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Editorial

Dear Colleagues,

March 2020 issue of Gülhane Medical Journal includes interesting articles of different disciplines that cover updated and scientifically valuable topics. Gülhane Medical Journal has changed the publication house and the online design with the new year and continues the way with passion as the previous years. This issue includes eleven articles. Nine of these articles are original researches and two of them are case presentations.

Our journal welcomes articles from all over the world and we are proud to publish them as strong contributors to the literature. Our journal is not a branch-specific journal so that it allows us to include articles from different disciplines. In this issue we include articles about; Gynaecology, Radiation Oncology, Physical Therapy and Rehabilitation, Neurology, Emergency Medicine also Dentistry and Nursing. The presented cases are rare and very interesting ones that would lead new point of views and treatment options.

Current medical news point an important infection. Nowadays, many countries are strongly struggling with Corona Virus that caused many deaths and severe health problems. Hope curable solutions would be found for this serious viral infection and also vaccines would be developed soon.

As Nelson Mandela said, 'Education is the most powerful weapon which you can use to change the world'. We would like to thank all authors for their precious contributions, the editors and reviewers for their valuable efforts and also the publisher for their interesting new design. Hope to receive more and more valuable articles for the upcoming issues.

Selcuk Sarikaya, MD FEBU
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The effect of maternal obesity on the success of labor induction with a cervical ripening double-balloon catheter and on pain perception during catheter insertion

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Presented in: The abstract of the manuscript represented as a poster at the 3. International Pregnancy, Birth and Puerperium Congress, on February 14-17, 2019, Bolu, Turkey.

Keywords: Double-balloon catheter, labor induction, multiparity, obesity, pain

ABSTRACT

Aim: To evaluate the effect of maternal body mass index (BMI) on the success of labor induction with a cervical ripening double-balloon catheter and maternal pain perception during the catheter insertion process.

Methods: This observational study included 103 women with singleton pregnancies, who underwent labor induction with a double-balloon catheter at ≥39 weeks of gestation for obstetric indications. The study population was divided into two groups according to the BMI (group 1 <30 kg/m^2 and group 2 ≥30 kg/m^2). The two groups were compared in terms of their clinical characteristics, labor outcomes, cesarean delivery rate, delivery rate within 24 hours of insertion, and maternal pain perception during catheter insertion.

Results: The two BMI groups showed no significant differences in the cesarean delivery rate (31.5% vs. 42.9%), the delivery rate within 24 hours of labor induction (85.2% vs. 81.6%), and Visual Analog Scale (VAS) score (4.8±2.9 vs. 4.6±2.5) (p>0.05). The cesarean delivery rate was 19.6% in multiparous women and 57.4% in nulliparous women (p<0.001). The median Bishop scores upon admission and at the time of balloon expulsion were higher in women who delivered vaginally than in those who underwent cesarean sections [4 (1-5) vs. 2 (1-5) and 7 (4-11) vs. 6 (2-8), respectively, p<0.001]. The VAS scores recorded during double-balloon catheter insertion (4.8±2.9 vs. 4.6±2, p=0.772) were also similar in both groups.

Conclusion: Maternal BMI did not affect the success of labor induction with a cervical ripening double-balloon catheter. Parity and Bishop scores were the factors influencing labor induction success.

Introduction

Over the last few decades, obesity [body mass ındex (BMI) ≥30 kg/m^2] has become one of the major health problems worldwide. Globally, the prevalence of overweight and obese adult women has increased from 29.8% in 1980 to 38.0% in 2013 (1). Obesity, which has also become common in women of reproductive age, increases the occurrence of obstetric complications, such as gestational diabetes mellitus, hypertension, fetal macrosomia, prolonged delivery time, and dystocia at birth (2-6). Obese women are also at increased risk for labor induction and their cesarean section rates are increased (7-9).

Labor induction with mechanical or pharmacological agents is now a commonly performed obstetrical intervention for various indications, such as prolonged gestation, fetal growth restriction, and oligohydramnios. Although some factors, such as the Bishop score and cervical length, can affect the success of labor induction, the factors that predict its success are not yet clear (10,11). The cesarean delivery rate is approximately 17% in women who undergo labor induction (12).

The efficacy of mechanical devices is comparable to that of pharmacological agents, as different mechanical devices have similar or higher vaginal delivery rates (13,14). One of the mechanical devices, the double-balloon catheter, enables cervical ripening by stimulating endogenous prostaglandin release (15). Balloon induction has a lower incidence of fetal tachysystole, but a higher need for oxytocin augmentation when compared to prostaglandin treatments (15,16). One disadvantage of balloon induction is a pain sensation during insertion.

This observational study was conducted to determine the impact of maternal BMI on the success of labor induction with a cervical ripening double-balloon catheter and to evaluate pain perception during catheter insertion. The cesarean section rate, delivery rate within 24 hours of labor induction, and Visual Analog Scale (VAS) pain score during double-balloon catheter insertion were compared between women with a BMI at or above 30 kg/m^2 and women with a BMI <30 kg/m^2.

Methods

The participants in this observational study were women with a single fetus in vertex presentation and a Bishop score of less than six, who underwent labor induction with a cervical ripening double-balloon catheter at 39 weeks' gestation or beyond at tertiary care center, between May 1 and November 1, 2018. The study protocol was approved by the Ethical Committee of the University of Health Sciences Turkey, Etlik Zubeyde Hanim Women's Health Training and Research Hospital (2018/8), and complied with the Helsinki Declaration, including current revisions. Signed written informed consent was obtained from all the participants who volunteered to participate in the study. Exclusion criteria included age under 18 years, multiple pregnancies, breech presentation, transverse position, prior cesarean delivery or uterine surgery, a Bishop score greater than or equal to six at admission, diabetes mellitus, hypertension, cardiac disease, premature rupture of membranes, chorioamnionitis, fetal demise, polyhydramnios, placenta previa, and a gestational age <39 weeks.

Prior to the cervical ripening double-balloon insertion, the gestational age of the participants was evaluated according to the last menstrual period and/or ultrasonographic findings in the first and early second trimester. Upon admission, a pelvic examination was performed to evaluate the fetal presentation and the maternal pelvic structure and to determine the baseline Bishop score. A reassuring fetal status was confirmed by a biophysical profile, non-stress test, and/or oxytocin challenge test. A double-balloon catheter was inserted into the cervical canal according to the previously described technique (17,18). The fetal heart rate was continuously monitored externally during induction. The double-balloon catheter was spontaneously expelled or it was removed upon completion of the 12-hour period or upon observation of a non-reassuring fetal heart rate. After the balloon removal, the Bishop score was re-evaluated via cervical examination, and oxytocin augmentation was performed in women who were not in an active phase of labor (defined as a period of labor from 5 cm of cervical dilatation with regular uterine contractions to delivery) (19). Oxytocin augmentation was also performed in cases of prolonged labor or labor arrest with uterine contractions of less than 200 Montevideo units. Unchanged cervical dilatation and effacement for four hours or a second stage of labor longer than two hours were defined as failures to progress.

The data collected included maternal age, BMI, gravidity, parity, gestational age, previous obstetrical history of multiparous women, the amniotic fluid index, indications for labor induction, Bishop scores upon admission, time to expulsion of the balloon, the duration of labor after induction, the need for oxytocin augmentation, the mode of delivery, indications for a cesarean section, and newborn birthweight, head circumference, and height. An amniotic fluid index of less than 5 cm was considered to indicate oligohydramnios (20). A gestational age greater than 41 weeks was defined as prolonged pregnancy. Pain perception during balloon insertion was evaluated using a 10-cm VAS score, as described previously (21).

The study population was divided into two groups according to BMI: group 1 <30 kg/m^2 and group 2 ≥30 kg/m^2. The clinical characteristics, labor outcomes, cesarean delivery rate, delivery rate within a 24-hour period of labor induction, and VAS scores for patient's pain perception during double-balloon catheter insertion were compared for the two groups. Other factors associated with labor induction success and maternal pain perception were also evaluated.

Statistical Analysis

Statistical analysis was performed with SPSS version 17 (SPSS, Chicago, Illinois, USA). The normality for continuous variables was analyzed using the Kolmogorov-Smirnov test. The descriptive statistics presented were the mean value and standard deviation or median (minimum-maximum) for the continuous variables and the numbers and percentages for the categorical variables. Differences in normally distributed continuous variables were analyzed using an independent sample t-test and variables without normal distribution were analyzed using the Mann-Whitney U test. Differences in

categorical variables were examined with the chi-square test. A p value of less than 0.05 was considered to be statistically significant.

Results

During the study period, 103 women who were eligible for the study underwent labor induction with a cervical ripening double-balloon catheter. Labor was induced for prolonged pregnancy in 49 women (47.6%), for oligohydramnios in 22 women (21.4%), and for non-reassuring fetal status in 32 women (31.1%). BMI was <30 kg/m^2 in 54 (52.4%) women (group 1), whereas, in the remaining 49 women (group 2), 32 (31.1%) had a BMI of 30-34.9 kg/m^2 and 17 women had a BMI ≥35 kg/m^2.

The clinical characteristics and labor outcomes of the two groups are shown in Table 1. The median maternal age was lower [24 (18-40) years vs. 27 (18-43) years, p=0.023] and gestational age was higher [41 (39-42) weeks vs. 40 (39-41) weeks, p=0.042] in group 1. No significant differences were detected for gravidity, parity, incidence of oligohydramnios, and Bishop scores upon admission and at the time of balloon expulsion between the groups (p>0.05). No association was found between the BMI and labor outcomes. The duration of labor (17.4±5.2 h in group 1, 17.5±6.1 h in group 2, p=0.960), cesarean section rate (31.5% in group 1, 42.9% in group 2, p=0.232), and delivery rate within 24 hours of balloon insertion (85.2% in group 1, 81.6% in group 2, p=0.628) did not differ between the two groups. No operative deliveries were required in either of the groups. The VAS scores recorded during double-balloon catheter insertion (4.8±2.9 in group 1, 4.6±2.5 in group 2, p=0.772) were also similar in both groups.

The overall cesarean delivery rate was 36.9% in the study population. The indications for cesarean delivery were fetal

Table 1. Clinical characteristics and labor outcomes of group 1 [body mass index (BMI) <30 kg/m^2] and group 2 (BMI ≥30 kg/m^2)

Characteristics	Group 1 BMI <30 kg/m^2 (n=54)	Group 2 BMI ≥30 kg/m^2 (n=49)	p value
Clinical characteristics			
Maternal age (y)	24 (18-40)	27 (18-43)	0.023**
Gravidity	2 (1-6)	2 (1-7)	0.119**
Parity	1 (0-3)	1 (0-3)	0.116**
Multiparous women	27 (50.0%)	29 (59.2%)	0.350***
Gestational age (w)	41 (39-42)	40 (39-41)	0.042**
Oligohydramnios	13 (24.1%)	10 (20.4%)	0.655***
Labor characteristics			
Bishop score upon admission	4 (2-5)	3 (1-5)	0.077**
Bishop score upon balloon expulsion	7 (4-11)	7 (2-10)	0.470**
Spontaneous balloon expulsion rate	27 (50.0%)	28 (57.1%)	0.468***
Balloon insertion to expulsion time (h)	12 (1-12)	10 (1-12)	0.175**
Balloon insertion to active labor onset time (h)	12.6±4.1	12.4±5.8	0.802*
Balloon insertion to delivery time (h)	17.4±5.2	17.5±6.1	0.960*
Balloon expulsion to delivery time (h)	7.9±4.6	9.3±4.8	0.389*
Oxytocin need	32 (59.3%)	30 (61.2%)	0.839***
Cesarean delivery	17 (31.5%)	21 (42.9%)	0.232***
Delivery within 24 h	46 (85.2%)	40 (81.6%)	0.628***
VAS score	4.8±2.9	4.6±2.5	0.772*
Newborn characteristics			
Birthweight (gr)	3406.9±422.0	3361.7±325.5	0.331*
Head circumference (cm)	34.9±1.4	34.5±1.1	0.078*
Height (cm)	51 (45-56)	51 (46-54)	0.449**

p>0.05
Data are the mean ± standard deviation, median (minimum-maximum), and number (%).
*The t-test was used.
**The Mann-Whitney U test was used.
***The Chi-square test was used.
VAS: Visual Analog Scale, BMI: Body Mass Index

distress in 22 women (21.4%), failure to progress in 15 women (14.6%), and a prolapsed umbilical cord in one woman (2.6%).

The characteristics affecting the success of induction and duration of labor are shown in Table 2. Significant differences were noted for gravidity (p<0.001), parity (p=0.001), the Bishop score upon admission (p<0.001), and the time to balloon expulsion (p<0.001) between the women with vaginal and with cesarean deliveries. The median Bishop scores at admission and at the time of balloon expulsion were 4 (minimum 1-maximum 5) and 7 (minimum 4-maximum 11) in women with vaginal deliveries, and 2 (minimum 1-maximum 5) and 6 (minimum 2-maximum 8) in women who had cesarean deliveries, respectively (p<0.001). Compared to the cesarean delivery group, balloon insertion to expulsion time (p=0.011), balloon insertion to delivery time (p<0.001), and balloon expulsion to delivery time (p=0.025) were shorter in the vaginal delivery group. Spontaneous balloon expulsion and the rates of need for oxytocin augmentation did not differ between the women with vaginal and cesarean deliveries. Similar results were observed in women who delivered within 24 hours of labor induction. Gravidity (p=0.011), parity (p=0.009) and the Bishop scores upon admission (p<0.001) and at the time of balloon expulsion (p<0.001) were higher; balloon insertion to expulsion time (p=0.001), balloon insertion to delivery time (p<0.001), and balloon expulsion to delivery time (p<0.001)

Table 2. Clinical characteristics and labor outcomes according to the delivery mode and labor time

Characteristics	Delivery mode			Delivery within 24 hours		
	Vaginal delivery n=65	Cesarean delivery n=38	p value	(+) n=86	(-) n=17	p value
Clinical characteristics						
Maternal age (y)	25 (18-40)	26 (18-43)	0.598*	26 (18-43)	25 (18-38)	0.203**
BMI (kg/m^2)	30.2±4.6	31.0±5.7	0.451*	30.6±4.9	30.3±5.5	0.857*
Gravidity	2 (1-7)	1 (1-5)	<0.001**	2 (1-7)	1 (1-3)	0.011**
Parity	1 (0-3)	0 (0-3)	0.001**	1 (0-3)	0 (0-2)	0.009**
Nulliparous	20 (42.6%)	27 (57.4%)	<0.001***	34 (27.7%)	13 (72.3%)	0.005***
Multiparous	45 (80.4%)	11 (19.6%)	<0.001***	52 (7.1%)	4 (92.9%)	0.005***
Gestational age (w)	40 (39-42)	41 (39-42)	0.163**	40 (39-42)	41 (39-41)	0.664**
Oligohydramnios	18 (27.7%)	5 (13.2%)	0.087***	19 (22.1%)	4 (23.5%)	0.897***
Interval between the births (y)†	5 (1.5-16)	6 (2-17)	0.385**	5 (1.5-17)	8 (7-16)	0.059**
History of prolonged pregnancy†	10 (25.6%)	2 (16.7%)	0.522***	11 (23.4%)	1 (25%)	0.671***
Labor characteristics						
Bishop score upon admission	4 (1-5)	2 (1-5)	<0.001*	3 (1-5)	2 (1-4)	<0.001*
Bishop score upon balloon expulsion	7 (4-11)	6 (2-8)	<0.001*	7 (4-11)	4 (2-8)	<0.001*
Spontaneous balloon expulsion rate	39 (60.0%)	16 (42.1%)	0.079***	53 (61.6%)	2 (11.8%)	<0.001***
Balloon insertion to expulsion time (h)	9.5 (1-12)	12 (5-12)	0.011**	10 (1-12)	12 (7-12)	0.001**
Balloon insertion to active labor onset time (h)	12.3±5.0	14.2±4.9	0.131*	12.0±4.5	19.4±5.5	<0.001*
Balloon insertion to delivery time (h)	16.7±5.5	21.2±6.8	<0.001*	16.4±4.7	28.1±3.9	<0.001*
Balloon expulsion to delivery time (h)	8.1±4.6	10.5±6.1	0.025*	7.5±4.1	16.6±4.0	<0.001*
Oxytocin need	37 (56.9%)	25 (65.8%)	0.375***	46 (53.5%)	16 (94.1%)	0.002***
VAS score	4.5±2.7	4.8±3.3	0.722*	4.6±2.8	4.9±3.6	0.715*
Newborn characteristics						
Birthweight (gr)	3389.2±388.6	3331.3±326.3	0.441*	3384.8±378.3	3282.1±293.1	0.293*
Head circumference (cm)	35 (31-38)	34.5 (33-37)	0.306**	35 (31-38)	35 (32-36)	0.952**
Height (cm)	51 (46-56)	51 (45-54)	0.737**	51 (45-56)	51 (48-52)	0.088**

†In multiparous women.
p<0.05 statistically significant.
The data are the mean ± standard deviation, median (minimum-maximum), and number (%).
*The t-test was used.
**The Mann-Whitney U test was used.
***The Chi-square test was used.
VAS: Visual Analog Scale, BMI: Body Mass Index

were shorter in the women who delivered within 24 hours than in those who needed a longer time to deliver. In addition, the percentage of women with spontaneous balloon expulsion was higher (p<0.001) while the interval from balloon insertion to active labor onset was shorter (p<0.001), and the additional oxytocin augmentation rate was lower (p=0.002) in the women who delivered within 24 hours.

In the total study population, the cesarean delivery rate was lower in multiparous women than in nulliparous women (19.6% vs. 57.4%, p<0.001). When the two groups were analyzed separately, it was found that the cesarean delivery rates were 18.5% in multiparous women and 44.4% in nulliparous women in group 1 (p<0.04), and 20.7% in multiparous women and 75% in nulliparous women in group 2 (p<0.001).

No significant association was found between the BMI and pain perception during double- balloon insertion. The VAS scores were 4.8±2.9 in group 1 and 4.6±2.5 in group 2 (p=0.772). The VAS scores also did not differ in women with Bishop scores of less than four or greater than four (4.7±3.2 vs. 4.7±2.7, respectively, p=0.974) upon admission. However, the VAS scores were significantly lower in women over 30 years old (3.4±2.4 vs. 5.1±2.9, p=0.006) and in multiparous women (3.9±2.6 vs. 5.4±3.1, p=0.012).

Discussion

The results of the current study show that the success of labor induction with a cervical ripening double-balloon catheter was not affected by maternal obesity. The duration of labor, mode of delivery, and maternal pain perception did not differ between women with a BMI <30 kg/m^2 and with a BMI ≥30 kg/m^2.

Previous studies investigating the obstetrical outcomes of labor induction with prostaglandins identified BMI as an independent risk factor for cesarean delivery (22-25). A significantly increased cesarean delivery rate was reported with increasing maternal BMI in the secondary analysis of the Misoprostol Vaginal Insert Trial data (22). Analysis of the labor induction outcomes of 1,273 women with a parity ≤3 with a singleton pregnancy at 36 weeks or more of gestation revealed a cesarean delivery rate of 21.3% in women with a BMI under 30 kg/m^2, 29.8% in women with a BMI of 30-39.9 kg/m^2, and 36.5% in women with a BMI of 40 kg/m^2 or higher. The time to delivery was also longer in obese women than in women with a BMI <30 kg/m^2 in this series. Another study also reported a significantly higher emergency cesarean rate among obese primigravida women who underwent labor induction with PGE2 (27.4% vs. 29.5%) (23).

Conversely, maternal weight did not affect the success of mechanical devices for labor induction according to the previous studies. Mechanical methods eliminate the dilutional effect of the increased distribution volume of ripening agents in obese women. Anabusi et al. (26) analyzed the outcomes in women who underwent labor induction with a double-balloon or a Foley catheter and reported no difference in the duration of labor and the cesarean delivery rate with mechanical ripening devices between obese (25%) and normal weight (17%) women. We observed similar results in women who underwent labor induction with a double-balloon catheter only. The vaginal delivery rate and the delivery rate within 24 hours after the initiation of labor induction did not differ between the obese and normal weight women in our series. According to these results, the success of the double-balloon method seems to be independent of maternal weight. According to the results of our study, cervical ripening with a double-balloon catheter might be superior to pharmacological labor induction in obese women.

Similar to previous reports, an unfavorable Bishop score was identified as one of the predictors of the success of labor induction in our study group (10,27). Lower Bishop scores at the time induction with a double balloon catheter and at the time catheter expulsion were observed in women who had cesarean deliveries.

The labor induction success rate was higher in multiparous women, as reported in previous studies (12,24,27,28). Thorsell et al. (24) reported that the emergency cesarean section rate during labor induction with PGE2 vaginal gel or a transcervical catheter was 42% in nulliparous women and 14% in multiparous women at or after 41 weeks of gestation. Roos et al. (28) reported a five-fold increase in the cesarean section rate in post-term nulliparous women who underwent labor induction. Similar results have been reported in studies evaluating the success of labor induction with mechanical devices alone. Delaney et al. (27) reported a rate of 28% for cesarean section among nulliparous women and a 6% rate in multiparous women induced with a Foley catheter. However, in our study group, a prior history of prolonged pregnancy or duration between two consecutive births did not affect the success of labor induction.

