpretation of results: İHR and EÇ; draft manuscript preparation: İHR and EÇ. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Ethical approval for this study was obtained from Sanko University Clinical Studies Ethics Committee (Approval number: 202310-19).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

A potential prognostic indicator in methanol intoxication: Body temperature

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Received: 3 March 2024, Accepted: 21 May 2024,
Published online: 29 June 2024

ABSTRACT

Objective: Methanol intoxication is a type of poisoning with high mortality and morbidity. The current study aims to examine patients diagnosed with methanol intoxication and treated with standardized treatment to collect data that may be used to predict patient outcomes and mortality.

Materials and Methods: The current study was a retrospective study and included patients over 18 years of age diagnosed with methanol intoxication between 1st March, 2011 and 1st March, 2021. All patients were treated with the treatment protocol determined by the clinic in accordance with the guidelines. Sociocultural characteristics, vital and laboratory findings, and clinical outcomes of the patients were analyzed.

Results: Of the 28 patients included in the study, 80% were male, and the median age was 49. Patients were divided into two groups: survived and deceased. The median time since last alcohol intake was higher in surviving group (7 hours (Q1-Q3:6-12) vs 4 hours (Q1-Q3:2-17), p=0.005) and the amount of alcohol per kilogram of weight was lower in surviving group (3.13 ml/kg (Q1-Q3: 1.34-4.46) vs 8.81 ml/kg (Q1-Q3:5.22-9.49), p=0.002). The body temperature was lower in deceased group (35.40 °C (Q1-Q3:34.95-35.50) vs 36.40 °C (Q1-Q3:36.10-36.55), p=0.001). The current study showed that the other diagnostic factors of mortality in methanol intoxication are serum pH, lactate levels, bicarbonate levels, base deficit, anion deficit, the level of consciousness of the patient at admission, the time since the last alcohol consumption, and the amount of methanol ingested.

Conclusion: In this study, it was concluded that moderate hypothermia may be an indicator of mortality in addition to classical findings. Thus, it has been shown that hypothermia will be effective in methanol intoxication in addition to other early markers for early diagnosis and rapid initiation of treatment.

Keywords: methanol, toxicity, temperature, hypothermia, mortality.

INTRODUCTION

Methanol (methyl alcohol) is the simplest aliphatic alcohol, biochemically consisting of a methyl group attached to a hydroxyl group [1]. The primary chemical characteristics of the substance include being lightweight, volatile, flammable, and colorless [2]. It has a slightly alcoholic odor similar to ethanol. It is called wood spirit because it was first created by distilling wood at high temperatures in an airless environment. Today, it is used industrially as a precursor to many chemicals such as formaldehyde, acetic acid, and methyl benzoate and as a solvent for some chemicals.

The elimination half-life of methanol in intoxication is 24 hours [1]. It reaches its peak distributional concentration in 30-60 minutes [1]. Methanol undergoes primary elimination in the liver. It is converted to formaldehyde via hepatic alcohol dehydrogenase. Although formaldehyde is a toxic metabolite, it is metabolized rapidly via aldehyde dehydrogenase, so its effect is not apparent. Formaldehyde is metabolized to formic acid via aldehyde dehydrogenase. Formic acid is the primary metabolite that causes methanol-related toxic symptoms [1,3]. It is rapidly converted to its conjugated base formate and free hydrogen ion. Tetrahydrofolate synthetase breaks down formic acid into carbon dioxide and water in the final stage of metabolism. Folinic acid is the cofactor of the last step in metabolism (Figure 1).

Formic acid is the leading toxic agent in methanol metabolism [1,3]. Formaldehyde is rapidly metabolized to formic acid, which binds to the cytochrome oxidase enzyme at the end of the respiratory chain in mitochondria. The inhibition of the cytochrome oxidase enzyme disrupts oxidative metabolism. Simultaneously, the rapid dissociation of formic acid into formate and free hydrogen ions causes a decrease in serum pH and an increase in the inhibition rate of cytochrome oxidase with the resulting acidosis. All physiologic changes trigger an increase in serum lactate concentration. Due to the inhibition of aerobic metabolism by formic acid, cells activate anaerobic metabolism pathways. As a result of increased anaerobic metabolism, serum lactate concentration increases, pH decreases further, and acidosis deepens [1,4,5]. Due to increased acidosis, the conversion of formic acid to formate slows down, and the toxic activity of formic acid increases. Therefore, an increase in serum lactate concentration is triggered. A vicious cycle of formic acid and lactate occurs in methanol toxicity. As methanol is broken down, the osmolar gap decreases, and metabolic acidosis with increased anion gap occurs (Figure 1) [1,4,6].

Metabolic acidosis with increased anion gap is the leading cause of mortality in methanol intoxication [1,7,8]. Therefore, treatment should be initiated rapidly for suspected methanol intoxication. Sodium bicarbonate, fomepizole, ethanol, folinic acid, and hemodialysis treat methanol intoxication [1,4,9].

Sodium Bicarbonate: The level of metabolic acidosis on admission is a prognostic marker [10-12]. In cases of suspected methanol intoxication, it is recommended to start intravenous sodium bicarbonate infusion if the pH is <7.3 [1]. Early correction of acidosis increases the conversion rate of formic acid to formate.

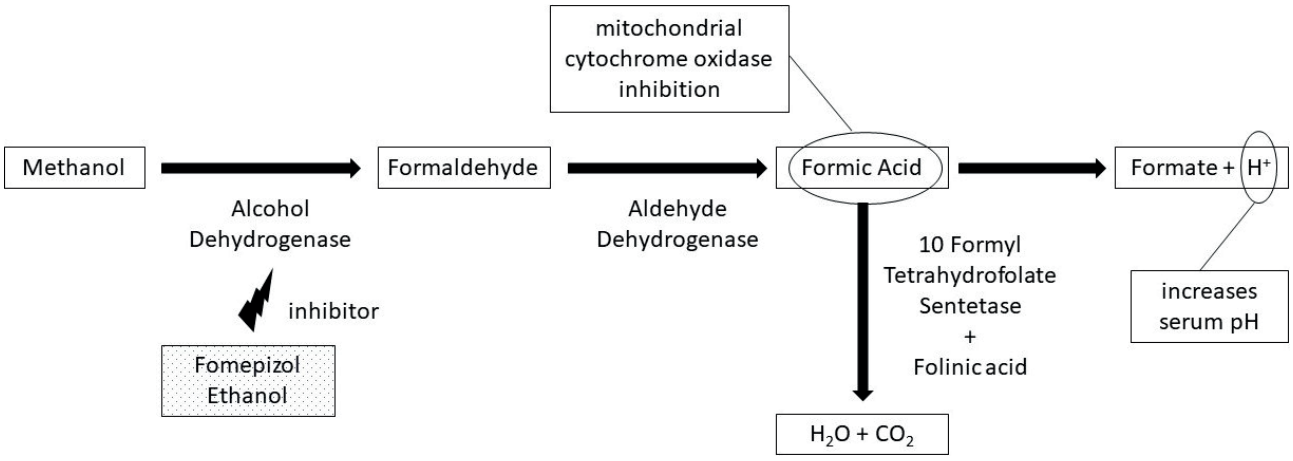

Figure 1. The metabolism of methanol

Fomepizole/Ethanol: It is a potent inhibitor of the alcohol dehydrogenase in the first step of metabolism. The affinity of ethanol for alcohol dehydrogenase is 20 times higher than methanol [13]. Therefore, it acts as a competitive inhibitor of alcohol dehydrogenase.

Hemodialysis: Removes methanol and its toxic metabolites from circulation and regulates serum pH [1,14]. The circulating half-life of methanol is prolonged in ethanol-treated patients. Hemodialysis should be started immediately to prevent prolonged methanol circulation and undesirable physiological effects.

The leading causes of methanol intoxication are accidental ingestion or inhalation of chemicals and oral ingestion due to using methanol to produce home-distilled alcohol. Although the rate of methanol intoxication in Turkey is not known, it is known that there was a relative increase in methanol intoxication cases in 2016 and 2020 [15].

The current study aims to examine patients diagnosed with methanol intoxication and treated with standardized treatment to obtain data that may be useful in predicting patient outcomes and mortality.

MATERIALS and METHODS

Approval for the study was obtained from the Clinical Research Ethics Committee of the Hacetttepe University (Project no: GO 21/494, decision no: 2021/08-29). The current study was planned as a single-center retrospective study. Patients over 18 years old diagnosed and treated for methanol intoxication in the emergency department were included in the study between 1st March, 2011 and 1st March, 2021. The data were scanned through the hospital information system and printed files.

Hospital records were retrospectively reviewed for cases reported as methanol poisoning. The American Academy of Clinical Toxicology criteria for fomepizole or ethanol treatment in methanol intoxication were used for the diagnose [1]. Patients who met at least one of the following criteria and received ethanol and folic acid treatment were included in the study. Patients had to fulfill the following criteria to be included. A total of 28 patients were included in the study.

1. Plasma methanol concentration > 20 mg/dl

or

2. Recent history of ingestion of methanol with serum osmol gap > 10 mOsm/L

or

3. History or strong clinical suspicion of methanol poisoning and at least two of the following criteria:

   a. Arterial pH <7.3

   b. Serum bicarbonate <20 meq/L (mmol/L)

   c. Osmolal gap >10 mOsm/kg L

All patients were treated with the treatment protocol determined by the clinic in accordance with the guidelines. Hemodialysis was performed immediately in patients who met the criteria determined by Extracorporeal Treatments in Poisoning as indications for hemodialysis in methanol intoxications [16] (Table 1).

Demographic characteristics such as age, gender, marital status, presence and duration of alcohol and smoking, laboratory results, and outcomes were recorded.

