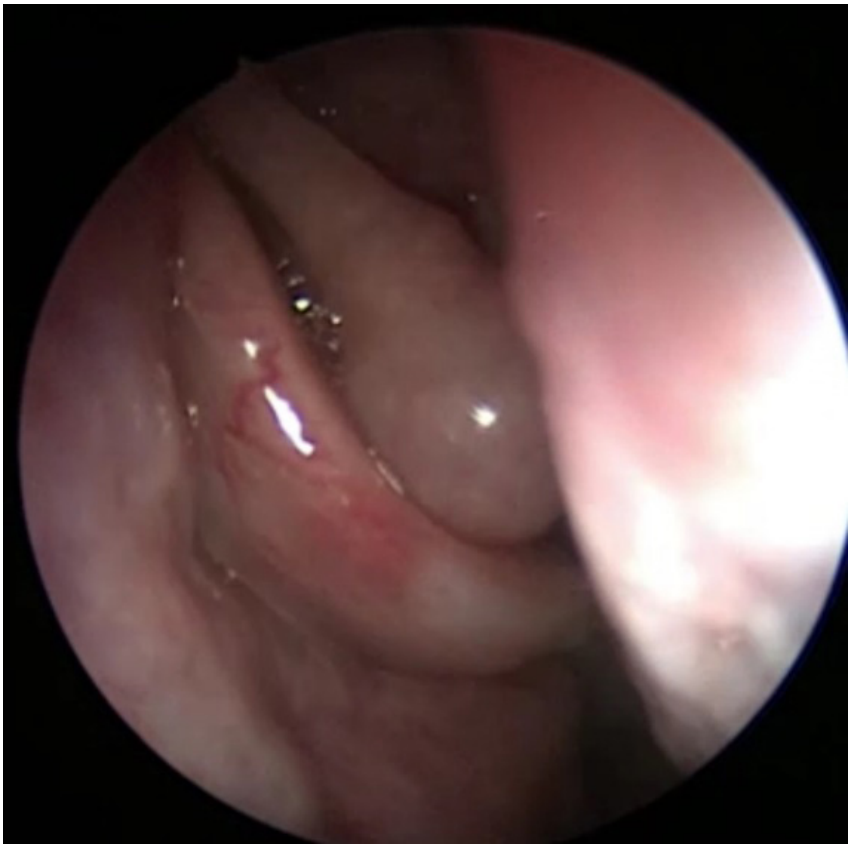
Journal of Experimental and Clinical Medicine

Vol: 38 • Issue: 1 • March: 2021



e-ISSN 1309-5129 JECM https://dergipark.org.tr/omujecm

Journal of Experimental and Clinical Medicine

e-ISSN 1309-5129

Vol: 38 Issue: 1 March 2021

e-ISSN 1309-5129

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Ondokuz Mayıs University
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Atakum / Samsun, Turkey

Publish Type
Periodical

Press
HT MATBAA
Hamdi TANRIKULU
Hançerli Mah. Atatürk Bulvarı No:112/A 55020 İlkadım / Samsun, Turkey
www.htmatbaa.com

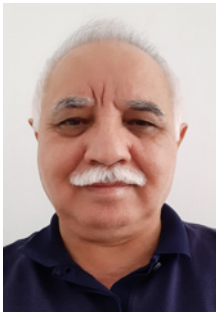
Online Published Date
26 / 01 / 2021

Acid-free paper is used in this journal.

Indexed: CEPIEC, Crossref, DOAJ, EMBASE, EBSCOhost, Google Scholar, Index Copernicus, J-Gate, NLM Catalog (PubMed), Research Gate, Turkiye Citation Index, World Cat.

Cover Art
Mehel et al., Page, 18; Fig. 1.

Farewell Message from the Editor-in-Chief



This will be the last issue of Journal of Experimental and Clinical Medicine (JECM) under my editorship. It has been a great pleasure and honour for me to have edited 53 issues (12 volumes) between 2009 and 2021.

As a newly appointed editor-in-chief, I focused the scope of the journal on experimental and clinical medicine, quickly preparing number of special issues from different medical disciplines so that the journal would attract a broad readership and authors. We published five special issues in the JECM in a very few years. We not only changed the name of the journal to "Journal of Experimental and Clinical Medicine," but also published it in English to attract a wider readership.

As the publishing team of this highly respected journal, we transformed it from a local publication to an international, scientific journal. From the very beginning of my editorship, the journal achieved international standards, was included in respected indexes and acquired a significant impact factor. The journal has been indexed in several prominent databases over the last decade. In that context, I wish to express my profound gratitude to the deans of the Medical Faculty, Prof. Haydar Sahinoglu, Prof. Ayhan Dağdemir and Prof. Cengiz Çokluk, and to the rectors, namely Prof. Hüseyin Akan, Prof. Sait Bilgiç and Prof. Yavuz Ünal, who gave me their full confidence and support as editor of the JECM.

During my editorship, we applied to Web of Science and PubMed for inclusion in their index system, but that application failed due to low numbers of citations and for other technical reasons. I believe that sustainable processes on the journal issues would contribute solving those issues and the journal would reach to deserve level.

Publishing a scientific journal is a very fruitful and complex activity. I would like to thank the editorial board for their patience in my first editorial experience and for their support for the journal, as well as for their friendship. I would also like to express my sincere gratitude to my editorial teams, Dr. Kıymet Kübra Yurt, Dr. Işınsu Alkan, Dr. Elfide Gizem Kıvrak, Dr. Erkan Erener, Arife Ahsen Kaplan, Adem Kocaman, Burcu Delibaş, Gamze Altun, Sümeyye Gümüş and others. These have given freely and unreservedly of their working time and have always prioritized journal issues.

I would also like to express my special thanks to the editor and associated editors of the journal, who come from different cities in different countries. These have given huge backing aimed at improving the quality of journal. One of them in particular, Prof. Yasin Temel from Maastricht University, has never been forgotten.

Without the authors of manuscripts and the reviewers, the journal would be unable to survive in the scientific world. It is thanks to their enormous contributions that the journal is able to appear on time.

I also have a very diligent volunteer team responsible for editing each accepted manuscript. This special team consists of my students, secretaries and publisher (the staff of HT Matbaa) who have invested much time and effort in facilitating the work of the editorial committee.

I wish the incoming editorial team on the JECM every success for the future, and believe new editorial teams will further enhance the quality of the journal.

It has been an honour and privilege to serve as editor-in-chief of the JECM, and one that I will never forget. So while I am sad to depart, I am also excited for the future.

My thanks and best wishes to you all.

January 2021
Professor Süleyman Kaplan, PhD

CONTENTS ***Page***

Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Clinical Research

J. Exp. Clin. Med., 2021; 38(1): 1-4
doi: 10.5835/jecm.omu.38.01.001

Propofol-ketamine versus propofol-tramadol sedation in children undergoing gastrointestinal endoscopy

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ARTICLE INFO

Article History
Received 27 / 03 / 2020
Accepted 28 / 06 / 2020
Online Published 26 / 01 / 2021

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Keywords:
Anesthesia recovery period
Deep sedation
Digestive system endoscopy
Pediatric nursing

ABSTRACT

Numerous combinations of drugs are used for sedation in upper gastrointestinal endoscopies. The aim of this study was to compare the quality of two sedation regimens in upper gastrointestinal endoscopy performed on pediatric patients. After the study approval by the local ethics committee of Ondokuz Mayıs University Hospital, written informed consent was obtained from parents. Eighty patients between the ages of 1 and 18 were randomized into two groups. Group K (n=40) received propofol 1 mg/kg + 1 mg/kg ketamine intravenously. Group T (n=40) received propofol 1 mg/kg + 1 mg/kg tramadol intravenously. In both groups, additional propofol (0.5 mg/kg) was administrated when a patient showed signs of discomfort, in order to maintain a Ramsey Sedation Scale of 4 to 5. In Group K, additional propofol requirements were significantly lower compared to Group T (p=0.003). Group K had significantly higher sedation scores than Group T at 3rd min. (p=0.028) and 20th min. (p=0.015). Recovery time increased significantly in Group K (p=0.002). Although there was no difference between two groups concerning the propofol consumption, both groups required additional propofol and tramadol resulted in a shorter recovery time compared to ketamine.

1. Introduction

Increasing numbers of gastrointestinal endoscopic procedures are being performed outside the operating room (Kuzhively and Pandit, 2019).

Gastrointestinal endoscopies (GIE) are the most useful procedures for diagnosing and treating gastrointestinal tract disorders (Van Beek and Leroy, 2012). This procedure requires moderate/deep sedation as described by the American Society of Anesthesiologists (ASA) (American Society of Anesthesiologists, 2002). Although at least moderate sedation is necessary to maintain spontaneous ventilation, some children undergoing endoscopy require deep sedation. As levels of sedation can change rapidly, maintaining spontaneous ventilation and patient safety is quite difficult. The most commonly used medications for pediatric sedation are barbiturates, benzodiazepines, propofol, ketamine, and opioids (Van Beek and Leroy, 2012). This study was aimed to compare the clinical efficacy and safety of a propofol–ketamine combination and of a propofol–tramadol combination in children undergoing GIE.

2. Materials and methods

After approval of the study by the local ethics committee of Ondokuz Mayıs University Hospital (OMU-KAEK 2012-113, 30.11.2012), written informed consent was obtained from parents. Eighty ASA physical status I–II patients, ages 1 to 18 who were scheduled for upper gastrointestinal endoscopies (UGIE), were randomized using a sealed envelope assignment. Patients were excluded from the study if they had a history of allergic reactions to the study drugs, eggs, or soybeans; a history of behavioral problems and neurological impairment; preexisting respiratory conditions and previous difficult intubations.

The patients, pediatric endoscopist, and anesthesiologist were blinded to the study groups. Another anesthesiologist administrated the study drugs and monitored the patient. No sedative premedication was administered, and patients fasted for at least 6 h before the intervention.

Patients were divided into two groups. The ketamine group (Group K, n=40) received propofol (propofol-lipuro; 10 mg/mL, Braun, Philippines) 1 mg/kg + 1 mg/kg ketamine (ketalar; 50 mg/mL ketamine hydrochloride, Pfizer USA) intravenously (IV), while the tramadol group (Group T, n=40) received propofol 1 mg/kg + 1 mg/kg tramadol (contramal; 100 mg/ampul, Abdi İbrahim, Turkey) IV. Patients in both groups received 1 mg/kg propofol for sedation induction. In both groups, additional propofol (0.5 mg/kg) was administrated when a patient showed signs of discomfort in order to maintain a RSS of 4 to 5. The heart rate (HR), mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), respiratory rate (RR), and Ramsay sedation scores (Ramsay et al., 1974) of all patients were recorded at baseline, after induction, and every five min thereafter during the procedure by an anesthesiologist blinded to the study.

The following data were recorded for each patient: Age, sex, weight, duration of the procedure (defined as the time from oral insertion of the endoscope to its withdrawal), recovery time (defined as the time to reach a Steward Recovery score (Steward, 1975), number of patients who needed additional propofol, and adverse effects during and after the procedure.

Adverse events included laryngospasm [wheezing, stridor, seizure (generalized tonic-clonic activity) and dyspnea], changes in the MAP and HR of at least 20% from baseline, oxygen desaturation with SpO_2 of < 90% for more than 15s, increased secretions (which require suction), nausea, vomiting, and agitation. After the end of procedure, during the recovery period agitation was evaluated by four-point scale (Watcha et al., 1992); 1= calm, quite, 2= crying, but can be consoled, 3= crying, cannot be consoled, and 4= agitated and thrashing around. Children with an agitation score of 3 or 4 were classified as agitated.

Statistical analysis was performed using Statistical Package for Social Sciences, version 20.0 (SPSS Inc., Chicago, IL, USA). Between-group comparisons of numerical data were analyzed using the Mann–Whitney U Test or a t-test. Adverse events and additional propofol required were analyzed using Fisher's exact test and Pearson's chi-square test respectively. A repeated measures analysis of variance was used to evaluate respiratory rate and hemodynamic data. Statistical significance was reached when the $p < 0.05$.

3. Results

Eighty patients ranging in age from 1 to 18 successfully completed the procedure. There were no statistically significant differences between groups with respect to age, sex, weight, duration of the procedure, agitation score, or adverse events.

Compared to Group T, Group K had significantly lower additional propofol requirements (p=0.002, Table 1) and significantly higher sedation scores at the 3th min (p=0.028) and 20th min (p=0.015) (Fig. 1). The recovery time was significantly higher in Group K than Group T (p=0.002, Fig. 2).

Table 1. Number of patients required one or more additional propofol boluses (p=0.002).

	Group K (n=40)	Group T (n=40)	P value
Additional propofol required	21 (52.5%)	34 (85%)	0.002

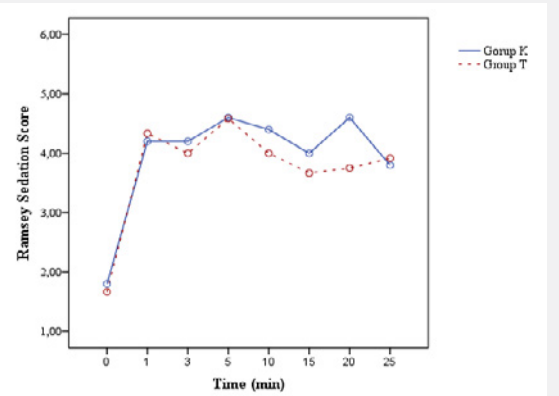

Fig. 1. Ramsey sedation scores in both groups. Significantly higher sedation scores 3th min (p=0.028) and 20th min (p=0.015) in group K.

Comparisons of the groups' HR, MAP, RR, SpO_2, duration of the procedure and number of adverse events did not reveal any statistical significance. One patient in each group experienced an adverse respiratory event. Respiratory depression requiring bag-valve-mask ventilation, occurred in one patient in each group. Other adverse events for ketamine group included tachycardia (4), nausea (1), laryngospasm (1), and increased secretions (1). As for the tramadol group bradycardia and hypotension occurred in 1 patient, but

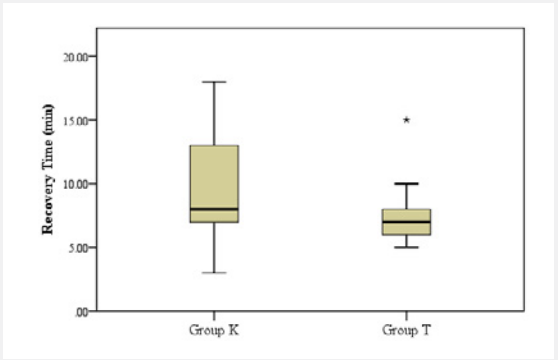

Fig. 2. Recovery times in both groups. The recovery time was significantly higher in Group K than Group T (p=0.002).

there were no significant differences between the study groups (Table 2). We observed emergence agitation only in one patient in Group K.

Table 2. Type and frequency of adverse events (p>0.005).

	Group K	Group T
Hypotension	-	1 (2.5%)
Bradycardia	-	1 (2.5%)
Tachycardia	4 (10%)	
Decrease in SpO2	1 (2.5%)	1 (2.5%)
Laryngospasm	1 (2.5%)	-
Increase in secretions	1 (2.5%)	-
Nausea	1 (2.5%)	-
Vomiting	-	-
Agitation	1 (2.5%)	-

4. Discussion

The aim of this study was to evaluate the effects of a propofol–ketamine combination and a propofol–tramadol combination on hemodynamics, quality of sedation, recovery profile and adverse events in pediatric patients undergoing UGIE. Endoscopic procedures are frequently performed outside the operating room. While medical centers perform different approaches, there is no ideal protocol for sedation in children during endoscopic procedures (Chung and Lightdale, 2016). The ideal sedative agent for endoscopic procedures should have a rapid onset and a short duration of action (Stogiannou et al., 2018). Propofol is commonly used for sedation outside the operating room. Beyond its sedative hypnotic effect, though, propofol has no analgesic properties. Therefore, it is frequently combined with analgesic drugs, especially opioids. The combination of propofol and ketamine has been associated with effective sedation and analgesia during UGIE.

Ketamine has many advantages. First, in addition to its analgesic effects, it acts as an anxiolytic and amnesic drug while protecting airway reflexes. It has a short duration of action and allows rapid recovery, (Roelofse, 2010). Sharieff et al. reported the patient receiving single dose 0.5:1 ratios of ketamine: propofol showed rapid recovery. In contrast, prolonged recovery was associated with continuous infusions, especially 1:1 ratio of propofol ketamine mixture (Sharieff et al., 2007; Kramer et al., 2012; Finn et al., 2014). In our study 1:1 ratio of propofol:ketamine combination was probably associated with prolonged recovery in group K. Besides its advantages, ketamine is associated with laryngospasm, hypersalivation, emergence delirium. Brecelj et al. reported potentially dangerous laryngospasm and hypersalivation in 5% of patients in both study groups (Brecelj et al., 2012). Incidence of laryngospasm was relatively higher (13.9%) in preschool-age children (< or =6) than school-age children (3.6%) (Green et al., 2001). In our study, laryngospasm occurred in one patient who was six years old and sedated with ketamine - propofol (2.5%). It is reported that using propofol and ketamine as combination may lead to lower rates of adverse events. Likewise, hypersalivation occurred in only one child who was also sedated with ketamine – propofol (Alletag et al., 2012). Another important adverse event is the emergence agitation, common undesired effects of ketamine, are significantly decreased with the addition of propofol (Alletag et al., 2012). Thus, we observed emergence agitations in only one patient who did not need any treatment.

Many studies have evaluated vomiting during pediatric procedural sedation. In three different studies in which the effects of sedation with ketamine were investigated, the frequency of vomiting among children was 17%, 19.4% and 18.9%, respectively (Wathen et al., 2000; Langston et al., 2008; Brecelj et al., 2012). In the present study, we observed nausea in only one patient in the ketamine group and none in the tramadol group. We did not observe any vomiting. This result may be related to the antiemetic property of propofol.

Combinations of drugs use lower doses of each agent and might reduce their hemodynamic effects. In our study, there were no differences in hemodynamic instability between the study groups. It was recommended a combination of ketamine–propofol, rather than fentanyl–propofol, for hemodynamic stability (Guit et al., 1991). UGIEs are among the most common outpatient procedures, and the most frequent adverse events during procedural sedation are respiratory (Van Beek and Leroy, 2012). Therefore, we used tramadol to avoid respiratory adverse events such as hypoxia and laryngospasm. In addition to a weak opioid analgesic effect, tramadol has less sedation potency, respiratory depression, and minimal

gastrointestinal dysfunction compared opioid drugs. In our study, the number of patients with additional propofol requirement were significantly higher in the tramadol group than the ketamine group. In addition, the tramadol group had significantly lower sedation scores than the ketamine group. In our opinion, these findings are related to the weak sedative property of tramadol. Thus, recovery time was significantly shorter in the tramadol group than the ketamine group. Rare adverse effect profile and shorter recovery time improving patient safety and lowering costs, reducing length of hospital stay can release capacity in the system (including beds and staff time) and enabling the hospital to serve more patients.

Our study has some limitations. First, we do not know whether patients experienced unpleasant dreams and hallucinations after the procedures. Different doses could be compared in larger patient groups undergoing UGIE. Finally, these regimens might not suitable for longer procedures.

The present study demonstrated that, combination of tramadol-propofol result in a faster recovery without increase the rate of adverse effects. However, patients required additional propofol due to insufficient sedation, so tramadol should be considered for short procedures.

Acknowledgments

Ethical approval

The experimental protocol of this study was reviewed and approved by the Clinical Research Ethical Committee of Ondokuz Mayis University, Samsun, Turkey (Ethical Committee Number: OMU-KAEK 2012-113, 30.11.2012).

Informed consent

Parental permission consent document was obtained from both parents/legal guardians in this study.

Conflict of interest

The authors declare that they have no conflict of interest.

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Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Clinical Research

J. Exp. Clin. Med., 2021; 38(1): 5-9
doi: 10.5835/jecm.omu.38.01.002

Breathing patterns response to the incremental exercise test in young males

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ARTICLE INFO

Article History
Received 02 / 04 / 2020
Accepted 09 / 06 / 2020
Online Published 26 / 01 / 2021

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Keywords:
Anaerobic threshold
Breathing frequency
Incremental exercise test
Respiratory compensation point
Tidal volume
Ventilation

ABSTRACT

Incremental exercise test contains three different metabolic regions, including aerobic region, partly anaerobic and anaerobic dominated region. The work load from warm up period to anaerobic threshold (AT) was accepted as aerobic region, workload above AT to respiratory compensation point (RCP) was accepted partly anaerobic region and above RCP was accepted as anaerobic region of incremental exercise test. We aimed to compare the ventilatory patterns during different metabolic sections of incremental exercise test. Fifteen healthy males performed an incremental exercise test (15 W/min) to exhaustion on a cycle ergometer. Metabolic and cardiopulmonary parameters were measured breath-by-breath using metabolic gas analyser system and turbine volume meter. AT and RCP were estimated using ventilator and pulmonary gas exchange parameters. Respiratory patterns, breathing frequency (Bf) and tidal volume (VT), showed great differences among the exercise regions. VT is the main factor increases minute ventilation (VE) during aerobic region. However, Bf becomes dominant factor increasing VE in anaerobic region of test. In the region between AT to RCP, Bf and VT showed similar effects on increase in VE. VT to inspiratory time ratio increased significantly in all region of test. However, work production capacity for each liter of VE decreased markedly when the exercise intensity changed from aerobic to anaerobic regions. Consequently, evaluation of breathing patterns for different metabolic regions of incremental exercise will provide information regarding individual's metabolic strength and ventilator response.