One of the main disadvantages of mechanical methods compared to pharmacological agents is the pain sensation during catheter insertion. Advanced age and previous birth experiences may affect the intensity of the pain perception and improve pain tolerance during double-balloon catheter insertion. Our results indicated that younger and nulliparous women had a higher VAS pain scores, but maternal obesity had no effect on pain perception. The mean VAS score was 4.8 in lean women and 4.6 in women with a BMI of 30 kg/m^2 or more. Anabusi et al. (26) also reported similar pain perception rates between the obese and normal weight women with overall lower mean VAS scores; the mean VAS score was 3.5 in women with a BMI lower than 30 kg/m^2 and 3.2 in obese women. Ethnic and cultural differences between the study populations may be the cause of the differences in VAS score effects reported in the two studies.

The main limitation of the present study was its observational design. The decision for labor induction or cesarean section was also made by different obstetricians. The other weakness of the study was that the study population included few morbidly obese women with BMI of 40 kg/m^2 or more. Larger studies are needed to allow the generalization of our results to morbidly obese women. However, the comparable clinical characteristics and the investigation of labor induction with a single mechanical method in the entire study population are the main strengths of this observational study. The effect of obesity on the success of labor induction was investigated without any confounding effects caused by different induction methods.

Conclusion

In conclusion, the current study demonstrated that maternal obesity had no influence on the outcome of labor induction with a cervical ripening double-balloon catheter. As reported in previous publications, parity and the Bishop score are the factors that affect labor induction success. A lower cesarean birth rate was observed in multiparous women and in women with a favorable Bishop score in this study. Therefore, a cervical ripening double-balloon catheter can be considered as one of the preferred options for labor induction in obese multiparous women.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethical Committee of the University of Health Sciences Turkey, Etlik Zubeyde Hanim Women's Health Training and Research Hospital (2018/8).

Informed Consent: Signed written informed consent was obtained from all the participants who volunteered to participate in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.K., B.D., Design: T.K., B.D., Ö.M.T., Data Collection or Processing: T.K., R.Ö., İ.K., Analysis or Interpretation: B.D., R.Ö., İ.K., Ö.M.T., Literature Search: R.Ö., İ.K., Writing: T.K.

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

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Evaluation of the radiotherapeutic management of refractory painful heel spur and plantar fasciitis: a single center experience of 45 years

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Keywords: Heel spur, plantar fasciitis, radiation therapy, refractory pain management

ABSTRACT

Aim: Heel spur is exostosis of the calcaneus. Plantar fasciitis and heel spur constitute a very common cause of plantar pain, which may be managed with radiation therapy (RT). In this study, we assessed the radiotherapeutic management of refractory painful heel spur and plantar fasciitis.

Methods: In this retrospective study, we report our single center experience with RT for refractory painful heel spur and plantar fasciitis management over a period of 45 years and describe patient and treatment characteristics.

Results: Between 1974 and 2019, a total of 4904 patients received RT at our department using cobalt-60 teletherapy machine for the management of refractory painful heel spur and plantar fasciitis. Out of the total 4904 patients, 2012 patients (41%) were male and 2892 patients (59%) were female. The median age was 51 (range: 41-85) years. All patients had received previous therapies for refractory painful heel spur and plantar fasciitis before the management with RT. Total RT dose was 8 Gy delivered in 2 consecutive days with daily fractions of 4 Gy using 2 opposing anterior-posterior RT fields to both heels without bolus material. Treatment response was assessed 3 to 5 weeks after the completion of RT. Response to RT was complete in 3579 patients (73%), partial in 1188 patients (24.2%), and none in 137 patients (2.8%). No therapy-related toxicity was observed in the whole series.

Conclusion: RT for refractory painful heel spur and plantar fasciitis may offer effective palliation of pain and may be considered as a viable therapeutic option for selected patients exhausted with other treatment modalities.

Introduction

Plantar fasciitis and associated bone formation, referred to as “plantar heel spur”, constitute a very common cause of plantar pain. Plettner, a German surgeon, was first to describe calcaneal spur in 1900 (1). Factors associated with plantar fasciitis include increased body weight, intensive workload and sportive activity and working on hard surfaces (2-4). Patient symptomatology typically includes stinging and severe heel pain with potential gait and mobility disturbances accompanied by worsened quality of life.

Several mechanisms are thought to play a role in the occurrence of pain from heel spur. Vertical compression leads to continual microtraumas and eventual degeneration of fascia at calcaneal insertion area, which is typically followed by inflammatory tissue reactions (5). Inflammation may result in thickening of the fascia along with exostotic bone formation as the heel spur. Staged development of heel spur has been described by Kumai and Benjamin (6). While patients with heel spur may typically suffer from severe pain, there may be cases without pain and also some patients with plantar fasciitis may present with pain albeit without radiographic evidence of heel spur formation. Diagnosis is based on history and physical examination findings with typical localization of pain (7). While sophisticated imaging techniques including ultrasonography or magnetic resonance imaging are not routinely utilized, radiographs may be used for showing heel spurs and facilitates

the exclusion of other diseases such as metastatic involvement of the bone.

Over a decade after its first description, several therapeutic modalities have been used for the management of painful heel spur and plantar fasciitis. Modification of life style to prioritize resting, losing weight and avoiding from intensive physical workload, analgesics, cold compresses, iontophoresis, antiinflammatory agent and steroid injections, stretching exercises and physical therapy, laser, microwave, ultrasound therapy, orthotics and shoe modifications, foot orthoses and insoles, heel pads, efforts to decrease pressure on the affected site, orthopedic interventions, and radiation therapy (RT) are among the methods for eradicating or alleviating pain from heel spur and plantar fasciitis (8-10). The use of foot orthoses and insoles may result in functional improvement and reduction of pain from plantar fasciitis and heel spurs (9,10).

RT has a long history in the management of painful heel spur and plantar fasciitis. Accumulated data from several centers have consistently reported effective palliation of painful plantar fasciitis and heel spur; however, dose fractionation schemes and treatment fields may vary among the institutions and are typically based on retrospective data and experiences (2,11-26).

In this study, we report our single center experience with RT for painful heel spur and plantar fasciitis management over a period of 45 years and describe patient and treatment characteristics including RT dose, fractionation, target volume, and pain response.

Methods

This retrospective study was conducted in accordance with the Code of Ethics of the World Medical Association, Declaration of Helsinki principles, and Uniform Requirements for manuscripts submitted to medical journals with the approval of Gülhane Faculty of Medicine, Radiation Oncology Department (date: 07.02.2020).

Informed consents of all patients were taken before RT.

A total of 4904 patients with painful heel spur and plantar fasciitis were treated at our institution over a period of 45 years between 1974 and 2019. All patients were referred for refractory painful heel spur and plantar fasciitis and had received previous medications including analgesics, cold compresses, iontophoresis, antiinflammatory agent and steroid injections, stretching exercises and physical therapy, laser, microwave, ultrasound therapy, orthotics and shoe modifications, heel pads, efforts to decrease pressure on the affected site and orthopedic interventions before RT. If available, imaging data of the patients were assessed for precise localization of plantar heel spur as shown in Figure 1.

Patient and treatment characteristics such as age, gender, RT dose and fractionation, toxicity and response to treatment were analyzed. Response to RT was stratified as no response, partial response, and complete response. Patients were simulated at X-ray 2D (dimensional) simulator available at our department. After 2D simulation for the designation of treatment portals and marking of the treatment fields on the patients' heels with permanent markers, setup of the patients was performed at cobalt-60 (Co-60) teletherapy unit with both soles apposing as shown on Figure 2. Total RT dose was 8 Gy delivered in 2 fractions using 2 opposing anterior-posterior (AP/PA) RT fields to both heels without bolus material (Figure 2). Treatment response was assessed 3 to 5 weeks after the completion of RT.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL) software (version 15.0) was used for analysis.

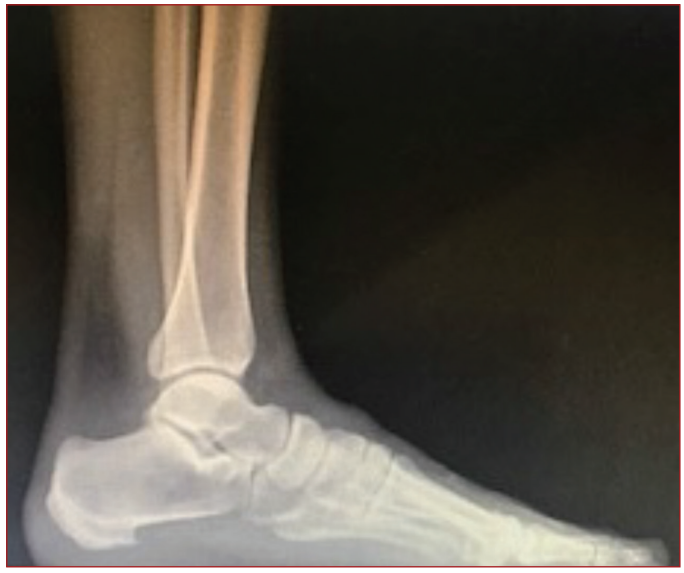

Figure 1. Plantar heel spur of a patient shown on radiograph

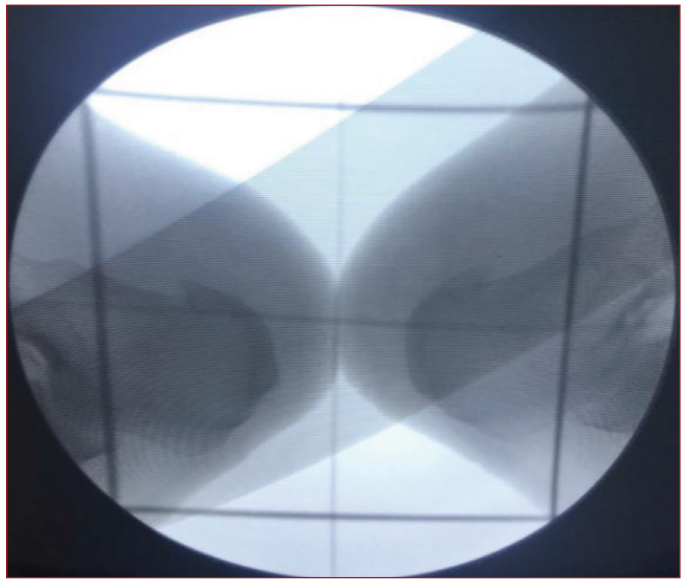

Figure 2. 2D simulation image showing treatment portal including bilateral heel spur

Descriptive statistics were used for the description of basic features of data in our study.

Results

Between 1974 and 2019, 4904 patients received RT for the management of refractory painful heel spur and plantar fasciitis. All patients were treated at our department using Co-60 teletherapy machine for refractory painful plantar fasciitis or heel spur. Patient characteristics, treatment characteristics and response are shown on Table 1 and Table 2, respectively.

Out of the total 4904 patients, 2012 patients (41%) were male and 2892 patients (59%) were female. The median age was 51 (range: 41-85) years. All patients had received previous therapies for painful plantar fasciitis or heel spur before RT. Total RT dose was 8 Gy delivered in 2 consecutive days with daily fractions of 4 Gy using 2 opposing AP/PA RT fields to both heels without bolus material. Treatment response was assessed 3 to 5 weeks after the completion of RT. Treatment response was complete in 3579 patients (73%), partial in 1188 patients (24.2%), and none in 137 patients (2.8%). No therapy-related toxicity was observed in the whole series.

Table 1. Patient characteristics

Patient characteristic	Number	%
Number of patients	4904	100
Male	2012	41
Female	2892	59
Median age (range)	51 (41-85) years	
Diagnosis		
Painful plantar fasciitis/heel spur	4904	100
Use of previous therapies	4904	100

Table 2. Treatment characteristics and response

Indication for RT Refractory painful plantar fasciitis/heel spur	4904 patients	100
RT dose per fraction	4 Gy	100
Total number of RT fractions	2	100
Total RT dose	8 Gy	100
Treatment length	2 consecutive days	100
Treatment modality EBRT	4904 patients	100
Treatment machine Co-60	4904 patients	100
RT technique Two opposing AP/PA RT fields including bilateral heels	4904 patients	100
Time period for treatment response assessment 3 to 5 weeks after completion of RT	4904 patients	100
Treatment response		
Complete response	3579 patients	73
Partial response	1188 patients	24.2
No response	137 patients	2.8

RT: Radiation therapy, EBRT: External beam radiation therapy, AP/PA: Anterior-posterior, Co-60: Cobalt-60

Discussion

Our study comprises a large series of patients treated over a long period of 45 years at a tertiary referral institution. Our single center experience confirms the efficacy of RT with Co-60 teletherapy machine for the management of refractory painful heel spur and plantar fasciitis.

Plantar heel spur has been defined as an exostotic bone formation localized at the insertion site of plantar fascia (1,12). While there is no established preponderance for gender in the literature, our series of 4904 total patients included more female patients than male patients. Typical age of presentation is over 40 years, which is consistent with our study population having a median age of 51 (range: 41-85) years. Affected patients may suffer from stinging and severe heel pain with potential gait and mobility disturbances accompanied by worsened quality of life. Repetitive microtraumas with resultant damage of the plantar aponeurosis and muscle insertions by excessive stress on the heels may have role in pathogenesis (27). Increased straining may stem from intensive sport activities, foot deformities, increased body weight, and working on hard surfaces (2-4,12,27-29). A plethora of treatments have been used for the management including modification of life style to prioritize resting, losing weight and avoiding from intensive physical workload, analgesics, cold compresses, iontophoresis, antiinflammatory agent and steroid injections, stretching exercises and physical therapy, laser, microwave, ultrasound therapy, orthotics and shoe modifications, heel pads, efforts to decrease pressure on the affected site, orthopedic interventions, and RT.

Traditionally, RT has been reserved for refractory cases due to concerns about adverse radiation effects such as carcinogenesis (15). While several countries in Europe have adopted RT for the management of several benign conditions including musculoskeletal, degenerative, and inflammatory disorders with encouraging treatment outcomes, the use of RT for nonmalignant benign conditions have been considered skeptical as well by several centers (15,30-34). Besides its utility in the management of several cancers throughout the whole human body, ionizing radiation may induce mutations and carcinogenesis. However, no carcinogenesis was reported in our series, and decision making for management with RT should be individualized based on a harm to benefit ratio (35). Mechanism of action for RT has been extensively studied, and may be possibly through modulating the intensity of inflammation along with possible neurolysis of the sural and posterior tibial nerves

responsible for dominant pain through the obstruction of the capillaries nourishing these nerves (8,15,16,36-38).

Several trials have been conducted to assess the utility of low dose irradiation in the management of heel spur and plantar fasciitis (11-26). While the exact mechanism of pain relief by irradiation is an area of research, RT may also induce a placebo effect in some patients (24). In terms of dose and fractionation, there is no standard fractionation scheme for the irradiation of painful heel spur and plantar fasciitis. Several dose-fractionation schemes have been evaluated, and total delivered doses in the range of 3 to 12 Gy have been found to be effective (24). In the study by Seegenschmiedt et al. (11), 3 dose-fractionation schemes were comparatively assessed, and 10x0.5 Gy to a total dose of 5 Gy was reported to be superior than 10x0.3 Gy to a total dose of 3 Gy and 12x1 Gy to a total dose of 12 Gy in terms of pain relief. In the retrospective study by Mücke et al. (12) assessing low dose irradiation for the management of painful heel spur in 117 patients, over 80% of the patients benefited from RT. The authors suggested commencing RT within 6 months of symptom onset to achieve effective pain palliation (12). Micke et al. (13) reported the results of a national patterns of care study from German. The study included a very high number of cases treated with RT for painful heel spur syndrome in several centers of Germany, and confirmed the safety and efficacy of irradiation for this indication (13). Complete relief of pain over 3 months has been achieved in median 70% (range: 25%-100%) of all treated patients (13). Persisting pain relief for at least 1 year has been reported in median 65% (range: 19%-99%) of the patients (13). The median percentage of patients without symptomatic improvement was 15% (range: 5%-50%), and no toxicity or secondary cancers have been reported during the follow-up period (13). Vast majority of radiation oncologists participating in the national survey has considered RT as a viable and essential treatment indication for painful heel spur syndrome (13). Schwarz et al. (14) assessed the use of single fraction RT for heel spur and plantar fasciitis, and concluded that irradiation with single fraction might be further investigated in future trials. Heyd et al. (16) prospectively evaluated 130 patients in a randomized study and found comparable results with both fractionation schemes of 6x0.5 Gy and 6x1 Gy. In a study by Niewald et al. (19), two fractionation schemes of 6x1 Gy and 6x0.1 Gy were comparatively assessed, and a total dose of 6 Gy delivered in 6 fractions of 1 Gy each was found to achieve superior pain relief than 6x0.1 Gy. Hermann et al. (20) assessed the effect of field size and plantar spur length on the outcome of RT for plantar fasciitis management. They reported that patients with short heel spurs benefited from RT equally as patients with no radiological evidence of spur (20). Also, they reported that the use of smaller field sizes was also effective and could be used for minimizing exposure of normal tissues (20). Koca et al. (21) reported the results of 62 patients treated using a Co-60 teletherapy machine. Their series of 62 patients included 53 female and 9 male patients with female preponderance consistent with our series (21). With a total dose of 8 Gy, response to RT was reported to be no response in 21%, partial response in 21%, and complete response in 58% of the total 62 patients (21).

Although irradiation for painful heel spur and plantar fasciitis has been considered as a last resort treatment traditionally, there is accumulating data supporting the utility of RT for the management of pain from heel spur and plantar fasciitis (2,11-26). Our study adds to the literature with high number of patients treated using a standard treatment machine and uniform dose-fractionation scheme at a single institution over 45 years. Since our results reveal satisfactory pain relief by the use of RT without treatment-related toxicity and secondary malignancies in accordance with the literature, we conclude that RT is safe and effective for the management of refractory painful heel spur and plantar fasciitis management. Clearly, comparative evaluation of different modalities for this indication in future studies may shed light on optimal decision making for the management of patients with painful heel spur and plantar fasciitis.

Conclusion

Our single center experience confirms the efficacy of RT for the management of refractory painful heel spur and plantar fasciitis. RT offers a non-invasive treatment modality and should be considered as a viable therapeutic option for this indication. Without downsizing of the spur, RT achieves effective pain relief which is a major cause of deterioration in quality of life. Future studies are warranted to assess the comparative efficacy of different modalities in the management of painful heel spur and plantar fasciitis.

Ethics

Ethics Committee Approval: This retrospective study was conducted in accordance with the Code of Ethics of the World Medical Association, Declaration of Helsinki principles, and Uniform Requirements for manuscripts submitted to medical journals with the approval of Gülhane Faculty of Medicine, Radiation Oncology Department (date: 07.02.2020).

Informed Consent: Informed consents of all patients were taken.

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Which treatment protocol is better in rehabilitation of joint contracture?

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ABSTRACT

Aim: To investigate demographic features, treatment response and factors affecting improvement in patients with joint contracture.

Methods: Three hundred sixty-one in patients with decreased range of motion were included in this retrospectively observational study. The demographic and clinical characteristics of patients were recorded. According to the physical therapy modalities, patients were divided into three subgroups. All patients received conventional therapy, which consisted of hot pack, therapeutic ultrasound, and stretching exercises. In addition to the conventional therapy, transcutaneous electrical nerve stimulation (TENS) was applied to the patients in group A, hydrotherapy (whirlpool) to the patients in group B, TENS and hydrotherapy to the patients in group C.

Results: There were 130 (36%) knee, 66 (18.3%) ankle, 58 (16.1%) elbow, 49 (13.6%) wrist, 40 (11.1%) shoulder, and 18 (5%) hip joint cases. Patients had statistically significant improvements of all decreased joint range of motion ($p<0.001$). Therapy of more than 30 sessions improved only knee flexion and wrist extension significantly. A negative correlation was detected between age and the difference in wrist extension ($r=-0.324$, $p=0.023$). Improvements of knee flexion and elbow flexion were significantly better in the acute group than in subacute and chronic groups ($p=0.03$, $p=0.036$). There was no statistically significant difference in range of motion of the elbow between the patients who used and those who did not use an adjustable elbow contracture orthosis. There was no statistically significant difference between the treatment protocols.

Conclusion: Therapy of more than 30 sessions is useful for only knee flexion and wrist extension contracture. Adding TENS or hydrotherapy have no additional benefit on conventional treatment.

Introduction

Contracture is the molecular shortening of connective tissue. Joint contracture is characterized by limited range of motion secondary to periarticular connective tissue changes (1). Multiple factors are associated with posttraumatic joint contracture most importantly occurring with pain, prolonged joint positioning (immobility), adhesions, heterotopic bone formation, joint incongruity and periarticular connective tissue changes (2). Upper limb joint contractures may lead to loss of ability to dress or to eat independently. Lower limb contractures may lead to imbalance and the inability to walk unaided with the consequent higher risk of being housebound or confined to bed (3). Also, joint contractures increase the risk of pain, pressure ulcers and fall. The main aim of improving range of motion is to reduce

impairments, to increase function for the daily life activities and work and leisure activities and to prevent long term disability (1,3). Therapeutic considerations in the treatment of joint contractures include safety, efficacy, availability, cost, and time. Therapy modalities for the management of joint contracture include passive stretching, splinting, application of serial plasters, joint mobilization, injection of botulinum toxin, electrical stimulation, and surgical manipulations (1,4).