Statistical analysis was performed using the IBM SPSS for Windows version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in median (Q1-Q3 values) for continuous variables and in number and frequency for categorical variables. The distribution of continuous variables was analyzed using the Shapiro-Wilk tests. For multiple group comparisons, the continuous variables were analyzed using the Kruskal-Wallis, and the categorical variables were analyzed using the Pearson chi-square test and Fisher exact test.

Table 1. Hemodialysis criteria

Hemodialysis criteria
1. Coma, Seizures, New Vision Deficits
2. Metabolic acidosis (blood pH ≤ 7.15)
3. Persistent metabolic acidosis despite adequate supportive measures and antidotes
4. Serum anion gap higher than 24 mmol/L
5. Serum methanol concentration:
a. greater than 70 mg/dL in the context of fomepizole therapy
b. greater than 60 mg/dL in the context of ethanol treatment
c. greater than 50 mg/dL in the absence of an alcohol dehydrogenase blocker
6. Renal Failure

The statistical analysis between two independent groups with non-normal distribution data was performed with the Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was used to demonstrate the accuracy of characteristics in mortality of methanol intoxication. The Youden index was used to adjust the best cut-off point. The calculation of sensitivity and specificity was performed with the 95% confidence intervals. A p-value of <0.05 was considered statistically significant.

RESULTS

Of the 28 patients included in the study, 80% were male, and the median age was 49. Of all patients, 19 were treated with hemodialysis, and 8 (28.6%) died. Patients were divided into two groups: survived and deceased. The characteristics of the two groups were analyzed. The median time since last alcohol intake was 7 hours (Q1-Q3: 6 - 12) in the deceased group and 4 hours (Q1-Q3: 2 - 17) in the surviving group (p=0.005). The amount of alcohol per kilogram of weight consumed at the last drink in the deceased group (8.81 ml/kg (Q1-Q3: 5.22 - 9.49)) was higher than in the surviving group (3.13 ml/kg (Q1-Q3: 1.34 - 4.46)) (p=0.002) (Table 2).

Differences in vital signs between the two groups were analyzed. The median body temperature was 35.40 °C (Q1-Q3: 34.95 - 35.50) in the deceased group and 36.40 °C (Q1-Q3: 36.10 - 36.55) in the surviving group (p=0.001). Among vital signs, only body temperature significantly differed between the two groups (Table 2).

The blood gas analysis was analyzed. Median pH was 6.79 (Q1-Q3: 6.72 - 6.85), bicarbonate was 4.85 mmol/L (Q1-Q3: 4.40 - 5.75), and lactate was 46,50 mmol/L (Q1 Q3: 13.45 - 18.55) in the deceased group, while the median pH was 7.18 (Q1-Q3: 7.13 - 7.24), bicarbonate was 8.75 mmol/L (Q1-Q3: 6,55 - 16.30) and lactate was 2.85 mmol/L (Q1-Q3: 1.70 - 8.95) in surviving group (p<0.001, 0.003 and <0.001, respectively) (Table 2). The median base deficit was 23.70 (Q1-Q3: 17.20 - 27.90) and the median anion gap was 23.70 (Q1-Q3: 16.15 - 28.00) in survived group, while the median base deficit was 32.50 (Q1-Q3: 27.75 - 37.45) and the median anion gap was 32.50 (Q1-Q3: 27.67 - 37.62) in deceased group (p=0.002, p=0.002, respectively).

Differences between deceased and surviving groups were analyzed regarding sociocultural characteristics such as marital status, being a parent and educational status, comorbidities, and complaints on admission. The two groups had no significant differences regarding sociocultural characteristics and comorbidities. Significant differences were found in cooperation and orientation on admission (p=0.033, p=0.011, respectively) (Table 3). All (100%) of the deceased patients received hemodialysis. In the surviving group, 55% received hemodialysis (Table 3).

ROC analysis was performed, and thresholds were calculated for the characteristics with statistically significant differences between the deceased and surviving groups (Table 4). In the ROC curve diagram for serum pH predicting mortality, the AUC was 0.959 (95% CI= 0.905 - 1.000). The serum pH threshold for death was 6.97 (sensitivity= 100%, specificity= 95%). In the ROC curve diagram for serum lactate, AUC was 0.950 (95% CI= 0.875 - 1.000), and the threshold was 9.8 mmol/L (sensitivity= 100%, specificity= 80%). AUC for the anion gap was 0.872 (95% CI= 0.739 - 1.000), the threshold was 26.95 (sensitivity= 100%, specificity= 70%), AUC for temperature was 0.925 (95% CI= 0.821 - 1.000), the threshold was 35.95 0C (sensitivity= 100%, specificity= 85%) (Table 4).

DISCUSSION

Methanol is a solvent in cleaners, antifreeze, and paint solvents [9]. Although it frequently causes poisoning by ingestion, it may also cause poisoning by inhalation and dermal route [17]. Home-distilled alcohol is produced predominantly in countries where alcohol sales are illegal and in low-income countries due to high alcohol prices [18]. Methanol, cheaper than ethanol, is used in home-distilled alcohol production [19]. For this reason, methanol toxicity outbreaks have emerged in many low-income countries and countries where alcohol sales are illegal [20-23]. In 2019, a consensus of clinical toxicologists defined 3 cases occurring within 72 hours in the same region as a methanol toxicity outbreak [24]. In 2018, it was reported that 31 people were affected by a methanol outbreak in Malaysia; 30 were male (96.7%), the average age was 32 years, and the mortality rate was 61.3% [21]. In a 2014 outbreak of methanol toxicity in Kenya,

Table 2. The effect of variables on mortality

Characteristics (median/Q1-Q3)	Total (N=28)	Survived (n=20)	Deceased (n=8)	p*
Age (year)	**49.0 (36.0 – 56.0)**	**39.0 (33.5 – 51.5)**	**58.00 (50.00 – 62.50)**	**0.012**
Duration of alcohol consumption (year)	**21.00 (10.00 – 30.50)**	**17.5 (7.50 – 24.0)**	**30.50 (26.00 – 39.00)**	**0.009**
Time since last alcohol intake (hour)	**6.0 (2.0 – 12.0)**	**4.0 (2.0 – 17.0)**	**7.00 (6.00 – 12.00)**	**0.005**
Systolic Blood Pressure (mmHg)	130.50 (113.50 – 140.00)	132.00 (115.50 – 143.50)	126.00 (104.00 – 138.00)	0.387
Diastolic Blood Pressure (mmHg)	78.50 (68.50 – 89.00)	80.50 (71.50 – 89.00)	78.00 (54.00 – 84.00)	0.297
Pulse (beat/min)	83.50 (72.00 – 97.00)	83.50 (75.50 – 96.00)	74.50 (55.50 – 98.00)	0.445
Temperature (°C)	**36.10 (35.45 – 36.50)**	**36.40 (36.10 – 36.55)**	**35.40 (34.95 – 35.50)**	**0.001**
Glascow Coma Scale Score	**14.5 (5.0 – 15.0)**	**15.0 (10.5 – 15.0)**	**3.00 (3.00 – 7.00)**	**0.002**
Saturation (%)	95.00 (91.50 – 97.00)	96.50 (94.00 – 97.00)	90.00 (85.50 – 97.50)	0.118
Sodium (mEq/L)	133.50 (132.00 – 138.00)	133.50 (132.00 – 136.50)	134.00 (129.00 – 140.00)	0.818
Potassium (mEq/L)	4.69 (4.02 – 5.11)	4.18 (3.74 – 5.05)	5.20 (4.69 – 5.45)	0.033
Chloride (mEq/L)	101.50 (97.0 – 103.00)	102.00 (98.50 – 107.50)	98.00 (96.00 – 101.00)	0.058
Calcium (mg/dL)	9.15 (8.79 – 9.52)	9.03 (8.71 – 9.38)	9.53 (9.16 – 10.15)	0.056
Phosphorus (mg/dL)	**4.90 (4.15 – 6.83)**	**4.70 (3.71 – 5.06)**	**7.71 (6.31 – 9.12)**	**0.002**
Creatinine (mg/dL)	**1.12 (0.89 – 1.27)**	**1.02 (0.82 – 1.21)**	**1.30 (1.14 – 1.43)**	**0.008**
Urea (mg/dL)	12.22 (7.80 – 15.98)	12.15 (7.95 – 14.64)	14.40 (7.55 – 20.49)	0.445
Uric acid (mg/dL)	8.00 (6.87 – 9.02)	8.20 (6.79 – 9.02)	7.86 (7.61 – 10.08)	0.525
Albumin (g/dL)	4.26 (3.66 – 4.66)	4.37 (3.98 – 4.67)	3.66 (3.55 – 4.25)	0.104
ALT (U/L)	28.00 (19.50 – 73.00)	30.00 (14.00 – 75.00)	28.00 (23.50 – 66.50)	0.703
AST (U/L)	47.00 (30.00 – 86.00)	43.00 (23.00 – 79.50)	64.00 (43.00 – 94.00)	0.222
ALP (U/L)	85.50 (69.50 – 102.50)	83.00 (57.00 – 114.00)	91.00 (84.50 – 100.50)	0.309
GGT (U/L)	77.00 (46.00 – 153.00)	65.50 (32.00 – 153.00)	91.00 (74.00 – 495.00)	0.178
Total Bilirubin (mg/dL)	0.56 (0.35 – 1.04)	0.45 (0.33 – 0.90)	0.70 (0.37 – 1.57)	0.558
INR	1.21 (1.06 – 1.51)	1.19 (1.06 – 1.40)	1.38 (1.14 – 1.54)	0.373
Hemoglobin (g/dL)	14.65 (13.55 – 15.85)	14.90 (13.95 – 15.90)	13.65 (12.60 – 15.10)	0.186
Hematocrit (%)	45.00 (41.90 – 48.30)	45.60 (41.90 – 48.30)	43.75 (41.50 – 48.95)	0.799
Leukocyte (x10^3/µL)	9.90 (8.30 – 14.20)	10.40 (7.90 – 14.40)	9.55 (9.15 – 11.70)	0.780
Lymphocyte (%)	26.15 (13.99 – 34.18)	24.96 (13.27 – 34.18)	31.30 (21.07 – 38.52)	0.263
Neutrophile (%)	62.32 (51.49 – 77.40)	70.05 (51.49 – 79.11)	60.80 (53.20 – 68.73)	0.334
Thrombocyte (x10^3/µL)	239.00 (194.00 – 280.50)	250.50 (198.00 – 288.00)	209.00 (182.00 – 239.00)	0.170
Mean Corpuscular Volume (fL)	**97.00 (94.50 – 103.50)**	**95.70 (91.70 – 97.80)**	**104.65 (103.70 – 107.95)**	**<0.001**
pH	**7.15 (6.85 – 7.21)**	**7.18 (7.13 – 7.24)**	**6.79 (6.72 – 6.85)**	**<0.001**
Glucose (mg/dL)	**124.00 (106.50 – 219.50)**	**113.50 (104.00 – 194.00)**	**220.50 (133.50 – 275.50)**	**0.025**
Lactate (mmol/L)	**8.45 (2.05 – 14.45)**	**2.85 (1.70 – 8.95)**	**16.50 (13.45 – 18.55)**	**<0.001**
PO_2 (mmHg)	**65.90 (58.75 – 80.70)**	**62.85 (54.90 – 72.70)**	**89.00 (63.90 – 91.25)**	**0.015**
PCO_2 (mmHg)	25.20 (17.95 – 32.40)	27.75 (19.15 – 35.35)	22.40 (17.10 – 24.95)	0.079
HCO_3 (mmol/L)	**7.25 (4.82 – 11.05)**	**8.75 (6.55 – 16.30)**	**4.85 (4.40 – 5.75)**	**0.003**
Base deficit	**26.95 (20.00 – 29.70)**	**23.70 (17.20 – 27.90)**	**32.50 (27.75 – 37.45)**	**0.002**
Serum osmolarity	281.41 (275.11 – 291.92)	279.44 (275.11 – 289.04)	284.06 (277.48 – 297.58)	0.416
Anion Gap	**26.95 (19.90 – 30.20)**	**23.70 (16.15 – 28.00)**	**32.50 (27.67 – 37.62)**	**0.002**