1. Introduction

Cardiopulmonary exercise test is an important tool that is widely used to evaluate functional capacity of body respiratory, metabolic and cardiac systems (Wasserman et al., 2012). Incremental ramp exercise protocols have become popular because they provide smooth and constantly increasing load stress to metabolic systems. Thus, increased metabolic demands from resting to maximal exercise should be associated with cardiorespiratory adjustment for maintaining homeostasis.

Incremental exercise test contains three important set point, including anaerobic threshold (AT), respiratory compensation point (RCP) and maximal exercise (Max) (Algul et al., 2017). During incremental exercise test, minute ventilation (VE) increases linearly with increasing workload and closely with increased CO_2 output (VCO_2) until the anaerobic threshold (AT) (Whipp et al., 1989). AT reflects highest workload without increase of blood lactate levels reflecting aerobic region of incremental exercise tests (Wasserman et al., 2012). Above AT, when work rate

increased further VE increases proportion to with increased VCO_2 until the RCP. However, beyond RCP VE increases out of proportion to VCO_2 until the end of test (Whipp et al., 1989). It is known that increases of VE is the result of wide range of change in breathing patterns, i.e. tidal volume (VT) and breathing frequency (Bf) (Milic-Emili and Cajani, 1957). Since its first clinical description, VT, Bf and VE are widely used in medicine and sport science (Hey et al., 1966). The breathing pattern changes have been evaluated at maximal exercise values and normal responses has been presented in some studies (Hansen et al., 1984; Blackie et al., 1991; Neder et al., 2003). In addition breathing patterns has been evaluated in response to the incremental exercise with different work increments (Scheuermann and Kowalchuk, 1999) or sinusoidal exercise (Nicola et al., 2018). However, the response of breathing patterns at the anaerobic threshold, at respiratory compensation point and at maximal of the incremental exercise test will provide important information concerning VE, Bf and VT triangle.

In the present study, we aimed to evaluate contribution of VT and Bf for increasing VE during an incremental exercise test and to compare the values at three different metabolic set points from onset to anaerobic threshold, from anaerobic threshold to RCP and from RCP to end of exercise test.

2. Materials and methods

Fifteen heathy male subjects were participated to this study after giving signed informed consents, which were approved by the local ethical committee. Their (mean±SE) age, weight and height are 21.06±0.5 year, 77.2±1.9 kg and 184.9±1.7 cm, respectively. The subjects were free of any metabolic, cardiac and respiratory disease. The subject's age should was between 18 to 25. The body composition analysis was made using BIA and subjects with normal body composition was participated to study (Kaya and Ozçelik, 2009).

Each subject performed an incremental exercise test (Whipp et al., 1981). The exercise work protocol started with 20 W cycling as a warm-up period for four minutes until the steady state of respiratory parameters. This period was carefully controlled for prior hyperventilation in which results pseudo-threshold phenomenon (Ozcelik et al., 1999). The workload increased by a workload controlled 15 W/min until the subjects' limit of tolerance. Then the workload reduced to 20 W as a recovery period for couple of minutes. The subjects had 12 lead-EKG and during exercise all cardiac values were controlled beat-by-beat especially ST segment for any deprivation.

During exercise, the subjects were instructed to breathe into low resistance, low dead space turbine volume transducer to measure ventilatory parameters. The metabolic parameters were measured using metabolic gas analyser. The data was evaluated breath-by-breath.

Anaerobic threshold was estimated using standard V-sloe method (Beaver et al., 1986). The other conventional methods including increases of ventilatory equivalent for VO_2 (VE/VO_2) and end-tidal partial pressure of O_2 ($PETO_2$ mmHg) also used to estimate AT (Whipp et al., 1986). Respiratory compensation point was estimated using increase of ventilatory equivalent for CO_2 (VE/VCO_2) and decrease in end-tidal partial pressure of CO_2 ($PETCO_2$ mmHg) (Algul et al., 2017). Anova test was used to analyse data for significant differences between three different regions. A Pearson correlation analysis was used to evaluate data between breathing patterns and respiratory time. $P<0.05$ was accepted as statistically significant.

3. Results

The subjects (mean±SE) work rate at the AT, RCP and maximal exercise were found to be 143.6±6 W, 171.3±7 W and 226.6±6 W, respectively. The AT and RCP were occurred at 63% and 75% of the maximal exercise capacity. The work production capacity and O^2 uptake for each kg of body weight at maximal exercise were found to be 2.94±0.08 W/min/kg and 39.9±1.2 ml/min/kg, respectively.

Ventilatory patterns response to incremental exercise test is shown in Fig. 1. The percent change of VE, Bf and VT from warm up to AT, from At to the RCP and RCP to maximal exercise test are shown in Fig. 2. Minute ventilation at the 20 W warm up period was found to be 16.73±0.48 L/min. VE increased to 49.4±2.0 L/min at the AT. The marked increase of VE in the aerobic region of exercise test occurred as 197%. Above the AT VE, continued to increase and it reached to 64.4±2.9 L/min at the RCP (i.e. 30% of increase). VE at maximal exercise was found to be 103.7±4.3 L/min (i.e. 62% of increase). Breathing frequency at the 20 W warm up period was found to be 19.4±0.6 br/min. Bf increased to 24.3±1.3 L/min at the AT. The increase of Bf in the aerobic region of exercise test was occurred as 25%. Above the AT, Bf increased slightly and it reached to 28.8±2.0 br/min At the RCP (i.e. 18% of increase). Bf at maximal exercise was found to be 42.1±2.2 br/min (i.e. 50% of increase). VT at the 20 W warm up period was found to be 0.87±0.03 Ln. VT increased to 2.10±0.13 L at the AT. The increase of VT in the aerobic region of exercise test was occurred as 142%. Above the AT, VT increased slightly and it reached to 2.343±0.16 L At the RCP (i.e. 11% of increase). VT at maximal exercise was found to be 2.538±0.15 L (i.e. 10% of increase).

The amount of workload for each litter of VE (WR/VE) in aerobic region of incremental exercise test was 3.875±0.16 (L/min/W). However, above the

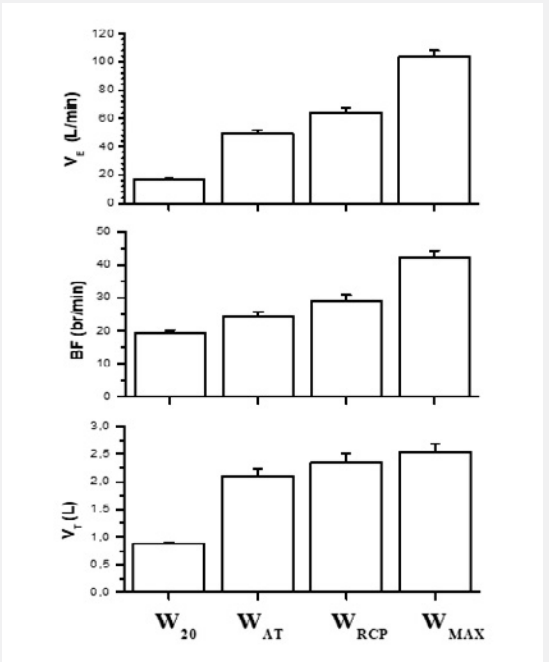

Fig. 1. The (mean±SE) values of minute ventilation (VE), breathing frequency (Bf) and tidal volume (VT) in response to the incremental exercise at the warm up (W20), at anaerobic threshold (WAT), at respiratory compensation point (WRCP) and at maximal exercise (WMAX).

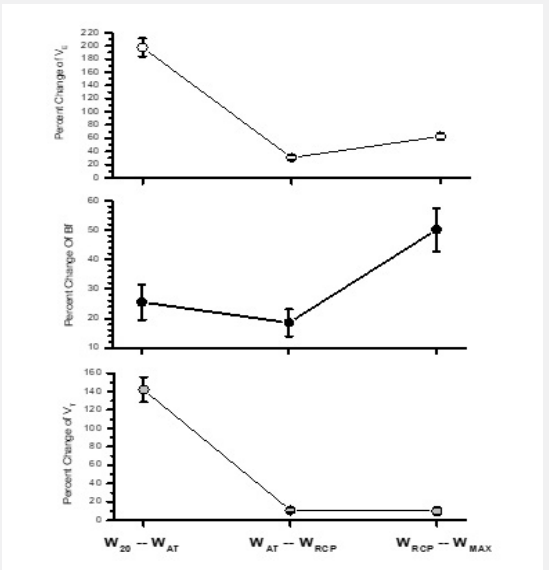

Fig. 2. The (mean±SE) percent change of minute ventilation (VE), breathing frequency (Bf) and tidal volume (VT) in response to the incremental exercise tests: from warm-up to anaerobic threshold (W20-- WAT), from anaerobic threshold to respiratory compensation point (WAT -- WRCP) and from respiratory compensation point to maximal exercise (WRCP --WMAX).

AT, WR/VE significantly decreased to 2.147±0.26 L/min/W ($p<.005$). Beyond the RCP, WR/VE continued to decreased and averaged 1.524±0.13 L/min/W ($p<0.005$) at maximal exercise. During incremental exercise test, VT to inspiratory time and inspiratory time to total breathing time response to the AT, RCP and maximal exercise are shown in Table 1. There is linear significant correlation between increase in VT/Ti and VE (Fig. 3).

Table 1. Relationships between tidal volume to inspiratory time ratio (VT/Ti) and inspiratory time to total respiratory time ratio (Ti/Ttot) in response to the incremental exercise at the warm up, at anaerobic threshold (WAT), at respiratory compensation point (WRCP) and at maximal exercise (WMAX) (mean±SE).

	V_T/Ti	Ti/Ttot
Warm-up	0.668±0.02	41.9±0.9
W_{AT}	1.848±0.06	45.8±0.8
W_{RCP}	2.326±0.09	47.1±0.9
W_{MAX}	3.509±0.13	49.1±0.9

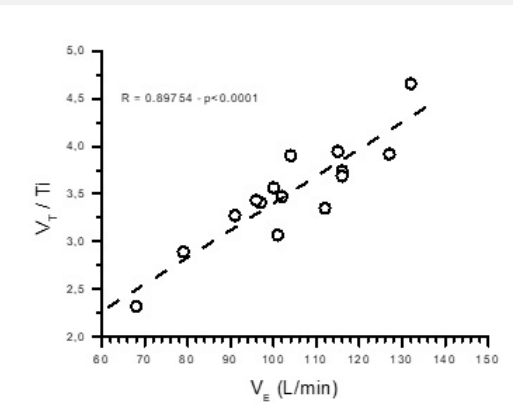

Fig. 3. The correlation between minute ventilation and tidal volume to inspiratory time ratio (VE/Ti at the end of the ramp test (n=15)).

4. Discussion

We have found different interaction in VT and Bf during each metabolic stage of incremental exercise test, i.e. aerobic region, isocapnic buffering period and anaerobic region. There was significant change in ventilator pattern regarding the exercise modality. Evaluating the differentiating between Bf and VT during different part of the incremental exercise test may improve our knowledge of exercise hyperpnoea, because Bf and VT seems to be regulated by different metabolic effects (Whipp and Ward, 1998).

AT describes the metabolic transition point from aerobic to anaerobic metabolism occurred at 63% of maximal exercise capacity, which is accepted as normal healthy range (Ozcelik et al., 2004; Wasserman et al.,

2012). During an incremental exercise test, increased metabolic demands of exercising muscle in response to the progressively increasing work load (i.e. from 20 W to 143 W) accompanied by a marked increase of VE (Fig. 2). In the aerobic region of incremental, exercise test, VE increased mainly by a marked increase in VT (142%) and also small but significant increase in Bf (25%) (Figs.1, 2).

Breathing patterns response to the incremental exercise work rate between AT and RCP was different than aerobic region of exercise. VE increased due to the rise in both VT and Bf (Fig. 2). Workload above the RCP, VE increased significantly (62%). In contrast to the aerobic region of increment exercise test, Bf is the main factor stimulating VE (Fig. 2). Bf begins to increase workload above AT and becomes more rapidly above RCP to maximal exercise (Cross et al., 2012).

VT/Ti increased thought the incremental exercise test (Naranjo et al., 2005) and reflect switch off inspiration regulating the rate of VT and Bf. The work production capacity for each liter of VE decreased when the work rate increased further (Benito et al., 2006). A high level of Bf relative to given VT above the AT and RCP will result in a less effective ventilation. The study performed trained subjects showed different breathing pattern in treadmill exercise compared to cycle ergometer especially lower VT observation (Power et al., 2012). The disparate response of respiratory pattern to metabolic activity under the condition of progressively increasing exercise stress reveal close relationships between metabolic activity level and breathing patterns.

Evaluating of the relationships between Bf and VT for assessing ventilatory response during incremental exercise at the AT, RCP and maximal values will provide useful information in the assessment of the response to each part of exercise in healthy people.

Acknowledgements
There is no acknowledgement to report.
Funding: This study was not funded.

Conflict of Interest: There is no conflict of interest to declare.

Ethical approval: The study was approved by the Ethics Committee of our hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Clinical Research

J. Exp. Clin. Med., 2021; 38(1): 11-15
doi: 10.5835/jecm.omu.38.01.003

Results of cardiologic evaluation at our newborns intensive care unit

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ARTICLE INFO

Article History
Received 13 / 05 / 2020
Accepted 27 / 06 / 2020
Online Published 26 / 01 / 2021

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Keywords:
Congenital heart disease
Incidence
Murmur
Newborn intensive care unit

ABSTRACT

Congenital heart disease (CHD) are the most common congenital anomaly in newborns. In this study, we aimed to evaluate the frequency and distribution of CHD among babies in the neonatal intensive care unit (NICU) of our center. Between June 2018 and February 2020, 109 babies were diagnosed with congenital heart disease among 1779 babies who were admitted to the NICU. The most frequent reasons of pediatric cardiology consultation were murmur and respiratory problems. Of newborns with CHD, 85.3%, have acyanotic and 11.1% have cyanotic CHD. The mean gestational age, postnatal age and the bodyweight of the cases were 33.4 weeks, 2.5 days and 1.58 kg, consecutively. 52.3% were male and 47.7% were female. The incidence of CHD in our center was 6.05%. The most common acyanotic CHDs were ventricular septal defect (24.8%), patent ductus arteriosus (23%) and atrial septal defect (16.6%). The most common cyanotic CHDs were Tetralogy of Fallot (3.7%) and transposition of the great arteries (1.8%). As a result, a significant portion of our patients were diagnosed acyanotic CHD. We think that the frequency of CHDs in our NICU will possibly change as the preferability of our center increases for pediatric cardiac surgery. Congenital heart diseases remain as common and important health problem in the neonatal period. Therefore, early cardiological evaluation is very important for management of these patients. The incidence of CHDs in the NICU is higher than in all live births.

1. Introduction

Congenital heart disease (CHD) is still responsible for 3% of all infant deaths and 46% of congenital malformation deaths despite advances in diagnosis and treatment (Hoffman and Kaplan, 2002). Although it varies through centers, the overall incidence in the neonatal period is between 0.5-0.8% (Wren et al., 2000).

There is an increasing interest in demonstrating cardiac pathologies by antenatal evaluations. As a result of this, the distribution of CHD in the neonatal intensive care unit (NICU) of the centers changes as the babies with complex CHD are transferred before birth to the centers' where they will be operated (Geggel, 2004). In newborns, symptoms of CHD can be severe, such as dyspnea, tachypnea, cyanosis, acidosis, shock, or mild, such as isolated murmur. The aim of this study is to determine the frequency and distribution of CHDs in newborns who are evaluated with suspicion of CHD in our NICU.

2. Materials and methods

In our study, newborns who were admitted to NICU of Ondokuz Mayıs University Faculty of Medicine between

June 2018 and February 2020 and who were asked for a pediatric cardiology consultation with suspicion of CHD were evaluated retrospectively. Postnatal age, gender, body weights and echocardiographic diagnoses of the patients were recorded. Local ethics committee approval was obtained for the study protocol.

In the NICU, newborns were evaluated by neonatologist. Pediatric cardiology consultation was requested for babies who had mild symptoms such as murmur, dysmorphic findings, infant of diabetic mother (IDM), or severe symptoms such as cyanosis, respiratory problems that could not be explained by pulmonary disease. Echocardiography was performed on all the newborns by the same pediatric cardiology specialist and the examination was repeated when necessary. Two-dimensional (2D), M-Mode, color Doppler, continuous wave (CW) and pulse wave (PW) Doppler capable device (Vivid 7 ultrasound-GE Medical Systems, Norway) and 10S sector probe is used. Cardiovascular anatomy was determined using two-dimensional and color doppler echocardiography using standard four chamber, long axis, parasternal, subcostal and suprasternal views. Valve-vessel stenoses were evaluated by CW and PW Doppler. Left ventricular internal diameters, interventricular septum thickness, posterior wall thickness of left ventricle were measured during diastole and systole by M-mode. Cases of atrial septal defect (ASD) (<3 mm), patent foramen ovale (PFO), and small asymptomatic patent ductus arteriosus (PDA) which closed spontaneously were not included to the CHD group and were considered normal. In cases where the anatomy could not be clarified by echocardiography, multislice computed tomography was performed.

Statistical analysis

"Statistical Package for Social Sciences for Windows", version 18.0 (SPSS Inc, Chicago IL, USA) was used for statistical analysis. Categorical variables were expressed as percentages. Descriptive statistics were used for frequency and percentage, which are descriptive parameters.

3. Results

1799 patients were admitted to the NICU between June 2018 and February 2020. Four hundred seventy-seven of these were consulted to the pediatric cardiology division for a total of 998 times. Of the consulted newborns, 261 (45.1%) were girls and 214 (54.9%) were boys; average gestational age 36.4 ± 3.1; postnatal age was 5.0 ± 5.6 days and body weight was 1.93 ± 0.84 kg.

The reasons for neonatologists to request pediatric cardiology consultation are shown in table 1, among which the most common were murmur and respiratory problems. CHD was found in 72 (33.4%) of the newborns with murmur and in 37 (14.1%) of those without a murmur and consulted for other reasons.

Table 1. Reasons of pediatric cardiology consultation

Reasons	n	%
Murmurs	215	45.07
Respiratory problems	112	23.48
Non-cardiac congenital anomalies	48	10.06
Low oxygen saturation	32	6.70
Cyanosis	21	4.40
Infant of diabetic mother	20	4.19
Antenatal diagnosis	14	2.93
Circulatory deterioration	10	2.09
Metabolic acidosis	5	1.04

60 (12.5%) of the newborns who were included in the study has normal cardiac anatomy. Three hundred eight cases [91 (19%) PFO, 133 (27.8%) ASD less than 3 mm, 41 (8.5%) small atrial septal aneurysm, 18 (3.7%) mild valve deficiencies lost at follow-up (tricuspid 11, pulmonary 2, aortic 2, mitral 3) and 25 (5.2%) asymptomatic small self-closing PDA] were considered normal. Thus, the number of newborns without significant CHD was found to be 368 (77.1%). Therefore, the rate of patients with CHD among all newborns who were admitted to the NICU was 6.05% (109/1799) and 109/477 (22.9%) among the newborns for whom pediatric cardiology consultation was requested.

In the study group, 57 (52.3%) of the cases were male; 52 (47.7%) girls; 43 (39.4%) were premature, 66 (60.6%) were mature. Average gestational age, postnatal age and body weight were 33.4 ± 2.8 weeks; 2.5 ± 3.1 days (0-30 days) and 1.58 ± 0.74 (0.525-4.260 kg), respectively.

93 (85.3%) of cases have acyanotic, 12 (11.1%) have cyanotic CHD. Echocardiography showed asymmetric septal hypertrophy (ASH) in two, hypertrophic cardiomyopathy in one and intracardiac mass in one case. Table 2 shows the types and frequencies of CHD detected in our study.