Joint contracture is a common problem in physical medicine and rehabilitation or orthopedic practices. However, there have been few studies which have investigated the management and long-term follow-up results of orthopedic joint contracture rehabilitation (5-7). In this retrospective study, the data on inpatients with joint contracture are presented and it was aimed to define the factors which affected rehabilitation outcomes. This study enlightens optimal therapy methods, therapy time, therapy period and other factors that can affect the outcomes in patients with joint contracture.

Methods

Approval of the Local Research Ethics Committee of our tertiary hospital was obtained before initiating the study (Gülhane Training and Research Hospital, January 02, 2013, 12th session). The research protocol complies with the Declaration of Helsinki and written informed consent was obtained from all participants.

In our study, we retrospectively evaluated the medical records of inpatients with decreased range of motion who were treated between January 2009 and January 2013. Patients with any central or peripheral nervous system disorder, primary muscle disease, congenital malformation, systemic arthritis, systemic or metabolic disease or burn were excluded.

This study was designed as a retrospective observational study in our national tertiary rehabilitation center. The medical records of the inpatients were obtained from the electronic database of our hospital. The demographic and clinical characteristics including the patient's age, gender, etiology of joint contracture, duration of disease, presence of fractures and fixator, range of motion before and after treatment, number of physical therapy sessions, use of orthotics, and type of physical therapy were evaluated. Passive range of motion was measured with a goniometer by the neutral zero method. Comparison between subgroups was performed. Time to the initiation of treatment was classified into three subgroups as follows; acute period (first 3 months of disease onset), subacute period (3-6 months) and chronic period (>6 months). According to the number of therapy sessions, patients were divided into two subgroups as follows; group 1 (up to 30 sessions) and group 2 (more than 30 sessions). Also, according to the physical therapy modalities, patients were divided into three subgroups. All patients received conventional therapy, which consisted of hot pack, therapeutic ultrasound, stretching exercises. In addition to the conventional therapy, transcutaneous electrical nerve stimulation (TENS) was applied to the patients in group A, hydrotherapy (whirlpool) to the patients in group B, and TENS and hydrotherapy to the patients in group C. Physiotherapists applied stretching exercises manually for 20 minutes per therapy session. The contracted joint was stretched until the patient felt discomfort, but not pain. Stretching was sustained for at least 20 seconds. TENS was administered for 20 minutes in each therapy session. The amplitude was increased until the patient felt a comfortable tingling sensation without motor contraction. Conventional TENS mode was used at high frequency and low intensity. The effects of the therapy session number and the physical therapy modalities on the rehabilitation outcomes were evaluated. An assessment was also made on the benefit of contracture orthosis in the management of elbow contracture.

Statistical Analysis

Statistical Package for Social Science (SPSS) version of 16.0 was used for analysis. (SPSS, Inc., Chicago, IL). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov, Shapiro-Wilk's test) to determine whether or not they were normally distributed. The Wilcoxon test was used to compare range of motion measurements before and after treatment. The Mann-Whitney U test was applied in the comparison of differences in range of motion according to therapy sessions. The Kruskal-Wallis test was used to compare measurements according to therapy groups and duration of the disease. The Mann-Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. While investigating the associations between non-normally distributed variables, the correlation coefficients and their significance were calculated using the Spearman test. A value of $p<0.05$ was considered statistically significant.

Results

Medical records of 423 inpatients with joint contracture were assessed for inclusion. Sixty-two patients were excluded due to concomitant peripheral nerve injury (n=24), incomplete medical records (n=13), traumatic brain injury (n=11), burn (n=9), and primary muscle disease (n=5). A total of 361 inpatients (10 female, 351 male) who were treated for joint contracture related to orthopedic conditions were included in this study. There were 130 (36%) knee, 66 (18.3%) ankle, 58 (16.1%) elbow, 49 (13.6 %) wrist, 40 (11.1 %) shoulder, and 18 (5%) hip joint cases. The mean age was 27.3±8.0 years. Most of the contractures were due to fall (39.6%). Other etiologies of joint contracture were as follows; strain 80 (22.1%), motor vehicle collision (inside vehicle) 45 (12.5%), gunshot wound 40 (11.1%), motor vehicle collision (outside vehicle) 26 (7.2%), crush injury 13 (3.6%), knife wound 10 (2.8%), malignancy 3 (0.8%), infection 1 (0.3%). The median

therapy period was 49.0 (minimum: 7.0; maximum: 300.0) days, 115 patients (31.9%) received up to 30 sessions therapy and 246 patients (68.1%) received more than 30 sessions.

According to range of motion before and after treatment, statistically significant improvements were determined in all joints with decreased range of motion (except hip internal and external rotation, Wilcoxon test) (Table 1). In terms of the number of sessions, therapy of more than 30 sessions resulted in significant improvements only in knee flexion and wrist extension (p<0.001, p=0.016 respectively, Mann-Whitney U test) (Table 2). Correlations between age and joint range of motion improvements were also assessed and a negative correlation was detected only between age and wrist extension (r=-0.324, p=0.023, Spearman test) (Table 3). No statistically significant difference was determined in range of motion between the groups in respect of the fracture and/or fixator (p>0.05, Mann-Whitney U test). Improvements in knee flexion and elbow flexion in patients who initiated therapy in acute period were significantly better than in other groups (p=0.03, p=0.036 respectively, Kruskal-Wallis test).

Twenty-three of 58 patients with elbow contracture used contracture orthosis. The median change in elbow flexion was 15 degree (minimum: 0, maximum: 60) in the patient group who used an adjustable elbow contracture orthosis and 10 degree (minimum: 0, maximum: 55) in the patient group who did not use. The median change in elbow extension was 10 degree (minimum: -10, maximum: 40) in the patient group who used contracture orthosis and 5 degree (minimum: 0, maximum: 60) in the patient group who did not use. Although changes in elbow flexion and extension degree tended to be higher in patients who used an adjustable elbow contracture orthosis than who did not use, this difference was not statistically significant (p>0.05, Mann-Whitney U test). The median changes in elbow pronation and supination degree were 10 degree, there was no statistically significant difference (p>0.05, Mann-Whitney U test).

According to the therapy groups, 109 (30.2%) patients were in group A, 138 (38.2%) patients were in group B, and 114 (31.6%) were in group C. There was no statistically significant difference among the treatment protocols of group A, B and C (all p>0.05, Kruskal Wallis test) (Table 4).

Discussion

This study on 361 inpatients investigated the long-term results of joint contracture rehabilitation. Statistically significant improvement was achieved in all joints and more than 30 treatment sessions provided beneficial effects that increased knee flexion and wrist extension. It has been previously suggested that the knee and the elbow joints are more prone to contracture, especially after injury or surgery (8). Concordant with these data, in our study, the joint most affected by

Table 1. Difference in range of motion

Joint	Motion	Before treatment	After treatment	p value
Shoulder (n=40)	Flexion	110,0 (40.0;180,0)	160.0 (45.0;180.0)	<0.001
	Abduction	90.0 (40.0;160.0)	155.0 (50.0;180.0)	<0.001
	Internal rotation	70.0 (10.0;90.0)	90.0 (45.0;90.0)	<0.001
	External rotation	60.0 (10.0;90.0)	90.0 (20.0;90.0)	<0.001
Elbow (n=58)	Flexion	110.0 (55.0;140.0)	130.0 (65;150.0)	<0.001
	Extension	-30.0 (-60.0;0.0)	-12.50 (-60.0;0.0)	<0.001
	Supination	80.0 (10.0;90.0)	90.0 (0.0;90.0)	<0.001
	Pronation	80.0 (10.0;90.0)	90.0 (0.0;90.0)	<0.001
Wrist (n=49)	Extension	40.0 (0.0;80.0)	65.0 (0.0;90.0)	<0.001
	Flexion	40.0 (0.0;80.0)	75.0 (0.0;90.0)	<0.001
Hip (n=18)	Flexion	90.0 (40.0;120.0)	115.0 (60.0;120.0)	<0.001
	Abduction	45.0 (45.0;45.0)	45.0 (45.0;45.0)	<0.001
	Internal rotation	25.0 (0.0;45.0)	27.5 (0.0;45.0)	0.619
	External rotation	27.5 (10.0;45.0)	32.5 (10.0;45.0)	0.223
	Extension	15.0 (15.0;45.0)	20.0 (20.0;30.0)	0.025
Knee (n=130)	Flexion	90.0 (15.0;135.0)	130.0 (5.0;140.0)	<0.000
	Extension	0.0 (-30.0;130.0)	0.0 (-25.0;0.0)	<0.001
Ankle (n=66)	Dorsiflexion	5.0 (-20.0;20.0)	10.0 (0.0;20.0)	<0.001
	Plantar flexion	30.0 (5.0;50.0)	40.0 (10.0;50.0)	<0.001

Data were presented as median (minimum; maximum). Wilcoxon test was used.
n: the number of patients

contracture in the lower extremities was the knee and that in the upper extremities was the elbow.

In daily practice, joint contracture, which is defined as a limitation of range of motion, is one of the most frequently encountered disorders in clinics of orthopedic and physical medicine and rehabilitation. Posttraumatic joint contractures, which are secondary to changes in joint structures, can be classified as intrinsic or extrinsic contractures. Knowledge of the affected structure in the joint contracture is essential for good management of contractures (9). Joint contracture is a sequel of trauma and it results from a combination of injury-related, diagnostic-related and therapy-related factors. Rehabilitation programs have an important role in obtaining the optimal range of motion, attaining independence in daily living activities and back to work (10).

In the current study, no statistically significant difference was found between the groups in respect of the treatment protocols. Therefore, the results of the current study suggest that conventional therapy is the most important part of the treatment. In a systematic review by Harvey et al. (7), it is reported that conventional therapy (stretching) provides an increase in joint range of motion. In the current study, although TENS and hydrotherapy results showed no statistical significance, there were improvements in these treatment groups but level of improvement did not reach a significant level. Future prospective studies may be helpful to assess the exact benefit of these traditional therapy methods.

Stretch is widely used for the treatment and prevention of contractures. Stretch can be administered with splints or serial casting. Also, stretch can be self-administered or applied manually by therapists. In addition to conventional physical therapy for contractures, dynamic and static splinting modalities are frequently applied (11-14). Furia et al. (6) reviewed the effects of dynamic splinting and reported that dynamic splinting was associated with improvements in joint range of motion. The most used dynamic splint among the participants of this study was elbow contracture orthosis. These patients gained more elbow flexion but the difference from the patients

Table 2. Comparison of range of motion differences according to therapy sessions

Joint	Motion	≤30 session	>30 session	p value
Shoulder		**n=17**	**n=23**	
	Flexion	40.0 (0.0;100.0)	50.0 (0.0;100.0)	>0.05
	Abduction	40.0 (5.0;120.0)	50.0 (0.0;130.0)	>0.05
	Internal rotation	10.0 (0.0;80.0)	15.0 (0.0;60.0)	>0.05
	External rotation	10.0 (0.0;80.0)	10.0 (0.0;60.0)	>0.05
Elbow		**n=6**	**n=42**	
	Flexion	5.0 (0.0;40.0)	10.0 (0.0;60.0)	>0.05
	Extension	5.0 (0.0;10.0)	10.0 (-10.0;60.0)	>0.05
	Supination	7.5 (0.0;20.0)	10.0 (-90.0;60.0)	>0.05
	Pronation	5.0 (0.0;80.0)	10.0 (-90.0;60.0)	>0.05
Wrist		n=17	n=32	
	Extension	10.0 (0.0;50.0)	20.0 (0.0;90.0)	0.016
	Flexion	20.0 (0.0;75.0)	15.0 (-5.0;70.0)	>0.05
Hip		**n=5**	**n=13**	
	Flexion	12.5 (0.0;65.0)	20.0 (0.0;60.0)	>0.05
	Abduction	5.0 (0.0;10.0)	5.0 (0.0;10.0)	>0.05
	Internal rotation	7.5 (0.0;20.0)	0.0 (-30.0;5.0)	>0.05
	External rotation	7.5 (0.0;10.0)	0.0 (-25.0;10.0)	>0.05
	Extension	5.0 (5.0;5.0)	5.0 (0.0;5.0)	>0.05
Knee		**n=40**	**n=90**	
	Flexion	20.0 (-20.0;60.0)	40.0 (-125.0;115.0)	<0.001
	Extension	1.0 (0.0;10.0)	1.1 (-130.0;25.0)	>0.05
Ankle		**n=20**	**n=46**	
	Dorsiflexion	5.0 (0.0;40.0)	5.0 (-20.0;20.0)	>0.05
	Plantar flexion	10.0 (0.0;40.0)	10.0 (-25.0;40.0)	>0.05

Data were presented as median (minimum; maximum). Wilcoxon test was used.
n: the number of patients

without contracture orthosis was not statistically significant. In the literature, there are studies that use different splinting protocols (1,15). In the literature, at least 30-60 min of splint use was recommended and we used splinting for at least 2 hours (16). Some positive outcomes, including increased range of motion, improved patient satisfaction and reduced use of pain medication, were shown by some researchers (17-20). No significant difference in improvement in motion between static progressive and dynamic splinting protocols was reported by another prospective study (21). According to a recently published review, authors concluded that stretch did not have clinically important effects on joint mobility in people with or without neurological conditions if performed for less than seven months. In addition, stretch did not have clinically important short-term effects on the quality of life or pain in people with non-neurological conditions (22). Similarly, the later meta-analyses of randomised trials by the same authors showed that stretch did not have clinically important effects on joint mobility (23).

A negative correlation was determined between age and increasing range of motion in wrist extension in this study. This result seems to be expected because younger patients are prone to show better results due to elastic properties (24). But among all measured parameters, this result was present in only one joint and therefore this correlation should be carefully taken into consideration.

In the literature, there are emerging data that recommend early diagnosis and treatment of contractures (25). Similarly, according to the current results, early initiation of treatment was seen to be an important factor in achieving better rehabilitation outcomes. The improvements in knee and elbow flexion were remarkable particularly in patients who started therapy in acute period of the disease.

The major limitation of this study is the retrospective design. The number of treatment groups was not distributed equally. Also, there were many different etiologies, all of which could influence outcome. Lack of data about duration of contracture was another limitation of the study. However, to the best of our knowledge, there has been no previous study, which has included all joints with a long therapy duration and long follow-up period. Therefore, the results of this study may be of importance in guiding physical rehabilitation teams.

Conclusion

In conclusion, joint contracture or decreased range of motion is one of the most frequently seen problems in physical medicine and rehabilitation practice. Also, it is one of the most frequent orthopedic problems to complicate back to work generally. However, the literature about this period has been very poor. Therapy of more than 30 sessions is useful for only knee flexion and wrist extension contracture. Adding TENS or hydrotherapy has no additional benefit on conventional treatment.

Table 3. Correlations between age and joint range of motion differences

Joint	Motion	r	p
Shoulder (n=40)	Flexion	0.095	>0.05
	Abduction	0.190	>0.05
	Internal rotation	0.267	>0.05
	External rotation	0.167	>0.05
Elbow (n=58)	Flexion	-0.168	>0.05
	Extension	0.246	>0.05
	Supination	-0.251	>0.05
	Pronation	-0.174	>0.05
Wrist (n=49)	Extension	-0.314	0.023
	Flexion	-0.090	>0.05
Hip (n=18)	Flexion	0.300	>0.05
	Internal rotation	0.199	>0.05
	External rotation	-0.410	>0.05
	Extension	0.118	>0.05
Knee (n=130)	Flexion	-0.045	>0.05
	Extension	-0.043	>0.05
Ankle (n=66)	Dorsiflexion	-0.059	>0.05
	Plantar flexion	-0.088	>0.05

Spearman test was used.
n: the number of patients

Table 4. Comparison of range of motion differences according to therapy groups

Joint	Motion	Group A	Group B	Group C	p value
Shoulder		**n=10**	**n=14**	**n=16**	
	Flexion	30.0 (0.0;60.0)	50.0 (0.0;100.0)	40.0 (0.0;100.0)	>0.05
	Abduction	30.0 (0.0;90.0)	50.0 (0.0;120.0)	40.0 (5.0;130.0)	>0.05
	Internal rotation	10.0 (0.0;20.0)	15.0 (0.0-80.0)	10.0 (0.0;60.0)	>0.05
	External rotation	20.0 (0.0;30.0)	15.0 (0.0-80.0)	10.0 (0.0;60.0)	>0.05
Elbow		**n=15**	**n=25**	**n=18**	
	Flexion	10.0 (0.0;10.0)	10.0 (0.0,55.0)	20.0 (5.0;60.0)	>0.05
	Extension	5.0 (0.0;30.0)	10.0 (-10.0;60.0)	10.0 (-10.0;40.0)	>0.05
	Supination	5.0 (0.0;10.0)	10.0 (-90.0;60.0)	10.0 (0.0;50.0)	>0.05
	Pronation	5.0 (0.0;15.0)	5.0 (-90.0;80.0)	10.0 (0.0;30.0)	>0.05
Wrist		**n=11**	**n=23**	**n=15**	
	Extension	0.0 (0.0;5.0)	20.0 (0.0;90.0)	20.0 (0.0;90.0)	>0.05
	Flexion	0.0 (0.0;0.0)	20.0 (-5.0;75.0)	27.5 (0.0;65.0)	>0.05
Hip		**n=6**	**n=7**	**n=5**	
	Flexion	37.5 (10.0;65.0)	20.0 (0.0;60.0)	20.0 (5.0;30.0)	>0.05
	Abduction	5.0 (0.0;10.0)	5.0 (0.0;10.0)	5.0 (0.0;10.0)	>0.05
	Internal rotation	-10.0 (-20.0;0.0)	5.0 (0.0;10.0)	0.0 (-30.0;20.0)	>0.05
	External rotation	-12.5 (-25.0;0.0)	10.0 (0.0;10.0)	0.0 (0.0;10.0)	>0.05
	Extension	5.0 (5.0;5.0)	5.0 (5.0;5.0)	2.5 (0.0;5.0)	>0.05
Knee		**n=47**	**n=44**	**n=39**	
	Flexion	20.0 (5.0;35.0)	30.0 (-125.0;115.0)	35.0 (-20.0;110.0)	>0.05
	Extension	5.0 (0.0;10.0)	0.0 (-130.0;25.0)	0.0 (0.0;20.0)	>0.05
Ankle		**n=20**	**n=25**	**n=21**	
	Dorsiflexion	10.0 (-5.0;10.0)	7.5 (-20.0;40.0)	2.5 (-15.0;10.0)	>0.05
	Plantar flexion	10.0 (5.0-10.0)	10.0 (-25.0;40.0)	10.0 (0.0;40.0)	>0.05

Data were presented as median (minimum; maximum). Kruskal-Wallis test was used.
n: the number of patients

Ethics

Ethics Committee Approval: Approval of the Local Research Ethics Committee of our tertiary hospital was obtained before initiating the study (Gülhane Training and Research Hospital, January 02, 2013, 12th session).

Informed Consent: The research protocol complies with the Declaration of Helsinki and written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Validation of the outcomes tools for urinary incontinence in Nursing Outcomes Classification system and their sensitivities on nursing interventions

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ABSTRACT

Aim: There are many scales to measure urinary incontinence (UI). Nursing Outcomes Classification (NOC) scales which include Urinary Continence, Urinary Elimination, Self-Care Toileting, Medication Response, and Tissue integrity: Skin and Mucous Membranes are ideal for use in the nursing process for comprehensive and holistic assessment, with surveys available. For this reason, the purpose of this study is to evaluate the validity of these NOC outcomes and indicators used for UI.

Methods: This research is a methodological study. Scope validations were applied and calculated according to Fehring 1987 work model. Total of 55 experts which were the sample of the study rated Fehring as a "senior degree" with a score of 90 according to the experts' scoring. These weighted scores obtained for NOC indicators were classified as critical, supplemental or excluded.

Results: In the NOC system, 5 NOCs proposed for nursing diagnosis of UI were proposed. These outcomes are; Urinary Continence, Urinary Elimination, Tissue Integrity, Self Care-Toileting, and Medication Response. After the scales were translated into Turkish, the weighted average of the scores was obtained from specialists for the coverage of all 5 NOCs. After getting the experts' opinion, 79 of the 82 indicators were calculated as critical, 3 of the indicators were calculated as supplemental. All NOCs were identified as valid and usable scales in Turkey.

Conclusion: The five NOCs were verified for the evaluation of the output of individuals who received nursing knowledge of UI and variant types. Recommendations include the testing of NOC outcomes in clinical practice and inclusion in nursing curriculum.