Table 3. The characteristics of study group

Characteristics (n,%)	Alive (n=20)	Exitus (n=8)	p*
Gender			
Male	16 (80)	8 (100)	0.295
Female	4 (20)	0 (0)	
Marital status			
Single	7 (35)	1 (12.5)	0.380
Married	11 (55)	5 (62.5)	
Divorced	2 (10)	2 (25)	
Being parent			
Yes	12 (63.7)	7 (87.5)	0.214
No	8 (33.3)	1 (12.5)	
Educational status			
Primary	11(55)	2 (25)	0.067
Secondary	5 (25)	6 (75)	
Higher	4 (20)	0 (0)	
Diabetes mellitus			
Yes	8 (40)	0 (0)	0.063
No	12 (60)	8 (100)	
Hypertension			
Yes	5 (25)	2 (25)	
No	15 (75)	6 (75)	>0.999
Coronary artery diseases			
Yes	4 8 (20)	0 (0)	0.295
No	16 (80)	8 (100)	
Cirrhosis			
Yes	2 (10)	2 (25)	0.555
No	18 (90)	6 (75)	
Chronic alcoholism			
Yes	17 (85)	8 (100)	0.536
No	3 (15)	0 (0)	
Home distilled alcohol			
Yes	7 (35)	4 (50)	0.671
No	13 (65)	4 (50)	
Blurred vision			
Yes	7 (35)	3 (37.5)	>0.999
No	13 (65)	5 (62.5)	
Headache			
Yes	9 (45)	4 (50)	>0.999
No	11 (55)	4 (50)	
Loss of vision			
Yes	3 (15)	1 (12.5)	>0.999
No	17 (85)	7 (87.5)	
Nausea			
Yes	12 (60)	5 (62.5)	>0.999
No	8 (40)	3 (37.5)	
Vomiting			
Yes	10 (50)	2 (25)	0.401
No	10 (50)	6 (75)	
Cooperation			
Yes	**13 (65)**	**1 (12.5)**	**0.033**
No	**7 (35)**	**7 (87.5)**	
Orientation			
Yes	**14 (70)**	**1 (12.5)**	**0.011**
No	**6 (30)**	**7 (87.5)**	

58 of 62 patients were reported to be male (93%), 13 patients died (21%), and the median age was 30 years [20]. In the current study, 26 of 28 patients were male (92.85%). The median age was 49, and the mortality rate was 28.57% (n=8). Similar results were obtained with the literature. The observed median age in the present study could potentially be attributed to middle-aged individuals of low socioeconomic position who engage in the utilization of methanol for the manufacturing of home-distilled alcohol. Mortality rates are similar to the literature.

In studies about methanol intoxications, medical history and complaints on admission were evaluated [18,25,26]. It was observed that patients admitted to the emergency department had dizziness, GI symptoms, visual symptoms, and dyspnea. However, no study was found in which these findings were analyzed as an indicator of mortality. The current study analyzed the patients' sociocultural and socioeconomic characteristics and presented complaints to predict mortality. Contrary to expectations, parameters such as marital status, having children, and educational status did not significantly affect mortality.

In the methanol outbreak in Taiwan, it was found that the Glasgow Coma Scale score (GCS) could be used to predict mortality (OR: 0.816, 95% CI: 0.682-0.976) [26]. Mahdavi et al. found that median GCS was lower in deceased patients than in survivors (5 vs. 15, respectively, p=0.001) [11]. In the current study, only GCS and impaired consciousness significantly predicted mortality among the complaints and symptoms on admission. These results can be explained by central nervous system depression caused by increased methanol metabolites.

In a study involving 795 patients examining the methanol outbreak in Iran in 2020, , the time elapsed after the last alcohol intake was 24 hours in patients who died and 48 hours in survivors (p=0.014) [11]. In the current study, the time since the last alcohol consumption was higher in the deceased group. The current result was accepted as a predicted situation. As the duration of methanol consumption increases, the severity of metabolic acidosis induced by methanol metabolism and formic acid will deepen. Increased metabolic acidosis and formate concentration are correlated with mortality [1]. Delays in hospital admission and medical intervention after methanol consumption

Table 4. The ROC analysis of the characteristics

Diagnostic Test	AUC	Standard error	P	95% CI		Threshold	Sensitivity	Specificity
				Lower Bound	Upper Bound			
pH	0.959	0.033	<0.001	0.905	1.000	≤6.97	100	95
MCV (fL)	0.991	0.013	<0.001	0.965	1.000	≥102.95	100	90
Temperature (°C)	0.925	0.053	0.001	0.821	1.000	≤35.95	100	85
Lactate (mmol/L)	0.950	0.038	<0.001	0.875	1.000	≥9.8	100	80
HCO_3 (mmol/L)	0.866	0.068	0.003	0.733	0.999	≤6.8	100	75
Base deficit	0.872	0.068	0.002	0.739	1.000	≥26.95	100	70
Anion gap	0.872	0.068	0.002	0.739	1.000	≥26.95	100	70
Phosphorus (mg/dL)	0.872	0.080	0.002	0.715	1.000	≥5.90	87.5	85
Glascow coma								
scale	0.847	0.089	0.005	0.672	1.000	≤8	87.5	80
Glucose (mg/dL)	0.775	0.102	0.025	0.574	0.976	≥130	87.5	70
Age (year)	0.890	0.083	0.012	0.647	0.972	≥46.5	87.5	60
Last alcohol intake (mL/kg)	0.888	0.076	0.002	0.738	1.000	≥5.01	85	87.5

are associated with increased mortality. Therefore, although the result obtained differs from previous studies, it should be considered that mortality increases as the time elapsed after methanol consumption increases.

Patients who died in the methanol outbreak in Norway were found to have lower serum pH levels (6.57 vs. 7.25, respectively, p=0.001) and higher base deficit (28 mmol/L vs. 18 mmol/L respectively, p=0.001) than the group who survived without sequelae [18]. In 2012, in the methanol outbreak in the Czech Republic (n=101), serum lactate level (6.75 mmol/L) was found to be more acidic in patients who died compared to patients who survived without and with sequelae (7.31 mmol/L vs 7.02 mmol/L respectively, p<0.001). The same study found median bicarbonate levels were lower in deceased patients than in survivors without sequelae (5.2 mmol/L vs. 17.8 mmol/L, p<0.001). The median base deficit (29.0 mmol/L vs 6.1 mmol/L, p<0.001) and the median anion gap (39 mmol/L vs 22 mmol/L, p<0.001) were higher in deceased patients [25]. In the current study, median pH and bicarbonate levels were lower in the deceased group than in the surviving group. Median lactate, median PO2, median base deficit, and median anion gap were higher in the deceased group. The data obtained were similar to the previous studies in the literature.