The most common CHD was VSD (27/109, 24.8%) in this group. 23 of these were small and 4 were large VSD. In the second frequency, wide PDA was detected in 25 patients (23%). Although 4 of them were large according to echocardiographic criteria, they were not clinically hemodynamically significant. These closed spontaneously within an average of 22 days at follow-up. Four newborns PDA has become smaller during follow-up and these were planned to be followed up in pediatric cardiology outpatient clinic with the diagnosis of small PDA. In 15 cases, PDA closure treatment was applied pharmacologically using ibuprofen or paracetamol depending on the clinical condition. Successful results were obtained in 13 cases.

Table 2. The types and frequencies of CHD detected in the neonatal intensive care unit

Type of CHD*	n	%
Ventricular septal defect (Total)	27	24.8
small (apical muscular)	8	7.4
(central muscular)	13	12
(perimembranous outlet)	2	1.8
large (central muscular)	1	0.9
(perimembranous outlet)	3	2.7
Patent ductus arteriosus (large)	25	23
Atrial septal defect (secundum)	18	16.6
Endocardial cushion defect	7	6.5
Tetralogy of Fallot	4	3.7
Pulmonary stenosis (mild)	4	3.7
Pulmonary stenosis (peripheral, mild)	4	3.7
Bicuspid aortic valve + Aortic regurgitation	2	1.8
Aortic coarctation	2	1.8
Transposition of the great arteries	2	1.8
Asymmetric septal hypertrophy	2	1.8
Single ventricle	2	1.8
Pulmonary stenosis (severe)	1	0.9
Hypoplasia of arcus aorta	1	0.9
Aortic stenosis (severe)	1	0.9
Tricuspid atresia	1	0.9
Pulmonary atresia / Ventricular septal defect	1	0.9
Hypoplastic left heart syndrome	1	0.9
Total pulmonary venous return anomaly	1	0.9
Hypertrophic cardiomyopathy / Pompe disease	1	0.9
Intracardiac mass	1	0.9
Aortic stenosis (mild)	1	0.9
Total	**109**	**100**

* Only major pathology of the patients with multiple heart diseases has been shown.

Two cases did not respond to pharmacological closure. In these, hemodynamically significant PDA continued, and surgical closure was successfully performed at our center.

Cyanotic heart diseases were 11.1% in our study group and the most common one was Tetralogy of Fallot (TOF) (3.7%). Balloon angioplasty for a patient with aortic coarctation, balloon valvuloplasty for a patient with severe PS and balloon atrial septostomy for a patient with transposition of great arteries (TGA) were performed successfully at our center. A patient with TGA and another with cyanotic CHD were transferred to another center for advanced surgery.

4. Discussion

Congenital heart diseases are the most common congenital anomalies with unknown etiology (Gürkan, 2004). Its incidence ranges from approximately 0.5-0.8% in all live births (Baş et al., 2013). In terms of developments in echocardiography, screening methods and NICU monitoring, the prevalence of CHD has increased over the years (Zan et al., 2015). Although the frequency of CHD varies from center to center, it is reported to be 1.6-6.6% in our country (Baş et al., 2013). In our study, the frequency of CHD among the patients hospitalized in our center was found to be 6.05%. In our study, we think that the reason for the high incidence of CHD in our center is the admission of the babies from the other centers of North Anatolian region whom were suspected to have CHD.

In the neonatal period, CHD may cause symptoms such as cyanosis, shock, restlessness, and lack of nutrition, and may not cause any symptoms (Güven et al., 2006). In neonatal units, evaluation of heart diseases should be prioritized by a team of newborn and pediatric cardiology specialists. Echocardiographic examination is very important for diagnosis and treatment at the neonatal period, since hemodynamic changes of CHD should be fast. Therefore, patients should be evaluated more than once if necessary. In our study, 477 cases were evaluated by echocardiography for whom neonatologists requested pediatric cardiology consultation. Four hundred seventy-seven cases were assessed by echocardiography a total of 998 times. Re-evaluations were due to clinical deterioration of some case with severe CHD and the persisting suspicion for CHD in some newborns who were found to be normal before. The gender distribution of the patients was screened. Of those diagnosed with CHD, 52.3% were boys and 47.7% were girls. Although there was no significant difference in our study, male newborns constituted the majority of cases in accordance with the literature (Morris, 2004). In two studies conducted in our country, 54.3% and 54.5% of babies with CHD in the neonatal intensive care unit were reported as males (Zan et al., 2015). According to these results, male gender appears to be disadvantageous in terms of the frequency of CHD.

Half of babies with congenital heart disease are diagnosed in the first week and the other half in the first month. In one study, the average time of diagnosis was determined as 11 (1-45) days, while in the other, the average age of diagnosis was 5.7 days in acyanotic patients and 2.7 days in cyanotic patients (Kadivar et al., 2008; Zan et al., 2015). In our study, the average age of diagnosis of our patients was found to be 2.5 ± 3.1. This situation made us think that we were successful in evaluating our newborn patients earlier than the studies in the literature.

Over 50% of murmurs heard in newborn babies are innocent murmurs with increased pulmonary blood flow (Zan et al., 2015). These innocent murmurs can be confused with pulmonary stenosis or PDA murmurs.

CHD type and severity can not be determined only with murmur. Murmur of tricuspid regurgitation in the neonatal period can also be confused with VSD. Also, murmur may not be present in severe CHDs such as aortic coarctation and TGA. Despite these, murmur in the neonatal period is still the most important symptom of CHD. In our study, murmur was the most common reason (45.07%) for requesting pediatric cardiology consultation.

Less than 50% of congenital heart diseases can be detected by routine examination of healthy newborns in the first weeks. In the presence of murmur, this rate rises to 54% (Güven et al., 2006). In one study, the sensitivity of murmur in detecting CHD was 54.1% and its specificity was 92.9% (Yıldız et al., 2015). In our study, CHD was found in 33.4% of newborns who were consulted for murmur, and in 14.1% of those who were consulted for other reasons. We think that the reason for the low rates in our study was the large number of cases that we did not include in the patient group like PFO (n=91), ASD (n=133), atrial septal aneurysm (n=41), mild valve insufficiency (n=18) and small-asymptomatic-spontaneously closed PDA (n=25). Indeed, in a study, it was reported that PFO, ASD and PS were found to be the most common in neonates with murmur (Yıldız et al., 2015). In another study, it was stated that PFO, ASD and VSD were the most common CHDs among 455 newborns who applied to the pediatric cardiology outpatient clinic (Özkan et al., 2016). Instead of performing echocardiography at the neonatal period only due to a prominent murmur, we prefer to perform echocardiographic evaluation in every suspicious auscultation finding. As a matter of fact, the frequency of CHD was found to be quite high (37.1%) than other studies in a study in which all patients hospitalized in NICU were evaluated with ECO (Ertuğrul et al., 2011). The fact that we have determined a flexible attitude towards the severity and quality of murmur is another reason for the low frequency of CHD in patients with murmur in our study.

In our study, acyanotic and 11.1% cyanotic CHD were detected in 85.3% of the patients diagnosed with CHD. Asymmetric septal hypertrophy in two (1.8%), hypertrophic cardiomyopathy in one (0.9%) and intracardiac mass in one (0.9%) were detected. Among the congenital heart diseases, the most common acyanotic diseases are ASD and VSD (Güven et al., 2006). In another large study, the most common acyanotic heart disease was found as VSD (Zan et al., 2015). In a meta-analysis, VSD prevalence was reported to be the first with 2.62/1000, second with ASD 1.64/1000 and third with PDA 0.87/1000 in all live births (Van der Linde et al., 2011). In our study, the most common CHD (n=27) was determined as VSD with 24.8%. However, it was noticed that huge part of them was small VSD (n=23). Large PDA was the second most common (23%) and despite the exclusion of small ASDs, ASD was the third most common (16.6%) CHD. The most common cyanotic CHDs in the literature are TOF and TGA (Van der Linde et al., 2011; Zhao et al., 2018) and the most common cyanotic heart disease in our study was TOF. Although the ranking of acyanotic and cyanotic CHDs are compatible with the literature in our NICU, low frequency of acyanotic CHDs attracts attention.

In the literature, different reports are present about the frequency of cyanotic heart diseases in patients followed up in NICU. In a study conducted in our country, the most common symptom was detected as cyanosis in neonates with 190 CHD (Tokel et al., 2001). In other studies, cyanosis was detected in 9.6% to 13.1% of newborns with CHD and it was stated that cyanosis was the second most common symptom of CHD (Zan et al., 2015). This situation is related to whether the study center is a reference center for complex heart disease treatment. As in our center, the centers without the division of "Pediatric Cardiovascular Surgery" are not the centers that these patients prefer primarily. In recent years, we think that cyanotic CHD rate is lessened in our unit due to admission of these patients to the advanced "Pediatric Cardiovascular Surgery centers and this is related with improvement of antenatal diagnosis techniques and transportation facilities.

The most common congenital heart anomalies in IDMs were reported ASH and VSD (Edwards et al., 2001; Güvenç and Güzeltaş, 2017). In one study, the frequency of ASH was 38% in IDMs and 7% in normal population (Weber et al., 1991). In our study, only two (10%) of the 20 newborns who were consulted as IDM were diagnosed as ASH. Although the relation between ASH and IDM remains a popular information, we think that the frequency of ASH is not high in IDMs.

In conclusion, it is difficult to diagnose CHD only by physical examination during the neonatal period. Due to the rapid hemodynamic changes in the neonatal period, early cardiological evaluation is required of early diagnosis and treatment for whom has suspicious signs of CHDs. For this reason, we think that even if there is no characteristic findings of CHD, suspicion may be an indication for echocardiographic examination which is non-invasive. Thus, early diagnosis, early treatment, reducing morbidity and mortality will be possible at NICU. Although, our results are generally consistent with the literature, we think that the frequency of CHD in our NICU will change as the preferability of our center increases for pediatric cardiovascular surgery.

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

Funding: The author received no financial support for the research and/or authorship of this article.

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Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Clinical Research

J. Exp. Clin. Med., 2021; 38(1): 17-20
doi: 10.5835/jecm.omu.38.01.004

Sinonasal neoplasms: A tertiar center experience

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ARTICLE INFO

Article History
Received 17 / 12 / 2019
Accepted 01 / 08 / 2020
Online Published 26 / 01 / 2021

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Keywords:
Histopathology
Sinonasal neoplasms
Symptom
Treatment

ABSTRACT

Primary tumors of the nasal cavity can be classified as benign or malignant. Patients with tumors of the nose and paranasal sinuses are usually diagnosed in the advanced stages of the disease. The aim of this study was to evaluate the data of patients who were operated for sinonasal masses in our clinic in light of the literature. Between January 2016 and December 2018, 357 cases of sinonasal masses presenting to the Otorhinolaryngology Department of the Health Science University at the Samsun Training and Research Hospital were retrospectively screened and included in the study. Of the 357 patients included in the study, 256 (72%) were male, and 101 (28%) were female. The most common symptom was nasal obstruction (90%). Most of the benign cases were nasal polyps (90.2%), while the next most frequent diagnosis was inverted papilloma (4.7%). Malign neoplasms were found in 11 cases, and five were found to be squamous cell carcinomas (SCC). All benign cases were treated surgically, and the malignant cases were treated according to the diagnosis. In conclusion, although the symptoms of the 357 patients with sinonasal mass were similar, histopathological evaluation revealed 96.9% benign and 3.1% malign pathologies. The malign/benign ratio was 3.08. Malignancy should therefore be considered as a possibility in patients with nasal bleeding and facial swelling.

1. Introduction

Primary tumors of the nasal cavity can be classified as benign or malignant, and epithelial ornon-epithelial (including soft tissue tumors, bone and cartilage-derived tumors, neuroectodermal tumors, germ cell tumors, and hematolymphogenic tumors) (Thompson and Franchi, 2017). Nasal and paranasal sinus tumors are very rare. Malignant tumors of the sinonasal tract comprise 0.2% to 0.8% of all malignant tumors, and only 3% of head and neck malignancies (Frierson, 1986; Maniglia and David, 1995).

Patients with tumors of the nose and paranasal sinuses are usually diagnosed in the advanced stages of the disease. Because sinonasal symptoms such as nasal congestion, toothaches, and nosebleeds are primarily caused by simple diseases, a tumor can grow in the closed cavity for a while after initiation, and can usually only be diagnosed when it reaches the bone. The time between the onset of the initial symptoms and the diagnosis has been determined to be six to eight months, and it has been reported that only 25% of maxillary sinus tumors could be diagnosed while the

tumor was still in the sinus (Frierson, 1986).

Smoking, exposure to wood dust, nickel, or formaldehyde, rhinitis, and sinoanasal diseases such as nasal polyps are among the predisposing factors of sinonasal cancer. More specifically, there is a direct relationship between chronic sinusitis and sinonasal cancers (Lund, 1983; Brinton et al., 1994).

The aim of this study was to evaluate the data of patients who were operated on for sinonasal masses in our clinic in light of the literature.

2. Materials and methods

A total of 357 patients who were treated for sinonasal pathology between January 2016 and December 2018 at the Otorhinolaryngology Department of the Health Sciences University at the Samsun Training and Research Hospital were included in the study. The study was approved by the local ethics committee (protocol number 31-2019BADK / 7-61). Demographic characteristics, complaints, operations, and histopathological findings of the patients were evaluated. Radiological evaluations (CT and/or MRI) were performed following the ENT examination (including endoscopic examination) of the patients who presented to the clinic. The patients who had malignant findings had first received biopsies, and the patients with benign masses were operated on without preoperative biopsies. The patients with malignant masses according to histopathological evaluation had surgery, surgery + radiotherapy (RT), or RT alone.

3. Results

Of the 357 patients included in the study, 256 (72%) were male, and 101 (28%) were female. The ages of the patients ranged from six to 83 years. The mean age was 43.2 for males and 38.5 for females. A total of 346 patients presented with benign neoplasm, 315 (91.0%) had nasal obstruction, 21 (6.06%) reported that they had been snoring, six (1.73%) had epistaxis, three (0.86%) had nasal mass prolapsus, and one (0.3%) had a nasal dorsum enlargement complaint. Of the 11 patients who had been diagnosed with malignant neoplasm, five (45.4%) presented with nasal obstruction, three (27%) had epistaxis, two (18%) had facial swelling, and one (9%) had nasal mass prolapsus (Table 1).

Table 1. Reasons of pediatric cardiology consultation.

Complaints	Benign neoplasm (n=346)	Malignant neoplasm (n = 11)	Total (n = 357)
Nasal obstruction	315	5	320
Nasal mass prolapsus	3	1	4
Epistaxis	6	3	9
Snoring	21	-	21
Facial swelling	1	2	3

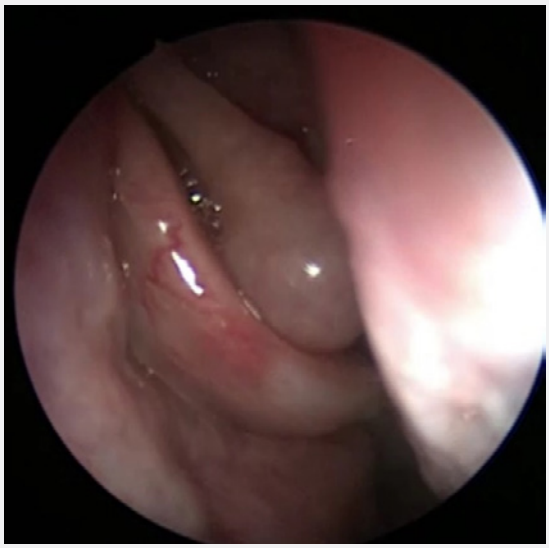

Fig. 1. Nasal polyp in right middle meatus.

According to histopathological evaluation, the most common benign neoplasm in 322 patients (90.2%) was nasal polyposis (Fig. 1). The second most common benign neoplasm was inverted papilloma, which had been diagnosed in 17 patients (4.7%). Other benign neoplasms included ameloblastoma (3), osteoid osteoma (2), hemangioma (1), and angiofibroma (1).

The most common malignant neoplasm was SCC (5%, 1.4%) (Fig. 2). Other malignant neoplasms included lymphoma (3), carcinoma ex pleomorphicadenoma (1), esthesioneuroblastoma (1), and hemangiopericytoma (1) (Table 2).

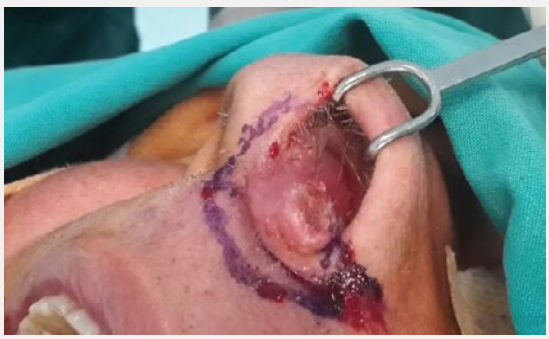

Fig. 2. Squamous cell carcinoma in left nasal vestibule.

Functional endoscopic sinus surgery (FESS) was performed in 322 patients with nasal polyposis. Transnasal endoscopic resection (TNER) was performed in 11 of 17 patients with inverted papilloma, while transnasal endoscopic medial maxillectomy was performed in five patients, and medial maxillectomy with lateral rhinotomy in one patient. In ameloblastoma cases, open surgery was performed, and transnasal endoscopic resection was performed in all other benign cases.

Table 2. Histopathologic diagnosis

Benign neoplasm		**(n=346)**
	Nasal polyposis	322
	Inverted papilloma	17
	Ameloblastoma	3
	Angiofibroma	1
	Hemangioma	1
	Osteoid osteoma	2
Malignant neoplasm		**(n=11)**
	Squamous cell carcinoma	5
	Lymphoma	3
	Carcinoma ex pleomorphic adenoma	1
	Esthesioneuroblastoma	1
	Hemangiopercytoma	1

The squamous cell carcinomas (SCC) originated from the vestibule in two cases, the maxillary sinus in two cases, and the lateral nasal wall in one case. The complaints of the patients with maxillary sinus-induced SCC were swelling on the face and eye. One of the patients with vestibule-originated tumors was treated only with surgery, and the other was treated with surgery and RT. Two cases that originated in the maxillary sinus were treated with RT only (the patients did not accept surgical treatment). The case originating from the nasal passage was treated with RT. Lymphoma cases received RT (Table 3).

Table 3. Treatment modalities

Histopathologic diagnosis	**Treatment**
Benign neoplasm	
Nasal polyposis	Functional endoscopic sinus surgery (FESS)
Inverted papilloma	Transnasal endoscopic resection (TNER) / endoscopic medial maxillectomy
Ameloblastoma	TNER + open surgery
Angiofibroma	TNER
Hemangioma	TNER
Osteoid Osteoma	TNER
Malignant neoplasm	
Squamous cell carcinoma	1 case surgery 2 cases surgery + radiotherapy (RT) 2 cases RT
Lymphoma	RT
Carcinoma ex pleomorphic adenoma	Resection with lateral rhinotomy
Esthesioneuroblastoma	Surgery + RT
Hemangiopericytoma	Endoscopic surgery

4. Discussion

Benign and malignant diseases of the paranasal sinuses may cause similar complaints among patients. The most common complaints are nasal obstruction, facial pain, headache, and intermittent epistaxis. Although patients may have one or more of these symptoms at the beginning stages of the disease, the time between the first symptom and the diagnosis varies between three and 14 months due to physician or patient reasons (Lund, 1983). Tritt et al. reported that they observed epistaxis in malignant diseases at a higher rate, whereas nasal obstruction, nasal congestion, and non-olfactory symptoms did not differ (Tritt et al., 2008). In our study, it was observed that the patients were admitted to our clinic with complaints of snoring, epistaxis, nasal mass prolapsus, and facial swelling. Intermittent epistaxis and facial swelling were common symptoms of malignant neoplasms.

In a study evaluating the histopathology of 44 patients with unilateral nasal pathology, 32 patients had polyposis, seven had inverted papillomas, two had SCC, one had mucocele, and one had esthesioneuroblastoma (Tritt et al., 2008). In our study, the most common benign neoplasm was nasal polyposis in 322 (90.2%) cases. The second most common was inverted papilloma in 17 (4.7%) cases. Other benign neoplasms included ameloblastoma (3), osteoid osteoma (2), hemangioma (1), and angiofibroma (1). The most common malignant neoplasm was SCC (5-1.4%). Other malignant neoplasms were lymphoma (3-0.9%), carcinoma ex pleomorphic adenoma (1-0.3%), esthesioneuroblastoma (1-0.3%), and hemangiopericytoma (1-0.3%).

The incidence of nasal polyposis in the population varies between 1% and 4%. Polyposis is four times more common in males than females, and it is usually seen at the age of 40 (Kitapçı et al., 2005). Sinonasal polyps are caused by an inflammatory condition. However, in most studies in the literature, they have been classified as the most common benign sinonasal tumors (Headman et al., 1999; Shirazi et al., 2015). In our study, the most common nasal pathology was nasal polyposis (90%), and these patients were frequently admitted to our clinic with the complaint of nasal obstruction. The mean age of the patients with nasal pathology was 40.8± 2.4, and the female/male ratio was approximately 1/3. FESS was performed in all nasal polyposis patients.