Introduction

Nurses perform the nursing care plan and then assess the executed plan in a systematic process (1). In literature, it is stated that in this systematic process, the results improve their objectivity and accuracy if they use the classification systems while considering a client's health condition and revealing his/her needs (2). These classification systems provide the coding of the data, inserting them into databases as systematized and certifying the nursing process. In this process, they allow the nurses to give the right decision making, to assess with quantitative data and to select the accurate interventions (3).

Among many of the nursing classification systems that are constituted for international usage, NANDA-I in making diagnoses, Nursing Outcomes Classification (NOC) in assessing severity of the issue and patient outcomes and Nursing Interventions Classification (NIC) for nursing interventions are the most used classification systems (4-7). NANDA-I is used actively in Turkey during both nursing education and practice, but NIC and especially NOC systems are not used during education and execution yet (7).

NOC, developed by Iowa University Research team in 1991, is a standard classification system that allows nurses to assess

the patients' before and aftercare status and changes. First NOCs are published in 1997. NOC consists of 7 domains and 31 classes. Each NOC has a code in the taxonomic structure. Lastly, a total of 540 NOCs were published including 52 new ones in 2018. Each NOC has 5 of Likert type scales. In all of the scales, the least wanted state is indicated by the number 1, the most wanted state is indicated by the number 5. In the scales, the point calculation is done through the total point average. Each scale has a different number of articles in itself. The scales should be used privately and in accordance with the need of the individual (2). Nursing care plans can be constituted with the combination of NANDA-I, NIC and NOC systems. In literature, these care plans are called as NNN linkages (5). The main purpose of this study is to be a model for the hospitals in Turkey and the caregivers in public and to provide the assessment of the nursing outcomes with NOC scales. In accordance with this purpose, it has been thought that doing the validities of some of the assessment scales can be a methodological tool in using these NOCs in the execution.

Urinary incontinence (UI) is the most common problem in the worldwide for among elderly, children, disabled ones, and dependent patients (8-11). Especially, it is very common in the aging process and also included in geriatric syndromes. UI is one of the most common one among these syndromes, frequently seen in nursing homes, living quarters, rehabilitation centers (43% to 77%) where elderly people live together (12,13). Although UI is a non-life threatening condition, it is a common health problem affecting the physical, social, work and educational activities of women and decreasing the quality of life (14). So, nurses have an important role to evaluate and improve UI. They need standard and systematic measurement criteria so that they can implement the right initiative. To measure UI, there are many scales and surveys (15-18). Beside them, NOC scales are ideal to be used in the nursing process for comprehensive and integrative assessment. Comprehensive assessment of UI-diseased individual regarding incontinence allows to indicate the incontinence type and therefore to provide accurate nursing care. For UI, NOC and NIC Linkages to NANDA-I and Clinical Conditions Supporting Critical Reasoning and Quality Care Book (page: 234-238) suggested eight NANDA-I Diagnoses (Urinary Elimination Impaired, Urinary Elimination Readiness for Enhanced, Urinary Retention, UI: Urge, UI: Functional, UI: Over Flow, UI: Stress, UI: Reflex), five NOC outcomes (Urinary Elimination, Self- Care Toileting, Urinary Continence, Medication Response, Tissue integrity: Skin and Mucous Membranes) include 92 indicators and 11 major NIC intervention/35 suggested NIC intervention (5).

Therefore, the purpose of this study was to evaluate the content validity and nursing sensitivity of the five incontinence outcomes included in the 5th edition of the NOC (2).

Research questions

1. Which of the five outcomes is most affected by nursing interventions?

2. Which of the outcomes is important for the nursing interventions?

Methods

Ethical issues

To execute the research, 50687469-1491-432-15/1648.4-1348 protocol numbered permission letter was taken from the Gülhane Military Medical Academy Ethics Committee. First of all, the research protocol was explained to each expert. After their written approval, scales were asked to score. Written and verbal consents were obtained before receiving opinions of the experts.

Study design

This study was designed methodologically to validate NOC scales, which can be used in the assessment of the conditions of the patients diagnosed with UI. In this study, it was also assessed by the experts how much the NOC Scales indicators contributed to the healing process after the nursing intervention.

Participants

Execution and calculation of extent validations were done according to the Fehring's work model (19). Expert nurses' inclusion criteria for the study were determined according to the Fehring's expertise criteria and the criteria of experts were scored (Table 1) (20-22). Including 9 nurses who were expert in the field of sampling, with master degree in a department related to incontinence (9 points), 24 academician nurses (48 points), 21 clinical nurses who used the nursing classification system for at least one year in the clinic (19 points) and an academician nurse with at least four years of clinical experience in urology (4 points), there were 55 experts in total. According to Fehring's expert scorings, these 55 experts scored 82 points and assessed as *Senior degree* (Table 1).

Outcome measures

In the assessment of NOCs that were used in collecting data for nursing diagnoses intended for UI, "NOC and NIC Linkages to NANDA-I and Clinical Conditions: Supporting Critical Thinking and Quality Care" guide, which was published in 2012, was used.

This NOC Scales are named as Urinary Continence, Urinary Elimination, Tissue Integrity, Self care-Toileting, and Medication Response. For the validation of these scales, the necessity/materiality of the NOCs and NOC indicators that were recommended for nursing diagnoses intended for UI and the level of contribution that nursing interventions to be executed provided in the healing of this indicators were asked to 55 experts in 2015.

According to the Fehring's model, it was asked to experts to score each of NOC and NOC indicators for arranged extent validation. For the necessity of these indicators, the scoring was described as: "1=not necessary, 2=slightly necessary, 3=necessary, 4=quite necessary and 5=very necessary". The scoring of the contribution of nursing interventions on these indicators was also assessed as: "1=no contribution, 2=slight contribution, 3=same contribution with other health personnel, 4=slightly more contribution than other health personnel, 5=full contribution" Before the data were collected, NANDA-1, NOC, NIC and NNN linkages systems' specifications, contents and their positions in nursing process were explained to the experts.

Statistical Analysis

SPSS 21.0 package program was used in the assessment of the data obtained in the research. The data were analyzed with descriptive statistics. For each NOC and NOC indicators, the scorings were calculated as follows: "1=0 points; 2=0.25 points; 3=0.50 points; 4=0.75 points; 5=1.00 point". After getting the expert opinion, these weighted points obtained for each NOC and NOC indicator were classified as "critical in >0.8 and supplemental in 0.8>, <0.5 and >0.5" was removed (23).

To assess the internal consistency between expert opinions, Cronbach alpha factors of all articles were assessed. If Cronbach alpha factor was between 0.00 and 0.39, then the test was assessed as not reliable, if between 0.40 and 0.59, then as quite reliable and if between 0.80 and 1.00, then as highly reliable (24).

Results

In NANDA-I system, in the third field named "elimination and exchange" and in the "urinary function" class, the nursing diagnoses of UI were published; 00019 urge UI, 00017 stress UI, 00018 reflex UI, 00020 functional UI, 00176 overflow UI, 00016 impaired urinary elimination, 00166 readiness for enhanced urinary elimination, 00022 risk for urge UI, 00023 urinary retention. 5 NOCs were recommended for these diagnoses. Extent validations of these 5 NOCs and weighted average of the expert scoring for the contribution of nursing interventions raised above 0.8 (Table 2).

Urinary continence outcome was defined as "control of elimination of urine from the bladder" and it consisted of 19 indicators (2). It evaluated the urinary continence with individual's responding to urge timely manner, void inappropriate receptacle, start and stop the stream, managing clothing independently, urine leakage between voiding, with increased abdominal pressure, wets clothing and urinary tract infection.

Table 1. Expert selection criteria and scoring

Criteria	Scoring	Number of experts	Scores for each expert
4 years of clinical experience in urology	4	1	**4**
Experience of at least one year in clinical teaching of the urology area and teaching of nursing classifications	1	21	**21**
Experience on research with articles published on nursing classification	1	-	-
Being joined at least 2 years to the research in the urology field	1	-	-
Having doctor's degree in nursing	2	24	**48**
Having master degree in a field related to incontinence	1	9	**9**
Having proficiency degree in nursing	1	-	-
Total	-	**55**	**82**

Table 2. Nursing Outcomes Validated as Critical and "Supplemental" for the Nursing Diagnosis of Acute Pain, with Weighted Ratios and Nursing Outcomes Classification Linkages to NANDA-I

Outcomes	Weighted ratio for content (CVI)*	Rank using outcomes content validity score	Weighted ratio for contributions of nursing interventions	Rank using outcome rating	Level of validation**	NNN linkages guideline***
Urinary Continence	0.94	4	0.95	4	**Critical**	**Major**
Urinary Elimination	0.95	2	0.95	3	**Critical**	**Major**
Tissue Integrity	0.92	5	0.92	5	**Critical**	**Major**
Self-care Toileting	0.96	1	0.96	2	**Critical**	**Major**
Medication Response	0.95	3	0.96	1	**Critical**	**Major**

*CVI: Content validity index.
**Critical=CVI >0.80; supplemental=CVI: 0.79-0.50; disposed=CVI <0.50.
***Major: Main outcome; suggested=recommended outcomes for measurement

Two of them ("Voids >150 milliliters each time" and "Manages clothing independently") were classified as "supplemental" and others as "critical". Besides, for average scoring taken after expert opinion regarding the contribution of "Manages clothing independently" indicator to interventions was calculated as 0.77, and as below 0.8, this indicator was identified as a "supplemental" indicator intended to contribute to nursing interventions (Table 3).

"Urinary Elimination" outcome was defined as "collection and discharge of urine" and consisted of 21 indicators (2). This NOC evaluated the urinary elimination with indicators which were elimination pattern, urine features as odor, amount, color, clarity, fluid intake status, the individual's ability to completely empty the bladder, types of incontinence as stress, urge, functional, urinary status as frequency, urgency, retention, nocturia, pain. All of the indicators in Urinary Elimination were classified as "critical" according to the experts' opinion.

"Tissue Integrity: Skin and Mucous Membranes" outcome was defined as "Structural intactness and normal physiological function of skin and mucous membranes" and it consisted of 22 indicators (2). Only "Hair growth on skin" indicator was classified as "supplemental" regarding its necessity and contribution to interventions. The other indicators were skin features as temperature, sensation, elasticity, hydration, perspiration, texture, thickness, integrity, tissue perfusion, hair growth on skin and abnormal pigment features as lesions, mucous membrane lesions, scar, erythema, blanching, necrosis, induration, corneal abrasion, skin cancers, flaking, scaling. All of them were evaluated as "critical".

"Self-Care-Toileting" outcome was defined as "Personal actions to toilet self independently with or without assistive device" and it consisted of 13 indicators (2). All of the indicators were classified as "critical" for the experts' opinion. They were patient's response to full bladder, response to urge to bowel movement in timely manner, patient's ability to get in and out of bathroom, to remove clothing, position seat on toilet or commode, to get toilet between urge and passage of urine, to get toilet between urge and evacuation of stool, to empty bladder and bowel, to wipe self after urinating and bowel movement, to get up from toilet or commode, to adjust clothing after to toileting.

"Medication Response" outcome was defined as "Therapeutic and adverse effects of prescribed medication" and it consisted of 10 indicators (2). All of the indicators in Self-care-Toileting outcome were classified as "critical" for the experts' opinion. They were therapeutic effects, change in blood chemistries and symptoms, behavioral, maintenance of expected blood levels allergic reaction, adverse effects, medication interactions, medication intolerance, and adverse behavioral effects.

Cronbach alpha factor calculated for internal consistency of the scorings given by the experts (n=55) was found to be above 0.80 (0.873-0.959) for 5 NOCs (Table 4).

As a result, 79 of the indicators were evaluated as critical and 3 of indicators as supplemental after expert opinion. These three indicators evaluated as supplemental are shown in Table 2. Besides, none of the articles was removed for not obtaining any scoring as 0.5>. All of NOC outcomes were identified as valid and usable scales in Turkey.

Discussion

All of 5 NOC outcomes were assessed as "critical" by the experts. These results have shown the importance of analyzing of the continence status, the urinary excretion status, the existence of skin lesions and the effects of self-care and medicine used in the nurses' assessment of individuals regarding UI. These outcomes can be used by the nurses to obtain comprehensive

Table 3. Indicators of the Nursing Outcomes Validates as "Supplemental" for the Nursing Diagnosis of Urinary Incontinence, with Weighted Ratios

Outcomes	Supplemental indicators	Weighted ratio for content (CVI)*	Weighted ratio for contributions of nursing interventions
Urinary Continence	Voids >150 milliliters each time	0.77	0.80
	Manages clothing independently	0.77	0.77
Tissue Integrity	Hair growth on skin	0.79	0.74

*CVI=Content validity index "supplemental"=0.79-0.50

Table 4. Nursing outcomes' Cronbach alpha coefficients for internal consistency

Outcomes	Cronbach alpha consistency	Coefficient of variation	Number of indicators
Urinary Continence	0.873	0.001	21
Urinary Elimination	0.959	0.002	19
Tissue Integrity	0.942	0.002	14
Self-care Toileting	0.902	0.001	13
Medication Response	0.949	0.000	8

and standard data in the assessment of the individual receiving nursing diagnosis of UI.

The indicators in the urinary continence outcome that assess the continence status of an individual like one's knowing of toilet need sense, not holding the urine after toilet need sense, urinary tract infection status, daily amount of liquid taken, knowing of the medicine that spoils urine control, going to toilet independently, urine leaking ways (as coughing, as sneezing, etc.) were assessed as critical. In the researches in which urinary continence status of individuals are assessed, not all but similar outcomes as incontinence type, medical drugs which effect urinary elimination, mobilizing, the status of infection have been questioned (23-26). "Voids >150 milliliters each time" and "Manages clothing independently" indicators' being assessed as "supplemental" by the experts may be for their thoughts of them being valid for elders and children and not being the indicators that appeal to the general population. Urinating more than 150 milliliters and addiction level have been emphasized as important factors in assessing the individual regarding UI (27,28).

The assessment of all of urinary elimination indicators as critical by the expert nurses shows us the importance of the assessment of each factor that fazes urinary tract infection, in parallel with the studies that assess the effectiveness of nursing interventions executed to UI-diseased individual (23,25).

In literature, there are study reports regarding the importance of perineal skin assessment of UI-diseased individuals, especially the ones using the diaper, and the big contribution of this assessment to selecting nursing interventions (29,30). In this study, the experts consider the indicators like skin temperature, sensation, elasticity, perspiration, skin integrity, skin cancer, skin lesion, skin scaling and necrosis valid as the indicators important to the assessment of skin integrity. However, in contrast to the literature, the indicator "Hair growth on skin" was assessed as supplemental. This case may be arisen from its being thought on the basis of children and this indicator not being considered as important as others for there not being hair growth on perineal skin in children.

The indicator of the Self-care-Toileting includes the relationship between people's incontinence status and self-care status (taking off the clothes before-after urinating, providing himself hygiene after urinating, addiction status, etc.) Experts accepted all indicators in Self-care-Toileting outcome valid as "critical" and stated that the assessment of these indicators provided a big contribution in selecting nursing interventions. In 2012, as a result of 5th International Consultation on Incontinence in Paris, it was stated that it was necessary the individuals be assessed in terms of self-care related to toileting because of peripheral arrangement and self-care being important interventions in incontinence management (31).

The indicators of the outcome of Medication Response provide to assess the medicine's healing or side effects seen on people as both behavioral and blood findings. Expert nurses found all articles of this NOC important as "critical". In literature, it is stated that some medicine used by patients, especially by elders, may lead to incontinence and it is emphasized that their pharmacological treatment and their effects should definitely be assessed (9).

In the light of these results, we can say that NOC scales are a valid tool to assess people regarding UI. We can say that the consistency between experts is high because of nearly all of the obtained scorings being very close to each other. Using them in nursing care plans will lead to comprehensive and accurate interventions as a result of the assessment with more standard and valid indicators and provide the chance for the assessment of intervention's effectiveness again with standard and valid indicators. In literature, NOC scales have been stated as an active assessment tool in the assessment of nursing diagnosis' degree in NNN linkages and in the assessment of activeness of executed interventions (32-34).

From the nurses who had at least 4 years of clinical experience in urology, there was only 1 nurse who made a return. If this number had been higher, a higher expert scoring would have been provided and an assessment of NOC outcomes with a more comprehensive overview would have been performed. Despite this, by keeping the number of our other experts high, scoring was held above 20 and *Senior degree* was reached.

Conclusion

In this study, five NOC outcomes were verified to assess the outcomes of people receiving nursing diagnosis of UI and its various types. It was also stated that these five NOC outcomes contributed to deciding on nursing interventions.

All 82 indicators were approved as valid. Seventy-nine of indicators were assessed as critical and 3 of indicators were assessed as supplemental according to the scoring from experts to verify the indicators. At the same time, the contribution to planning nursing interventions of 2 of the indicators that were assessed as supplemental was assessed as supplemental.

Despite NANDA-I's being executed by students and in hospitals in our country, NOC and NIC were being lectured only as a theoretical lesson. With this study, an awareness has been created for using an international and standard nursing assessment system that can be used in the assessment of people's health issues or risks.

As a suggestion for future studies, we recommend using these NOC outcomes in execution after they are repeatedly used on people who are from different age groups and have different diseases.

Ethics

Ethics Committee Approval: To execute the research, 50687469-1491-432-15/1648.4-1348 protocol numbered permission letter was taken from the Gülhane Military Medical Academy Ethics Committee.

Informed Consent: Written consents were obtained before receiving opinions of the experts.

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Authorship Contributions

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Evaluation of the efficacy of bite wafer chewing in pain reduction in fixed orthodontic appliance treatment

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ABSTRACT

Aim: The purpose of this study was to assess the efficacy of bite wafer (BW) in reducing pain levels, which is a highly complex and subjective phenomenon by assessing the substance P level in the gingival crevicular fluid (GCF) at different time intervals after initial arch wire placement.

Methods: A parallel 2-group prospective case control study was designed for the estimation of substance P levels in GCF after bite-wafer chewing to validate orthodontic pain reduction. The sample size consisted of 80 subjects (47 males and 33 females, mean age of 18.94±2.87 years), who were randomly divided into two groups as the BW group (BWG) and the control group (CG). Fixed orthodontic appliance was placed in each patients of both groups and 0.014-inch nickel-titanium wire was placed and ligated. GCF was collected from the BW and CG before and 8, 24 and 72 hours after the initiation of orthodontic treatment. Unpaired T test was applied between the control and experimental group to evaluate the significant difference between the groups.

Results: The substance P level in GCF for both the BWG and CG followed a similar curve i.e., their levels increased after 8 hours, reached its peak at 24 hours and decreased gradually at 72 hours. The mean substance P level was significantly lower in the BWG compared to the CG, which implied that rhythmic chewing of BW helps in alleviating pain.

Conclusion: Bite wafers offer an excellent non-pharmacological option in reducing substance p level, thus indicating pain alleviation after orthodontic procedures.

Introduction

Pain and discomfort are often reported in patients undergoing fixed orthodontic treatment. Patients complain of pain interfering with their normal activities like biting, chewing, and sleep and some even consider terminating their treatment. Certain procedures like separator placement, placement and activation of arch wires are considered painful by the patients (1). Pain sensation usually begins by 2-4 hours following the placement of wire, and peaks at 24 hours; it gradually disappears over next 7 days (2). Pain perceived by the patient during orthodontic treatment is often ignored by the orthodontist and the option of pain-free treatment is not considered.

Studies have shown that pain following arch wire placement is the response due to the combination of pressure, edema, inflammation and ischemia in compressed periodontal ligament (PDL) (3). According to Proffit, pain experienced by the patients can be reduced by making them chew on the bite wafer (BW) repetitively for the first 8 hours after the activation of appliance (4). Chewing on the BW temporarily displaces the teeth thus allowing blood flow in the compressed areas of PDL, thus preventing build-up of pain-inducing metabolites.

Pain is a sensory experience that is highly subjective. The most commonly used method by a clinician to measure pain is visual analogue scale. Various factors such as age, sociocultural, psychological and environmental factors profoundly alter the

perception of pain (5). Hence for accurate assessment of change in pain levels, substance P is measured in gingival crevicular fluid (GCF). Substance P is a neuropeptide which is found in GCF and is a inflammatory mediator (6). Substance P plays an important role in the induction and maintenance of inflammation and dental pain (7). Studies have shown that levels of substance P are elevated in painful teeth, indicating that they may have an important role in the mechanism of pain (8). Application of orthodontic forces significantly increases substance P level in GCF after 8, 24 and 72 hours following orthodontic activation (9).

The use of non-steroidal anti-inflammatory drugs (NSAIDs) is the most preferred method for pain control in orthodontics but the overuse of analgesics and their potential side effects particularly in children have raised a concern over their use (10). Experimental and clinical studies have shown that NSAIDs can delay or inhibit tooth movement by inhibiting periodontal inflammatory response. Hence this clinical trial was conducted to evaluate the efficacy of BW in pain reduction by measuring substance P level at different time intervals, i.e. before and 8, 24 and 72 hours after the placement of arch wire.

Methods

Patients reporting for the orthodontic treatment were included in this prospective study, after getting an approval from the Institutional Review Board (IRB) and Ethical Committee (IRB. no. 2012/P/OR/15) and patients' consent.