Among the studies examining methanol intoxications, a limited number of studies analyzed data on body temperature. Many external and patient-related factors determine body temperature. However, the typical features of methanol outbreaks are that patients from the same geographical region and with the same climatic characteristics present to the emergency department. A study involving 32 patients diagnosed with methanol intoxication in Taiwan found that hypothermia developed in 50% of the patients [26]. Cox regression analysis in the same study showed that hypothermia was associated with mortality (OR: 168.686, 95% CI: 2.685-10595.977, p=0.015) [26]. The current study found lower body temperature in the deceased group than in the surviving group. In a study conducted by Mohler et al., it was observed that hypothermia occurred within 1 to 2 hours in rats given methanol compared to those given saline, and behavioral responses that could be exhibited to get away from hypothermia were disrupted [27]. Thus, it was experimentally proven that methanol intoxication has a negative effect on thermoregulation. Since methanol metabolism is clearly explained, metabolic changes that may occur can be predicted. The severity of these metabolic changes may be associated with mortality. However, using an easily measurable and simultaneous assessment, such as body temperature as a possible marker of mortality, is valuable data.

A multivariate regression analysis was performed in a study of the methanol outbreak in the Czech Republic. In this study, serum pH level <7.0 (OR 0.04 (0.01-0.16), p < 0.001), patient presenting with coma (OR 29.4 (10.2-84.6), p < 0.001) and negative

serum ethanol (OR 0.08 (0.02-0.37), p < 0.001) were found to be independent parameters that could be used to predict mortality [25]. In the Cox regression analysis performed in the study analyzing methanol intoxications in Taiwan, GCS (OR: 0.816, 95% CI: 0.682-0.976, p= 0.026), hypothermia (OR: 168. 686, 95% CI: 2.685-10,595.977, p= 0.015) and serum creatinine level (OR: 4.799, 95% CI: 1.321-17.440, p= 0.017) were associated with mortality [26]. In the current study, regression analysis could not be performed due to insufficient patients. However, ROC analysis was performed for the variables in which a statistical difference was found between the deceased and surviving groups. As expected, serum pH, lactate, bicarbonate, base deficit, and anion gap had thresholds with high sensitivity and specificity. After serum pH and lactate, body temperature was the parameter with the highest AUC value and high sensitivity and specificity. It was concluded that hypothermia caused by methanol suppression of the thermoregulation system in the central nervous system is a parameter that can be used to predict mortality.

CONCLUSION

Methanol intoxication has a high mortality rate. However, early diagnosis and treatment will reduce possible mortality and morbidity rates. The diagnostic factors of mortality in methanol intoxication are serum pH, lactate levels, bicarbonate levels, base deficit, anion deficit, the level of consciousness of the patient at admission, the time since the last alcohol consumption, and the amount of methanol ingested. In methanol intoxications resulting in death, the presence of central nervous system and metabolic disorders, as well as moderate hypothermia, was observed. If the patient's history suggests methanol intoxication, investigating the presence of hypothermia before obtaining laboratory results may help predict mortality. Especially in patients with a preliminary diagnosis of methanol intoxication, hypothermia on initial physical examination should lead to immediate initiation of methanol intoxication treatment. Thus, mortality due to methanol intoxication can be reduced.

Limitation

Since the current study was conducted in a single center with a limited number of patients, the targeted regression analysis models could not be created. Although standardized treatment protocols were carried out in the center where the study was conducted, the lack of fomepizole might have a negative effect on mortality.

Author contribution

Study conception and design: AB, GK, OAU; data collection: AB, GK; analysis and interpretation of results: AB, OAU, MA; draft manuscript preparation: AB, MA. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Hacettepe University (Protocol no: GO 21-494/06.04.2021).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

The role of reconstructive plastic surgery in the treatment of victims of the 2023 Kahramanmaraş earthquake

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Received: 4 April 2023, Accepted: 22 May 2024,
Published online: 29 June 2024

ABSTRACT

Objective: As a result of the 2023 Kahramanmaraş earthquake, medical institutions experienced a large influx of patients requiring acute multidisciplinary surgical and medical care. This study aimed to evaluate the patient demographics and treatment management of survivors admitted to our reconstructive plastic surgery department.

Materials and Methods: We retrospectively analyzed the age, sex, time under the wreckage, time of admission, types and locations of injuries, treatment modalities, receipt of hyperbaric oxygen therapy, and receipt of vacuum-assisted closure therapy of the earthquake victims referred to our department.

Results: The definitive management of all 42 earthquake survivors admitted to our department was reviewed. This included five free flaps, four regional flaps, 18 split-thickness skin grafts, and one maxillofacial fracture repair. Eight patients were treated conservatively including two with non-displaced maxillofacial fractures. Of the 26 patients treated for lower extremity injuries, four were already amputees. Among the remaining 22 patients with such injuries, one underwent Charcot amputation plus free flap reconstruction to preserve extremity length and one underwent below-the-knee amputation. Of the 16 upper extremity injuries, two patients referred with extensive forearm necrosis underwent forearm amputation. To preserve extremity length and ensure the limbs were suitable for biomechanical orthoses, free transverse upper gracilis musculocutaneous flaps and free chimeric Anterolateral- Vastus Lateralis musculocutaneous flaps were performed.

Conclusion: This study illustrates the value of multi-modal reconstructive plastic surgery in the treatment of disaster survivors, particularly in the management of multi-trauma.

Keywords: amputation, earthquake, fasciotomy, flap, skin graft.

INTRODUCTION

As a country spread over three major fault lines, Turkey is particularly vulnerable to earthquakes, with 61% of the damage caused by natural disasters in Turkey over the last 60 years attributable to earthquakes [1].

The injuries caused by earthquakes are most often due to victims being hit by or buried under parts of collapsed or collapsing buildings. This can result in compartment syndrome, soft tissue damage, fractures, and crush injuries, with the upper and lower extremities the most frequently affected areas [2]. These are important causes of morbidity and such injuries can be life-threatening. Most require fasciotomies under emergency conditions. However, the majority of fasciotomies opened under emergency conditions are inadequate, while others fail because metabolites produced as a result of crush injuries cause acute renal failure, increasing the mortality rate [3, 4]. Therefore, the appropriate and effective management of survivors is critical, beginning with the first intervention.

On February 6, 2023, two major earthquakes occurred in the Southeastern Anatolia region of Turkey. The first occurred at 04.17 local time in the Pazarcık district (37.288N–37.043E), with a depth of 8.6 km and a magnitude of 7.7 Mw. The second hit at 13.24 local time in the Elbistan district (38.089N–37.239E) at a depth of 7 km and a magnitude of 7.6 Mw. Together, they affected 11 provinces with a total population of over 16 million, killing over 50,000 people in the region [1, 5].

However, the emergency and advanced examination and treatment of earthquake survivors was hindered by damage to healthcare facilities and injured healthcare workers. For this reason, most of the seriously injured survivors had to be transferred to higher-level centers in other cities, including Istanbul, Ankara, Izmir, Adana, and Konya.

Our facility is one of the largest tertiary-level hospitals in Turkey. Eligible wards were converted into intensive care units, which were filled only with earthquake survivors. In our department, all non-urgent elective surgical operations were postponed. Patients awaiting surgery and those eligible for discharge were released from the hospital.

In this study, we aim to share the demographic data of the survivors admitted to the plastic surgery department of our center after the 2023 Kahramanmaraş earthquake, to describe the treatment and management protocols utilized, and to demonstrate the importance of a multidisciplinary approach in overcoming various obstacles while managing a large influx of patients following a disaster.

MATERIALS and METHODS

This study was approved by our institutional ethics committee (Istanbul Faculty of Medicine Clinical Research Ethics Committee) on the 9th February 2024 (approval no. 255).

We performed a retrospective analysis of the medical records of earthquake survivors treated in the Plastic Reconstructive and Aesthetic Surgery Clinic of Istanbul University Faculty of Medicine between the 8th of February 2023 and the 1st of March 2023.

Earthquake victims with the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnostic code X34 (victim of cataclysmic earth movements caused by earthquake) or X39 (exposure to forces of nature) admitted with open wounds, neural deficits, hand or wrist fractures, or maxillofacial fractures were referred to our clinic from the Orthopedics and Traumatology Clinic, the Emergency Medicine Department, the Intensive Care Unit, the Department Of Pediatrics, the Internal Medicine Department, the Undersea And Hyperbaric Medicine Department, and the General Surgery Clinic. The data of these patients were retrospectively reviewed.

The age, sex, time of admission, time under the wreckage, hyperbaric oxygen therapy (HBOT) application, vacuum-assisted closure (VAC) therapy, length of hospital stay, injury type and location, preferred treatment approach, and comorbidities of the patients were analyzed.

Statistical analysis was performed using SPSS v.26.0 (IBM Corp., Armonk, NY, USA). Categorical measurements were expressed as numbers and percentages, means ± standard deviations (SDs), and medians (min-max) as applicable.

RESULTS

A total of 42 (54.8% [n=23] female, 45.2% [n=19] male) patients were included. Patient ages ranged from 2–86 (mean 25.9) years and 45.2% (n=19) were under 18 years old. Time under the wreckage ranged from 1–261 (mean 19.55) h (Table 1).

While 13.95% (n=6) of the patients were directly admitted to the plastic surgery clinic from the Emergency Medicine Department, 16.3% (n=7) were referred from the pediatric ICU and 4.65% (n=2) were referred from the adult ICU.

Three (7.1%) of the patients were referred due to isolated maxillofacial trauma, one of whom underwent naso-orbito-ethmoidal fracture correction by open reduction and internal fixation. One patient had a non-displaced lateral orbital wall fracture and one had a non-displaced condylar fracture. The latter two patients were treated conservatively.

There were 11 (26.2%) patients with isolated upper extremity trauma. One of these (70 h under the wreckage) underwent forearm amputation and the stump was reconstructed with a free anterolateral vastus lateralis chimeric flap (Fig. 1). Three presented with traumatic upper brachial plexus palsy, for which electromyography (EMG) was ordered for 3 weeks later. Three patients underwent split-thickness skin grafting for defect closure. Other three patients were treated conservatively because of presenting with simple abrasions.