Inverted papilloma is a benign epithelial tumor characterized by invagination of the epithelium originating from the sinonasal mucosa toward the stroma. They constitute 0.5-4% of all nasal tumors (Constantino et al., 2007; Zhao et al., 2016). In our study, inverted papilloma was detected in 17 (4.7%) of the cases of sinonasal masses. TNER was applied in 11 of these cases, and TNER with medial maxillectomy

was applied in five. One patient underwent medial maxillectomy with lateral rhinotomy.

Nasal and paranasal sinus tumors are very rare. Malignant tumors of the sinonasal tract comprise 0.2% to 0.8% of all malignant tumors and only 3% of head and neck malignancies. Surgical planning should be done according to the stage of the disease. Surgical resection is applied in stage 1 tumors. If there is doubt in the surgical margins, RT should be administered. In stage 2 and 3 tumors, surgery is performed after primary RT. Propagation of the skull base and nasopharynx in stage 4 tumors is relatively contraindicated for surgery. In this situation, high-dose RT is applied (Frierson, 1986; Maniglia and David, 1995).

SCC is the most common malignancy of the sinonasal region (Lee et al., 2007). In our study, the most common malignant neoplasm (five cases) was SCC. Two of these cases were caused by the maxillary sinus and invaded the orbita, and these patients did not accept the proposed surgery and received RT. The other two cases originated from the nasal vestibule, and surgery was performed, with RT administered to one patient after surgery. In one case, the tumor originated from the lateral nasal wall, and endoscopic transnasal medial maxillectomy was performed.

In conclusion, the diversity of the masses in the sinonasal region, the similarity of their symptoms, and the advent of mostly benign neoplasms delay the diagnosis and treatment of rare malignant neoplasm. Patients with epistaxis and facial swelling should be evaluated with caution for malignant neoplasm. Further, patients with sinonasal masses should undergo endoscopic examination and radiological screening, and biopsies must be taken in cases of malignancy suspicion. Detailed information should be provided to the patient and their relatives in the selection of the treatment method for malignant neoplasms.

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Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Clinical Research

J. Exp. Clin. Med., 2021; 38(1): 21-25
doi: 10.5835/jecm.omu.38.01.005

Could the ratio of the second finger to the fourth finger (2D:4D) be a new morphological marker in predicting preoperative anxiety and postoperative agitation in pediatric patients?

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ARTICLE INFO

Article History
Received 13 / 05 / 2020
Accepted 27 / 06 / 2020
Online Published 26 / 01 / 2021

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Keywords:
2D:4D
Marker
Postoperative agitation
Preoperative anxiety

ABSTRACT

Studies have reported that the ratio of the second finger to the fourth finger (2D:4D) indicating the effects of intrauterine andogene exposure. It is stated that it can be used as a morphological marker in evaluating developmental/ psychopathological disorders. 90 children between the ages of 5-10, who were planned to undergo deciduous tooth extraction under deep sedation, were included in the study. Measurements were made on the second and fourth fingers of children's right and left hands. The behaviors of the patients during the preoperative period (m-Yale Preoperative Anxiety Scale), vascular access insertion and separation from the family were evaluated in determining the anxiety levels of the patients. During the recovery process, agitation status was evaluated using Watcha Scale. And there was no significant relationship found between 2D:4D and these parameters. In conclusion, 2D:4D did not succeed as a morphological marker in predicting preoperative anxiety and postoperative agitation in the preoperative period.

1. Introduction

Anxiety is one of the most important problems we encounter before medical procedures. In general, anxiety can occur in 10-30% of hospitalized patients. This rate increases in preoperative anxiety. It is reported that especially in pediatric patients, the anxiety rate exceeds 60% in the preoperative period, and this rate increases as the age decreases (West et al., 2020). General anesthesia / sedation applications are needed for many medical procedures of children. Many processes such as preparations procedures, preoperative waiting time and invasive procedures are increasing the anxiety level of the children. Apart from these, reasons such as not having full information about the procedure to be performed, anxiety of pain, fear of death are also effective (Meletti et al., 2019). Especially in children, the lack of cooperation and fear of leaving the family increase the level of anxiety. In dental practice, dental anxiety, a more specific and important condition, is encountered. Dental anxiety causes delayed dental treatments and impaired oral hygiene, negatively affecting the patient's oral health. Previous experiences and fear of losing an organ cause serious anxiety especially in children (Dixit and Jasani, 2020).

It has been associated with anxiety level and many complications such as postoperative pain, nausea, behavioral disorders, burnout, and sleep disturbance (Dwairej et al., 2020). This causes an increase in postoperative complications and difficulties for the hospital staff to continue their treatment. It also causes health personnel not to work efficiently and increases hospital costs.

Postoperative agitation, like preoperative anxiety, is a condition that negatively affects healthcare and can cause complications. Postoperative agitation appears as a picture that causes delirium, confusion, disorientation, uncontrolled crying, irritability, and elongation at recovery time (Hino et al., 2017; Ali et al., 2020). In this process, the patient may hurt himself. Additional medications applied to prevent excitation may delay the recovery process. In the preoperative period, some scales and determinant tests can be used to predict postoperative agitation risk and to take precautions against factors that trigger and cause postoperative agitation.

It is known that intrauterine testosterone is effective in determining gender and behavior patterns. Richard et al. investigated the effects of the ratio of the second finger [index finger] to the fourth finger [ring finger] (2D:4D) and have shown a relationship between prenatal sex hormone measurements (amniocentesis and perinatal cord blood) (Ventura et al., 2013; Richards, 2017). Many studies have reported that low 2D:4D ratio is an indicator of intrauterine androgen exposure and may be associated with many diseases (Ribeiro et al., 2016; Eichler et al., 2018; Myers et al., 2018). The relationship between physical, psychological, social and developmental disorders and 2D:4D have been investigated (O'Briain et al., 2017; Butovskaya et al., 2019; Togo et al., 2019).

In this study, the hypothesis is that 2D:4D ratio may be low in patients with high preoperative anxiety and postoperative agitation. If this relationship is determined, the 2D:4D ratio can be used as a morphological marker to predict preoperative anxiety and postoperative agitation. For such patients, regular application of behavioral management techniques, special time allocation, calling to operation when the ambient conditions are at the optimum level and pharmacological techniques can be recommended. It may also be recommended that the physician be cautious for the reasons that increase postoperative agitation.

In this study, it was aimed to investigate whether there is a significant relationship between 2D:4D ratio and preoperative anxiety and postoperative agitation in pediatric patients who are planned to deciduous tooth extraction under deep sedation.

2. Materials and methods

This is a double-blind, randomized study. The study started after the permission of the Ondokuz Mayis University Clinical Research Ethics Committee (B.30.2.ODM.0.20.08/537). This study was carried out in accordance with the Helsinki Declaration Principles. 90 children between the ages of 5-10, ASA I-II, male and female who were planned to deciduous tooth extraction under deep sedation, were included in the study. Patients with high anxiety and incompatibility were directed to tooth extraction under deep sedation. Deciduous teeth that should be removed due to caries or root resorption were included in the study. Patients with skeletal deformity, developmental retardation and mental disability were excluded from the study. First of all, relatives and patients were explained in the waiting room and informed volunteer consent form was approved. Relatives accompanied the patients until the anesthetic drug was given. Anxiety levels of all patients were evaluated using the m-Yale Preoperative Anxiety Scale (m-YPAS) in the preoperative waiting room. Afterwards, finger measurements of the children were made, and patients who did not allow measurement were excluded from the study. Measurements were made on the second and fourth fingers of children's right and left hands. The distance between the basal wrinkle and the fingertip was measured with the help of a ruler (vernier caliper). All measurements were made by the same assistant medical staff. Patients' behaviors were evaluated and recorded during intravenous vascular access and leaving the family and taken to the operating table. Minute heart rate, arterial oxygen saturation, and mean arterial pressure measurements were performed before surgery, after local anesthesia injection and every five minutes in all patients. Patients were administered intravenously (iv) with propofol 1 mg kg-1, midazolam 0.5 mg kg-1, fentanyl 1 μg kg-1. Propofol 0.5 mg kg-1 iv was administered to patients whose Ramsey Sedation Score was less than 5 (Table 1). Articain (40 mL mg-1) was administered to all patients as a local anesthetic. Demographic and intraoperative hemodynamic data were recorded. During the recovery process, agitation status was evaluated using Watcha

Table 1. Ramsey Sedation Score and Watcha Scale.

Ramsey Sedation Score	Response	Watcha Score	Response
1	Patient anxious oragigated or both	0	Asleep
2	Patient cooperative, oriented and tranquil	1	Calm
3	Patient responds to commands only	2	Crying, but can be consoled
4	A brisk response to a light glabellar tab	3	Crying, but cannot be consoled
5	Asluggish response to light glabellar tab	4	Agitated, and trashing around
6	No response		

Scale (WS). Complications, operation time and number of extracted teeth were recorded. No information was given to the patient about the finger measurements, the patient's relative and the physician who made the behavioral evaluations. All tooth extractions were done by the same dentist.

Statistical method

The data were analyzed with IBM SPSS V23. Comparisons by groups were compared with independent samples t-test and ANOVA. Categorical data were analyzed with chi-square test. The significance level was taken as $p<0.05$.

3. Results

Finger measurements were evaluated as mean ± standard deviation and multiple or small. When the average age, weight, procedure duration and number of extracted teeth were evaluated, there was no significant difference between 2D:4D ratios. The patient were aged a median of 7 (5-10) and 42 of these were female and 48 were male.

When the number of teeth extracted from the study was evaluated, it was found to be 5 ± 1 in patients with 2D:4D<1, and 6 ± 1 in patients with 2D:4D≥1 (p=0.664). When the processing times were evaluated, it was found to be 6 ± 1 minutes in patients with 2D:4D <1, and 7 ± 1 minutes in patients with 2D:4D≥1 (p=0.969).

When the preoperative anxiety level was evaluated, the the m-YPAS was found to be 29 (15-48) in patients with right hand 2D:4D ratio less than one, and 28 (16-48) in patients greater than one. (p=0.504). When the left hand was evaluated, 2D:4D ratio was determined as 29 (16-48) in patients with less than one, and 30 (18-46) in patients with greater than one (p=0.732) (Table 2).

When the behavior patterns shown by patients during vascular access insertion were evaluated, there was no significant relationship with right and left 2D:4D. Right hand 2D:4D ratio was determined as 0.96 ± 0.4 in shouting, impregnable patients, 0.98 ± 0.4 in patients with crying anxious, 1.00 ± 0.5 in patients withdrawing his hand, and 0.99 ± 0.5 in inactive calm patients (p=0.068). Left hand 2D:4D ratio was 0.97 ± 0.5 in shouting, impregnable patients, 0.97 ± 0.4 in patients with crying anxious, 0.97 ± 0.5 in patients withdrawing his hand, 0.98 ± 0.4 in inactive calm patients (p=0.863) (Table 3).

When the behavior patterns shown by the patients during family separation were evaluated, there was no significant relationship with right and left 2D:4D. The ratio of right 2D:4D was 0.98 ± 0.5 in calmly allowed families to leave, and 0.98 ± 0.4 in non-calm (p=0.463); the left 2D:4D ratio was 0.97 ± 0.5 in calmly allowed families to leave and 0.98 ± 0.4 in non-calm (p=0.885) (Table 3).

When hemodynamic data was evaluated, it was found that there was no significant difference with the right and left 2D:4D ratios in terms of heart rate, mean arterial pressure and arterial oxygen saturation (Table 4).

When the postoperative agitation status of the

Table 2. M-Yale Preoperative Anxiety Scale according to finger ratios.

	Right 2D:4D		Left 2D:4D	
	<1	≥1	<1	≥1
M-Yale Preoperatif Anxiety Scale	29 (15-48)	**28 (16-48)**	29 (16-48)	30 (18-46)
p	0.504		0.732	

Data presented as median (min-max). 2D: 4D; ratio of second finger to fourth finger.

Table 3. 2D:4D ratios according to the Vascular Access İnsertion, Family Seperation, Watcha Scale.

Vasculer access insertion	Shouting, impregnable patients (0)	Crying anxious (1)	Withd-rawing hand (2)	Inactive calm (3)	p
Right 2D:4D	0.96±0.4	0.98±0.4	1.00±0.5	0.99±0.5	0.068
Left 2D:4D	0.97±0.5	0.97±0.4	0.97±0.5	0.98±0.4	0.863
Family separation	**Calm**	**Non-calm**			
Right 2D:4D	0.98±0.5	0.98±0.4	-	-	0.463
Left 2D:4D	0.97±0.5	0.98±0.4	-	-	0.885
Watcha scale	**Watcha 1**	**Watcha 2**	**Watcha 3**		
Right 2D:4D	0.98±0.5	0.98±0.4	0.98±0.2	-	0.997
Left 2D:4D	0.97±0.4	0.97±0.4	1±0.4	-	0.724

Data presented as mean ± standard deviation. 2D: 4D; ratio of second finger to fourth finger.

Table 4. Hemodynamic data according to right and left 2D:4D ratios.

	Right 2D:4D<1	Right 2D:4D≥1	p	Left 2D:4D<1	Left 2D:4D≥1	p
Preoperative HR	**103±13**	100±20	0.213	101±15	101±20	0.724
HR after local anest-hesia	**123±10**	105±13	0.183	103±12	129±12	0.077
Minute 5 HR	**108±13**	**105±14**	**0.342**	**105±13**	**108±13**	**0.665**
Minute 10 HR	**112±11**	102±10	0.638	105±11	112±14	0.607
Preoperative MAP	**82±10**	81±11	0.400	81±10	81±12	0.053
MAP after local anesthesia	**84±12**	**80±11**	**0.392**	**82±11**	**81±13**	**0.106**
Minute 5 MAP	**78±11**	79±12	0.548	78±10	79±12	0.068
Minute 10 MAP	**77±9**	74±10	0.979	74±8	79±12	0.497
Preoperative SpO_2	**99(99-100)**	99(99-100)	0.107	99(99-100)	99(97-100)	0.233
SpO_2 after local anesthesia	**99(99-100)**	99(99-100)	0.638	99(99-100)	99(98-100)	0.454
Minute 5 SpO_2	**99(98-100)**	99(99-100)	0.586	99(99-100)	99(99-100)	0.783
Minute 10 SpO_2	**99(98-100)**	99(99-100)	0.230	98(98-100)	99(99-100)	0.774

Data presented as mean ± standard deviation and median (min-max). 2D:4D; ratio of second finger to fourth finger. HR; heart rate. MAP; mean arterial pressure. SpO2; arterial oxygen saturation.

patients was evaluated, the right hand 2D:4D ratio was 0.98 ± 0.5 in patients with Watcha 1, 0.98 ± 0.4 in patients with Watcha 2, and 0.98 ± 0.2 in patients with Watcha 3 (p=0.997). Left hand 2D:4D ratio, it was 0.97 ± 0.4 in patients with Watcha 1, 0.97 ± 0.4 in patients with Watcha 2, and 1 ± 0.4 in patients with Watcha 3 (p=0.724). There were no patients with Watcha score of 4 and 5 (Tables 1 and 3).

4. Discussion

High anxiety level can cause many problems during the operation and postoperative period. It has been stated that an anxiety-induced neurohormonal response may increase the need for anesthetics during operation and particularly cardiovascular complications. Increased catecholamine and cortisol levels can cause many systemic side effects (Moura et al., 2016; Malik et al., 2018). Similarly, postoperative agitation can cause many problems in children such as general anxiety, separation anxiety, sleep anxiety, eating disorders, disobedience to parents and environmental authority, and apathy in the postoperative period (Cho et al., 2020; Devroe et al., 2020). In addition, dental anxiety especially affects pediatric patients in the procedures applied in dentistry. Dental anxiety is more specific and important, and is a reaction to bad dental experience (Bux et al., 2019). In the preoperative period, it can be tried to be kept under control by keeping pediatric patients in appropriate environments, explaining the procedures to be applied and using behavior management techniques (Appukuttan, 2016). In cases where it is not sufficient, pharmacological methods are frequently used in dentistry applications (Wang et al., 2020). Determining the patients anxiety levels before and appropriately approaching them will have a positive impact on the patients treatment experience and therefore their dental health. The prevalence of preoperative anxiety and postoperative agitation and the frequency of its occurrence can be reduced by taking precautions (Hino et al., 2017; West et al., 2020). Many studies have shown that there is a negative relationship between many psychopathological conditions such as behavioral disorder, suicide, autism, and 2D:4D, and the 2D:4D ratio is less than one in such disorders (O'Briain et al., 2017; Butovskaya et al., 2019; Togo et al., 2019). In a study by Lenz et al. in cadavers, they reported that the rate of 2D:4D was lower in men who died by suicide than those who died normally. They stated that intrauterine androgen exposure may cause suicidal tendencies (Lenz et al., 2016). In another recent study, they did not find a significant relationship between 2D:4D ratio and the aggressive behaviors they display during the video game in college age teens (Hilgard et al., 2019). O'Brian et al. investigated the relationship between aggression-related injuries and 2D:4D ratio in patients who applied to the pediatric emergency department and reported that this rate was lower in girls (O'Briain et al., 2017). We investigated whether 2D:4D ratio can be a morphological marker in predicting preoperative anxiety and postoperative agitation. In this study, the behaviors of the patients during the preoperative period, vascular access insertion and separation from the family were evaluated in determining the anxiety levels of the patients However, no significant difference was determined in terms of these parameters and 2D:4D. This may be related to the average age group of patients included in this study. The anxiety to feel pain, inability to understand the events that develop around and fear of leaving the family were common results in this age group (West et al., 2020). In this study, the addition of dental anxiety to preoperative anxiety may have caused similar anxiety levels in all patients. Studies on the relationship between preoperative anxiety and 2D:4D are insufficient in the literature. Further studies are needed.

In order to predict postoperative agitation in the preoperative period, some scales are tried to be developed in addition to the clinical features of the patient and surgery (Berghmans et al., 2015; Hino et al., 2017; Lerman, 2018). Hino et al. investigated the validity of the scale they created using age, Pediatric Anesthesia Behavior Score, type of operation and duration of operation, and reported that it was effective in predicting postoperative agitation. They also stated that using this scale, preventive measures can be taken (Hino et al., 2017). In this study, it was hypothesized that the 2D:4D ratio may be a morphological marker in predicting postoperative agitation based on the studies we mentioned earlier. However, there was no significant relationship between postoperative agitation and 2D:4D ratio.

This study has some limitations. Some factors that increased the risk of postoperative agitation were not present in this study. Many factors such as long operation time, inhaler anesthetics and risk of postoperative pain were not included in the plan of this study. Deep sedation was provided to patients with intravenous anesthetics and the duration of anesthesia was very short. Local anesthesia was applied to all patients for postoperative analgesia. The relationship between postoperative agitation and 2D:4D ratio can be investigated after general anesthesia with inhaler anesthetics in further studies.

In conclusion, 2D:4D did not succeed as a morphological marker in predicting preoperative anxiety and postoperative agitation in the preoperative period. New studies can be planned considering the limitations of this study.

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Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Clinical Research

J. Exp. Clin. Med., 2021; 38(1): 27-31
doi: 10.5835/jecm.omu.38.01.006

The experience of interleukin-1 inhibition in patients with familial Mediterranean fever

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ARTICLE INFO

Article History
Received 07 / 09 / 2020
Accepted 25 / 09 / 2020
Online Published 26 / 01 / 2021

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Keywords:
Anakinra
Canakinumab
Familial mediterranean fever
Interleukin-1 inhibition

ABSTRACT

This study aimed to present our single-center experience of anakinra and canakinumab treatment in patients with Familial Mediterranean fever (FMF). This study included 48 patients who were treated with anti-interleukin-1 (anti-IL-1) treatment for at least six months. Initially, all patients with colchicine-resistant or intolerant FMF were received anakinra treatment. Then those resistant to anakinra were given canakinumab treatment. Of the 48 (female/male:29/19) patients using anti-IL-1, their age was 31.2 ± 10.7 years, the duration of drug use was 15±8 months. 30 patients were already using anakinra and 18 patients were using canakinumab. Treatment was found to be switched to canakinumab in 9 patients due to non-adherence to daily injection, and inadequate response to anakinra in 9 patients. After the anti-IL-1 treatment the number of attacks, erythrocyte sedimentation rate, C-reactive protein, fibrinogen levels, colchicine dose and proteinuria (for all $p<0.001$) were decreased. Anti-IL-1 treatment is effective for controlling attacks and reducing proteinuria in patients with colchicine-resistant or intolerant FMF. In addition, canakinumab appears to be an alternative treatment option when there is a inconvenience to daily injection or resistance to anakinra treatment.