In this study 80 patients (47 males and 33 females, mean age of 18.94±2.87 years) requiring fixed appliance therapy in at least one arch were consulted and selected. Only patients having mild to moderate crowding (1-6 mm of crowding) according to Little's irregularity index were included in this study (11). Informed consent was obtained from patients and parents/guardians. Patients with periodontitis or any other periodontal problems were not included in the study. Patients with any skeletal anomalies were excluded from the study. Also patients on daily medication for systemic conditions or any medication taken 3-4 days before the start of the treatment or those undergoing any surgical procedures in the previous four weeks were excluded from the study.

The study was designed as a comparative prospective 2-group parallel clinical trial. The subjects were randomly divided into two groups of 40 subjects each. The first group was designated as the BW group (BWG) and the second as the control group (CG). The Bite-wafers used for study would be the standard Elastobyte wafers provided by the Ortho Technology, Inc. Florida, USA (Figure 1). All subjects received superficial prophylaxis three days before sample collection and they were instructed to follow good oral hygiene measures. All the subjects were bonded in at least one arch with Pre-Adjusted edgewise appliance with MBT prescription (0.022" slot) and 0.014" NiTi was used as the initial arch wire.

Subjects in the BWG were asked to bite or chew on the wafer for 8-10 minutes before the placement and then within an hour after the initial arch wire placement, and they were asked about experiencing any discomfort (Figure 2). They were specifically instructed to avoid any analgesic rescue medication. Substance P levels in GCF was evaluated at 4 instances, i.e., pretreatment, 8 hours, 24 hours and 72 hours after the initial arch wire placement. The patients were made to sit comfortably on the dental chair with proper illumination.

The marginal gingiva was dried with a stream of air and isolated using cotton rolls. Average of 2 µL of GCF was collected from the mesial as well as distal gingival crevices of the upper premolar using 1-5 µL calibrated volumetric micropipettes by capillary action (Figure 3). Each sample was examined upon removal and samples containing blood were discarded until an uncontaminated sample was obtained from each patient. The samples were diluted in phosphate buffer solution (100 µL, pH:

Figure 1. The Bite-wafers: The standard Elastobyte wafers by the Ortho Technology, Inc. Florida, USA

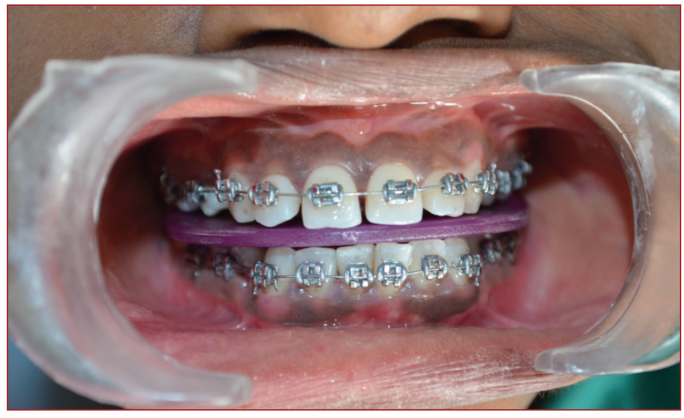


Figure 2. Patients in the Bite wafer group were asked to bite or chew on the wafer for 8-10 minutes

7.2). The collected samples were stored at -20 °C till analysis. Estimation of substance P levels was done using ELISA (human substance P immunoassay, R&D Systems, Minneapolis, USA) according to manufacturer's instructions.

Statistical Analysis

All the data collected were transferred to a computer, the results were statistically analyzed using the statistical software SPSS (version 20.0 Armonk, NY: IBM Corp). The mean difference and standard error values of substance P value were calculated at different time intervals. The comparison of the mean values between the two groups was performed using unpaired t test and within the groups at different time points (0 hours, 8 hours, 24 hours and 72 hours) by using ANOVA. A p value <0.05 was considered to indicate statistical significance.

Results

Results showed that the mean value of substance P level in GCF reported by the BWG was less than the CG at 4 instances i.e., before the placement of arch wire, 8 hours, 24 hours and 72 hours after the initial arch wire placement. The reduced pain scores in the BWG could be attributed to the repetitive chewing of the wafer which caused temporary displacement of the teeth that allowed some blood flow through the compressed areas of the PDL, thus preventing the build-up of metabolites that could in turn stimulate pain receptors. Readings also showed that the mean value of substance P level in GCF was maximum in both CG and BWG at 24 hours, indicating that maximum pain was perceived at 24 hours after the placement of arch wires (Graphic 1).

Unpaired t test showed statistically significant difference between the control and BWG at four different time intervals, i.e., T0, T1, T2, T3 since p<0.05. This results indicate that subjects in the BWG showed substance P level in GCF to be less than that of the CG at 4 different time intervals. Anova test showed that substance P level in GCF increased from the time orthodontic force was applied in both BW and CG groups, It reached its peak value at 24 hours and after that its value decreased gradually (Table 1).

Intragroup comparison of substance P level in GCF samples among the CG at 4 different time interval showed that there was a significant difference between all pairs (p=0.000, <0.05). This shows that the substance P level was significantly higher at 8 hours, 24 hours and 72 hours. The values reached a peak at 24 hours after which they reduced, but still the value remained more than the baseline value (Table 2).

Intra group comparison of substance P level in GCF samples among the BWG at 4 different time intervals showed that there was a significant difference between all pairs as p<0.05. This shows that the substance P level was significantly higher at 8 hours, 24 hours and 72 hours. The values reached a peak at 24 hours after which the values dropped, but still the value remained more than the baseline value (Table 2).

Discussion

Pain is sensory experience that is very subjective. Fear of pain is highly common among patients undergoing any dental treatment. This fear of discomfort and pain discourage patients from undergoing orthodontic treatment (12). Discomfort and pain are experienced by some patients immediately after the placement of arch wire. Studies have shown that intensity of pain peaks at 24 hours following the application of force and it gradually decreases over the next seven days (13).

In orthodontics, the application of forces to induce tooth movement is the main cause of pain. The force applied to move the tooth through brackets and arch wire through alveolar bone may be perceived as a nociceptive input and might result in specific pain and inflammation receptors. On the application of orthodontic forces, ischemia, edema and inflammation occur in the compressed PDL, releasing mediators such as bradykinin

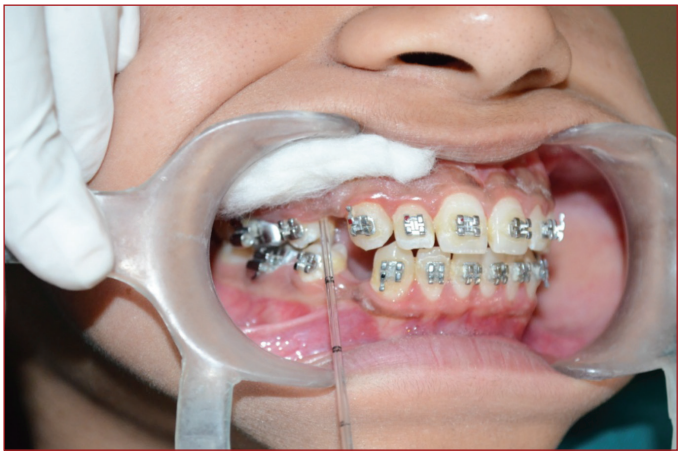
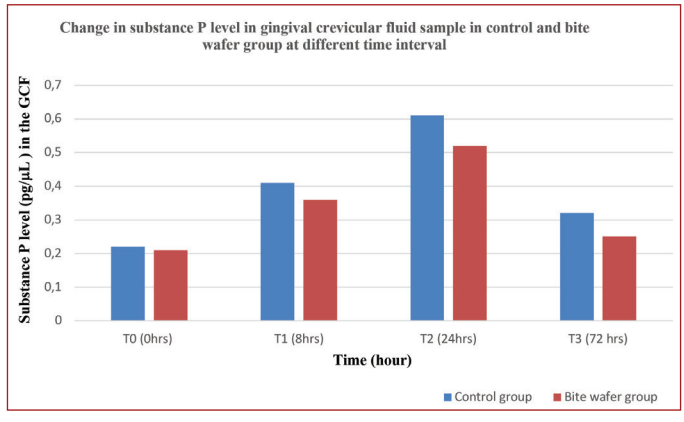


Figure 3. Gingival crevicular fluid was collected from the mesial as well as distal gingival crevices of the upper premolar using 1-5 µL calibrated volumetric micropipettes by capillary action



Graphic 1. Changes in substance P level in gingival crevicular fluid in the control and bite wafer groups at different time intervals

GCF: Gingival crevicular fluid, hrs: Hours

Table 1. Unpaired test showing statistical difference in substance P level between the control and bite wafer groups

Group	T0 (0 hrs)	T1 (8 hrs)	T2 (24 hrs)	T3 (72 hrs)
Control group	0.22±0.02	0.41±0.02	0.61±0.02	0.32±0.03
Bite wafer group	0.21±0.02	0.36±0.02	0.52±0.03	0.25±0.02
t value	1.31	9.27	12.70	9.56
p value	0.19	0.001*	0.001*	0.001*

*p<0.05 is considered statistically significant.
hrs: Hours

Table 2. Pairwise comparison of substance P level between the control and wafer groups at different time intervals

Group	Time	Mean ± SD	Wilk's Lambda	p value
Control	T0 (0 hrs)	0.22±0.02	0.006	0.001*
	T1 (8 hrs)	0.41±0.02		
	T2 (24 hrs)	0.61±0.02		
	T3 (72 hrs)	0.32±0.03		
Bite wafer	T0 (0 hrs)	0.21±0.02	0.016	0.001*
	T1 (8 hrs)	0.36±0.02		
	T2 (24 hrs)	0.52±0.03		
	T3 (72 hrs)	0.25±0.02		

*The mean difference is significant at the 0.05 level.
SD: Standard deviation, hrs: Hours

substance P, prostaglandins, serotonin, histamine and this irritates the nerve ending of pain receptors which in turn causes pain (14).

Pain is a subjective response that shows a vast individual variations depending on the magnitude of force applied, individual pain threshold, gender, age, emotional state, cultural differences and previous pain experiences (15). The same stimuli may be perceived by different individuals as the amelioration or aggravation of pain. Thus it is difficult to measure pain which is a highly complex and personalized phenomenon.

Various methods have been recommended for controlling pain in orthodontic patients such as vibratory stimulation of PDL (16), low level laser therapy (17), NSAIDs (1), and transcutaneous electric nerve stimulation (18). Among these, NSAIDs were the most commonly used method for reducing pain, but due to side effects such as skin rash, headaches, thrombocytopenia, etc. seen with the use of these drugs especially in young patients, non-pharmacological approach like chewing on a BW is recommended for controlling orthodontic pain.

According to Stanfeld et al. (19), pain occurring during orthodontic treatment is due to inflammatory response taking place in PDL. In this study, we used BW to relieve pain because chewing on the BW reduced pain by causing loosening of the tightly grouped fibers around blood vessels and nerves, thus restoring normal vascular and lymphatic circulation, thus preventing and/or relieving inflammation and edema. According to Furstman and Bernik (3), orthodontic pain is a combination of pressure inflammation ischemia and edema. Chewing something hard can temporarily displace teeth, thus relieves the pressure and prevents the formation of ischemic areas which in turn releases pain.

An appreciable amount of substance P is present in the GCF in teeth on which orthodontic force is applied (9). Substance P level is increased in GCF during the incidence of pain (8). Studies have shown that initial orthodontic tooth movement incites pain and rapid release of biochemical mediators such as substance P, interleukin 1B, prostaglandin E2, and substance P in GCF. When orthodontic forces are applied, substance P level is increased in GCF and its values were significantly higher after 8, 24, and 72 hours of orthodontic activation, with its peak value at 24 hours after which its value decreased by reaching almost its baseline measurement at 168 hours (9). Hence in this study, substance P level in GCF was measured at 4 different time intervals, i.e. before the arch wire placement, 8 hours, after 24 hours, after 72 hours after the arch wire placement.

Conclusion

In the present study, it was found that there was a definite increase in substance P level in GCF in both the CG and the BWG with its value increasing 8 hours after orthodontic force loading, its value peaked at 24 hours and then gradually decreased at 72 hours. Rhythmic chewing of BW reduced substance P level in GCF in the BWG when compared to the CG at all the time intervals, thus indicating that BW chewing can be used to alleviate pain at any stage of orthodontic treatment and not just at the initial arch wire placement. The BW is an

excellent non-pharmacologic option for pain management during orthodontic treatment without any of the side effects of analgesic medicines and it can easily be used at home or school without adult supervision.

Ethics

Ethics Committee Approval and Informed Consent: Patients reporting for the orthodontic treatment were included in this prospective study, after getting an approval from the Institutional Review Board (IRB) and Ethical Committee (IRB. no. 2012/P/OR/15) and patients' consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Vasomotor reactivity in the ophthalmic artery

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ABSTRACT

Aim: The aim of this study was to obtain information about reactivity differences in ophthalmic artery (OA) and middle cerebral artery (MCA) presented as a change in blood flow velocity (BFV) induced by the breath holding in healthy individuals.

Methods: Cerebral vasomotor reactivity (VMR) is interpreted indirectly with the increase in the BFV detected in the basal arteries, secondary to a vasodilatory stimulus as breath holding. Bilateral MCA and OA were evaluated by using transcranial Doppler ultrasonography in 15 volunteers.

Results: The basal velocities obtained from MCAs and from bilateral OA were symmetrical and did not change according to the side ($p>0.05$). The ratio of MCA to OA flow velocities had no significant difference between the sides ($p>0.05$). The OA flow velocities were significantly lower than the ipsilateral MCA flow velocities. Breath-holding index (BHI) was used to evaluate the VMR. Although the BHI values were not symmetrical and statistically different between the sides ($p>0.05$), the difference between the ipsilateral MCA BHI and OA BHI was significant ($p<0.05$). We determined the ratio of MCA VMR to OA artery VMR as 1.47±0.15.

Conclusion: We found out that the VMR measurement with the BHI method could be used in the OA and VMR in the OA was decreased compared to the MCA on the same side. Future studies on OA VMR in patients with different degrees of carotid stenosis and determination of changes in the OA VMR as a result of angioplasty or stenting will provide valuable information.

Introduction

Transcranial Doppler ultrasonography (TCD) is a noninvasive technique in which sudden cerebral blood flow velocity (CBFV) changes in the basal cerebral arteries can be evaluated. The most important feature is the ability to monitor these sudden changes. It is assumed that the velocity changes during breath-holding are caused by varying resistance secondary to diameter changes in small vessels distal to the M2 segment of the middle cerebral artery (MCA). These changes observed in the velocity are considered to be indicative of the cerebro-vascular reserve of cerebral vascular structures formed in response to hypoxia (1).

The vasodilation capacity of cerebral arterioles can be measured indirectly by changes in the BFV in the main cerebral arteries. This capacity, defined as a cerebrovascular reserve or vasomotor reactivity (VMR), can be evaluated by carbon dioxide inhalation, acetazolamide injection, and breath-holding and vasodilator stimulation (2-4).

The ophthalmic artery (OA) is the first branch of the internal carotid artery responsible for arterial supply of the eye and other structures in the orbita. The MCA is one of the three main vessel pairs responsible for the arterial supply of the cerebrum. The MCA originating from the internal carotid artery continues its course in the lateral sulcus and gives many branches to the lateral cerebral cortex. The vasomotor features of the M1, M2, and posterior cerebral arteries of the MCA have been previously discussed (1,5).

Little is known about the VMR capacity of the OA, and results obtained from healthy individuals and the findings are inconsistent.

The aim of this study was to obtain information about changes in the BFV induced by the breath-holding movement of theM1 segment of the MCA and the OA and thus VMR in healthy individuals.

Methods

Fifteen healthy volunteers were included in the study (mean age 26.2±7.8 years). The study described was carried out in accordance with the Declaration of Helsinki for researches involving humans. The ethical approval date and number is 30 Jun 2009/135 (GATA). Informed consent was obtained from all volunteers prior to the study. Strict exclusion criteria were applied with the assumption that comorbidities or treatments might change the measurements. Hypertension, diabetes mellitus, obesity, congestive heart failure, chronic obstructive pulmonary disease, stroke (history of any stroke or transient ischemic attack), carotid artery disease (detection of luminal narrowing at a higher rate than the intima-media thickness), hematological disease or cancer were applied as strict exclusion criteria. None of the volunteers were smokers. Magnetic resonance angiography was performed to exclude possible intracranial stenosis, arteriovenous malformation, aneurysm, or Willis polygon variation (6).

Volunteers were accepted to the ultrasonography laboratory after 8 hours of night sleep on a full stomach at 08:00 in the morning. As sleep deprivation may lead to VMR change, at least 8 hours of night sleep was required. The study was performed with a DWL Multi-Dop X4 TCD device while patients were lying in the supine position on an ultrasonography examination table. Pulsed-wave Doppler probes (2 MHz) were fixed on the bilateral temporal window with a probe holder and stabilizer. The optimal signal from the MCA was obtained from a mean depth of 45-55 mm on both sides. For the OA examination, Pulsed-wave Doppler probes (2 MHz) were placed manually to receive signals from the transorbital window. In the transorbital window examination, the power of the device was reduced to 16 mW/cm^2. The optimal signal from the OA was obtained from a mean depth of 11-24 mm on both sides. The mean BFV of the arteries under sonographic examination during both basal and breath-holding maneuver were continuously recorded by the software of DWL device. The basal BFV was accepted as the mean of the last 3 minutes BFV of a 10-minute period after the probes were fixed. The breath-holding maneuver was performed to evaluate VMR in vascular structures. The breath-holding maneuver was performed in sets of three at a time. For mean BFV, vascular structures were recorded in ipsilateral pairs. The right MCA and right OA were recorded together, while the left MCA and left OA were recorded together. Volunteers were asked to hold the breath for 30 seconds at 3-minute intervals. If the breath-holding for 30 seconds was not successful, the test was interrupted for 3 minutes. Velocity measurements were made offline afterwards. During the breath-holding maneuver, no side effects were observed to stop the study, but the volunteer was informed again before the procedure and instructed during the procedure so that the volunteer could cooperate.

All measurements were made offline using the software of the DWL TCD device. At the selected time window and the specified exact time, the mean flow velocities were calculated by the device.

Cerebrovascular reactivity was measured by the breath-holding index (BHI). The percentage of increase in the mean BFV observed after 30 seconds of breath-holding by the volunteers was determined as the BHI. BHI = mean BFV at the end of the breath-holding maneuver - mean BFV at rest / mean BFV at rest x100 / breath-holding time (sec) (1).

Statistical Analysis

Data were entered into SPSS v.15.0 statistics program. The Kolmogorov-Smirnov test was used for continuous variables. All measurements with normal distribution were performed with the t-test. Quantitative data were presented as mean±standard deviation, and the p value <0.05 was accepted to be significant.

Results

Bilateral MCA and OA were evaluated in 15 volunteers (6 females and 9 males, mean age 26.2±7.8 years). The basal velocity obtained from the right MCA was 40.3-83.9 cm/s (mean 59.19±11.65 cm/s), and the basal velocity obtained from the left MCA was 46.8-89.9 cm/s (mean 64.79±12.51 cm/s). The recorded velocities were among the normal values of our laboratory (7). The basal velocity obtained from the OA was 13.0-23.1 cm/s (mean 18.37±2.86 cm/s) on the right and 11.8-24.3 cm/s (mean 17.30±3.91 cm/s) on the left. Table 1 shows the flow velocities obtained. The basal flow speeds were symmetrical and did not change according to the recorded side (p>0.05). When the ratio of MCA flow velocity to OA flow velocity, which can be considered as an indicator of possible distal stenosis, was evaluated, the ratio of MCA to OA flow velocity was 3.30±0.93 on the right and 3.87±0.94 on the left. There was no significant difference in flow velocity between the two sides (p>0.05). As expected anatomically, the OA flow velocities were significantly lower than the ipsilateral MCA flow velocities (Table 2).

When flow velocities were measured from both the MCA and OA after 30 seconds of breath-holding, the BHI was 0.7-3.6 (mean: 1.64±0.53) in the right MCA and 0.8-3.1 (mean 1.57±0.50) in the left MCA. In the OA, the BHI was 0.3-2.7 (mean 1.04±0.59) on the right and 0.2-3.0 (mean: 1.15±0.68) on the left.

Table 1. Comparison of lateralization of middle cerebral artery and ophthalmic artery flow parameters

	Right	Left	p value
MCA	59.19±11.65	64.79±12.51	0.215
OA	18.37±2.86	17.30±3.91	0.402
MCA/OA	3.30±0.93	3.87±0.94	0.108
MCA BHI	1.64±0.53	1.57±0.50	0.483
OA BHI	1.04±0.59	1.15±0.68	0.427
MCA BHI/OA BHI	2.15±1.51	2.15±2.05	0.993

MCA: Middle cerebral artery, OA: Ophthalmic artery, BHI: Breath-holding index

Although the BHI values were not symmetrical and statistically different between the sides (p>0.05), the difference between the ipsilateral MCA BHI and OA BHI was significant (p<0.05) (Table 2). The BHI values are shown in Figure 1 and Figure 2. The ipsilateral MCA and OA flow velocities were 3.30±0.93 on the right and 3.87±0.94 on the left. The ratio of MCA BHI to OA BHI was 2.15±1.51 on the right and 2.15±2.05 on the left (p>0.05).