Table 1. Demographic characteristic of the patients

	N (count)	% (percentage)	Mean
Female	23	54.8	
Male	19	45.2	
Age Classification (year)			
0-10	11	26.2	
11-20	12	28.6	
21-30	3	7.1	
31-40	6	14.3	
41-50	3	7.1	
51-60	4	9.5	
61-70	1	2.4	
70 up	2	4.8	
Length of the stay under the rubble (h)			
0-6	8		1.81 h
6-12	6		8.66 h
24-48	7		35.71 h
72 up	4		135 h

Of those admitted to our clinic, 52.4% (n=22) were referred due to isolated lower extremity trauma. One of these (12 h under the wreckage) was already a transfemoral amputee and a pedicled tensor fascia lata musculocutaneous flap was used on the contralateral side for a stage 4 ischial decubitus ulcer reconstruction. One pediatric patient presented with a transmetatarsal amputation (12 h under the wreckage) and was treated with a free vastus lateralis musculocutaneous flap. Another pediatric patient who presented with an open forefoot defect (1 h under the wreckage) underwent a free anterolateral thigh flap reconstruction for defect closure. A free vastus lateralis muscle flap was lost due to venous insufficiency and split-thickness skin grafting was performed for the final reconstruction with this patient. One patient (262 h under the wreckage) underwent a Charcot amputation and a free chimeric suprafascial anterolateral vastus lateralis thigh muscle flap was used to protect limb length. (Fig. 2) One patient underwent heel reconstruction using a reverse sural flap. Ten patients underwent STSG for defect closure. Other patients treated conservatively without requiring any surgical intervention.

Multiple significant side injuries were seen in 27.2% (n=6) of the patients, necessitating a multidisciplinary approach. One patient had lacerations to the intraoral mucosa and a non-displaced thoracolumbar vertebral fracture. A conservative approach was deemed preferable for this patient. One pediatric patient (40 h under the wreckage) was admitted to the facility with a humerus fracture, lung injury, and upper and lower extremity open fasciotomy defects. STSG for defect closure was performed. The humerus fracture was non-operative and a cast was applied. A temporary chest tube was considered for the pneumothorax injury. One patient (112 h under the wreckage) presented with a necrotic forearm and grade 4 sacral decubitus. The forearm stump was reconstructed with a free transverse upper gracilis musculocutaneous flap to preserve limb length and a gluteal musculocutaneous rotation flap was used for defect closure. Two patients (8 h and 112 h under the wreckage) had multiple open wounds and fasciotomy defects of the upper and lower extremities. Both underwent STSGs for closure of

Figure 1. a. An earthquake survivor with extensive dry necrosis on the volar side of the forearm and hand after 70 h under the wreckage. **b.** The appearance of the patient's limb and remaining humeral length after adequate debridement, HBOT, VAC therapy, and broad-spectrum antibiotics. **c.** An ALT-VL musculocutaneous flap with two skin perforators, before the ligation of the main pedicle. **d.** The flap was inset for final closure and the skin-grafted VL muscle, remnant radial artery and its concomitant veins, and cephalic vein were anastomosed to the lateral circumflex femoral artery and its concomitant veins. **e.** The patient with a biomechanical prosthetic following successful treatment.

ALT-VL, Anterolateral Thigh- Vastus lateralis; HBOT, Hyperbaric Oxygen Theraphy; VAC, Vacuum-Assisted Closure; VL, Vastus Lateralis

the defects and were treated with hemodialysis in the ICU for acute kidney injury. One patient (96 h under the wreckage) already had a below-the-knee amputation and a skin-grafted traumatic ear amputation but was referred for grade 4 sacral decubitus and peripheric facial paralysis. A tensor fascia lata static sling was used for facial palsy reconstruction and a gluteal fasciocutaneous rotation flap for grade 4 sacral decubitus reconstruction.

Negative pressure wound therapy (NPWT) was performed on 14.2% (n=6) of the patients with fasciotomy defects and 50% (n=21) of those with soft tissue infections and open wounds that could not be controlled by simple debridement. The treatment was repeated every 3 days and final wound closure was performed after 2–8 sessions of NPWT. To prevent the separation of wound edges in those patients with fasciotomy defects, either rubber bands or sutures were applied to the wound edges during the NPWT. This reduced lateral strain around the suture lines and decreased the need for skin grafts during final closure.

Cases requiring hyperbaric oxygen therapy (HBOT) underwent the treatment daily for 30 min to 2 h in a chamber pressurized at 1.5–3.0 atmospheres with 100% oxygen. This was received by 23 of the 42 patients (54.8%) with open wounds. Two

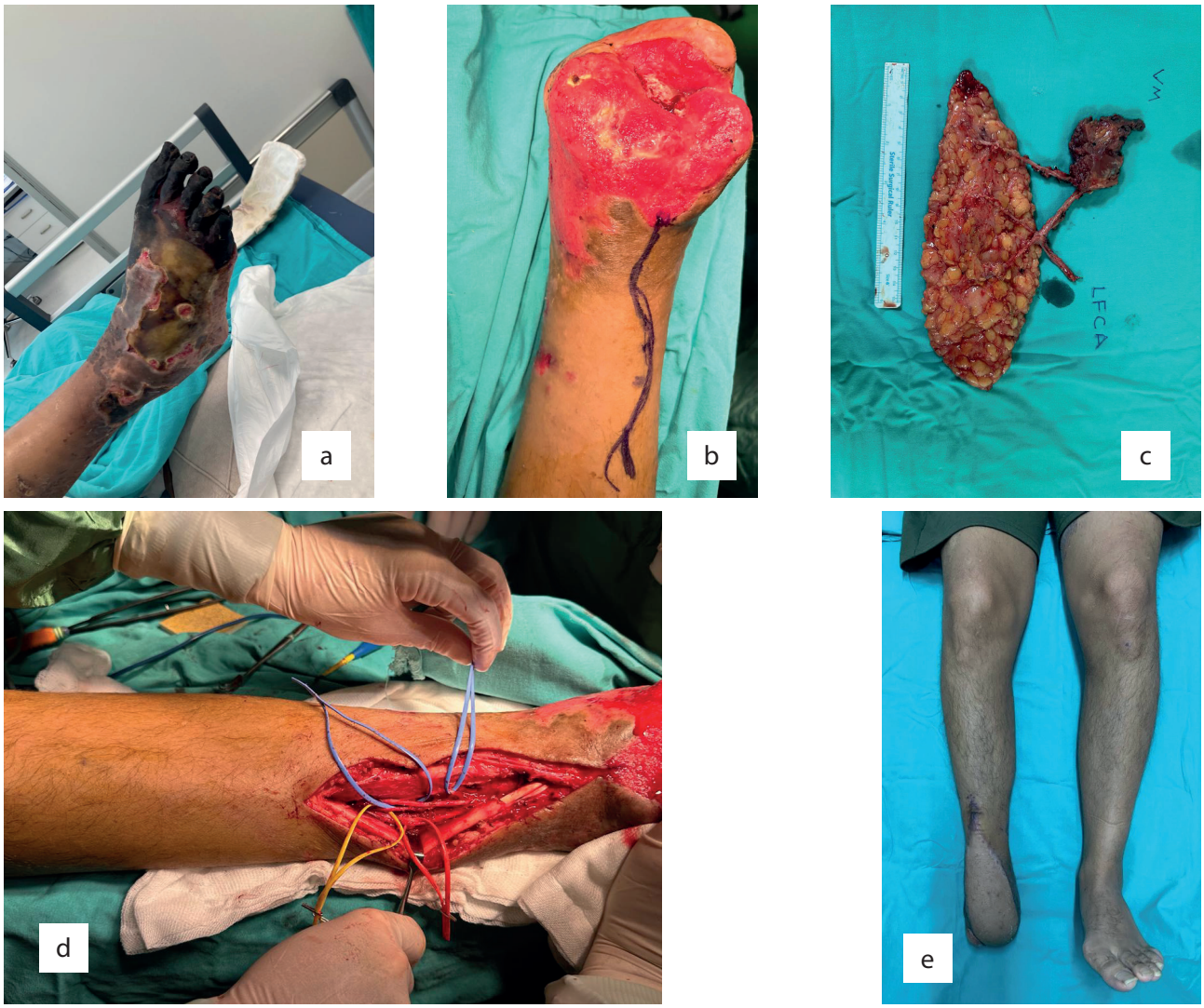

Figure 2. a. An earthquake survivor referred with foot necrosis after 262 h under the wreckage. **b.** The appearance of the patient's foot and lower limb after multiple debridements, VAC treatment, HBOT, and broad-spectrum antibiotics. **c.** A chimeric suprafascial ALT flap with the VL muscle.

patients with isolated upper extremity trauma, 16 patients with isolated lower extremity trauma, and five patients with lower and upper extremity fasciotomy defects underwent this treatment for 4–16 days (Table 2).

Table 2. The reconstruction types of the defects

Treatments	N (count)	% (percentage)
Non surgical intervention	8	19
Primary wound closure	4	9.5
STSG+NPWT	18	42.8
HBOT	23	54.7
Regional flap	4	9.52
Free flap	5	11.9
Maxillofacial fracture repair	1	2.38
Amputation	6	14.2

STSG: Split thickness skin grafting NPWT: Negative pressure wound theraphy HBOT: Hyperbaric oxygen theraphy

DISCUSSION

As our facility was some distance from the incident area, we primarily treated patients presenting with multiple injuries and those in critical condition requiring collaboration between different medical and surgical disciplines. The majority of the patients had already undergone acute-urgent procedures such as fasciotomies or amputations before they were seen at our clinic.