1. Introduction

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease - mainly prevalent in Eastern Mediterranean descents (i.e. Turks, Armenians, Arabs and Jews). It is characterized by recurrent fever and inflammation of the serosal membranes (Sari et al., 2014; Petrushkin et al., 2016). The attacks are self-limiting and terminate spontaneously within 1-5 days (Sohar et al., 1967).

The MEFV gene, which is responsible for the pathogenesis of the disease, encodes a protein called pyrin-an element of the NLRP3 inflamasom complex (The French FMF Consortium, 1997; Abderrazak et al., 2015). Inflammasomes are molecular platforms responsible for caspase-1 activation. The caspase-1 enzyme converts pro-interleukine (IL)-1 to IL-1 (Papin et al., 2007; Franchi et al., 2009). The mutated pyrin causes the overexpression of IL-1β and consequently leads to inflammation and increase of serum amyloid A (SAA) which is responsible for amyloidosis (Bozkurt et al., 2015).

Colchicine, which is considered as revolutionary and started being used in 1972 in the treatment of patients with FMF, reduces attacks, improves the quality of life and prevents amyloidosis. It is the first option of treatment that should be started once the

clinical diagnosis is made (Cronstein and Terkeltaub, 2006; Nuki, 2008).

While complete remission was achieved in 60-65% of the patients under the treatment of colchicine, 30-35% had a partial response, and 5-10% did not respond at all. 2-5% of the patients cannot use colchicine due to side effects such as diarrhea and hepatotoxicity (TerHaar et al., 2013).

In recent years, FMF patients with resistance or intolerance to treatment with colchicine have been reported to give very good clinical and biochemical responses when they were given treatments of anakinra (recombinant human IL-1 antagonist), canakinumab (human anti-IL-1 beta monoklonal antibody), rilonacept (a receptor fusion protein acting as IL-1 decoy receptor) many patients with FMF have been reported to have given very good clinical and biochemical responses (Van der Hilst et al., 2005; Ozen et al., 2011; Akar et al., 2015; Kucuksahin et al., 2017). We thought that our treatment experience of using anti-IL-1 agents in our FMF patients can potentially contribute the literature.

2. Materials and methods

All the patients, diagnosed with FMF between 1 February 2013 and 31 December 2018 at our rheumatology department, were included in the study. The patients were retrospectively screened. This study protocol was approved by the institutional Ethics Committee, and all the participants gave an informed consent before enrolling in the study.

This retrospective study included 48 FMF patients who can not tolerate treatment with high-dose colchicine (1.5-3.0 mg/day) and in those with uncontrolled FMF attacks, treatment of anti-IL-1 was started. In our country, anakinra and canakinumab treatments are given off-label with the permission of the Ministry of Health who permits anakinra treatment first. Therefore, anakinra 100 mg daily injection treatment was administered as the first choice of treatment.

48 out of the total 338 patients with FMF were treated with anti-IL-1 treatment. Data for a total of 48 patients were retrospectively evaluated and included the following: 1. ID information, age and gender 2. Age of onset of symptoms 3. Age at diagnosis 4. History of additional disease (hypertension, diabetes mellitus, cardiovascular diseases, chronic renal failure) 5. Family history in terms of FMF and amyloidosis 6. Patient symptom and clinic (fever, peritonitis, pleuritis, pericarditis, arthritis, myalgia, amyloidosis, erysipelas like skin rash, vasculitis) 7. Dose of colchicine used before and after treatment with anti-IL-1 treatment 8. Gene analysis 9. Laboratory values (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, proteinuria) 10. Reason for switching to anti-IL-1 treatment 11. Duration of use of anti-IL-1 treatment 12. Number of attacks before and after treatment and 13. Reasons for switching from anakinra to canakinumab 14. Screening for tuberculosis, hepatit B and C, malignancy.

The statistical method used: Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 11.0, Chicago, IL, USA). Results were given as mean ± standard deviation. Statistical differences among the groups were identified with paired-7 test. Chi-squared test was used to compare categorical variables. P values less than 0.05 were considered as significant.

Computer tomography (CT) of the pelvis showed an enlarged prostate with protrusion bladder posterior to the submucosal area. The chest CT showed diffuse lung emphysematous micro bullae. There was no bone metastasis in whole body bone scintigraphy. Other biochemical parameters were normal.

Chemotherapy and radiotherapy were planned. The daily radiotherapy dose was 1.8 Gy and the total dose was 63 Gy. In total, 35 fractions were given. Six chemotherapy cycles (carboplatin, 450 mg/AUC 5) were also administered every 21 days concomitantly and consequently to radiotherapy. The patient was asymptomatic 8 months after treatment. He died 13 months after initial diagnosis because of the metastatic lesions.

3. Results

In 48 out of 338 FMF patients, anakinra treatment was initiated because of inadequate response to colchicine in 24 patients, colchicine triggered elevated liver function test in seven patients, colchicine related diarrhea in three patients, and amyloidosis in 14 patients. Having received anakinra treatment (100 mg/day), with 18 patients (out of 48) it is switched to canakinumab treatment (150 mg/ month) due to insufficient response observed in nine patients and inconvenience to daily injection observed in another nine patients. Treatment with colchicine was also continued in patients who received anti-IL-1 treatment (Zemer et al., 1986; Ozen et al., 2016).

Patients who received anti-IL-1 treatment for at least six months were included in the study. The mean duration of drug use was 15 ± 8 months. All the patients treated with canakinumab neither had any side effect that required to terminate the treatment, nor remained non-responsive to the treatment. Anakinra treatment was discontinued for a short period of time in two of the patients because of allergic skin rash in one patient and streptococcal pneumonia in another patient. No further complication was observed in the follow-up of these patients and the treatment was continued successfully. None of the patients had malignancy in the follow-up period. The demographic and some clinical data of the patients were shown in Table 1. The laboratory values of the patients before and after anti-IL-1 treatment

are were shown in Table 2. When the gene analysis was investigated in 48 patients with whom anti-IL-1 treatment was initiated, 31 (64.5%) patients were M694V homozygous, 5 (10.4%) were compound heterozygous (M694V heterozygous M680I heterozygous) and M694V heterozygous mutation was detected in 5 (10.4%) patients. In addition, two patients were M694I heterozygous, two patients were M680I heterozygous, two patients were V726I heterozygous and one patient was compound heterozygous (M694I heterozygous M680I heterozygous). When the gene analyzes of the patients with amyloidosis were examined, 11 (78.5%) were found to be M694V homozygous, one (7.14%) patient was M694V heterozygote. Additionally, two (14.3%) M694V homozygote + M680I heterozygote mutation were detected. The number of attacks was 5.7 ± 1.2/six months before in the 30 patients receiving anakinra treatment and the number of attacks after anakinra treatment was 1.3 ± 0.6/six months ($p<0.001$), anakinra treatment provided complete remission in 24 patients. The number of attacks before treatment of 18 patients treated with canakinumab was 4.9 ± 0.9/six months, and the number of attacks after treatment was 1.1 ± 0.3/six months ($p<0.001$), canakinumab treatment provided complete remission in 16 patients.

Table 1. Demographic and clinical characteristics of patients with FMF included in the study.

Age	31.2 ± 10.7
Female	29 (60.4%)
Male	19 (39.6%)
Age at onset of symptom	13.4 ± 9.7
Age at diagnosis	19.9 ± 13.4
Additional diseases	16/48 (33.3%)
Family history	28/48 (58.3%)
Fever	45/48 (93.7%)
Peritonitis	45/48 (93.7%)
Pericarditis	1/48 (2.1%)
Pleuritis	24/48 (50%)
Arthritis	37/48 (77.1%)
Myalgia	24/48 (50%)
Erysipelas like rash	12/48 (25%)
Amyloidosis	14/48 (29.1%)
Vasculitis	1/48 (2.1%)

Table 2. Before and after the anti-IL-1 treatment.

	Before Anti IL-1 Treatment	After Anti IL-1 Treatment	P value
ESR (mm/h)	30.9 ± 22.4	15.8 ± 8.4	<0.001
CRP (mg/L)	22.9 ± 12.4	3.3 ± 3.9	<0.001
Fibrinogen (g/L)	5.4 ± 1.6	2.2 ± 0.9	<0.001
Proteinuria (mg/day)	69.7 ± 146.8	18.1 ± 39.1	<0.001
Attack Frequency (/six months)	5.4 ± 1.1	1.2 ± 0.5	<0.001
Colchicine Dose (mg/day)	1.8 ± 0.3	1.5 ± 0.5	<0.001

IL-1; Interleukin-1, ESR; Erythrocyte sedimentation rate, CRP; C-reactive protein

4. Discussion

The importance of this study is that the anti-IL-1 treatment is isvestigated with such high numbers of patients, yet without multiple-centers. In other words, we have carried this study out in a single center which effectively provides more homogeneity. Regarding the result of our study, it verifies the results of previous studies indicating that when the anti-IL-1 agents are used regularly, they provide remission by significantly decreasing the number of attack episodes in colchicine resistant or intolerant FMF patients (Hilst et al., 2016; Akar et al., 2018).

In a systemic review published by Van der Hilst et al., complete remission was achieved in 76.5% of patients treated with anakinra and in 67.5% of patients treated with canakinumab (Van der Hilst et al., 2016) In 2017, the data obtained by Akar et al., have shown a remission of 40% and 65%, respectively (Akar et al., 2018). In our country, anakinra and canakinumab treatments are used off-label with the permission of the Ministry of Health. Anakinra treatment is preferred for the transition to anti-IL-1 treatment because of the lower cost, and then canakinumab treatment is started in case of insufficient response to anakinra treatment or inconvenience to daily injection It has been considered that canakinumab maybe more effective than anakinra with a longer half-life, canakinumab can block IL-1 action for a longer time and it has higher patient compliance. In this respect, the comparison of the response rates of these two treatments in our study would not be appropriate. Of those 48 patients who were already under anti-IL-1 treatment, 30 are receiving anakinra treatment. While %80 of patients receiving anakinra treatment had complete remission, the remaining %20 has still experienced FMF attacks. However, it should be recalled that nine patients using anakinra underwent canakinumab treatment due to treatment failure. Current status in terms of treatment with canakinumab, 16 patients out of 18 patients had complete remission, and two patients had one episode in three months. The success rate of remission achieved in patients using canakinumab was 88.8%, supporting the view that the treatment efficacy increases as a result of high compliance to treatment and stable plasma concentration. In conclusion, canakinumab treatment is considered to be an effective alternative treatment for patients who do not comply or respond to anakinra treatment.

In our study, when the gene analysis of the patients who could not achieve remission with anti-IL-1 treatment was investigated, of the six patients who could not be remedied with anakinra, five of them were M694V homozygous, one was M694V heterozygote and according to the gene analysis of nine patients who were treated with canakinumab due to anakinra resistance, five patient were M694V homozygote, three

patients were M694V heterozygote one was M694V heterozygote.

Homozygosity for the M694V mutation is generally thought to be associated with a more severe FMF phenotype (Cazeneuve et al., 2000), as well as with amyloidosis and colchicine resistance (Soylemezoglu et al., 2010). In a study conducted by Küçükşahin et al (Kucuksahin et al., 2017) the non-responsiveness to anti-IL-1 treatment was connected to presence of additional chronic multiple diseases in patients. In our study, there was no relationship between additional chronic disease and treatment non-responsiveness. In our country, Turkey, anakinra and canakinumab treatments are used off-label. There are occasional difficulties in patient's access, and the attacks are usually seen when patients cannot get regular treatment.

The results of our study support the results of other studies (Urieli-Shoval et al., 2000; Hilst et al., 2005; Chae et al., 2009; Stankovic et al., 2012; Kucuksahin et al., 2017; Ozdogan and Ugurlu, 2017) reporting that anti-IL-1 treatment used in colchicine resistant FMF patients prevented FMF attacks and decreased proteinuria. In previous studies, colchicine resistance was reported as 30-35% (Cerquaglia et al., 2005; Seyahi et al., 2006). In our study, 48 (14.2%) out of 338 patients had anti-IL-1 treatment. The reason for such a difference, we think, is due to the patients who are considered resistant to the treatment of the colchicine but refused the transition to anti-IL-1 treatment.

This study has some limitations. There was a significant decrease in proteinuria in the follow-up of patients but we did not perform a biopsy to prove the regression of amyloidosis. In addition, serum amyloid A level could not be evaluated in our patients. Although anti-IL-1 treatment decreased the number of attacks and the acute phases in the follow-up of our patients, we did not standardize the effects of these drugs on quality of life by measuring with any scale. In fact, despite the fact that they did not report an attack, the patients with persistent elevation in their acute phase reported an increase in performance after anti-IL-1 treatment and stated that they no longer get tired easily. Evaluating what with the quality of life scale could have revealed this situation. Patients using anti-IL-1 treatment reported that they had difficulty in accessing drugs and were unable to use their medication at regular intervals and, therefore, experienced attacks. Since our patients were evaluated retrospectively, we could not determine the frequency of this condition. Therefore, when evaluating the data of patients with anti-IL-1 treatment, this situation should be taken into consideration.

As a result; anti-IL-1 treatment appear to be effective and safe in the treatment of patients who are resistant to the treatment of the colchicine and cannot tolerate the treatment of the colchicine. On the other hand, in patients resistant to anakinra treatment, canakinumab treatment controlled the attacks and achieved high treatment compliance in patients with inconvenience to daily injection. Anti-IL-1 treatment under an acceptable safety profile is an effective alternative not only to control exacerbations but also to reduce proteinuria in patients with colchicine-resistant FMF in routine clinical practice. In addition, canakinumab may be considered as a good alternative in case of resistance to anakinra treatment and non-compliance.

Acknowledgements:
The authors would like to thank Enago (www.enago.com) for English language review.

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Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Clinical Research

J. Exp. Clin. Med., 2021; 38(1): 33-38
doi: 10.5835/jecm.omu.38.01.007

State-trait anxiety levels in Turkey during COVID-19 pandemic and its relationship to somatosensory amplification

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ARTICLE INFO

Article History
Received 22 / 09 / 2020
Accepted 02 / 12 / 2020
Online Published 26 / 01 / 2021

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Keywords:
Coronavirus
COVID-19
Somatosensory amplification
State anxiety
Turkey

ABSTRACT

Novel Coronavirus (COVID-19) pandemic which is a global public health problem continues to affect humans both physically and psychologically all around the world. So, it is important to diagnose and manage the anxiety while fighting the COVID-19 pandemic. The present study aimed to separately evaluate state and trait anxiety in the COVID-19 pandemic in Turkey. In addition, it was aimed to investigate the relation of demographic variable with state anxiety in the COVID-19 pandemic, as well as the relationship between trait anxiety and somatosensory amplification with state anxiety.726 participants who responded to online survey between March 30th and April 20th, 2020 were evaluated. All participants answered the survey that covered sociodemographic data and questions specifically about COVID-19 pandemic as well as State-Trait Anxiety Inventory and Somatosensory Amplification Scale. Pearson test was used for correlation analysis, ordinal variables were analyzed with Spearman correlation test. State anxiety is higher, if the participant is woman, has an acquaintance with the COVID-19 positivity, has a chronic medical condition and currently receiving or has history of psychiatric treatment. Age, monthly income, trait anxiety level and somatosensory amplification are also factors related to state anxiety. In conclusion, it is considered that those populations may be more vulnerable to the psychological effects of pandemic and they should be closely followed up for longer periods.

1. Introduction

Novel Coronavirus (COVID-19) pandemic continues to affect humans both physically and psychologically all around the world. Disease and uncertain future are major psychological stress factors for populations; moreover, social isolation precautions during the pandemic also seem a threat to public mental health (de Medeiros Carvalho et al., 2020). Considering prior pandemics, it is known that people may vary in terms of their anxiety levels (Wheaton et al., 2012), some people experience very intense anxiety and manifest clinically significant distress which may even require treatment (Rubin et al., 2009). While a moderate anxiety can generally motivate people to cope with health threats, it is also known that severe anxiety might be overwhelming (Kilgo et al., 2019).

Somatosensory amplification (SSA), a concept related to somatization, refers to a tendency to experience physical sensations more intensely and disturbing than usual (Barsky et al., 1988). SSA is shown to be related to both health anxiety and general anxiety levels in the literature (Korkmaz et al., 2017). Ability to conceive somatic sensations functions as an important construct for people in a pandemic that

is characterized by intense anxiety. People with high anxiety levels can consider symptoms that indicate presence of the COVID-19 for somatic signs, such as transient and harmless dizziness or fatigue and they may behave nonfunctionally. When misconception of somatic sensations is associated with increased anxiety, people may seek healthcare services which may not only increase the risk of spread, but also hinder duly delivery of healthcare services to patients who actually need them.

Studies conducted during the COVID-19 pandemic evaluated general anxiety level in populations and factors associated with this anxiety (Huang and Zhao, 2020; Shevlin et al., 2020). In addition, we believe that more realistic data on state anxiety which may be related to the pandemic can be obtained if pre-pandemic anxietic nature of people and the condition-based anxiety are addressed separately, when anxiety is evaluated during a pandemic. Spielberger et. al. suggests division of anxiety conditions into state anxiety (SA) and trait anxiety (TA). SA implies transitory psychological reactions that are directly related to negative conditions at a certain interval of time, while TA points to a personal trait that identifies personal variations and it is conceptualized as the tendency to perceive the threat and affect the SA (Spielberger, 1970).

It is important to diagnose and manage the anxiety while fighting the COVID-19 pandemic which is a global public health problem. Psychoneuroimmunological studies demonstrated that high stress level can suppress the immune system and therefore, make the individual more vulnerable to the infection (Kiecolt-Glaser, 2009). In the light of these data, we aim to separately evaluate SA and TA levels in Turkey during the COVID-19 outbreak using a web-based cross-sectional study. Our objective was to evaluate the relation of demographic with state anxiety in the COVID-19 pandemic, and to determine whether TA and SSA are related to the SA. We hope that the study findings will give an opinion on understanding the SA during a pandemic and provide data support for targeted interventions in the field of psychological health.

2. Materials and methods

Study design and participants

"Survey monkey", an online survey software and tool (https://tr.surveymonkey.com/), was used to prevent spread of COVID-19 via droplet and contact. The link of questions created with the online survey software was sent online to users over various social media platforms. This web-based questionnaire was completely voluntary.

Data collection

The participants anonymously answered the survey questions from March 30th to April 20th, 2020. The survey was either e-mailed to participants or sent to them over various social media platforms. Inclusion criteria were residents who: 1) aged 18 years and older, 2) aged 75 years and younger; (2) living in Turkey during the outbreaks of COVID-19; (3) have provided informed consent electronically prior to registration. Since it is aimed to evaluate the general population, eexclusion criteria other than being under 18 years old or over 75 years old were not determined. All participants answered the survey that covered sociodemographic data and questions specifically about COVID-19 pandemic as well as State-Trait Anxiety Inventory (STAI) and Somatosensory Amplification Scale (SSAS).

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki and it was approved by the Ethical Committee of Üsküdar University. Electronic informed consent was obtained from each participant before they were enrolled.

Measures

Demographic data and questions about COVID-19

Demographic variables include gender, age, marital status, place of residence, working status, history of chronic medical disease and history of psychiatric treatment. Participants were asked whether they should be in crowded places due to work after the COVID-19 outbreak and whether they have an acquaintance in their neighborhood with the COVID-19 positivity.

The state and trait anxiety inventory (STAI)

The scale was developed by Spielberger et al. to evaluate the state and trait anxiety levels separately (Spielberger, 1970) and it was adapted to Turkish population (Öner, 2006). State Anxiety Inventory determines how a person feels at a certain time, while Trait Anxiety Inventory indicates how a person feels in general regardless of situations and conditions. Both are 1-to-4 Likert scales that have 20 items and they include reverse-scored items. Total score of the scales varies from 20 to 80 points. Higher scores indicate higher anxiety level. Internal consistency coefficient varies from 0.94 to 0.96 for Turkish version of STAI-State and from 0.83 to 0.87 for Turkish version of STAI-Trait.

Somatosensory amplification scale (SSAS)

SSAS evaluates the extent a person amplifies somatic sensations. It is a Likert-type self-report instrument that consists of 10 items and the score varies from 1 to 5 points. Total score is regarded as the amplification score. It was developed by Barsky et al. and Turkish reliability study was conducted by Sayar et al. (Barsky et al.,1988; Sayar et al., 2003).

Statistical analysis

Descriptive statistics were used to analyze sociodemographic data and answers of participants to questions about COVID-19. Distribution of variables was measured with Kolmogorov–Smirnov test. Student-t test and one-way ANOVA were used for comparative analysis of quantitative independent data. If significant difference was found between groups, pair post-hoc comparisons were made with Tukey's test. Pearson test was used for correlation analysis, while ordinal variables were analyzed with Spearman correlation test. A p-value less than 0.05 was considered statistically significant.