Discussion

Transcranial Doppler is a noninvasive, fast and dynamic method that can be applied bedside, can reflect instantaneous changes and provides information about stenosis or occlusion of the main intracranial arteries, BFV and flow directions. At the same time, the VMR test can be performed, providing information about cerebral autoregulation and collateral circulation, and the intracranial hemodynamic status can be evaluated with TCD.

The size of the ischemic region that may develop after cerebral artery occlusion depends on whether cerebral collateral vascularization is sufficient to compensate for decreased blood flow (8-10). The anterior communicating artery and posterior communicating artery, which are intracranial anastomoses of the Willis polygon, are two of the primary collateral circulations (11-14). Anastomoses between the internal maxillary artery, the branch of the external carotid artery, and the OA and leptomeningeal anastomoses are considered as secondary collateral vascularization. The patent secondary collateral pathways may be indicative of inadequate cerebral hemodynamics (14). Many studies have been conducted to evaluate the patent structure and effects of primary and secondary collateral pathways on cerebral hemodynamics in occlusion or severe stenosis of cerebral arteries (8,9,13-15).

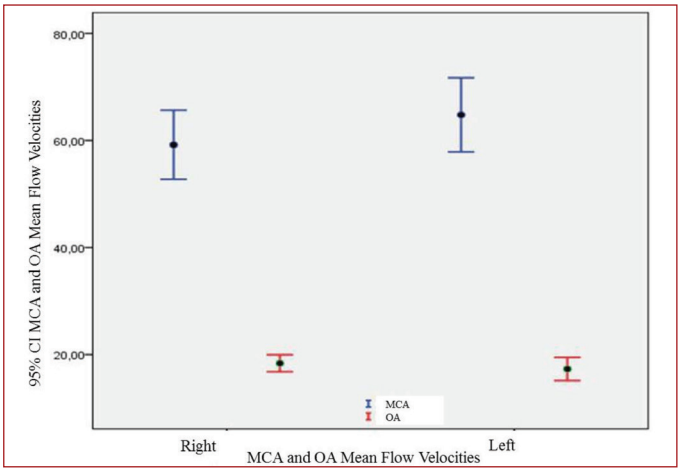

Figure 1. Middle cerebral artery and ophthalmic artery mean flow velocities

MCA: Middle cerebral artery, OA: Ophthalmic artery, CI: Confidence interval

Table 2. Comparison of middle cerebral artery and ophthalmic artery flow parameters bilaterally

	MCA	OA	p value
Right	59.19±11.65	18.37±2.86	<0.001
Left	64.79±12.51	17.30±3.91	<0.001
	MCA BHI	**OA BHI**	
Right	1.64±0.53	1.04±0.59	<0.001
Left	1.57±0.50	1.15±0.68	<0.001

MCA: Middle cerebral artery, OA: Ophthalmic artery, BHI: Breath-holding index

Patients with moderate to severe atherosclerotic lesions in the internal carotid artery have more hemodynamic disorders than those without them (9). In order to understand the hemodynamic status, the contribution of the Willis polygon and OA to the collateral circulation should be known (16).

Collateral clinical importance of the OA in patients with carotid artery occlusion has been reported in the literature. VMR studies performed on the OA are both few in number, and the findings obtained are contradictory (17-21). Kerty et al. (17) found that the OA flow velocity decreased after acetazolamide infusion in 15 healthy individuals, while Harer and Thomas found that a decrease occurred in the OA flow velocity and reactivity index after CO_2 inhalation in 15 healthy individuals. Rassam et al. (18) reported that the OA flow velocity increased after acetazolamide infusion as a result of their study on 10 healthy individuals. Harris et al. (20) found out that CO_2 or acetazolamide infusion had no effect on the OA flow velocity in 12 healthy individuals (19). Bornstein et al. (21) found that the VMR value of the OA increased significantly on the side with an internal carotid artery stenosis of 70-99% and that there was no significant increase on the side with normal or hemodynamically insignificant internal carotid artery stenosis, but they could not explain the underlying

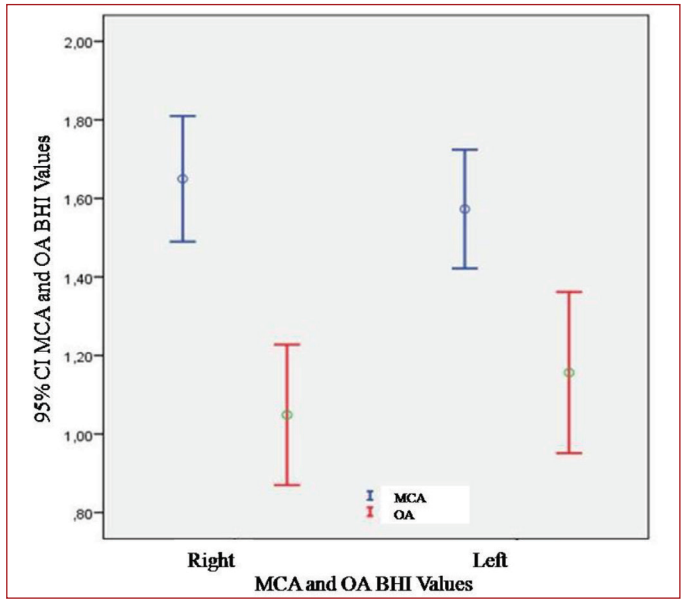

Figure 2. Middle cerebral artery and ophthalmic artery breath-holding index

MCA: Middle cerebral artery, OA: Ophthalmic artery, BHI: Breath-holding index, CI: Confidence interval

cause. In our study, it was aimed to determine the VMR value of the OA and to compare it with the MCA VMR by using the BHI in healthy individuals.

In this study, the ipsilateral OA BHIs of 15 healthy individuals both on the right and left sides were significantly lower ($p<0.05$) compared to the MCA BHIs. When the ninety BHIs measured from the OA were evaluated, the mean value was 1.10, and SEM was 0.06745. When the 95% confidence interval of the OA BHI of healthy individuals was evaluated, the lower limit was 0.97, and the upper limit was 1.24. The results of our study show that the vascular reserve of the OA is different and lower than the cerebrovascular reserve of the MCA in healthy individuals. In healthy individuals, the OA does not respond to the systemic vasodilator stimulus as much as intracerebral arteries.

The BHI calculated in healthy individuals should be brought to a certain standardization. Although the OA BHI values in healthy individuals were found to be lower than the BHI values of basal cerebral arteries, we think that these values should be accepted within normal limits.

Cerebral VMR is interpreted indirectly with the increase in the BFV detected in the basal arteries secondary to vasodilatation in cerebral arterioles. While there is no calibration change in the M1 and M2 segments of the MCA against a vasodilator stimulus, the more distal segments are considered reactive (1).

It is not wrong to state that VMR in the OA is decreased compared to the MCA. In this study, the BHI was used to evaluate the OA VMR. In the literature, it is observed that acetazolamide and CO_2 inhalation are used as a vasodilator stimulus in OA studies.

Although the mechanism is not the same as in the MCA, reactivity to a vasodilator stimulus is also observed in the OA, and this response is lower than in the MCA. The reduced reactivity in the OA determined in this study is consistent with other studies in the literature (17-19). Kerty et al. (22) examined healthy individuals and patients with internal carotid artery occlusion or severe internal carotid artery stenosis greater than 75%. They also divided the patient group into 3 subgroups according to the direction of flow in the OA after basal and acetazolamide injections. Group 1 consisted of patients in whom the OA flow was anterograde after basal and acetazolamide injection, it was basal anterograde and retrograde after injection in group 2, and retrograde in both cases in group 3. In this study, it was important that the flow velocity of the OA decreased in healthy volunteers after injection, there was no change in group 1, and it increased after injection in groups 2 and 3. In the same study, the basal anterior cerebral artery and MCA flow velocities were found to be lower on the symptomatic side compared to the contralateral side in groups 2 and 3, but the flow velocity after acetazolamide injection was found to be low only in group 3. These results show that in internal carotid artery occlusion or severe stenosis, VMR is increased as a compensatory mechanism in the OA, but if there is retrograde flow in the OA in the basal state, this increase is insufficient at the central level. These results are consistent with the results we found in healthy volunteers.

When the cerebral blood flow is decreased in the theoretical framework, it can be assumed that the risk of ischemic stroke increases with the decrease in systemic arterial blood pressure. If there is a serious stenosis or occlusion in the internal carotid artery that causes this disorder, it would not be wrong to say that VMR evaluation before applying with recanalization treatment modalities and even VMR results may be effective in the decision of recanalization or even the selection of a recanalization method.

In clinical practice, “blackout” defined by patients without a loss of consciousness in presyncope due to hypotension may be caused by reduced VMR in the OA. Again, in the case of amaurosis fugax, it may be stated that reduced VMR is more effective than the source of an embolism, which is almost always considered.

In this study, we demonstrated that the MCA BFV on both sides were similar at rest and that the OA flow hemodynamics of both sides were similar in terms of BFV at rest. We found that the MCA/OA BFV were similar between the two sides, and the flow rates between the two sides were identical. In the VMR parameters evaluated by the BHI, we demonstrated that the MCA and OA hemodynamic changes of both sides were similar after a dynamic test as at rest. As a result of this hemodynamic test performed in healthy individuals, we determined the ratio of MCA VMR to OA artery VMR as 1.47±0.15.

Conclusion

At the end of this study, we found out that the VMR measurement with the BHI method could be used in the OA and VMR in the OA was decreased compared to the MCA on the same side. In future studies, we think that evaluating the OA VMR in patients with different degrees of carotid stenosis and determining changes in the OA VMR as a result of angioplasty or stenting will provide valuable information.

The low OA VMR is actually regarded as an expected result in a healthy individual. In case of the insufficient central flow, VMR may increase in the OA as the collateral circulation becomes active and the OA begins to show central flow characteristics, and the fact that it begins to show central cerebral artery characteristics while it should be accepted as a peripheral artery, together with successful collateralization, can actually be considered as an indirect indicator of significant stenosis in central pathways.

In prospective studies to be planned in carotid artery patients with and without active collateral circulation, the association of VMR observed in the MCA and OA with the risk of recurrent stroke can be demonstrated.

Ethics

Ethics Committee Approval: The ethical approval date and number is 30 Jun 2009/135 (GATA).

Informed Consent: Informed consent was obtained from all volunteers prior to the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Importance of complete blood count parameters and neutrophil-to-lymphocyte ratio in central and peripheral vertigo

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Keywords: Central vertigo, complete blood count, neutrophil-lymphocyte ratio, peripheral vertigo

ABSTRACT

Aim: The present study investigated the diagnostic value of complete blood count (CBC) parameters, neutrophil-to-lymphocyte (NLR), mean platelet volume-to-platelet (MPV/PLT), and platelet-to-lymphocyte (PLR) ratios in patients with central vertigo (CV) compared to the value in patients with peripheral vertigo (PV).

Methods: This retrospective study included 31 patients with CV and 132 patients with PV. CBC parameters and NLR, MPV/PLT, and PLR were statistically analyzed in all patients with vertigo.

Results: Statistically significant differences were found between the CV and PV groups for white blood cell (WBC) count 9.55±2.33 and 8.24±2.34×10^6/mm^3 (p=0.006), NLR 3.58±2.16 and 2.96±2.47 (p=0.014), neutrophil count 6.49±2.38 and 5.27±2.23×10^6/mm^3 (p=0.007), and monocyte count 0.68±0.24 and 0.55±0.21×10^6/mm^3 (p=0.003).

Conclusion: WBC, neutrophil, and monocyte counts and NLR may be useful in the differential diagnosis of CV and PV.

Introduction

Vertigo is a common cause of admission to health centers, from family health centers to emergency departments (EDs) (1). It is classified into two main groups according to its underlying factors: central vertigo (CV) and peripheral vertigo (PV).

Differentiation between CV and PV requires clinical and laboratory examinations of acute cardiac, metabolic, toxic, local, and systemic infection and exclusion of ischemic and hemorrhagic disorders related to the central nervous system. The importance of physical examinations alone in the diagnosis of patients with acute vestibular syndrome is well known in EDs and is tested using head impulse, nystagmus, and test of skew (HINTS), which is a three-step examination (2). HINTS was shown to be more useful than magnetic resonance diffusion-weighted imaging (DWI) for differentiating between CV and PV. However, ED physicians may prefer to employ a brain computed tomography (CT) scan and/or DWI if there is suspicion of a central event related to ischemia or bleeding in the posterior fossa structures in vertigo patients (3).

Acute ischemic stroke (AIS) is a type of brain injury that develops as a result of thrombotic or embolic occlusion of the brain's blood flow and is affected by inflammatory processes (4). Complete blood count (CBC) parameters and the proportional values obtained from these parameters were reported to have diagnostic values as biomarkers (5-8). From the perspective of an ED physician, tests such as a CBC are simply components of routine practice and often have no direct impact on ED applications or diagnostic/prognostic value (9). Furthermore, the combined assessment of all laboratory results and clinical findings lead to preference for expensive, often unnecessary, central imaging methods.

The present study investigated the role of CBC parameters and neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume-to-MPV/PLT) ratio, which

are calculated from CBC parameters, in the differential diagnosis between CV and PV.

Methods

This retrospective study was designed in the ED of University of Health Sciences Turkey, Gülhane Training and Research Hospital, which is a tertiary hospital of the University of Health Sciences Turkey. The study was approved by the Ethics Committee for the Non-invasive Research at the Gülhane University of Health Sciences Turkey (no: 18/366). Informed consent was not received due to the retrospective nature of the study.

Study design and patient selection

Patients >18 years old who had been to the ED in Gülhane Training and Research Hospital between August 2016 and December 2018 with a pre-diagnosis of vertigo and who had undergone CBC tests and magnetic resonance imaging (MRI) examinations were screened retrospectively using the hospital information management system (FONET, Information Technology Incorporation, Turkey). Age, sex, DWI reports requested by the ED, all consultation results, and hospitalization and discharge information of the screened patients were examined using the patients' files.

Patients with CV and PV were identified, and CBC sub-parameters including NLR, MPV/PLT ratio, and PLR were statistically analyzed in all the patients. Patients were divided into two groups, as those with CV and those with PV, after definitive diagnoses using total examinations.

Exclusion criteria were as follows: patients <18 years old, patients with supratentorial ischemic stroke, pregnancy, history of recently performed surgery, trauma, major systemic diseases (renal or hepatic disease, hematologic and autoimmune disorder) that may affect NLR and PLR levels, evidence of infection (excluding ear, nose, and throat and central nervous system-related infections), and use of drugs (iron preparations, chemotherapeutic agents, vitamins, and corticosteroids) that could influence CBC measurements.

Power analysis

A minimum of 27 patients was calculated to be required for each group based on the findings from a previous study [NLR value for AIS of 4.87±3.48 (7), and NLR value for PV of 2.20 (10) with 80% power and a two-sided error margin of 0.05].

Laboratory analysis

Blood samples taken for CBC examination in the ED of the hospital were analyzed using Sysmex XN-1000 (Sysmex America Inc., Lincolnshire, IL, USA) and Beckman Coulter UniCel DxH800 (Beckman Coulter, Miami, FL, USA) analyzers. Neutrophils, lymphocytes, PLT, red blood cells, and white blood cells (WBCs) were measured as part of the automated CBC. NLR and PLR were calculated as NLR and PLR, respectively.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows v18.0 (SPSS Inc., Chicago, IL, USA) software package. Descriptive data were expressed in mean±standard deviation. Kolmogorov-Smirnov test was used to evaluate normally distributed data. Student's t-test was used for the comparison of normally distributed paired groups whereas Mann-Whitney U test was employed for non-normally distributed groups. All p values <0.05 were considered statistically significant. Receiver operating characteristic (ROC) analysis was performed to identify cutoff thresholds for WBC count, neutrophil, monocyte, and NLR. Sensitivity, specificity, and area under the ROC curve were used for overall estimation of the accuracy in distinguishing CV cases.

Results

A total of 163 patients underwent MRI examination in addition to CBC tests. In the CV group (n=31), only ischemia was detected in the infratentorial region, and all CV patients were hospitalized. Ischemia, hemorrhage, space-occupying lesion, and infection were not detected in any region of the central nervous system in the PV group (n=132), and all PV patients were discharged from the ED.

There was no statistically significant difference for age between the CV and PV groups (62±16 and 59±17, respectively; p=0.35). Sex distribution analysis showed 52% of the patients in the CV group were male (n=16) and 48% were female (n=15). In the PV group, 46% of the patients were male (n=61) and 54% were female (n=71). There was no statistically significant difference between the groups regarding sex (p=0.37).

WBC, neutrophil, and monocyte counts were significantly higher in the CV group compared to those in the PV group (p=0.006, p=0.007, and p=0.003, respectively). There was no significant difference between the two groups for lymphocyte and PLT counts and MPV (p=0.67, p=0.21, and p=0.72, respectively) (Table 1).

NLR was significantly higher in the CV group compared to that in the PV group (p=0.014). However, there was no statistically significant difference between the groups in terms of PLR and MPV/PLT ratio (p=0.273 and p=0.453, respectively) (Table 2).

A cutoff value of 8.55 for WBC count, which was derived from the ROC analysis, showed sensitivity and specificity values of 74.19% and 62.88%, respectively, for the prediction of CV. However, the area under the curve (AUC) value for NLR to distinguish between CV and PV groups was 0.642. NLR had the best cutoff value of 2.25, with a sensitivity of 61.29% and a specificity of 56.06%. On the other hand, the AUC value for

monocytes to distinguish between CV and PV patients was 0.676, with a cutoff value of 0.56, sensitivity of 74.19%, and specificity of 54.55%. Other CBC parameters and ROC analysis related to NLR are shown in Table 3. ROC analysis is shown separately in Figure 1.

Discussion

Vertigo is a common symptom that may be encountered in many diseases, including most benign disorders. However, to avoid misdiagnosis, effective differential diagnosis of vertigo is required, particularly in patients admitted to the ED. Vanni et al. (11) performed CV-PV differential diagnosis using clinical examination only and showed that 16.4% of patients were diagnosed with CV whereas 33.4% were diagnosed with PV. The authors also emphasized that CT and MRI examination rates were low among CV patients, and patients were hospitalized on the basis of physical examination alone. Consequently, the use of adjuvant diagnostic tools with clinical examination was suggested to provide an optimal benefit for the differential diagnosis between CV and PV. The results of the present study indicated that WBC, neutrophil, and monocyte counts and NLR might contribute to the differential diagnosis of CV and PV and hospitalization (independent of clinical findings).

It was previously reported that increased WBC count might be an indicator of high risk for acute myocardial infarct and acute cerebrovascular events (12,13). Zheng et al. (14) reported that increased WBC count on admission was related

Table 1. Comparison of complete blood count parameters between the central and peripheral vertigo groups

	CV (n=31) Mean ± SD	PV (n=132) Mean ± SD	p value*
WBCs (×10^6/mm^3)	9.55±2.33	8.24±2.34	0.006
Neutrophils (×10^6/mm^3)	6.49±2.38	5.27±2.23	0.007
Lymphocytes (×10^6/mm^3)	2.15±0.78	2.22±0.85	0.67
Monocytes (×10^6/mm^3)	0.68±0.24	0.55±0.21	0.003
Platelets (K/µL)	270.23±67.01	253.46±66.62	0.21
MPV (fL)	9.38±1.66	9.29±1.17	0.72

*Student's t-test.
CV: Central vertigo, MPV: Mean platelet volume, PV: Peripheral vertigo, SD: Standard deviation, WBCs: White blood cells

Table 2. Comparison of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume-to-platelet ratio between the central and peripheral vertigo groups

	CV (n=31) Mean ± SD	PV (n=132) Mean ± SD	p value*
NLR	3.58±2.16	2.96±2.47	0.014
PLR	144.95±75.49	133.23±68.28	0.273
MPV/PLT ratio	0.04±0.01	0.04±0.01	0.453

*Mann-Whitney U test.
CV: Central vertigo, MPV/PLT: Mean platelet volume-to-platelet, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PV: Peripheral vertigo group, SD: Standard deviation

Table 3. Receiver operating characteristic curve analysis of complete blood count parameters and neutrophil-to-lymphocyte ratio for differentiating between central vertigo and peripheral vertigo

	Cutoff	AUC	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	LR+ (95% CI)	LR− (95% CI)	p value*
WBCs (×10^6/mm^3)	8.55	0.675	74.19 (55.39-88.14)	62.88 (54.04-71.12)	2.00 (1.47-2.71)	0.41 (0.22-0.76)	0.002
Neutrophils (×10^6/mm^3)	5.40	0.664	74.19 (55.39-88.14)	62.12 (53.27-70.42)	1.96 (1.45-2.65)	0.42 (0.23-0.77)	0.005
Monocytes (×10^6/mm^3)	0.56	0.676	74.19 (55.39-88.14)	54.55 (45.65-63.23)	1.63 (1.23-2.16)	0.47 (0.26-0.88)	0.002
NLR	2.25	0.642	61.29 (42.19-78.15)	56.06 (47.16-64.68)	1.39 (0.99-1.96)	0.69 (0.43-1.10)	0.014

*Chi-square test.
AUC: Area under curve, CI: Confidence interval, LR−: Negative likelihood ratio, LR+: Positive likelihood ratio, NLR: Neutrophil-to-lymphocyte ratio, WBCs: White blood cells

to poor prognosis at 3 months in patients with ischemic stroke independent of other inflammation factors. Similar to these findings, the present study found the WBC count was higher in CV patients with ischemic stroke compared to that in the PV group.