We observed that the level of injury, the incidence of compartment syndrome, and the amputation and reconstruction requirements were related to the time spent under the wreckage. This could not be proven statistically as the reconstructions required became more complex as the time spent under the rubble increased.

Overall, the definitive management of all 42 patients was comprehensive and included five free flaps, four regional flaps, 18 split-thickness skin grafts, and one maxillofacial fracture repair. Among the 26 lower extremity injuries treated, four patients were already amputees (one below-the-knee amputation, one transfemoral amputation, and two metatarsophalangeal amputations), one patient underwent Charcot amputation plus a free ALT-VL flap to preserve extremity length and one underwent a below-the-knee amputation. Of the 16 upper extremity injuries treated, two patients who had already been referred with extensive forearm necrosis underwent forearm amputation. To preserve extremity length and ensure the limbs were suitable for biomechanical orthoses, free transverse upper gracilis flap and free chimeric ALT-VL musculocutaneous flaps were performed. Additional nerve coaptations were also performed to preserve muscle volume (Table 3).

Only one free flap was lost. This was in a patient (40 h under the wreckage) with a forefoot defect and transmetatarsal amputation. The patient was mobilized on the fifth day after defect reconstruction using a free vastus lateralis muscle flap but, the next day, the flap failed due to venous insufficiency. A venous Doppler ultrasound examination showed that the patient had suffered superficial and deep vein reflux during the Valsalva maneuver, suggesting that the flap failure was due to deep and superficial venous insufficiency resulting from the patient's crush injury. Subsequently, other patients with lower extremity injuries who required free flap reconstruction underwent venous Doppler ultrasound preoperatively and mobilization was initiated eight days after the reconstruction, beginning with the dangling procedure.

The optimal method of trauma management in patients presenting with dirty or contaminated soft tissue and bone infections is multiple debridements followed by vacuum-assisted wound closure, broad-spectrum antibiotics, and hyperbaric oxygen treatment if required. These procedures prepare the patient for proper functional anatomical and aesthetic reconstruction [6].

VAC narrows wound edges; removes exudate, including inflammatory and infectious material; and increases angiogenesis, all of which help to reduce the wound area and facilitate the formation of granulation tissue [7]. Previous research has found that, after 4 days of vacuum-assisted therapy, tissue bacterial counts are significantly decreased [8]. Therefore, vacuum-assisted therapy was repeated every 3 days 6–8 times as part of our wound management protocol.

Among the interventions used with these patients, HBOT has the unique ability to improve tissue oxygenation, decrease pathological inflammation, and repair ischemia-reperfusion injury. Although there is a lack of high-quality evidence for the efficacy of HBOT in acute wound management, it is thought to increase various growth factors, mobilize bone marrow-derived stem/progenitor cells, and induce changes in the synthesis of monocyte chemokines, hemoxygenase-1, heat shock proteins, and hypoxia-inducible factor-1, leading to the inhibition of inflammation [9, 10]. Not all tertiary centers have access to a hyperbaric chamber. Our facility has one chamber and 24/7 access was provided for the treatment of these patients. It is contraindicated in patients with pneumothorax, restrictive lung diseases, pregnancy, concomitant topical mafenide use, viremia, and concomitant chemotherapy [10,11].

Table 3. The distribution of the injury area and preffered reconstruction option, amputation levels

	STSG	Regional Flaps	Free Flaps	Amputation levels
Upper Extremity	6 patients		Chimeric ALT-VL flap	Forearm
			Transverse upper gracilis flap	Forearm
Lower Extremity	12 patients	Gluteal rotation flap	Chimeric suprafascial ALT-VL flap	Transfemoral amputation
		Gluteal rotation flap	VL muscle flap	Below knee amputation
		Sural flap	ALT fasciocutaneous flap	Transmetatarsal amputation
		Tensor fascia lata flap		Transmetatarsal amputation
				Below knee amputation
				Charcot amputation

ALT: Anterolateral thigh flap. VL: Vastus lateralis muscle flap

Therefore, one pediatric patient with multiple side injuries and forearm fasciotomy defects was unable to undergo this treatment due to additional lung injury.

There were some limitations in this study. Firstly, although the medical records were double-checked, due to the retrospective nature of the study and the chaotic conditions following the disaster, some medical records might have been compromised. Secondly, we focused on the musculoskeletal and maxillofacial injuries of those earthquake survivors referred to our plastic surgery clinic. The details of injuries to major organs or other forms of trauma were not assessed. Thirdly, due to the remote location of the facility in relation to the disaster site, we were only able to treat 42 of the thousands of survivors.

Essentially, the role of reconstructive plastic surgeons is to make critical treatment decisions, to provide open wound reconstruction, and to determine how much of a damaged extremity can be saved and to leave a healthy stump that is long enough for the use of orthoses and prostheses.

CONCLUSION

We believe that after the first intervention in the disaster area, ongoing management of earthquake victims in critical condition should be conducted in tertiary health centers with adequate intensive care support and orthopedic, general surgery, plastic surgery, cardiovascular surgery, hyperbaric and underwater medicine, internal medicine, infectious disease, pediatric, and psychiatric departments.

Collaboration between medical and surgical disciplines is crucial for the comprehensive and effective management of disaster survivor care.

Author contribution

Study conception and design: DA, EK, BM, RAA; data collection: DA, ÖFA BEA, ESB, ÖB; analysis and interpretation of results: DA, ESB, BM, ÖB; draft manuscript preparation: DA, EK, BEA, ÖFA, RAA. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Istanbul Faculty of Medicine (Protocol no. 255).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

Central nervous system involvement of chronic lymphocytic leukaemia: A rare case report

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Received: 12 January 2024, Accepted: 10 April 2024, Published online: 29 June 2024

ABSTRACT

Central nervous system (CNS) involvement in chronic lymphocytic leukemia (CLL) is unfamiliar. The diagnosis is delayed commonly, because of underdiagnosis or subclinical symptoms. We describe a 80-year-old woman with a previous diagnosis of CLL who presented to the emergency service with tonic clonic seizure. The new therapies, eg, ibrutinib and venetoclax, can be effective treatment strategies for CLL with CNS involvement. In our case, treatment with ibrutinib led to a resolution of the cerebralspinal fluid (CSF) neoplastic infiltration, but the patient died afterwards.

Keywords: chronic lymphocytic leukemia, central nervous system, cerebralspinal fluid.

INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in adulthood with a frequency 1% of all cancer cases [1]. The disease typically affects elderly patients with an age of diagnosis around 70 years. Generally, CLL is considered as an indolent lymphoma, whereas some cases with a more aggressive disease may associated with lower overall survival [2].

Non-lymphoid tissue is rarely associated with CLL infiltration, and defined as extramedullary CLL. Extramedullary CLL with central nervous system (CNS) infiltration and neurologic complications are reported only in 1% of patients [3,4]. As the diagnosis of CLL with CNS involvement is rare, there are no definitive data on clinical and radiological imaging findings. A wide variety of symptoms have been reported, including headache, convulsions, diplopia, ataxia and facial paralysis. Here, we report a case with CLL presented with tonic clonic epileptic seizure.

CASE PRESENTATION

An 80-year-old woman diagnosed with CLL (Rai, Stage I) in 2017. The patient only had hypertension as a chronic disease. Fluorescence in situ hybridization detected trisomy 12 with a normal karyotype cytogenetic analysis. She had been followed by a wait-and-see approach, until significant disease progression associated with lymphocytosis and axillary lymphadenopathy. In October 2020, the patient was treated with chlorambucil

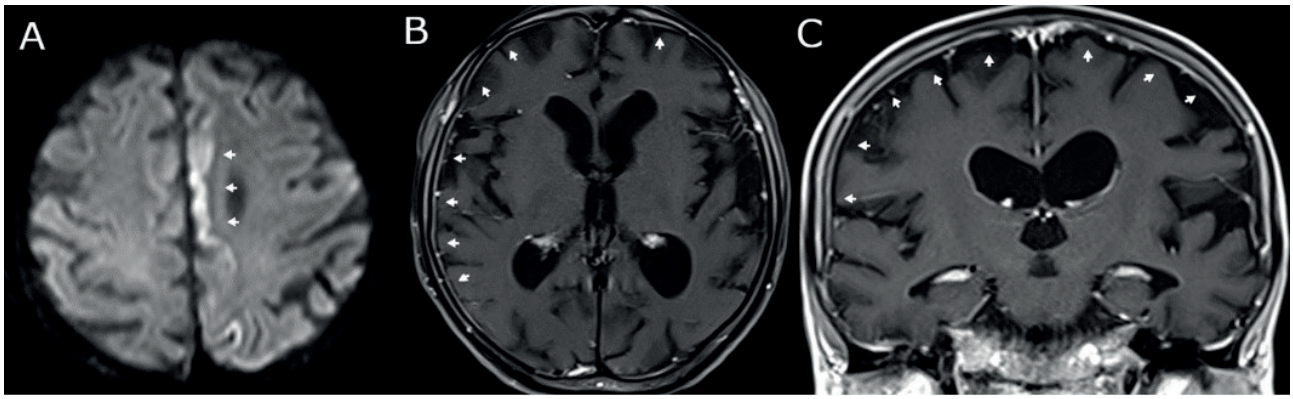
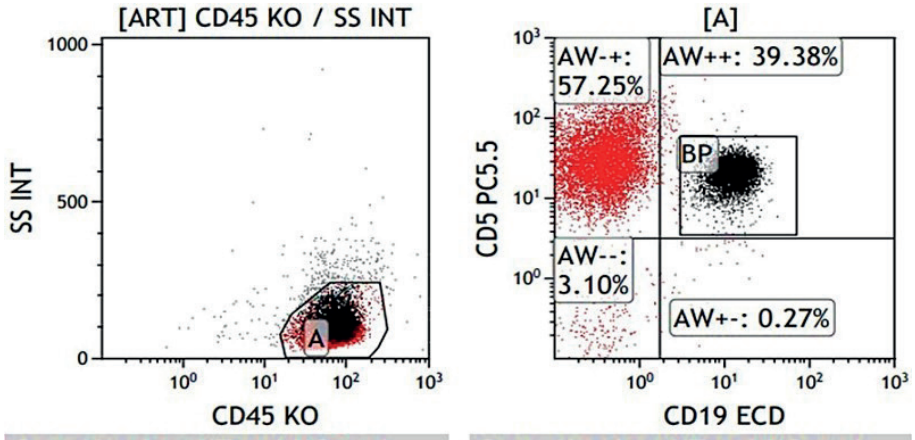