3. Results

Seven hundred and 26 participants aged between 18 and 75 (37.4±12.4) were enrolled. Table 1 reports the distribution of participants across socio-demographic variables and answers to COVID-19 pandemic-related questions (Table 1).

Average STAI-State, STAI-Trait and SSAS scores of participants are 46.2±10.8, 41.9±7.9 and 26.3±7.1, respectively. STAI-State ($p<0.001$), STAI-Trait ($p<0.001$) and SSAS ($p<0.001$) scores of female and male participants were significantly different and scores of female participants were higher. No significant difference was noted in STAI-State scores of married and single participants ($p>0.05$); however, STAI-Trait and SSAS scores were different. STAI-Trait and SSAS scores of single participants were significantly higher comparing to married ($p=0.02$, $p=0.001$). No statistically significant difference was noted between STAI-State, STAI-Trait and SSAS scores of participants living in Marmara region and other regions. When anxiety levels of participants were compared in terms of their working status, no significant difference was observed between STAI-State scores ($p>0.05$), while STAI-Trait and SSAS scores were different ($p=0.02$, $p=0.004$). Post-hoc analysis revealed out that STAI-Trait and SSAS scores of the non-working group were significantly higher than other groups. Moreover, no significant difference was observed between STAI-State, STAI-Trait and SSAS scores of groups that consist of participants who have to be in crowded places due to their work and who do not ($p>0.05$). STAI-State scores of the group of participants who have an acquaintance in their neighborhood diagnosed with COVID-19 were significantly higher than the group of participants who do not have; however, no significant difference was found between STAI-Trait and SSAS scores of two groups ($p>0.05$). STAI-State scores of participants with chronic medical condition were significantly higher than scores of participants without a chronic disease

Table 1. Comparison according to demographic data and coronavirus related variables.

	%	STAI-State		STAI-Trait		SSAS	
		Mean±SD	*p*	Mean±SD	*p*	Mean±SD	*p*
Gender			**<0.001[t]**		**<0.001[t]**		**<0.001[t]**
Female	59	47.9±10.5		42.8±7.5		27.7±7.1	
Male	41	43.7±10.7		40.5±8.3		24.2±6.6	
Marital Status			0.16[t]		**0.02[t]**		**0.001[t]**
Married	61	45.7±10.8		41.3±7.9		25.6±7.1	
Not married	29	46.9±10.7		42.8±7.9		27.4±7.0	
Living region in Turkey			0.92[t]		0.19[t]		0.70[t]
Marmara region	50	46.2±11.0		41.5±7.9		26.4±7.0	
Outside the Marmara region	50	46.2±10.5		42.2±8.0		26.2±7.2	
Chronic medical disease			**0.04[t]**		0.16[t]		0.49[t]
Yes	25	47.6±11.3		42.6±8.3		26.6±7.5	
No	75	45.7±10.5		41.6±7.8		26.2±7.0	
Psychiatric treatment history			**<0.001[A]**		**<0.001[A]**		**<0.001[A]**
Maintained treatment	8	50.9±10.7		47.7±9.2		27.4±7.7	
Treatment history in the past	24	47.5±10.9		43.9±7.7		27.5±6.7	
Treatment-naïve group	68	44.3±10.6		40.6±7.4		25.8±7.1	
Working status			0.87[A]		**0.02[A]**		0.004[A]
Not currently working	24	45.8±10.8		43.3±8.6		28.1±7.4	
Working in government institutions	22	46.6±11.0		42.2±8.4		25.7±7.3	
Working in private institutions	41	46.1±11.2		40.8±7.4		25.6±6.7	
Working in their own business	13	46.6±8.9		41.8±7.0		26.4±6.9	
Do you have to continue to be in crowded environments because of your job?			0.65[t]		0.34[t]		0.37[t]
Yes	53	46.4±10.9		41.6±8.1		26.1±7.2	
No	47	46.1±10.7		42.2±7.8		26.6±7.0	
Do you have any acquaintances in your neighborhood who are positive for COVID-19?			**0.01[t]**		0.36[t]		0.30[t]
Yes	20	48.2±10.9		42.4±8.3		26.9±7.5	
No	80	45.7±10.7		41.7±7.8		26.2±7.0	

[t] *Student t test*, [A] *ANOVA*

(p=0.04); however, no significant difference was noted between STAI-Trait and SSAS scores of two groups (p>0.05). Participants were divided into three groups according to their history of psychiatric treatment: 1-those who are maintained on psychiatric treatment, 2-those with history of psychiatric treatment, but no actual treatment, 3-those who are naïve to psychiatric treatment. A statistically significant difference was noted between STAI-State (p<0.001), STAI-Trait (p<0.001) and SSAS (p=0.01) scores of these groups. It was revealed out that the psychiatric treatment-naïve group was responsible for the intergroup differences in terms of scores; STAI-State, STAI-Trait and SSAS scores of this group were significantly lower than scores of other groups (Table 1).

According to results of correlation analysis, there was a negative correlation between ages of participants and STAI-State (r=-0.11, p=0.002), STAI-Trait (r=-0.13, p=0.001) and SSAS (r=-0.13, p=0.001) scores. There was negative correlation between income levels and STAI-State (r=-0.11, p=0.005), STAI-Trait (r=-0.26, p<0.001) and SSAS (r=-0.27, p<0.001) scores and it was noted that as income levels increase, anxiety and SSA levels decreased. In addition, there was a significant positive correlation between STAI-State scores and STAI-Trait (r=0.51, p<0.001) and SSAS scores r=0.34, p<0.001) (Table 2).

Table 2. Correlation of age, monthly income level, STAI-trait and SSAS scores with STAI-State scores (r).

Age	*-0,11***
Monthly income level	*-0,11***
STAI-Trait	*0,51***
SSAS	*0,34***

Pearson correlation analysis,

Spearmen correlation analysis was applied for Monthly income level and STAI-State relationship,

STAI: State and Trait Inventory, SSAS: Somatosensory Amplification Scale

*p<0.05, **p<0.01

4. Discussion

According to results of the study, SA is higher, if the participant is woman, has an acquaintance in their neighborhood with the COVID-19 positivity, has a chronic medical condition and receiving or has history of psychiatric treatment. In addition, age, monthly income, TA level and SSA level are also the factors related to the SA.

Results of this study revealed that female and single participants have higher TA and SSA levels. Findings related to those two variables which dates back to the pre-pandemic period and are also accepted as personal trait are as expected and consistent with the literature. Studies have reported that both incidence of anxiety disorders and levels of TA are generally higher in women (Peleg and Messerschmidt-Grandi, 2019). Pre-pandemic studies have also demonstrated that psychological load and TA level are higher in single individuals (Lindström and Rosvall, 2012). Similarly, it has been shown that SSA levels are higher both in women and in single participants (Nakao et al., 2005; Kivrak et al., 2016). In this study, SA, which can be helpful to evaluate effects of the pandemic more specifically, is also significantly higher in female participants. When the pandemic data reported in the literature are reviewed, women feel more anxious and stressed during pandemic period (Taha et al., 2014). Animal studies have shown that female rats demonstrated stronger emotional changes against the stressor comparing to male rats (Yang et al., 2019). Some evidences regarding the more potent response to the stressor in women were linked to the fluctuation of ovarian hormones due to the menstrual cycle and it has been argued that those fluctuations lead to tendency for psychiatrics pictures (Soni et al., 2013).

In this study, it is observed that SA level is negatively correlated to age of participants. Studies conducted in both previous pandemic periods and the COVID-19 pandemic showed that anxiety levels were higher in younger individuals (Matsuishi et al., 2012; Limcaoco et al., 2020). Higher anxiety levels in younger population is somewhat a discrepancy, as it was reported that elderly population was at higher risk. However, considering that individuals who stay more focused on the outbreak in the pandemic period experience more severe anxiety (Huang and Zhao, 2020), we believe that the relation between age and SA may be caused by the fact that younger people follow the social media news more frequently and they are exposed to pandemic-related information more than the elderly population. In addition, previous studies have demonstrated that psychological resilience defined as the ability to cope with various challenges and trauma experienced in their lives is higher in elderly people comparing to younger ones (Gooding et al., 2012), and it is considered that this situation may be a protective factor for elderly people during the pandemic period. Results of our study have shown that SA of people who have a relative or friend with the COVID-19 positivity is higher. This condition is considered secondary to the fact that the pandemic risk is more closely and more seriously perceived by such people and it is also related to the concern of being infected by such immediate circle. Although there is no detail on this subject in literature, it is generally considered that negative conditions related to health problems of individuals' relatives and friends, especially the family members, play a critical role on health anxiety (Fernandez et al., 2005).

It is expected that the COVID-19 pandemic will affect individuals' economic status and may generally result in decreased income due to less working hours (Hafiz et al., 2020). According to this study, income level is negatively related to the SA that seems higher

in people with lower income level. Similar to our study, a U.K. study evaluated the COVID-19 related anxiety and found that lower income level is a predicting factor for higher anxiety (de Medeiros Carvalho et al., 2020). In the period of pandemic which is expected to cause negative economic influences, the fact that income level is related to SA of individuals is considered to be related to concerns about future and the feeling of uncertainty in people with low income levels. Moreover, when the working status of participants is taken into consideration, no difference has been noted in the SA among groups of people who work in governmental organizations or private sector or who are self-employed or unemployed; however, it was observed that TA and SSA levels of unemployed individuals were higher. Those results suggest that the COVID-19 pandemic affect all people similarly irrespective of working status and psychological problems of unemployed individuals have already been persisting before the pandemic and can be generalized.

Furthermore, this study has demonstrated that participants with a chronic medical condition have higher SA levels. The literature has also shown that individuals who have a medical condition and specified poor health status in previous pandemic periods were more anxious. For example, in a study that assessed the factors affecting the perception of risk for pandemic influenza in Australia, it was determined that the group that reported negative health status and had diseases was more concerned about their own and their families' health compared with the group that had a good health status (Jacobs et al., 2010). And also, it is considered that people with psychiatric diseases are more vulnerable to the pandemic and will be affected more profoundly during the COVID-19 pandemic (Yao et al., 2020). This study has demonstrated that anxiety levels are higher in individuals who receive or has history of psychiatric treatment.

Our study has determined a positive relation between TA and SA. Spielberger et.al. suggested that people with higher levels of TA are more prone to the stress, they perceive threat in various conditions and show SA reactions more frequently (Spielberger, 1970). The literature has shown that the higher TA levels are, the more SA increases in different threatening conditions (Leal et al., 2017). In this study, the relation between TA and SA is also shown in the pandemic period which is perceived as a serious threat. Moreover, a positive relation is observed between SSA level and SA level in our study. It is well known that psychological problems are related to increased physical symptoms (Katon and Walker, 1998). After the anxiety is divided into state and trait forms, another study group demonstrated that anxiety can be manifested by a wide spectrum of symptoms and attention has been drawn to the somatic component of the anxiety (Ree et al., 2008). SSA represents learned automated and emotional evaluation pattern of the body. In other words, it is suggested that the less strict evaluation criteria for body in individuals with high SSA level aggravate the anxiety by causing higher expectations regarding potential damages (Köteles and Witthöft, 2017). When this fact is taken into consideration, it is understandable that individuals with high SSA in the pandemic period experience more intense SA due to their tendency to perceive their somatic symptoms and disease-related potential harms more negatively.

In conclusion, the COVID-19 pandemic is a source of potential direct and indirect trauma for many people; however, the effect of pandemic on mental health draws more attention due to disturbing case reports of suicides caused by the fear of getting sick or transmit the disease (Montemurro, 2020). Therefore, developing and implementing mental health check-up and intervention programs for seem important. We hope that our study provides data support for interventions in the field of mental health. Among all findings of our study, the higher SA in people who receive or have history of psychiatric treatment seem important. In addition, the fact that SA is higher in people with high TA and SSA levels is important to determine the people who are at higher risk regarding the mental health. It is considered that those populations may be more vulnerable to the effects of pandemic and they should be closely followed up for longer periods.

This study has some limitations. First, the data submitted in this study is based on a short-term observation; therefore, it is difficult to make causative inferences and long-term follow-up studies are warranted to evaluate longer term effects of the pandemic. Moreover, the data have been collected in early stage of the pandemic and they are important to evaluate the initial reactions of the general population to the pandemic; however, it should be repeated in late phases of the pandemic. Second, the study used a web-based survey method. This survey method results in over-representation of the people who use online tools more frequently; therefore, a selection bias should be taken into consideration. Third, pre-pandemic mental conditions of individuals could not be evaluated, as the outbreak occurred suddenly; this fat hinders stating a certain opinion about effects of the COVID-19 pandemic on mental condition.

Acknowledgement
There are no any acknowledgements.

Financial support and sponsorship
Nil.

Conflict of Interest
There is no conflicts of interest.

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Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Clinical Research

J. Exp. Clin. Med., 2021; 38(1): 39-41
doi: 10.5835/jecm.omu.38.01.008

Our surgery experience of non-oesophageal varices upper gastrointestinal bleeding

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ARTICLE INFO

Article History
Received 25 / 08 / 2020
Accepted 19 / 10 / 2020
Online Published 26 / 01 / 2021

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Keywords:
Bleeding
Outcomes
Surgery
Upper gastrointestinal

ABSTRACT

Necessity for surgery in the treatment Acute Upper Gastrointestinal Bleeding (AUGIB) is gradually decreasing. In spite of the decrease in the need for surgery, there is no decrease in rates of mortality and complication following surgery. The aim of this study is to present outcomes of the patients operated on AUGIB. Files of the patients operated on AUGIB, from 1 January 2010 to 2020, were examined. Age, gender and diagnosis of the patients, conservative treatment methods prior to surgery, surgery, duration of hospital stay, rates of mortality and complications were retrospective analyzed. 15 patients with UGH diagnosis were involved in the study. Out of 15, 12 male and 3 female, and their mean age was 61.26 (22-88). All the patients received endoscopic examination before the surgery. 2 patients received total gastrectomy, 1 distal gastrectomy, 3 gastrostomy and haemorrhage control, 6 HM pyloroplasty and bilateral truncal vagatomy, 2 HM pyloroplasty + gastrojejunostomy and bilateral truncal vagatomy, and 1 Whipple surgery. Average hospital stay was 10.53 (1-19) days. Mortality rate was 33%, complication was 26%. Surgical need for AUGIB was decreased by 2% over the years. Despite decrease in the need of surgery, rates of mortality and complication were 30% and 55% respectively. Mortality is generally caused by co-morbid disease.

1. Introduction

Acute Upper Gastrointestinal Bleeding (AUGIB) is commonly seen in emergency cases. Depending on medical development, need for surgery is rare, which, however, still stands as a nightmare for surgeons. Because of decreasing need of surgery, experience of the surgeons is getting limited within the last 20 years. Our aim in this study is to present the outcomes of the patients who were operated on AUGIB.

2. Material and method

The patients, who came to general surgery clinics of Ondokuz Mayıs University, and could not be treated with conservative treatment, and operated with AUGIB diagnosis, were examined.

Age, gender, and diagnosis of the patients, conservative treatment methods prior to operation, surgery, duration of hospital stay, rates of mortality and complication were analysed retrospectively.

Since it was retrospective study, approval of ethic committee was not necessary.

3. Result

15 patients, 12 male and 3 female, whose mean age was 61. 26 (22-88) years, were included into the study. All of the patients got endoscopic intervention before the

surgery but bleeding could not be brought under control. 6 patients received computed tomography angiography, 1 scintigraphy, 1 conventional angiography. Surgical indications were unstable hemodynamically or bleeding which could not be stopped with endoscopic interventions.

Location of bleeding were anatomically 2 in stomach cardia, 3 in stomach corpus, 9 in bulbus, 1 in duodenum second part. Total gastrectomy was performed to 2 patients, distal gastrectomy to 1 patient, gastrostomy and haemorrhage control to 3 patients, Heineke-mikulicz pyloroplasty and bilateral truncal vagatomy to 6 patients, Heineke-mikulicz pyloroplasty + gastrojejunostomy and bilateral truncal vagatomy to 2 patients, and Whipple surgery to 1 patient. Patients who underwent Heineke-mikulicz pyloroplasty and bilateral truncal vagatomy were given gastroduodenal artery ligation in 3 locations.

Whipple surgery was performed to a patient because of bleeding occurred on the second day of following the Heineke-mikulicz pyloroplasty+ bleeding control.

Average length of hospital stay was 10.53 (1-19) days. Compications were found in 4 patients, which were pneumonia in 1; surgical wound infection in 1, intraabdominal abscess in 1, pneumothorax in 1 patient. 5 patients died. Rates of mortality and complication were 33% and 26% respectively.The features of patients are presented at Table 1.

4. Discussion

The bleeding originated proximal to treitz ligament is named asAUGIB. Patients generally admit to hospital with presenting hematemesis, hematochezia and/or melena.

According to USA data, frequency of AUGIB is 65/100.000 people/year (Wuerth and Rockey, 2018). Upper gastrointestinal bleeding was six time more frequent than Lower gastrointestinal bleeding. Upper gastrointestinal bleeding was seen more in male patients than female ones in terms of increasing age (Longstreth, 1995; Lanas et al., 2005)

A common reason for AUGIB is gastrodoudenal ulcer. The risk factors of gastrodoudenal ulcer bleeding are Helicobacter pylori infection, emotional stress, nonsteroidal anti-inflammatory drugs use and excessive gastric acid production. Eliminating or reducing those factors decrease the risk of ulcer reoccurrence and repetitive bleeding (Rockey et al., 2017).

The other reasons for AUGIB are as follows; Mallory Weis tears, gastric stress, Dieulafoy lesion, gastroosephageal varices, GIS malignite, hemobilia and aorta duodenal fistules (Feinman and Haut, 2014). Depending on the bleeding level, hipovolemic shocking symptoms such as hypotension and tachycardia can accompany. The primary aim in the treatment is to stabilize hemodynamically and then to establish the aetiology. The factors leading to bleeding in a patient who is stabilized hemodynamically are NSAID, anticoagulant, antiplatelet agent and selective serotonin uptake inhibitors. They should certainly be questioned. Systemic examination should be performed. While performing rectal examination, surgeons must check if there is any active bleeding or melena. Finding peritonitis symptoms in abdominal examination should suggest bleeding along with ulcer perforation. During the systemic examination, according to the level of bleeding; hypotension, tachycardia, tachypnea, reduced urine, confusion and lethargy can be taken into

Table 1. Table 1. Features of patients

Age	Sex	Forreastclassification	Operation	Cause of death	Comorbidity
72	*E*	*1B*	*Pyloroplasty ,BTV*		*None*
61	*E*	*2B*	*Total gastrectomy*	*Pneumonia*	*CKD, DM*
68	*E*	*1B*	*Gastrostomy,Haemorrhagecontrol*		*None*
22	*E*	*1A*	*Pyloroplasty ,BTV*		*None*
56	*E*	*2B*	*Pyloroplasty ,BTV*		*DM,*
46	*K*	*1B*	*Pyloroplasty ,BTV, gastrojejunostomy*		*None*
50	*E*	*1B*	*Gastrostomy,Haemorrhage control*		*DM*
85	*E*	*1B*	*Whipple operation*	*MODS*	*HT, CAD*
75	*E*	*2B*	*Distal gastrectomy*		*HT, CKD,*
58	*K*	*1B*	*Pyloroplasty ,BTV*		*HT,*
59	*E*	*1A*	*Pyloroplasty ,BTV*		*None*
74	*E*	*1A*	*Gastrostomy,Haemorrhagecontrol*	*MODS*	*COPD*
38	*E*	*1A*	*Pyloroplasty ,BTV, gastrojejunostomy*		*DM*
88	*E*	*1B*	*Total gastrectomy*	*SEPSİS*	*HT, CAD*
67	*K*	*2B*	*Pyloroplasty ,BTV*	*SEPSİS*	*HT*

BTV: bilateral truncal vagotomy, MODS: Multiple organ disease, CKD: Chronic kidney disease, DM: Diabetes mellitus, HT: Hypertension CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease

consideration (Gutierrez et al., 2004; Kamboj et al., 2019).

Hemodynamic stability can generally be achieved with aggressive fluid therapy. If hemoglobin value is less than 7 g/dl or gets lower 2 g/dl or more, packed red blood replacement may be needed. In addition, PPI treatment on these patients must get started. Proton pump inhibitor use can decrease re-bleeding, surgical need, and mortality (Greenspoon et al., 2012; Srygley et al., 2012; Feinman and Haut, 2014).

Endoscopy is the first method to be selected for diagnosis and treatment., Epinephrine injection, thrombin injection, and thermocoagulation interventions can stop bleeding during endoscopic interventions. If an active bleeding can occur due to ulcer and/or an active bleeding vein during endoscopy, then bleeding rate is high, and need for surgery is increasing (Feinman and Haut, 2014).