Ozbay et al. (10) conducted a prospective controlled study and compared WBC, PLT, neutrophil, and lymphocyte counts and MPV and NLR values in PV patients and in the control group. No differences were found between the study groups, and all parameters were within the reference intervals. Furthermore, the sub-parameters of the hemogram (CBC) analysis were all within the normal limits. This was an important and distinctive factor in the exclusion of the effects of additional pathologies due to possible inflammation in our patient groups. Thus, the levels of cell count within the normal limits avoided a possible bias while demonstrating the importance of WBC levels in CV and PV distinction.

Neutrophil levels are expected to increase during inflammatory responses activated by ischemia and reperfusion (15,16). Zhou et al. (17) studied AIS patients undergoing clopidogrel treatment for 90 days and demonstrated that new ischemic strokes developed in patients with high neutrophil levels. In the present study, neutrophil counts were higher in CV patients compared to those in PV patients, which may be because all patients were diagnosed with AIS in the infratentorial region. In addition, the degree of neutrophil accumulation, particularly in the early stages and in regions of cerebral ischemia, correlates with stroke severity and poorer stroke outcomes (18). Therefore, targeting neutrophils to reduce brain injury in ischemic stroke may be beneficial by blocking

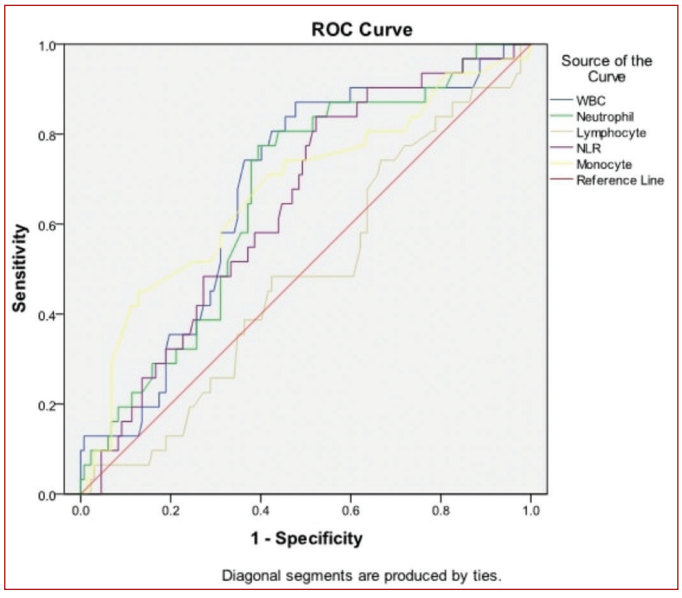

Figure 1. Receiver operating characteristic curves of white blood cells, neutrophils, lymphocytes, neutrophil-to-lymphocyte ratio, and monocytes levels for differentiating between central vertigo and peripheral vertigo

ROC: Receiver operating characteristic, WBC: White blood cells, NLR: Neutrophil-to-lymphocyte ratio

neutrophil adhesion to endothelial cells, neutrophil transmigration, and neurovascular interactions (19). The increase in neutrophils observed in patients in the CV group compared to those in the PV group, particularly in the early stages, although within normal limits, justifies the need to investigate the role of antineutrophil therapy in these patient groups.

Following AIS, monocyte levels increase and migrate to the infarct area, contributing to the enlargement of the ischemic lesion (20,21). Bolayır (20) reported that the monocyte count was significantly higher in AIS patients compared to controls. The same study also reported that monocyte count was statistically higher in AIS patients who died within 30 days compared to those who survived. In accordance with these findings, the present study also showed that monocyte levels were significantly higher in CV patients compared to those in PV patients (Table 1). These similar findings may depend on the early involvement of monocytes in the inflammatory processes of acute brain ischemia.

In the present study, lymphocyte levels were lower but not statistically significant in the CV group compared to those in the PV group. This was attributed to the adaptive lymphocytic response in the late phase of the inflammatory process. Bolayır (20) took blood samples from patients hospitalized in the neurology clinic within 24 h of hospitalization whereas the present study used blood samples taken at admission to the ED. In this context, the CBC parameters obtained in this study may reflect the early stage of the inflammatory response in AIS patients and are more valuable to initial diagnoses. Some studies have reported decreased levels of lymphocytes in AIS patients after ischemia (22,23). Pagram et al. (23) suggested that lymphocyte levels decreased after the first 24 h compared to lymphocyte levels at admission in patients with ischemic stroke. In the present study, lymphocyte levels were within the normal limits in both groups, and it was concluded that lymphocyte levels had limited value in differentiating between CV and PV patients.

The diagnostic and prognostic values of increased NLR in AIS have previously been demonstrated (16,24-26). In accordance with previous studies, the present study showed increased levels of NLR accompanied by acute ischemia in the infratentorial region in CV patients. This increase was mainly due to elevated neutrophil counts. The difference in neutrophil levels was more significant compared to that for NLR values. Furthermore, since neutrophil counts were within the normal limits in both groups, they were not considered to have diagnostic value alone. On the other hand, neutrophil counts were significantly higher but within normal limits in CV patients, highlighting the need for a marker that reveals this significant difference in the early stages of the disease. Since there was also no difference between the groups in terms of lymphocyte and PLT counts, PLR was shown to have no

diagnostic value, and the importance of NLR derived from neutrophil indices became more prominent. Therefore, NLR is recommended as an effective, inexpensive, and fast indicator for the differential diagnosis between CV and PV in the early stage of vertigo. In addition, Ozbay et al. (10) were the first to report the relationship between the CBC parameters in PV patients and they showed that NLR in PV patients was higher compared to that in healthy controls. In the present study, NLR was higher in the CV group than that in the PV group. Although this finding seems to conflict with those of Ozbay et al. (10), the present study showed meaningful results that included CV patients. Moreover, we found significant NLR levels in the CV group compared to those in the PV group.

In a retrospective study by Lok et al. (27), who investigated AIS patients, MPV was found to have no predictive or prognostic value. This study also showed similar findings in CV patients, and it was concluded that MPV had no value regarding the differential diagnosis between CV and PV. Ozbay et al. (10) found that PV patients had PLT counts and MPV within the normal limits, and there was no difference compared to the control group. Consistent with these findings, PLT parameters, including PLT count and MPV, had no value in the diagnosis and differential diagnoses of CV and PV in the present study.

The main limitation of this study is a lack of data for proinflammatory cytokines and/or inflammation markers (e.g., C-reactive protein), which may play a key role in the inflammation process in PV and CV. Another limitation is the relatively small sample size. The present data should, therefore, be interpreted with caution and need to be confirmed in a larger cohort.

Conclusion

In conclusion, WBC, neutrophil, and monocyte counts and NLR may be helpful in the differential diagnosis between CV and PV in patients who present with the complaints of vertigo to the ED. Regarding the differential diagnosis between CV and PV, the use of simple, easily available, and inexpensive CBC parameters, NLR, and monocyte counts, along with the clinical diagnostic tools, may prevent the unnecessary implementation of advanced and expensive imaging methods such as CT and MRI.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee for the Non-invasive Research at the Gülhane University of Health Sciences Turkey (no: 18/366).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally and internally peer-reviewed.

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Analysis of traumatic cardiorespiratory arrest cases in a level 3 emergency department

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Keywords: Advanced trauma life support care, cardiopulmonary resuscitation, heart arrest, return of spontaneous circulation, trauma severity indices

ABSTRACT

Aim: Our study aims to investigate the return of spontaneous circulation (ROSC) outcomes in traumatic arrest patients that were admitted to the emergency department (ED).

Methods: This study retrospectively investigates traumatic cardiorespiratory arrest (TCA) cases that were admitted to the level 3 ED of a university hospital between October 1, 2016 and April 30, 2019. The study includes TCA cases where cardiopulmonary resuscitation was performed in the preclinical phase, and/or after admission to the ED. Additional data were collected for statistical analysis: ROSC, age, gender, mechanism of injury, laboratory findings, injury severity scores (ISS), imaging methods, and consultation requests. The exclusion criteria were as follows: (a) non-traumatic arrest, (b) incomplete records.

Results: A total of 41 TCA patients were included in the study. ROSC was achieved in 16 patients (39.0%). Ten subjects (24.4%) were female and 31 (75.6%) were male, and the mean age of the sample group was 46.56±26.49 years. ROSC did not significantly depend on gender or age (p=0.612, 0.064, respectively). Most of the traumatic injuries were in the head-neck region, the extremities, and the thorax. ROSC did not significantly depend on the mechanism of injury (p=0.620). ROSC was significantly correlated with ISS scores (p=0.006).

Conclusion: According to our data, TCA mostly occur due to blunt trauma among the young adult male population and ISS scores seem useful in predicting ROSC. Trauma team formation should be directed to reversible causes of TCA, such as bleeding control, blood/blood product transfusions, and thoracostomy, to improve patient outcomes.

Introduction

Traumatic cardiac arrests (TCA) make up 12-13% of all cardiac arrest cases. Four out of 100,000 people experience TCA every year (1,2). TCA also constitutes 7% of all out-of-hospital cardiac arrest cases. It is a substantial cause of death for the younger population (3). TCA is mostly caused by blunt trauma, and penetrating trauma is associated with better outcome (4,5).

Despite being common, there currently is not a standard cardiopulmonary resuscitation (CPR) guideline for TCA cases. In fact, several authors claim that CPR efforts are futile for TCA patients whereas others debate this statement (6,7). As trauma is caused by one of the reversible causes of cardiac arrest (hypoxia, tension pneumothorax, cardiac tamponade, and hypovolemia), forming trauma teams in emergency department (EDs) that largely deal with trauma cases can effectively improve mortality (6,8). It is important to note that the survival rates of traumatic and non-TCA are similar (9). Regional data regarding mortality will prove valuable, as there are regional disparities in traumatic arrest outcomes. There is limited information regarding the effectiveness of using trauma scoring systems [e.g. injury

severity scores (ISS)] in EDs. One study estimates the rate of complete neurological recovery to be 1.6% for all traumatic arrest cases (2). Achieving return of spontaneous circulation (ROSC) or respiratory activity at any point in resuscitation is associated with better outcome (9).

Our study aims to investigate ROSC outcomes among traumatic arrest cases based on their ISS, vital findings, laboratory findings, and physicians' imaging and consultation preferences.

Methods

This study retrospectively investigates TCA cases in the level 3 ED of University of Health Sciences Hospital between October 1, 2016 and April 30, 2019. Ethical approval for this study was obtained from University of Health Sciences Turkey, Gülhane Non-invasive Investigation Ethics Committee (2019-19/252). The study includes TCA cases where CPR was performed in the preclinical phase, and/or after admission to the ED. The data were obtained from the electronic database of the hospital and the patients' files. The following information was recorded: age, gender, mechanism of injury, laboratory finding, ISS, duration of CPR, ROSC outcome, preferred imaging methods, requests for consultation. The exclusion criteria were as follows: (a) non-traumatic arrest, (b) incomplete records. The ethics committee waived the requirement for patient informed consent because no patient re-contact was established for the study.

Statistical Analysis

The frequencies, percentages and normally distributed continuous variables were reported as means with standard deviation while non-normally distributed continuous variables were presented as medians with interquartile ranges (IQR). Categorical variables of the subject groups were compared using the chi-square test. Mann-Whitney U test was used for the paired comparison of the continuous data that were not normally distributed whereas Student's t-test was used for the paired comparison of the continuous data that were normally distributed. SPSS 18.0 software was preferred for statistical analysis, significance level was set as below 5% ($p<0.05$).

Results

A total of 41 TCA patients were included in the study. ROSC was achieved in 16 patients (39.0%). The mean CPR duration was 41.24±23.16 minutes (minimum: 3, maximum: 125), and the median time to achieve ROSC was 10 minutes (minimum: 5, maximum: 30). ROSC did not significantly depend on the duration of CPR (Table 1). The CPR duration did not significantly depend

Table 1. Demographics of the groups

Parameter	ROSC	n	Mean ± SD	95% CI	p
Age	Non-sustained	25	52.68±25.40	-0.93-32.29	0.064*
	Sustained	16	37.00±26.05		
Gender (male/female)	Non-sustained	19/6	N/A	N/A	0.612**
	Sustained	12/4	N/A		
GCS	Non-sustained	23	4.70±3.90	-3.23-2.08	0.572***
	Sustained	15	5.27±4.01		
Heart rate	Non-sustained	18	95.50±6.34	-21.24-4.86	0.209***
	Sustained	13	103.69±26.18		
Systolic blood pressure (mmHg)	Non-sustained	18	106.11±30.08	-9.62-37.85	0.234***
	Sustained	13	92.00±34.28		
Diastolic blood pressure (mmHg)	Non-sustained	18	65.94±22.33	-6.44-25.26	0.235***
	Sustained	13	56.54±19.73		
ISS	Non-sustained	24	28.25±9.60	4.49-19.99	0.003***
	Sustained	15	16.07±14.14		
Duration of CPR	Non-sustained	25	45.92±12.04	-1.02-32.20	0.084***
	Sustained	13	32.23±35.09		
PRBC transfusion (Yes/No)	Non-sustained	9/16	N/A	N/A	0.334**
	Sustained	9/7	N/A		
Sedative administration (Yes/No)	Non-sustained	15/10	N/A	N/A	0.003**
	Sustained	16/0	N/A		

*Student's t-test.
**Chi-square test.
***Mann-Whitney U test.
CI: Confidence interval, CPR: Cardiopulmonary resuscitation, GCS: Glasgow Coma Scale, ISS: Injury severity score, N/A: Non-applicable, PRBC: Packed red blood cell, ROSC: Return of spontaneous circulation, SD: Standard deviation

on the mechanism of injury (blunt or penetrating, p=0.599, Mann-Whitney U test). Ten patients (24.4%) were female and 31 (75.6%) were male, and the mean age of the sample group was 46.56± 26.49 years. ROSC did not significantly depend on gender or age (p=0.612, 0.064; respectively) (Table 1).

Among the 41 patients, 38 (92.7%) were brought to the ED through emergency ambulance services (112 in Turkey). The median length of stay in the ED was 60 minutes (IQR: 45-143). The mean Glasgow Coma Scale (GCS) score at the time of admission was 4.92±3.90. This value was not significantly different for the two subject groups (Table 1). It was observed that among the laboratory findings, only the hemoglobin, pH, HCO_3, and lactate levels were significantly different between the two subject groups (Table 2).

The injury mechanisms among the patients were as follows: motor vehicle collision, 43.9% (n=18); penetrating injury, 14.6% (n=6); falls, 22% (n=9); other, 19.5% (n=8). ROSC did not significantly depend on the mechanism of injury (Table 3).

The anatomical locations of the sustained injuries were as follows: head-neck region, 32 (78.1%); extremities, 25 (60.9%);

Table 2. Laboratory parameters in relation to return of spontaneous circulation outcomes

Parameter	ROSC	n	Mean ± SD	95% CI	p
White blood cell count (10^9 cells/mL)	Non-sustained	25	10.19±3.79	-6.62-0.81	0.122*
	Sustained	12	13.09±7.71		
Hemoglobin (g/dL)	Non-sustained	25	12.42±2.53	0.03-0.02	0.046*
	Sustained	12	10.39±3.59		
Hematocrit (%)	Non-sustained	25	37.62±6.86	-0.76-10.61	0.087*
	Sustained	12	32.70±10.68		
Platelets (10^9 cells/mL)	Non-sustained	25	171.48±74.74	-52.56-56.52	0.942*
	Sustained	12	169.50±90.53		
Glucose (mg/dL)	Non-sustained	22	154.68±90.51	-88.92-31.35	0.338*
	Sustained	15	183.47±85.29		
Urea (mg/dL)	Non-sustained	22	37.50±25.78	-19.24-16.51	0.878*
	Sustained	15	38.87±27.04		
Creatinine (mg/dL)	Non-sustained	22	1.20±0.48	-0.50-0.21	0.405*
	Sustained	15	1.35±0.58		
Sodium (mmol/L)	Non-sustained	22	141.86±3.62	-4.64-1.65	0.342*
	Sustained	14	143.36±5.71		
Potassium (mmol/L)	Non-sustained	20	5.06±1.66	-1.12-0.78	0.723*
	Sustained	14	5.23±0.62		
pH	Non-sustained	19	7.16±0.15	0.02-0.28	0.024*
	Sustained	12	7.01±0.21		
PaO_2 (%)	Non-sustained	19	38.67±22.60	-43.07-7.89	0.169*
	Sustained	12	56.26±46.63		
pCO_2 (%)	Non-sustained	19	54.14±15.27	-22.44-11.86	0.533*
	Sustained	12	59.43±31.33		
Lactate (mmol/L)	Non-sustained	19	7.54±3.60	-6.96-0.15	0.06*
	Sustained	12	10.94±6.11		
HCO_3 (mmol/L)	Non-sustained	19	18.39±4.17	1.01-8.13	0.014*
	Sustained	12	13.83±5.49		
INR	Non-sustained	18	2.55±5.66	-3.73-3.77	0.188**
	Sustained	11	2.53±2.66		
Prothrombin time (seconds)	Non-sustained	18	14.13±3.71	-25.51-0.98	0.146**
	Sustained	11	27.37±25.21		

*Student's t-test.
**Mann-Whitney U test.
CI: Confidence interval, INR: International normalized ratio, ROSC: Return of spontaneous circulation, SD: Standard deviation

abdomen, 12 (29.3%); pelvic region, 9 (22%); vertebrae, 6 (14.6%); blood vessels, 6 (14.6%). Multiple trauma was not significantly correlated with ROSC compared to other trauma (p=0.079, chi-square test). A total of 2 patients (4.9%) underwent tube thoracostomy.

The preferred imaging methods were as follows: X-ray imaging, 6; ultrasound imaging, 7; computed tomography (CT), 17; magnetic resonance imaging, 2. None of the imaging methods were significantly correlated with ROSC (p=0.643, 0.672, 0.295, N/A, respectively; chi-square test). The CT findings of 17 patients were as follows: maxillofacial fracture, 6 (35.3%); hemothorax, 5 (29.4%); pneumothorax, 2 (11.8%); fractured scapula, 3 (17.6%); rib fracture, 3 (17.6%); intra-abdominal hemorrhage, 3 (17.6%); pelvic fracture, 4 (23.5%); vertebral fracture, 7 (41.2%).

The consulted departments were as follows: neurosurgery, 18 (43.9%); anesthesia, 13 (31.7%); thoracic surgery, 11 (26.8%); general surgery, 11 (26.8%); orthopedics, 10 (24.4%); pediatric surgery, 2 (4.9%); cardiovascular surgery, 2 (4.9%); other, 13 (31.7%). The total number of consultations was found to be correlated with ROSC outcome (p=0.014, Mann-Whitney U test).

The ISS findings were as follows: 25 and above, 22 (53.7%); 16-24, 7 (17.0%); below 16, 10 (24.3%). The ROSC outcomes of the three groups were found to be significantly different where increasing ISS score indicated a lower probability of ROSC (p=0.006) (Figure 1) (Table 4).

The blood and blood product replacement findings were as follows: packed red blood cell (PRBC) transfusion, 18 (44.9%); fresh frozen plasma (FFP) transfusion, 5 (12.2%); tranexamic acid administration 3 (7.3%). PRBC transfusion was not correlated with ROSC outcome (p=0.334) (Table 1).