Figure 1. Magnetic resonance imaging of the case. **A)** Axial diffusion-weighted imaging revealing a hyperintensity in the left parasagittal area (arrows), secondary to seizure on the right side. **B)** Axial T1 sequence displays meningeal contrast enhancement (arrows) predominantly on the right side. **C)** Coronal T1 sequence shows contrast enhancement of the meninges on both sides.

monotherapy as first-line treatment. In December 2021, she showed worsening of preexisting lymphocytosis and lymphadenopathy, ascribed to CLL progression. Treatment with Rituximab plus Bendamustine (RB) was commenced.

In the following month, she applied to the emergency service because of a tonic clonic seizure in right arm and leg, unremarkable neurological examination. Magnetic resonance imaging (MRI) revealed restricted diffusion in the left frontal parasagittal area secondary to seizure (Figure-1A). Two weeks later, a secondary MRI with contrast showed contrast-enhancement (lesional enhancement after administration of contrast agents in MRI scans due to impaired blood-brain barrier in CNS pathologies) (Figure-1B,C). A diagnostic lumbar puncture was performed, and the cerebrospinal fluid (CSF) analysis revealed normal glucose, elevated protein (5.13 g/L). It was negative for gram stain and culture, enterovirus PCR, HSV 1 and 2, VZV, EBV, CMV, HHV 6 and 7 PCR. The flow cytometry analysis of the CSF revealed the presence of lymphocytes positive for CD19+/CD5+ (AW++), CD20weak, CD43weak, CD45, CD23, CD3, CD200strong, and findings were consistent with CNS infiltration by CLL cells indicating meningeal carcinomatosis (Figure 2). The CIRS (Cumulative



Gate	Number	%Total	%Gated
All	17,706	96.28	100.00
A	17,285	93.99	97.62

Gate	Number	%Total	%Gated
All	17,285	93.99	100.00
AW--	536	2.91	3.10
AW-+	9,896	53.81	57.25
AW+-	47	0.26	0.27
AW++	6,806	37.01	39.38
BP	6,715	36.51	38.85

Figure 2. Dot plots illustrating cerebral spinal fluid (CSF), (ART) Artefact, (SS) Side Scatter, immunophenotyping CD 45+ (black dots); **(A)** CD19−/ CD5+ (AW− +) cells (red dots) and CD19+ /CD5+ B-CLL (AW+ +) cells (black dots); Fluorochromes (KO) Krome Orange, (ECD) Phycoerythrin-Texas Red-x, (PC5.5) Phycoerythrin-Cyanin 5.5.

Illness Rating Scale) score of the patient was nine. The patient received dexamethasone (intravenous, 40 mg/day, 4 days) followed by intrathecal methotrexate (12 mg/day), cytarabine (40 mg/day), and dexamethasone (4 mg/day), twice a week (6 cycles). Thereafter, because the patient is of advanced age, treatment efficacy and ease of use are known, treatment with ibrutinib monotherapy 420 mg/day was started and her general condition improved with CSF normalisation. Prior to treatment with ibrutinib, the patient underwent electrocardiography, echocardiography and cardiology consultation, and no contraindications were found. She died of an unknown cause at home after one month on ibrutinib treatment.

DISCUSSION

In our case, the patient was diagnosed by CSF flow cytometry analysis that could be predicted malign cells up to 40% [5-7]. The incidence of CNS infiltration in CLL is clearly common in autopsy series than real life [7,8]. This can be the heterogeneity of neurologic symptoms patients with CLL and CNS involvement [9]. The most common symptoms are vision changes (22%), encephalopathy (29%) and weakness with paresthesias (22%) [10]. The clinical presentation of our patient was seizure which Strati et al. reported as the incidence of 7% [7]. The reports revealed that, indeed, neurologic presentations are nonspecific (Table 1). In some reports, it has been suggested that CNS involvement neither related to disease stage (according to Rai or Binet), nor poor prognostic chromosomal factors (e.g. deletion 17p or 11q) [9,11].

There is a lack of consensus on the treatment of patients with CNS involvement in CLL (e.g. intrathecal chemotherapy, chemo-immunotherapy, radiotherapy, combined or alone). Wanquet et al. reported rituximab combined with chemotherapies [RB or RFC (Rituximab, Fludarabine, Cyclophosphamide)] had significantly better progression free survival, and also ibrutinib may be an effective therapy for CNS involvement [12]. In our case, intrathecal chemotherapy with ibrutinib was an option with lower toxicity, and seemed to have led to a decrease in the CLL cells from CNS with flow cytometry analysis. In addition, some reports suggest that venetoclax may be a potent therapeutic option, in patients who progressed under ibrutinib treatment (Table 1) [13,14].

CNS involvement in CLL is uncommon and should be considered in all CLL patients with neurological symptoms.

Author contribution

Study conception and design: DK, RY, and PT; data collection: DK, KUB and NA; analysis and interpretation of results: DK, RY, and PT ; draft manuscript preparation: DK, RY, and PT. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Ankara University School of Medicine (Protocol no. 11.05.2022; İ05-275-22).

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Table 1. Patient's characteristics central nervous system (CNS) involvement in CLL

Age/Sex	Symptoms	Stage	Blood lypmhocyte count (×109 /L)	FISH	Treatment	Response	Reference
57/male	Bradypsychia, headaches, nausea, vomiting	Rai-III	85.5	17p	High-dose methotrexate	High-dose methotrexate	4
43/male	Dysphasia, repeated unconsciousness, urinary, incontinence	Rai-IV	23	Normal	Rituximab, fludarabine, cyclophosphamide	Rituximab, fludarabine, cyclophosphamide	4
49/male	Diplopia, bilateral eyelid swelling, and tumors	Rai-IV	86.5	N/A	Cisplatine; cytosine arabinoside; dexamethasone	Cisplatine; cytosine arabinoside; dexamethasone	4
72/male	Dyslexia, lack of fine motor control, diplopia	Rai-IV	103.9	13q14	Cisplatine; cytosine arabinoside; dexamethasone	Cisplatine; cytosine arabinoside; dexamethasone	4
33/male	Diplopia, headaches	Rai low, Binet A	464	Normal	Methotrexate, vincristine, procarbazine; Rituximab subsequent whole-brain radiotherapy; Rituximab, fludarabine, cyclophosphamide; İbrutinib	Methotrexate,vincristine, procarbazine; Rituximab subsequent whole-brain radiotherapy; Rituximab, fludarabine, cyclophosphamide; İbrutinib	9
64/male	Hypoesthesia	Binet B	251	Normal	Rituximab, bendamustin	Rituximab, bendamustin	10
71/male	Transient epileptic seizure, Decreased left upperlimb strength, left hemianopsia, visual hallucinations	Not available	Not available	11q/TP53; IGHV unmutated	Ibrutinib; Methotrexat, rituximab, Venetoclax (relapse); Venetoclax, rituximab, prednisone	Ibrutinib; Methotrexat, rituximab, Venetoclax (relapse); Venetoclax, rituximab,prednisone	14
58/male	Not available	Not available	Not available	Trisomy 12; IGHV unmutated	Ibrutinib; Venetoclax	Ibrutinib; Venetoclax	15

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LETTER TO THE EDITOR

Isolated sphenoid sinus mycetoma: An unusual cause of chronic headache

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Received: 28 August 2023, Accepted: 4 April 2024, Published online: 29 June 2024

Dear editor,

A 58-year-old male patient was admitted to our neurology clinic with headache and blurry vision. The mean symptom duration was approximately five years for headache, and one year for blurry vision. He had no personal history of neurological and internal diseases. He was on analgesic therapy almost daily and was experiencing dizziness. Neurological and ophthalmological examinations showed no significant findings. Brain magnetic resonance imaging (MRI) revealed a T2 hypointense, diffusion-restricted, and intensely heterogeneous contrast-enhancing mass lesion in the left sphenoid sinus, suggestive of fungal infection (Figure 1). Paranasal sinus computed tomography (CT) disclosed total loss of aeration, increase in wall thickness, mild expansion, and sclerosis of the sphenoid sinus left compartment (Figure 2). These radiological findings raised suspicion of fungus ball (mycetoma). Functional endoscopic sinus surgery was performed. The macroscopic appearance during surgery strengthened the suspicion of non-invasive fungal infection. Therefore, the lesion was removed completely. Pathological examination of the specimens detected fungal hyphae with septate and narrow-angle branching features consistent with aspergillus. These results were compatible with mycetoma. The patient received nasal steroid therapy. At approximately two years of follow-up, he did not experience any neurological symptoms, and complaints were resolved entirely. Pre-operative and post-operative visual acuity was 20/30 and 20/20, respectively.