In case of endoscopic failure, angioembolization is the second choice to be considered before surgery (Loffroy et al., 2010).

AUGIB surgical need has gradually got lower as 2% throughout the years. Despite this fact, mortality and complication rates due to surgical reason were reported as 30% and 55% respectively (Clarke et al., 2010). Surgery was compulsory in those patients who were unstable, or bleeding could not be stopped by any means apart from surgery. If reasons stand unknown for UGH, then the subject surgery turns to be a nightmare for surgeon.

The patients, over 65 years old, presenting with hypotension, serious cardiopulmonary problems, ulcer diameter more than 2 cm, 5 units or more blood replacement, and repetitive bleeding in the last 72 hours are considered to be in high risk group. They need due surgery more than the other patients (Tırnaksız and Yorgancı, 2005)

Choosing surgical procedures depends on the source of bleeding. Peptic ulcer haemorrhage is originated from duodenum (75%), stomach (20%), and pylor ulcers (5%) (Bulut et al., 1996). According to the source, oversew, ligation of gastroduodenal artery, pyloroplasty and vagotomy, antrectomy and/or vagotomy, wedge resection, and distal or total gastrectomy may be needed (Feinman and Haut, 2014). In high risk group patients who underwent surgery, bilateral truncal vagotomy should added in order to prevent complication originated from ulcer (Tırnaksız and Yorgancı, 2005).

While the necessity for UGH surgery is decreasing, mortality and complication rates are still high following the surgery. Surgery must be performed on the patients who are unstable hemodynamically and bleeding cannot be stopped.

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Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Case Report

J. Exp. Clin. Med., 2021; 38(1): 43-46
doi: 10.5835/jecm.omu.38.01.009

Successful treatment with intravenous lipid emulsion of severe tricyclic antidepressant intoxication

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ARTICLE INFO

Article History
Received 18 / 05 / 2020
Accepted 12 / 10 / 2020
Online Published 26 / 01 / 2021

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Keywords:
Coma
Dysrhythmia
Intoxication
Lipid emulsion
Treatment
Tricyclic antidepressant

ABSTRACT

An overdose of amitriptyline has neurological and cardiovascular side effects (psychosis, lethargy, coma, hypotension, and dysrhythmia). A 19-year-old female patient was admitted to our emergency service after a suicide attempt by amitriptyline ingestion of unknown amount. Her follow-up demonstrated deteriorating consciousness and vital signs, she had a generalized tonic-clonic seizure, and her electrocardiogram (ECG) revealed QRS interval widening followed by a ventricular tachycardia (VT) attack. The patient was treated with intravenous (IV) diazepam (Diazem®) to control the epileptic seizure, IV lidocaine (Aritmal®) to stop the VT attack, and IV sodium bicarbonate due to QRS interval widening. The patient was given norepinephrine bitartrate (Steradine®) and dopamine hydrochloride (Dopamine®) due to low blood pressure. Intravenous lipid emulsion (ILE) therapy was started due to the uncontrolled rhythm and hypotension. Here, we present a case report of a comatose patient with dysrhythmia due to amitriptyline overdose who responds to ILE therapy.

1. Introduction

Amitriptyline is the most commonly used tricyclic antidepressant (TCA) for suicide (Caksen et al., 2006). TCA overdose results in a toxicity syndrome characterized by neurological and cardiac side effects. Poisoning-related clinical manifestations vary from mild muscarinic effects and severe cardiotoxicity due to sodium channel blockade to death. Change in mental status is the most common symptom after TCA toxicity (Bateman et al., 2005). The general treatment approach to TCA toxicity includes gastrointestinal decontamination, fluid replacement, sodium bicarbonate, and magnesium sulphate in case of resistant dysrhythmias. Although there is today no consensus on the use of lipid emulsion therapy for the treatment of TCA toxicity, the current literature includes case reports on its usefulness (Agarwala et al., 2014; Levine et al., 2014; Ozcan et al., 2014; Odigwe et

al., 2016). Here, we present a case report of a comatose patient with dysrhythmia due to amitriptyline overdose who responds to ILE therapy.

2. Case report

A 19-year-old female patient was admitted to our emergency department due to deterioration of her general condition after a suicide attempt by amitriptyline ingestion of unknown amount. She underwent gastric lavage followed by activated charcoal, her follow-up demonstrated deteriorating consciousness and vital signs, she had a generalized tonic-clonic seizure, and her electrocardiogram (ECG) revealed QRS interval widening followed by a ventricular tachycardia (VT) attack. The patient was treated with intravenous (IV) diazepam (Diazem®) to control the epileptic seizure, IV lidocaine (Aritmal®) to stop the VT attack, and IV sodium bicarbonate (1-2 mEq/kg) due to QRS interval widening. The patient was given norepinephrine bitartrate (Steradine®) at 30 mcg/minute and dopamine hydrochloride (Dopamine®) IV at 30 mcg/minute of serum physiologic solution due to low blood pressure. The patient was intubated because of her GCS score was 3/15. Despite the positive inotropic support, her vitals were blood pressure 70/40 mmHg, and pulse 180 beats/min. When the ECG of the monitored patient revealed VT (Fig. 1), three rounds of synchronized cardioversion of 100-100-200 joules were performed on the hypotensive patient with ongoing VT despite IV lidocaine administration (Fig. 2). The laboratory tests were normal. The patient was given IV magnesium sulphate 2 g due to resistant VT. ILE therapy was started due to the uncontrolled rhythm and hypotension. She was given a bolus of 100 mL (1.5 mL/kg) IV 20% lipid emulsion followed by an infusion of 400 mL. The patient was extubated 48 hours after her admission to the hospital and there was no need for vasopressors on the third day of admission. The patient who had stable vital signs and no additional problem was discharged with full recovery on the fifth day of admission in line with psychiatric recommendations (Fig. 3).

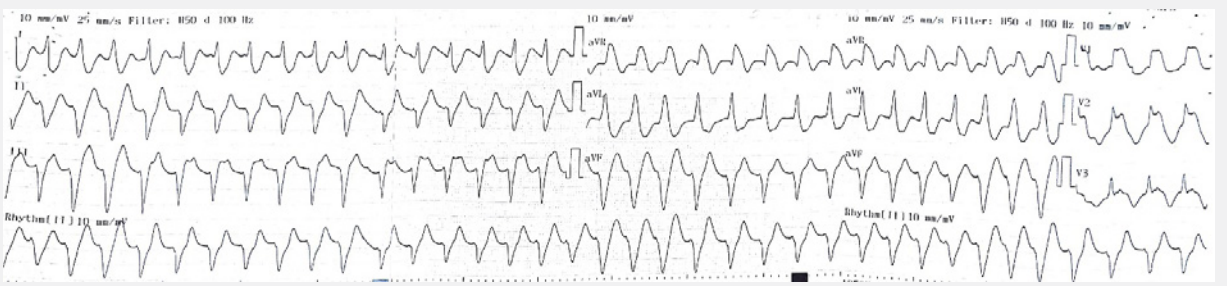

Fig. 1. Wide QRS tachycardia (Ventricular tachycardia) on admission.

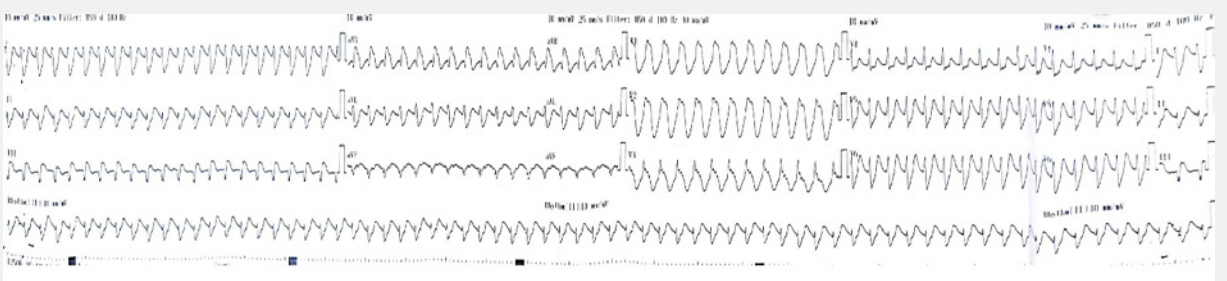

Fig. 2. Electrical cardioversion applied for ventricular tachycardia.

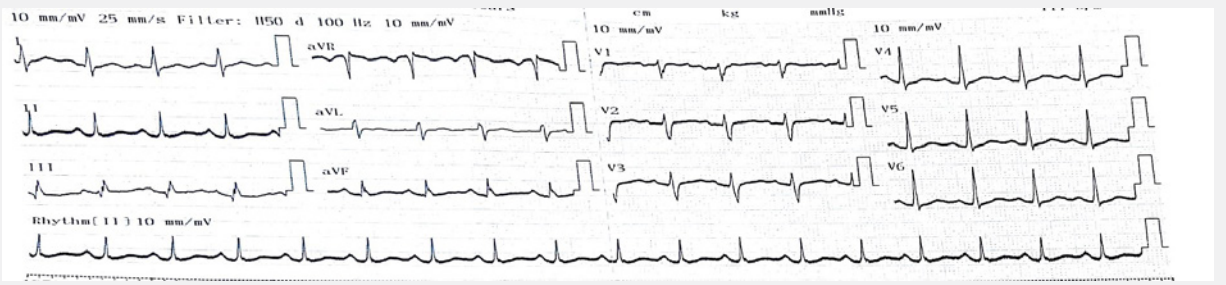

Fig. 3. Normal electrocardiogram after treatment.

3. Discussion

An intentional overdose of tricyclic antidepressants (TCAs) is a major cause of death. TCAs produce their pharmacological effects by inhibiting presynaptic serotonin and norepinephrine uptake. TCAs are rapidly absorbed from the intestine and reach high plasma levels within 2-8 hours (Odigwe et al., 2016). Our patient had altered mental status (coma), epileptic seizure, hypotension and resistant dysrhythmia approximately 3 hours after the overdose of amitriptyline.

Cardiotoxicity is the main cause of death in TCA overdose, mainly due to myocardial sodium channel blockade (Levine et al., 2014). Lipid emulsion therapy is a potentially new treatment used to reverse the cardiotoxicity caused by TCA overdoses (Chan et al., 2010; Levine et al., 2014). Sodium channel blockade caused by TCAs prolongs the refractory period and delays atrioventricular (AV) node conduction. This delay causes QRS widening, and QTc and PR prolongation on the ECG (Thanacoody et al., 2005; Aksakal et al., 2010). A QRS duration longer than 100 msn is an indication for bicarbonate therapy in cases of TCA overdose (Odigwe et al., 2016). QRS and QT intervals of our patient with resistant VT were 200 and 360 msn on the admission ECG. PR, QRS, QTc and QT/QTc intervals on the discharge ECG were within the normal range and 166, 94, 392 and 328/392 msn, respectively.

Today, no specific method is available in clinical practice to determine that sodium bicarbonate proves unsuccessful and other treatments should be initiated, thereby presenting challenges for clinicians to decide. Clinicians tend to initiate other treatments depending on disease severity and the response of electrocardiographic and hemodynamic parameters to sodium bicarbonate (Odigwe et al., 2016). We started ILE treatment for our patient who did not respond to other therapies including electrical cardioversion and had hemodynamic impairment and resistant VT attack. The mechanism of action of lipid therapy is not fully understood (Agarwala et al., 2014; Odigwe et al., 2016). Its role in humans remains uncertain (Odigwe et al., 2016). ILE therapy reduces bioavailability by forming a "lipid sink", i.e. trapping lipophilic agents in an expanded plasma lipid compartment, thereby inhibiting the effect of TCA and prevents toxicity (Chan et al., 2010). According to an alternative theory, ILE improves myocardial free fatty-acid availability by reversing the shift from lipid to glucose metabolism in stunned myocardium. ILE may also prevent the inhibition to oxidative phosphorylation in toxic myocardium (Levine et al., 2014). In patients with cardiotoxicity resistant to other treatment modalities, it is recommended to administer a 100 mL IV bolus injection of 20% lipid emulsion (1.5 mL/kg) for 2-3 minutes and a continuous IV infusion of 0.25 mL/kg/min (18 mL/min) at a total dose of 10 mL/kg (American College of Medical Toxicology, 2011). We initiated ILE therapy for our patient in the ICU due to resistant VT. Our patient received a total of 1000 mL IV lipid emulsion throughout her entire hospital stay.

The current literature includes a considerable number of case reports on the success of ILE in the treatment of TCA-induced cardiotoxicity. ILE therapy may be beneficial in the management of severe amitriptyline toxicity characterized by resistant hemodynamic instability and malignant dysrhythmias in case of failure to respond to other treatment modalities. Early-onset relative high-dose ILE therapy may be life-saving in patients with resistant hemodynamic instability due to TCA-induced severe cardiotoxicity.

Conflict of Interests

The authors declare that there is no conflict of interest.

Financial disclosure

The authors declare that no funding was granted for this research.

Statement of informed consent

A written informed consent form obtained from the patient at the time of discharge.

Author's contributions

HUA, YC, NUA conceived the study and design the trial, supervised the conduct of the trial, data collection and drafted the manuscript. HUA, YC, MU under took recruitment of participating patient. HUA, NUA managed the data, including quality control. HUA, NUA, YC supervised the conduct of the trial and data collection. HUA, MU, YC, NUA drafted the manuscript and managed the data, including quality control and all authors contributed substantially to its revision.

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Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Case Report

J. Exp. Clin. Med., 2021; 38(1): 47-50
doi: 10.5835/jecm.omu.38.01.010

Small cell prostate cancer: A very rare entity

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ARTICLE INFO

Article History
Received 20 / 01 / 2020
Accepted 12 / 10 / 2020
Online Published 26 / 01 / 2021

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Keywords:
Neuroendocrine carcinoma of prostate
Neuroendocrine differentiation
Prostate cancer
Small cell carcinoma

ABSTRACT

Small cell prostate cancer which is associated with a high disease specific mortality is a rare disorder accounting for less than 1% of all prostate cancers. We present here a case of 64 years old male patient presented with lower urinary tract symptoms. The prostate needle biopsy result was reported as prostate adenocarcinoma (predominant component small cell carcinoma) Gleason 5 + 3=8 (eight). Chemotherapy and radiotherapy were planned. The patient was asymptomatic 8 months after treatment. He died 13 months after initial diagnosis because of the metastatic lesions.

1. Introduction

Extrapulmonary small cell carcinoma which may originate from different parts of the body is very rare. Neuroendocrine tumors are almost the same as small cell carcinomas. Immunohistochemical staining tests such as synaptophysin, chromogranin, neuron-specific enolase and CD-56 are used for identification (Walenkamp et al., 2009; Demirtaş et al., 2013). Primary small cell prostate cancer is a rare pathologic entity accounting for less than 1% of all prostate cancers (Weprin and Yonover, 2017). Small cell prostate cancer has a poor prognosis and main age of presentation is 65 years. It was first described in 1977 (Wenk et al., 1977). It clinically behaves like small cell carcinoma of the lung and It commonly presents with lymph node, bone, or organ metastases. Survival expectancy is less than 1 year in diffuse disease (Spiess et al., 2007; Weprin and Yonover, 2017). Morphologically, small cell prostate cancer is similar to small cell carcinoma of the lung and small cell prostate cancer treatment is different from classical prostate cancer treatment. But patients often present with lower urinary tract symptoms

(Karaköse et al., 2013; Weprin and Yonover, 2017). The symptoms of presentation may be related to metastases and rarely to paraneoplastic syndromes. A relative decrease in prostate specific antigen production and androgen receptor expression was observed compared to adenocarcinoma (Petraki et al., 2005; Spiess et al., 2007).

Herein, we describe a 64-year-old man with small cell prostate cancer who was operated for benign prostate enlargement 1 year ago. His transurethral resection of prostate pathology was benign.

2. Case report

A 64 years old man initially presented to another clinic with lower urinary tract symptoms. His complaints were aggravated gradually. He applied to our clinic with symptoms of urinary retention. He was operated for benign prostate enlargement 1 year ago and his transurethral resection of prostate pathology was benign. The prostate gland was homogeneously enlarged and firmer than normal on digital rectal examination. Total prostate specific antigen (PSA) value was 4.50 ng/mL. Transrectal ultrasonography showed a prostate size of 85 mm. His serum creatinine value is normal. Pelvic MRI revealed a mass extending from the bladder posterior to the submucosal area (Fig. 1). A twelve-quadrant transrectal ultrasound guided prostate needle biopsy was taken. The pathology of the sample was reported as prostate adenocarcinoma Gleason 5 + 3=8 (eight). The predominant component in the tumor is small cell carcinoma of the prostate. The lesion was stained positive for CD56, chromogranin, synaptophysin. Histopathological examination was showed at figures (Fig. 2 - 6).

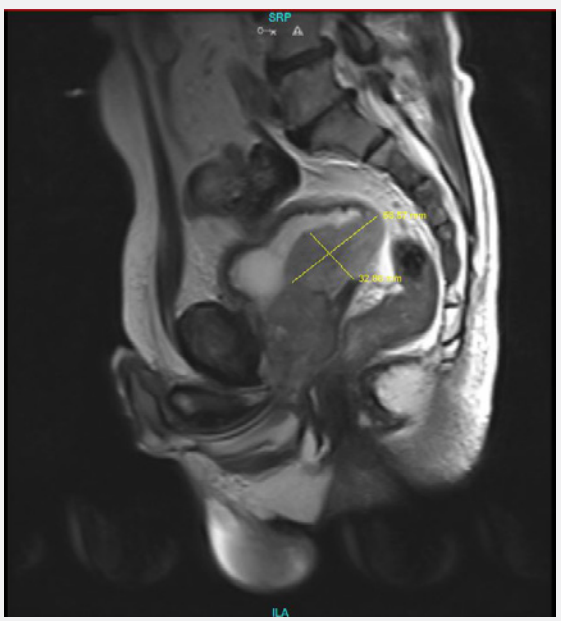

Fig. 1. Pelvic MRI image of the patient.

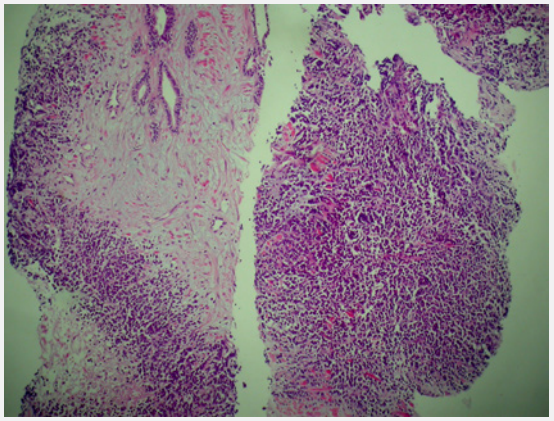

Fig. 2. Small cell carcinoma area with benign prostatic glands (HE; x100).

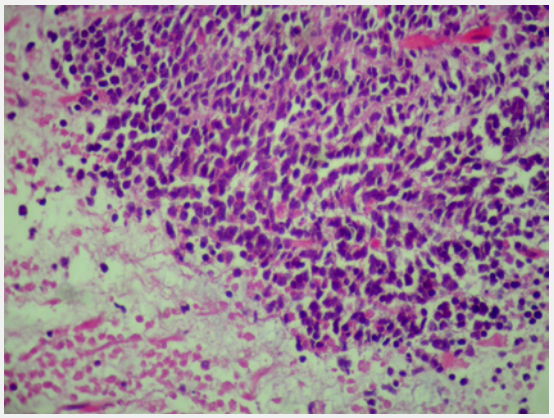

Fig. 3. Oval, round nucleus, without nucleoli specificity, narrow cytoplasm, Carcinoma field consisting of cells and necrosis(HE; x200).

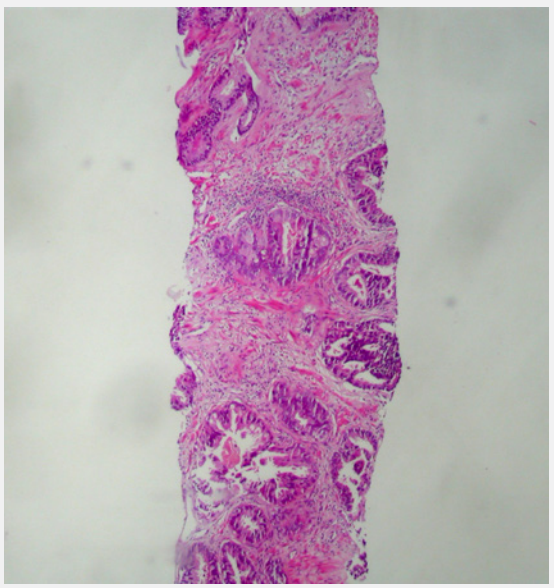

Fig. 4. Acinar carcinoma area in conventional Gleason 3 pattern (HE, x100).