Fungal infections of the paranasal sinus occur rarely, and the responsible agent is often aspergillus [1]. Fungal sinusitis is classified into allergic fungal sinusitis, mycetoma, acute fulminant form, and chronic invasive form. While the first two of these four types are non-invasive, the last two are invasive, progress rapidly, and cause severe disease. Invasive fungal sinusitis has been described more frequently in immunosuppressed individuals, while fungal balls have been reported generally in immunocompetent individuals [2,3].

Fungus ball refers to extra mucosal fungal proliferation, usually localized in a single sinus. Its pathogenesis and formation mechanism are not fully known. Cytotoxic metabolites formed during mycelium growth can lead to tissue and bone damage, and thus various complications develop [1-3]. There is no development of immune reaction against fungi. The incidence of atopy in patients suffering from mycetoma is similar to healthy individuals. Generally, skin tests and immunoglobulin E levels are normal [4].

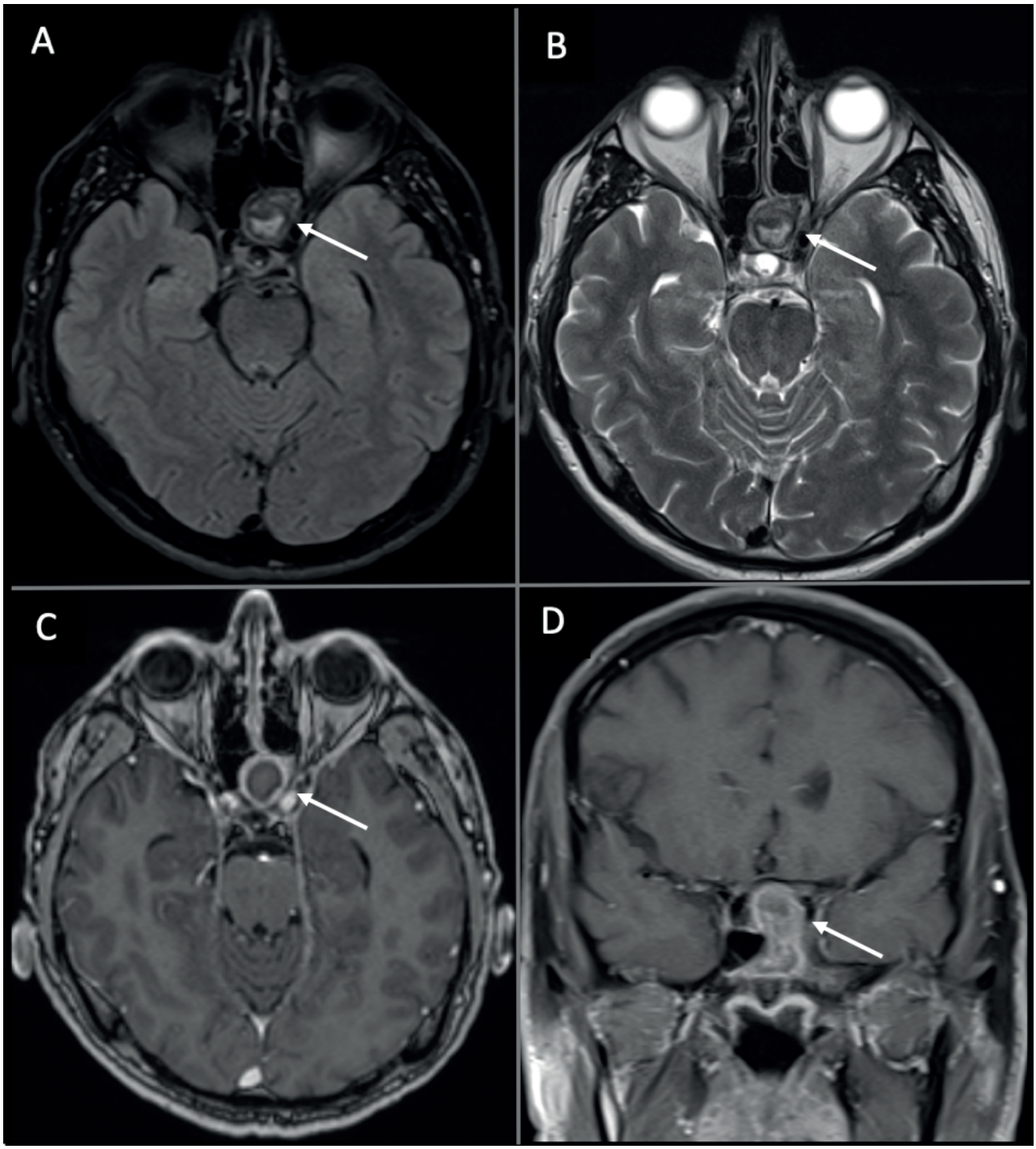

Figure 1. The initial brain magnetic resonance imaging, axial fluid-attenuated inversion recovery (FLAIR) image (A, arrow), and sagittal T2-weighted (W) image (B, arrow) discloses hypointense and diffusion-restricted mass lesion in the left sphenoid sinus. The axial (C, arrow) and coronal (D, arrow) contrast-enhanced T1-W images shows intensely heterogeneous contrast-enhancing of this lesion.

The sphenoid sinus is anatomically close to the neural and intracranial vascular structures such as optic nerve and chiasm, pituitary gland, internal carotid artery, and cranial nerve (III, IV, V1, V2). Therefore, delays in diagnosing and treating pathologies localized to the sphenoid sinus may result in serious complications [2]. Headache is the main complaint in isolated sphenoid sinus diseases, and there is no distinct type of pain. It can also lead to proptosis, ptosis, and visual symptoms [3]. There was no evidence of mucosal invasion of the pathogen in our patient. Orbital symptoms may have arisen as a result of pressure ischemia [2].

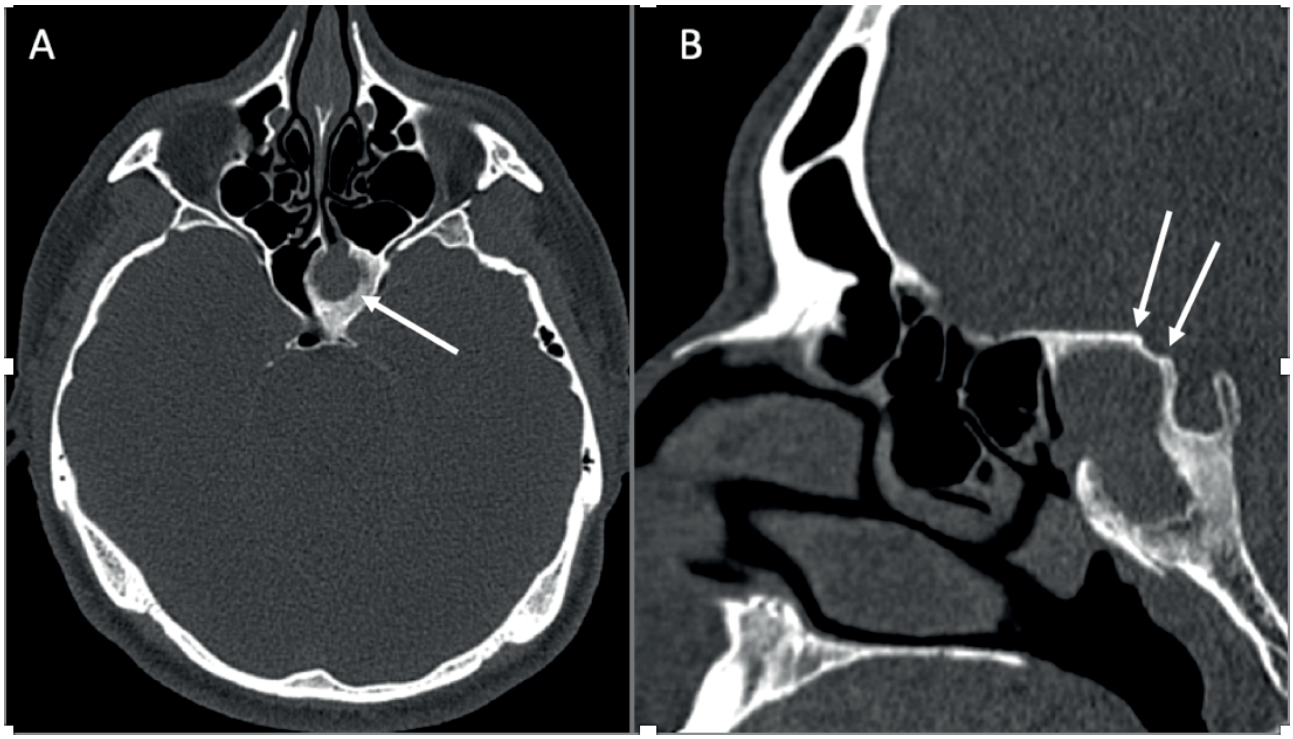

Figure 2. Paranasal sinus computed tomography axial (A, arrow) and sagittal (B, arrows) imaging demonstrates fungus ball (mycetoma).

Functional endoscopic sinus surgery is the primary treatment in this entity. Microbiological and histopathological studies of surgical material confirm the diagnosis. Surgical debridement and sinus ventilation are the main steps of treatment. It was discussed whether antifungal treatment was necessary or not, and it was emphasized that it was unnecessary [1-3].

In summary, paranasal sinus pathologies often present with non-specific symptoms. Brain MRI should be performed in patients with lesions detected in the sphenoid sinus on paranasal CT. It should be kept in mind in the presence of nasopharyngeal and vision loss in addition to atypical headaches.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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