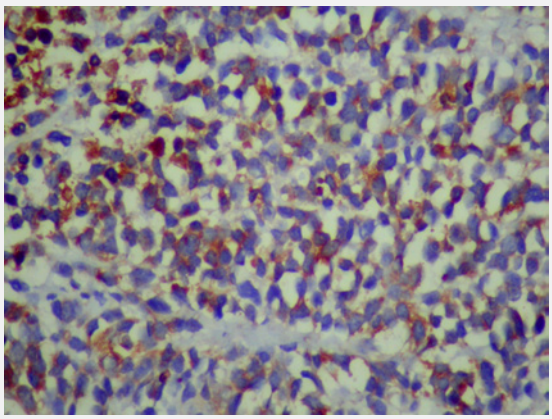

Fig. 5. Focal synaptophysin positivity in small cell carcinoma (DAB; x400).

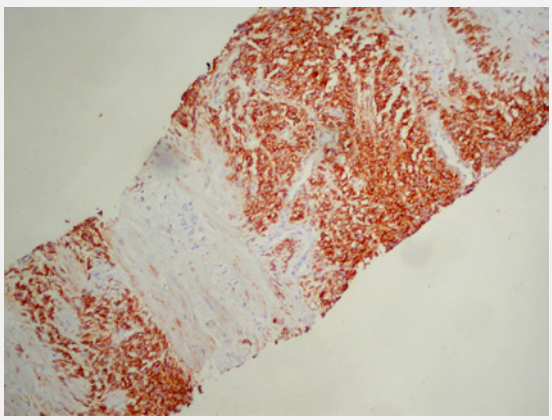

Fig. 6. Diffuse CD56 positivity in the area of small cell carcinoma (DAB; x100).

Computer tomography (CT) of the pelvis showed an enlarged prostate with protrusion bladder posterior to the submucosal area. The chest CT showed diffuse lung emphysematous micro bullae. There was no bone metastasis in whole body bone scintigraphy. Other biochemical parameters were normal.

Chemotherapy and radiotherapy were planned. The daily radiotherapy dose was 1.8 Gy and the total dose was 63 Gy. In total, 35 fractions were given. Six chemotherapy cycles (carboplatin, 450 mg/AUC 5) were also administered every 21 days concomitantly and consequently to radiotherapy. The patient was asymptomatic 8 months after treatment. He died 13 months after initial diagnosis because of the metastatic lesions.

3. Discussion

The prostate is one of the more common sites of extrapulmonary small cell carcinomas. Small cell prostate cancer is rare, accounting for 0.5–2% of all prostatic malignancies (Papandreou et al., 2002; Palmgren et al., 2007). Men with lower urinary tract symptoms are an important part of patients who apply to the urology outpatient clinic. But small cell prostate cancer is different from classic prostate cancer. Small cell prostate cancer is a tumor that tends to systematically metastasize. Even at the time of diagnosis, approximately 75% of patients are at an advanced stage. Small cell prostate cancer has similar characteristics with small cell lung cancer. Small cell prostate cancer has a poor prognosis with an average survival of less than 12 months (Erasmus et al., 2002; Deorah et al., 2012; Ateşçi et al., 2014; Karakose et al., 2014).

Small cell prostate cancer metastasizes early in its course and therefore the clinical presentation is often in an advanced stage. It most commonly metastasizes to the lungs, lymph nodes, brain, liver, bone, pericardium, rectum, and urinary bladder. Small cell prostate cancer cases have normal levels of prostatic acid phosphatase and PSA (Capizzello et al., 2011).

The transrectal ultrasound guided needle biopsy is used for the diagnosis of the small cell prostate cancer initially. However, morphology and immunohistochemical staining for neuroendocrine markers remain the reference point to confirm the diagnosis of small cell carcinoma. Neuroendocrine markers CD56, Chromogranin A, and Synaptophysin are highly specific for small cell carcinomas. Neuroendocrine cells are commonly found in isolated patches along prostate adenocarcinomas. However, immunohistochemical staining against PSA, androgen receptor, prostatic acid phosphatase and p504s (AMACR) are used to demonstrate high sensitivity to eliminate the presence of adenocarcinoma and mixed small cell/adenocarcinoma tumors. Differentiating the different forms of prostate cancer (adenocarcinoma, pure small cell carcinoma, mixed) is necessary to choosing the most effective form of treatment (Capizzello et al., 2011; Weprin and Yonover, 2017). The optimal treatment for small cell prostate cancer is not still defined because of the limited cases. Extra pulmonary small cell cancers are less susceptible to chemotherapy than pulmonary small cell carcinomas. Chemotherapy and radiotherapy can provide a cure for local disease. Survival after a diagnosis of small cell prostate cancer is less than 1.5 years (Palmgren et al., 2007; Weprin and Yonover, 2017).

We diagnosed combined prostate adenocarcinoma and small cell prostate carcinoma in our case. It took about eight months from initial diagnosis to development of diffuse disease. We have limited knowledge of the average survival time at combined prostate adenocarcinoma and pure small cell prostate carcinoma due to limited number of case reports on these cancers in the literature. In one study, the total survival time was 9.5 months for combined prostate adenocarcinoma and small cell prostate carcinoma (Asmis et al., 2006). In another study, the average

survival time found for metastatic small cell prostate cancer was 12.5 months (Spiess et al., 2007).

The majority of men with small cell prostate cancer are associated with both locally advanced lesions and distant metastatic spread. For this reason, the treatment modality should include both local control using radiation therapy to the primary tumor and systemic treatments with chemotherapy. As a result, optimal treatment specific to small cell prostate cancer has not been established with clinical experience or scientific research (Weprin and Yonover, 2017). In a study, they found that, the chemotherapy protocol consisting of cyclophosphamide, doxorubicin, and vincristine in a case with diffuse bone and solid organ metastases could provide a remission period of only 4 months (Hindson et al., 1985). In another study, the author reported a period of full remission of 36 months in a case with metastatic combined adenocarcinoma and small cell prostate carcinoma with radiotherapy, systemic chemotherapy and antiandrogen therapy (Brammer et al., 2011).

We planned chemotherapy and radiotherapy in our case. The daily radiotherapy dose was 1.8 Gy and the total dose was 63 Gy. In total, 35 fractions were given. Six chemotherapy cycles (carboplatin, 450 mg/AUC 5) were also administered every 21 days concomitantly and consequently to radiotherapy. The patient was asymptomatic 8 months after treatment. He died 13 months after initial diagnosis because of the metastatic lesions.

Conclusion

Small cell prostate cancer presents an aggressive tumor histology associated with a high disease-specific mortality rate. It seems that intense systemic chemotherapy, antiandrogen therapy, and radiotherapy extended the remission period and increase survival time for patients with localized disease.

Competing interests

None declared.

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Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Case Report

J. Exp. Clin. Med., 2021; 38(1): 51-54
doi: 10.5835/jecm.omu.38.01.011

Non-schistosomal verrucous carcinoma of the bladder

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ARTICLE INFO

Article History
Received 20 / 01 / 2020
Accepted 12 / 10 / 2020
Online Published 26 / 01 / 2021

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Keywords:
Bladder
Neoplasm
Schistosoma
Verrucous carcinoma

ABSTRACT

Verrucous carcinoma (VC) of the bladder is a malignant neoplasm associated with schistosomal infection. Non-schistosomal VC of the bladder is highly unusual; to the best of our knowledge, only 16 such cases have been reported to date. We report a case of non-schistosomal VC of the bladder, also review the literature and discuss the possible causes, management, and treatment of this unusual and malignant neoplasm.

1. Introduction

Verrucous carcinoma (VC) is a well-differentiated form of squamous cell carcinoma (SCC) that generally occurs in the oral cavity, larynx, vagina, penis, or perianal regions (Hassan et al., 2016). VC of the bladder is rare and has been linked to schistosomal infection (Lewin et al., 2004). Non-schistosomal VC of the bladder is a highly unusual malignant neoplasm; to the best of our knowledge, only 16 such cases have been reported to date in the English-language literature. In contrast to other bladder carcinomas, VC does not metastasize, and therefore complete local excision is curative. However, VC is locally aggressive and is therefore regarded as malignant (Hassan et al., 2016). We report a case of non-schistosomal VC of the bladder and review the current literature.

2. Case report

A 60-year-old male smoker (20 cigarettes per day) presented with severe dysuria, pollakiuria, and urinary urgency. No macroscopic hematuria was reported. The patient had received various treatments involving antibiotics, alpha blockers, antimuscarinic agents, and combinations thereof, but had failed to benefit from them. The physical examination, prostate-specific antigen, and serum biochemistry values

were normal. Microscopic hematuria was present at complete urinalysis. The bladder ultrasound showed no pathology. Flexible cystoscopy revealed a 7 x 5 mm solitary exophytic mass between the bladder neck and trigone.

Transurethral resection (TUR) of the mass was performed, and all visible lesions were completely removed. Macroscopic examination of the resection material revealed gray-white necrotic and flaky lesions. Microscopic examination revealed a well-differentiated malignant tumoral formation, which typically arise from squamous epithelial islands exhibiting acanthosis and papillomatosis and exophytic growth toward the surface (Fig.1). The tumor cells were large, consisting of squamous cells, moderately chromatin-rich nuclei, abundant eosinophilic cytoplasm, and minimal nuclear and structural atypia, with keratin pearls forming in some areas (Fig. 2).

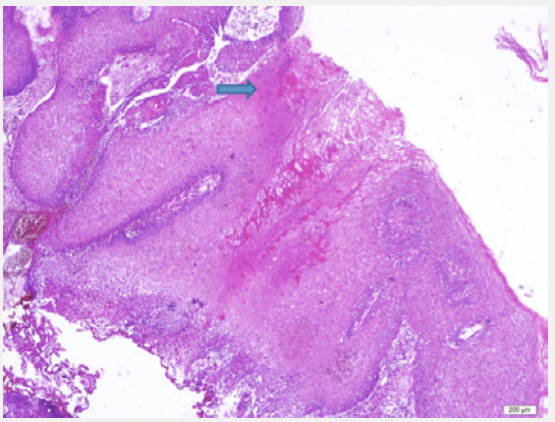

Fig. 1. H&E section (x 40). Tumoral structure consisting of epithelial acanthosis, papillomatosis (blue arrow), and minimal nuclear atypia, the main features of verrucous carcinoma.

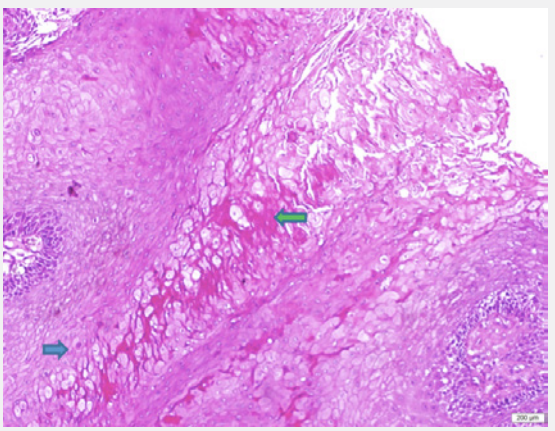

Fig. 2. H&E section (x 200). Squamous pearl (green arrow) formation in epithelial cells and minimal atypia (blue arrow).

Non-schistosomal VC of the bladder was diagnosed. A tumor invading the subepithelial connective tissue (pT1) was detected, but not schistosoma eggs. The surgical margins exhibited no signs of neoplasm. No complication occurred in the early or late postoperative periods, and abdominal computed tomography imaging scans revealed no pathology. The patient received no adjuvant therapy. Control cystoscopy at the third month postoperative also revealed no pathology, and the patient was placed under close clinical follow-up. Subsequent cystoscopy was repeated every three months for a period of one year. No recurrence was observed after the surgery.

3. Discussion

VC is a well-differentiated squamous cell carcinoma of the bladder. It is a rare, clinically inert form of bladder cancer that is primarily linked to schistosomal infection, but it can also occur without such infection (Park et al., 2019). Non-schistosomal VC of bladder is a highly unusual tumor, with only 16 cases having been reported in the English-language medical literature (Table 1). The mean age of these 16 patients (nine women and seven men) was 61.18 (range, 33-83) years.

The pathognomonic symptom of bladder tumors is macroscopic hematuria. This was observed in only three patients (Cases 2, 13, 15) (Holck and Jorgensen, 1983; Lewin et al., 2004; Flores et al., 2009). One patient (Case 1) presented with lumbar pain, and the others presented with irritative lower urinary tract symptoms (LUTS) (Wyatt and Craig, 1980). The reason for admission in our case was LUTS that was resistant to medical treatment.

The etiology of non-schistosomal VC of the bladder is unknown. However, various risk factors have been associated with this disease, such as smoking (Cases 8 and 12), urinary tract infection (Cases 9 and 10), condyloma acuminatum (Cases 3 and 6), urinary stones (Case 11 and 14), and interstitial cystitis (Case 12) (Walther et al., 1986; Batta et al., 1990; Blackmore et al., 1995; Ellsworth et al., 1995; Hamm et al., 1997; Oida et al., 1997; Sohn et al., 1997; Usta et al., 2006). All of these diseases feature chronic inflammation, and thus we think that non-schistosomal VC of the bladder can develop in association with chronic inflammation.

VC of the bladder is not metastatic, but malignant, since it is locally invasive (Hassan et al., 2016). Wide, aggressive resection or partial cystectomy with wide margins is sufficient for treatment. Total cystectomy was performed in 11 of the previously reported cases (Cases 1, 3, 6 – 13, and 15) (Wyatt and Craig, 1980; Walther et al., 1986; Batta et al., 1990; Horner et al., 1991; Blackmore et al., 1995; Ellsworth et al., 1995; Hamm et al., 1997; Oida et al., 1997; Sohn et al., 1997; Lewin et al., 2004; Flores et al., 2009). Four different patients (Cases 1, 3, 6, and 15) initially underwent

Table 1. Summary of non- schistosomal verrucoz carsinoma of bladder cases in the literature.

Case no.	Author, reference	Date	Age/ Sex	Plaint	Risk factor	Tumour size	Treatment	Recurrence	Adjuvanttherapy	Follow-up (Months)	Outcome
1	Wyatt&Craig	1980	73/M	Pain	-	VL	TUR	Yes	TC	24	Survived
2	Holck&Jørgen-sen	1983	75/M	H	-	VL	PC	Yes	PC	3	Survived
3	Walther et al.	1986	43/F	LUTS	CA	VL	TUR	Yes	TC	30	Survived
4	Boileau et al.	1986	83/M	LUTS	-	15 x 10 mm	RT	No	-	3	Died (Uremia)
5	Pierangeli et al.	1989	48/F	LUTS	-	VL	PC	Yes	TUR	6	Survived
6	Batta et al.	1990	43/F	LUTS	CA	VL	TUR	Yes	TC	12	Survived
7	Horner et al.	1991	68/F	LUTS	-	VL	TC	No data	-	No data	No data
8	Ellsworth et al.	1995	58/F	LUTS	Smoking	VL	TC	No	-	36	Survived
9	Blackmore et al.	1995	58/F	LUTS	UTI	VL	TC	No	-	24	Survived
10	Oida et al.	1997	66/F	LUTS	UTI	110 x 80 mm	TC	No	-	23	Survived
11	Sohn et al.	1997	69/F	LUTS	Urinary stone	VL	TC	No	-	12	Survived
12	Hamm et al.	1997	66/F	LUTS	IC	VL	TC	No	-	No data	Survived
13	Lewin et al.	2004	64/M	H	Smoking	VL	TC	No	-	3	Died (Unknown)
14	Usta et al.	2006	54/M	LUTS	Urinary stone	Small	TUR	Yes	TUR	3	Survived
15	Flores et al.	2009	33/M	H	-	VL	PC	Yes	TC	36	Survived
16	Hassan et al.	2016	78/M	LUTS	-	30 x 20 mm	TUR	Yes	TUR I-MMC	3	Survived
17	Present case	2019	60/M	LUTS	Smoking	7 x 5 mm	TUR	No	-	12	Survived

CA: Condyloma acuminatum, H: Hematuria, IC: Interstitial cystitis, I-MMC: Intravesical mitomycin, LUTS: Lower urinary tract symptoms, MM: Millimeter, PC: Partial cystectomy, RT: Radiotherapy, TC: Total cystectomy, TUR: Transurethral resection, UTI: Urinary tract infection, VL: Very large (occupying minumum 50% of bladder)

bladder sparing surgery but later received total cystectomy due to recurrence at follow-up (Wyatt and Craig, 1980; Walther et al., 1986; Batta et al., 1990; Flores et al., 2009). Four patients underwent bladder sparing surgery, two with partial cystectomy (Cases 2 and 5) two with TUR (Cases 14 and 16) (Holck and Jorgensen, 1983; Pierangeli et al., 1989; Usta et al., 2006; Hassan et al., 2016). One patient (Case 4) received radiotherapy (Boileau et al., 1986). This patient's general condition was unsuitable for surgery, and mortality occurred due to uremia on the third month postoperative.

The size of tumors in patients in the early years was sufficient to encompass more than 70% of the bladder, although the tumors' dimensions subsequently gradually decreased. This reduction was reflected in the type of treatment administered; treatments in the earlier publications consisted of aggressive surgery, but they were gradually modified to be minimally invasive. The rarity of this cancer and the resulting scarcity of reports and studies make it difficult to define and optimize therapy. We applied TUR in our case due to the small size of the tumor. We observed no recurrence throughout the 12-month follow-up period.

Non-schistosomal VC frequently involves a solitary lesion with an exophytic and filiform appearance. Microscopically, it is characterized by papillary proliferation accompanied by epithelial acanthosis and hyperkeratosis (Park et al., 2019). Histopathologically, since VC bears a close resemblance to lesions such as giant condyloma, verrucous hyperplasia, and SCC, diagnosis may be problematic (Hassan et al., 2016; Park et al., 2019). VC of the bladder must be distinguished from the more common neoplasias, including ordinary SCC and transitional cell carcinoma, with squamous differentiation. The majority of authors recommend that, in the presence of dysplasia in VC or small foci of SCC that resemble VC, patients should be treated as they would for SCC (Patel et al., 2015).

The prognosis for non-schistosomal VC of the bladder is generally good. Mortality was reported in only two cases (Cases 4 and 13) in the 15-patient series (Boileau et al., 1986; Lewin et al., 2004). The first patient (Case 4) was elderly, in poor general condition, and was not indicated for surgery, instead receiving radiotherapy. Mortality occurred due to uremia (Boileau et al., 1986). Mortality in the other patient (Case 13) occurred three months after total cystectomy (Lewin et al., 2004). No cause of death could be determined. No metastasis was observed in any of the 16 patients. Recurrence was identified in all eight patients (Cases 1-3, 5, 6, and 14-16) that underwent bladder sparing surgery at initial treatment (Wyatt and Craig, 1980; Holck and Jorgensen, 1983; Walther et al., 1986; Pierangeli et al., 1989; Batta et al., 1990; Usta et al., 2006; Flores et al., 2009; Hassan et al., 2016). Adjuvant

total cystectomy was performed on four patients (Cases 1, 3, 6, and 15), and adjuvant bladder sparing surgery was performed on four (Wyatt and Craig, 1980, Walther et al., 1986; Batta et al., 1990; Flores et al., 2009). One patient (Case 16) received intravesical mitomycin therapy as well as TUR, but this failed to prevent recurrence (Hassan et al., 2016). No recurrence was observed in our cases during the 12-month follow-up. The tumor in our case was detected incidentally and was very small (7 x 5 mm). In the other cases, tumors represented more than 50% of the bladder. The lack of recurrence over a 12-month follow-up may be due to the size of the tumor.

Due to the rarity of non-schistosomal VC of the bladder, there are no clear guidelines regarding its treatment. Based on a literature review, there is no answer regarding which is the treatment of choice, although it is difficult to recommend a standard therapy. If the tumor has invaded the perivesical tissue or is of a high volume (i.e., occupying at least 50% of the bladder), then radical cystectomy may be required. Radiotherapy can be applied in inoperable cases or with patients for which surgery is not indicated. In cases of low-volume tumors, minimally invasive approaches, such as partial cystectomy or TUR, may be employed if the patient will attend follow-ups, although close surveillance must be recommended due to the risk of recurrence. Subsequent cystoscopy should be repeated every three months, and semiannual or annual surveillance with pelvic CT studies should be recommended to evaluate the perivesical tissue.

To summarize, non-schistosomal VC of the bladder is observed in patients in their 60s, and it is slightly more common in women. It does not metastasize, but it has a very high recurrence rate. Although the etiology is unknown, the most likely cause is chronic inflammation. Further epidemiologic and clinical studies are required to evaluate the need for therapy and potential long-term recurrence in patients with non-schistosomal VC of the bladder.

Informed consent

Written informed consent was obtained from the patient for his clinical data to be published in this article.

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