Table 3. Return of spontaneous circulation rates in relation to mechanism of injury

	ROSC non-sustained n	ROSC sustained n	Total	p*
Motor vehicle collisions	13 (52.0%)	5 (31.3%)	18	0.620
Penetrating injuries	3 (12.0%)	3 (18.8%)	6	
Falls	5 (20.0%)	4 (25.0%)	9	
Others	4 (16.0%)	4 (25.0%)	8	
Total	25 (100%)	16 (100%)	41	

*Chi-square test.
ROSC: Return of spontaneous circulation

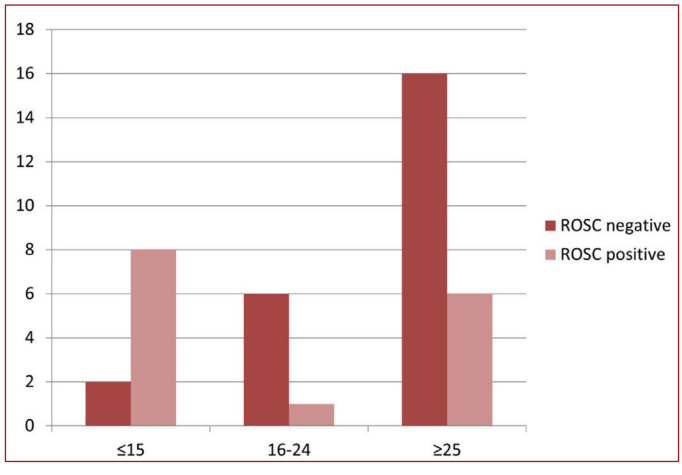

Figure 1. Distribution of return of spontaneous circulation in relation to injury severity score

ROSC: Return of spontaneous circulation

Discussion

There are several regional and national studies regarding the ROSC outcomes of TCA patients. These studies found the ROSC rates of TCA patients to be between 14.0% and 49.1% (1-3,10,11). The sizeable differences between these studies can be explained by the exclusion of TCA cases that were preclinically pronounced dead, and the differences in the data of Utstein style reports. In our hospital, CPR is performed for all cardiac arrest cases in accordance with hospital policy, regardless of traumatic/non-traumatic cause. All cardiac arrest patients that received CPR in the hospital (traumatic/non-traumatic) were included in our study. We found that ROSC was achieved in 39.0% of TCA patients, which is consistent with current literature.

The CPR duration findings in our study are compliant with those of Elkbuli et al. (12), who indicate that the duration of CPR was 1-120 minutes for TCA cases. There are several reasons that cause CPR durations to significantly vary, especially in the context of TCA. Unlike medical arrests, TCA cases may require additional interventions, such as thoracostomy, blood product transfusion, and consultation to specialists, all of which will increase the duration of CPR. Furthermore, it is possible that the patient will be pronounced dead shortly after admission due to irreparable trauma. Also, CPR procedures may vary due to local law or institutional standards. Some researchers suggest the development of a specific CPR protocol for TCA cases will

Table 4. Return of spontaneous circulation rates in relation to injury severity score

ISS groups	ROSC non-sustained n	ROSC sustained n	Total	p*
≤15	2 (8.3%)	8 (53.3%)	10	0.006
16-24	6 (25.0%)	1 (6.7%)	7	
≥25	16 (66.7%)	6 (40.0%)	22	
Total	24 (100%)	15 (100%)	39	

*Chi-square test.
ISS: Injury severity score, ROSC: Return of spontaneous circulation

be effective in addressing the CPR duration. Smith et al. (6) indicated that neither external chest compressions (ECC) nor the administration of epinephrine were found to be effective in TCA cases; however, they needed to be resumed due to the absence of an alternative. The standard CPR protocol was administered to all our TCA subjects as well, including ECC and epinephrine applications.

TCA is mostly observed in the younger population. Different studies report the mean age of patients to be between 33.0 and 48.9 (13-15) years. Consistently, we have found the mean age of our subjects to be 46.56±26.49.

TCA is more common among males, studies report, between 59% and 92%, all TCA patients are men (1-3,14,15). Pekdemir et al. (16) have found that in Turkey, males make up 59% of all trauma cases, and 67.9% of the trauma cases that require hospitalization. Moore et al. (11) found that males made up 87.3% of all TCA cases; however, gender or age was not found to be correlated with ROSC outcomes. Our findings are consistent with the literature. It can be concluded that men are more commonly subject to severe trauma, but gender does not influence overall ROSC outcomes of TCA.

Irfan et al. (1) found that 91% of trauma cases are transported with ground ambulances. This is consistent with our findings, where 97.2% of the patients were transported to the hospital with emergency ambulance services. In contrast, Pekdemir et al. (16) reported that in 1997, only 9.2% of trauma cases were transported to the hospital with an ambulance. The mode of transport was not found to be correlated with mortality. Another study that was conducted in the same hospital in 2017 found that this number had increased to 80.9%, indicating an increased use of emergency medical services over the years, allowing most cases to be treated on site (17). This supports the notion that well-trained paramedics can be an important part of trauma management systems.

It is crucial to determine the level of consciousness in TCA patients. Studies have found the mean GCS scores to be between 3 and 5.6 for TCA patients (1,5,15). Similarly, our subjects' mean GCS score was 4.92±3.90. Bleeding is the most common preventable cause of trauma-related deaths (11). There are several indicators that can be used to evaluate blood circulation, such as heart rate, blood pressure and hemoglobin levels. The mean systolic blood pressure (SBP) of TCA cases at the time of admission was reported to be between 49.6 and 80.1 (5,15). We did not find that SBP at the time of admission was an indicator of ROSC outcome. Huber-Wagner et al. (5) have found the mean hemoglobin value to be 8.2 mg/dL for TCA patients. We found this value to be 11.69±3.07, and that it was significantly different for the positive and negative ROSC outcome groups. When determining the stage of hypovolemic shock, heart rate, blood pressure and level of consciousness are not enough, and hemoglobin levels cannot not used. Thus, Mutschler et al. (18) indicate that hemoglobin levels at the time admission can be misleading as an indicator, and also that only 10.3% of trauma patients can be adequately classified according to the Advanced Trauma Life Support (ATLS) guideline, which indicates that a relevant update is necessary. A recent update included blood base deficit, a blood gas parameter, as an indicator in shock staging. Consistently, we found that blood gas parameters were significantly different for patients with different ROSC outcomes.

Blunt trauma is a more common cause of TCA, rates are reported to be between 85.2 and 96.53%, and the most common cause of blunt trauma is motor vehicle accidents (1,5,13,14,16). It is important to differentiate blunt and penetrating trauma, as resuscitative thoracotomy is significant in the management of penetrating TCA, despite having limited use in blunt trauma cases (9). It should be noted that the mechanism of the trauma is not found to be directly correlated with mortality. We have similarly found that blunt traumas, and specifically motor vehicle accidents are the major cause of TCA, and that the mechanism of trauma does not significantly affect ROSC outcomes.

According to the studies of Huber-Wagner et al. (5) and Avci et al. (15), traumas mostly affect the head-neck region and the thorax among TCA patients. Similarly, Irfan et al. (1) found that 66.0% of TCA patients had sustained head trauma, and Barnard et al. (13) found that 86.8% of patients had traumatic brain injury and severe hemorrhage. We have correspondingly found that most traumatic injuries were in the head-neck region, the extremities, and the thorax. In primary and secondary examinations, it is important to thoroughly assess head-neck and thorax regions. It is worth noting that thorax traumas are among the reversible reasons of cardiac arrest.

Current ATLS guidelines suggest that the radiological exams should only be done after the primary examination, when the patient's condition has improved, and bedside if possible. As mentioned before, the reversible causes of cardiac arrest, including hypoxia, tension pneumothorax (TPX), cardiac tamponade and hypovolemia, need to be rapidly diagnosed and treated (6). As radiological imaging will be helpful in the detection of these causes, it will be beneficial to carry out focused assessment with sonography in trauma (FAST) and bedside ultrasound examinations in early stages, provided that they do not get in the way of the resuscitation process. In our study, most subjects were examined with CT. The reason for lower rates of FAST and ultrasonography may be that not all physicians in the ED have adequate experience with FAST, or the poor condition of certain patients may have prevented them from being transported to the radiology department for further examinations. We were unable to find any studies that specifically researched imaging methods in the context of TCA.

There are several scoring systems that are used to determine the severity and mortality of trauma cases, ISS is one of the most

common scoring systems. ISS is the best system at predicting mortality, and an ISS score below 25 is an indicator of good outcome for TCA (9,19). Huber-Wagner et al. (5) found that the mean ISS score was 41.0 for TCA patients, and Barnard et al. (13) found it to be 29 (minimum-maximum: 21-75). Georgescu et al. (14) indicate that the ISS results of TCA patients were between 30 and 75 and were correlated with the ages of the patients. We have similarly found that ISS scores could have predictive value regarding ROSC outcomes.

Barnard et al. (13) found that an approach that focuses on reversible causes of cardiac arrest can increase the survival rate to 7.5%. Treating specifically reversible causes with hemorrhage control, thoracostomy, blood transfusion, and surgery were associated with improved ROSC and survival among TCA patients (1). Evans et al. (7) suggest focusing on reversible reasons for TCA patients, instead of ECC. They recommend using direct pressure, tourniquet and pelvic bandage to control hemorrhage. Tube thoracostomy is recommended as a lifesaving treatment for TPX. Smith et al. (6) even suggest that if tube thoracostomy is an available option, the physician should avoid needle decompression. Empiric bilateral chest decompression is recommended for all other TCA cases if there are no other possible explanations (7). Resuscitative thoracotomy should be considered for all TCA cases that have sustained penetrating trauma unless there is severe head injury, multisite trauma, or no sign of cardiac activity (9). In their study, Huber-Wagner et al. (5) found that 5.7% of TCA patients had TPX, 23.2% underwent chest tube insertion, and 10.2% underwent emergency thoracotomy. Irfan et al. (1) reported the rates of need and tube thoracostomy to be 3.4% and 6.0%, respectively. We found the rate of thoracostomy to be 4.9% and concluded that the prevalence of thoracostomy wouldl depend on several factors, such as institutional policies, training, experience of the physician and available equipment.

Smith et al. (6) recommend 0 Rh (-) PRBC infusion for traumatic arrest patients with hypovolemia, and according to the outcome, to follow this with plasma, platelet and cryoprecipitate transfusions, all of which need to be warmed prior to application. In the Huber-Wagner study, the mean amount of PRBC that was administered before admission to the ICU was 9.2±12.1 (5). In the Irfan study, 15% of the subjects received blood transfusions (1). In our study, 44.9% and 7.3% of the subjects had PRBC and FFP transfusions, respectively. Despite these relatively high blood product administration rates, the ROSC rates were not significantly different. We conclude that it is crucial to provide the patient with blood and blood products in the early stages of hypovolemic shock; however, this alone cannot resolve the risk of mortality, and it should be reinforced with effective hemorrhage control and early surgical intervention.

The current study has several limitations. Cardiac rhythm at the time of admission was not evaluated. Post-ROSC operation outcomes and discharge statuses were not evaluated. Preclinical intubation, thoracostomy or other medical interventions were not recorded.

Conclusion

Our findings indicate that most TCA cases occur among the young adult male population, and mostly due to blunt trauma from motor vehicle accidents. Injuries were most common in the head-neck region, the extremities, and the thorax, and ISS scores were useful in predicting ROSC outcomes in these patients. Our results suggest that TCA cases differ from non-traumatic arrest cases especially in reversible causes. Reinforcement of trauma team efforts to improve lifesaving attempts, such as bleeding control, blood/blood product transfusions, and thoracostomy, can improve patient outcomes.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from University of Health Sciences Turkey, Gülhane Non-invasive Investigation Ethics Committee (2019-19/252).

Informed Consent: The ethics committee waived the requirement for patient informed consent because no patient re-contact was established for the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Does the efficacy of different doses of Botulinum neurotoxin in chronic migraine change in terms of age and sex?

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ABSTRACT

Aim: The aim of this study was to investigate the effectiveness of Botulinum toxin A (BoNTA) treatment at different doses according to age and sex.

Methods: In this study, 53 patients diagnosed as chronic migraine (CM) were evaluated. The patients were divided into four groups. Group 1a (n=13) were elderly patients who received 5 U BoNTA. Group 1b (n=13) were elderly patients who received 2.5 U BoNTA. Group 2a (n=14) were young patients who received 5 U BoNTA. Group 2b (n=13) were young patients who received 2.5 U BoNTA. In all patients, the number of headache days and the severity of pain were compared before and after the treatment.

Results: There was a statistically significant difference between the number of headache days and the severity of pain in group 1a, group 1b, and group 2a at 3-month post-treatment ($p<0.05$). In the comparison between the groups, there was a statistically significant decrease in pain intensity in group 1b compared to group 2b in which 2.5 U BoNTA was applied ($p<0.05$).

Conclusion: In the treatment of CM, 5 U BoNTA applications were found to be an effective treatment method in both young and old population. However, the efficacy of 2.5 U of BoNTA treatment was seen to be superior in the elderly population compared to the younger population.

Introduction

Headaches constitute an important part of the burden of neurological diseases. Migraine is one of the most important causes of disability among these headaches. In community-based studies, chronic migraine (CM) was found at different rates. Studies have shown that CM costs are three to four times higher than the cost of episodic migraine. Poor clinical status of CM has been cited as the reason for these high costs. Migraine has an impact both on direct health costs and indirectly on labor costs as it causes labor loss. Studies have shown that CM also has negative effects on school and family life (1).

Trigeminovascular system, which is comprising of sensory neurons arising from the trigeminal ganglion and the upper cervical dorsal roots, generates the migraine pathophysiology (2). Neurogenic inflammation is known to be most important parameter of migraine pain, and substance P, the calcitonin gene-associated peptide and neurokinin A are accepted to be vasoactive neuropeptides that released with stimulation of the trigeminal ganglion. In addition, neurogenic inflammation can lead to a sensitivity process. There is a continuous activation of the trigeminovascular system in patients with CM. Increased vasoactive neuropeptide levels in cerebrospinal fluid have been found to be associated with this condition (3,4).

When the studies on the preventive treatment of CM are reviewed, there are important deficiencies regarding the study design. Because the study designs are heterogeneous, it is difficult to compare the results of similar studies and it leads to conflicting results in terms of treatment efficacy (5). CM is a headache that is difficult to treat. Analgesics, anti-epileptics, antidepressants, beta blockers, calcium channel blockers, greater occipital nerve blockade, Botulinum toxin applications and cognitive behavioral therapy are used in the treatment (6-9).

In recent years, OnabotulinumtoxinA (BoNT-A) injections to the muscles in the head and neck region have been used in the treatment of CM (10,11). It has been understood that BoNTA is effective through different mechanisms. Due to its axonal

transport feature, it affects anatomically different regions besides the area where it is injected. In addition, it has been determined that BoNTA regulates neurotransmitter release and makes changes in the expression of receptors and cytokines. Some randomized, placebo-controlled studies have reported that CM patients respond well to BoNTA injections to the muscles (in the head and neck region), which are effective in treatment (10,11).

The aim of this study was to define the efficacy of different BoNTA dosing treatments in terms of age and gender in the treatment of CM patients.

Methods

All patients underwent the procedure after obtaining written informed consent. This study was approved by the LIV Hospital Local Ethics Committee (protocol no: 2019/002-008).

Patients older than 18 years of age who were diagnosed with CM in accordance with the diagnostic criteria (third edition of the International Classification of Headache Disorders) published by the International Headache Association were included in the study. CM patients with a history of headache for more than 6 months from onset and having a headache of 15 days or more per month were selected. In order to exclude secondary causes, the data of patients who underwent whole blood, routine biochemistry, thyroid function tests, vitamin B12, folic acid, ferritin levels and brain imaging methods were analyzed.

Patients that received any kind of preventive treatment for CM at the last 6 months were excluded from the study. Patients with a history of neuromuscular junction disease, those receiving aminoglycoside group antibiotics or curar-like pharmacological agents affecting neuromuscular functions, pregnant patients, those with a history of malignancy, those with cervical and cranial surgery history, those who received non-pharmacological treatment during BoNTA administration, those with major psychiatric disease history in the last 3 months before the study, those taking antipsychotics, antidepressants, antiepileptic drugs, and those with drug overuse headache were not included in the study.

Fifty-three patients [39 female, 14 male-26 (49.1%) were in the geriatric age group and 27 (50.9%) were in the adult age group] were analyzed retrospectively and were included in the study according to inclusion and exclusion criteria. Botox injections were applied by the same specialist (neurologist) to half of the patients in a single session for a total of 60 units, 5 units to each muscles and the other half of the patients in a single session for a total of 30 units, 2.5 units to each muscles (bilaterally to frontal muscles, temporal muscles, occipital muscles, semispinalis capitis, splenius capitis and trapezius muscles in the cervical region). The injections were performed at the myofascial trigger points, the dominant areas of pain in the pericranial muscles. Pain intensity in the headache diaries of all patients before and after the third month was recorded using Visual Analogue Scale (VAS).

Statistical Analysis

In the analysis of descriptive statistical data, mean±standard deviation, median, minimum, maximum values were used for continuous variables, and number and “%” expressions were used for discrete data. The comparison of categorical data between the groups was made by the chi-square test. For the analysis of continuous data, firstly, normality was analyzed by the Kolmogorov-Smirnov test. Parametric tests were used for the analysis of the data that fit the normal distribution and nonparametric tests were used for the data not suitable for the normal distribution.

Student’s t-test was used for dependent variables in student dependent groups and Student’s t-test was used for independent variables in dependent groups. The differences between the groups were taken as 95%. SPSS 22.0 software was used for statistical analysis.

Results

Of the 53 CM patients included in the study, 26 (49.1%) were in the geriatric age group and 27 (50.9%) were in the adult age group. In the geriatric age group (group 1), half of the patients received 5 U (group 1a) and the other half received 2.5 U (group 1b) BoNTA treatment. In the adult age group (group 2), 14 patients (group 2a) received 5 U and 13 patients received 2.5 U (group 2b) BoNTA treatment. The mean age of group 1 patients was 68.0 (65-73) years, while the mean age of group 2 patients was 37.0 (24-49) years. When the gender distribution was examined, a similar distribution was observed in both groups. 73.1% (n=19) of the patients in group 1 were female and 26.9% of the patients (n=7) in group 1 were male; 74.1% (n=20) of the patients in group 2 were female and 25.9% of the patients (n=7) in group 2 were male ($p>0.05$). There was no statistically significant difference between the subgroups in terms of age and sex ($p>0.05$) (Table 1).

In group 1, the median number of headache days before the treatment was 19.0 (15-25) days but decreased to 12.5 (5-17) days after the treatment ($p<0.01$), and the median values of VAS for pain severity was 80 ($p<0.05$) (70-95) and decreased to 60 (30-80) after the treatment ($p<0.01$). These decreases were statistically significant in terms of both the number of headache days and the severity of pain. There was a statistically significant decrease in the number of headache days and VAS pain severity after the treatment in group 2 (Table 2).

In group 1 patients, the median value of headache days was decreased by 8 days [minimum-maximum (-1) and 15 days], and the median value of VAS pain was decreased by 35 (0-55) points. When the treatment efficacy rates were compared to pre-treatment, the mean number of headache days after the

treatment was 38.5% in group 1 and 41.3% in group 2. The decrease in VAS pain intensity was 38.1% in group 1 and 37.4% in group 2. The mean number of headache days receiving 2.5 U treatment was 37.5% in group 1, 20.7% in group 2, while the decrease in VAS pain severity was 38.5% in group 1 and 3.5% in group 2.

Before and after the treatment, there was a statistically significant decrease in the number of headache days in both group 1 and group 2 patients with both 2.5 U and 5 U BoNTA treatment (p<0.01). Reduction in VAS pain intensity was statistically significant in both treatment doses in group 1 patients (p<0.01). The decrease in VAS pain intensity before and after the treatment was not statistically significant in group 2 patients who received only 2.5 U treatment (p=0.27) (Table 3).

There was no statistically significant difference in the number of headache days before and after the treatment in both group 1 and group 2 patients who received BoNTA treatment. There was no statistically significant difference between the groups in terms of the number of headache days and the severity of VAS pain before the treatment in the groups that received 2.5 U treatment. There was a statistically significant decrease in the number of headache days and VAS pain score after the treatment in group 1 patients compared to group 2 patients (p=0.01 and p<0.01, respectively) (Table 4).

Table 1. Comparison of age and sex characteristics of the groups

Groups*		Age, year**	p[1]	Sex (n, %)		p[2]
Group 1 (n=26)	Group 1a (n=13)	68 (65-73)	0.80	F	10 (76.9)	0.74
				M	3 (23.1)	
	Group 1b (n=13)	68 (65-72)		F	9 (69.2)	
				M	4 (30.8)	
Group 2 (n=27)	Group 2a (n=14)	37 (24-79)	0.92	F	10 (71.4)	0.66
				M	4 (28.6)	
	Group 2b (n=13)	35 (24-49)		F	10 (76.9)	
				M	3 (23.1)	

*Group 1: Patients in the geriatric age
Group 2: Patients in the adult age
Group 1a: Patients in the geriatric age that received 5 U Botulinum toxin A (BoNTA)
Group 1b: Patients in the geriatric age that received 2.5 U BoNTA
Group 2a: Patients in the adult age that received 5 U BoNTA
Group 2b: Patients in the adult age that received 2.5 U BoNTA
**Mean, minimum-maximum.
F: Female, M: Male.
p[1]: Student's t-test for independent variables, p[2]: Chi-square test

Table 2. Comparison of the number of headache days and Visual Analogue Scale values before and after the treatment in groups

Groups		Headache days before treatment	Headache days after treatment	p**
Group 1 (n=26)	Mean ± SD*	19.6±3.0	11.9±3.5	
	Mean	19.0	12.5	
	Min.-max.	15-25	5-17	<0.01
Group 2 (n=27)	Mean	19.9±2.5	13.67±4.1	
	Median	20.0	13.0	
	Min.-max.	16-25	6-21	
		VAS before treatment	VAS after treatment	
Group 1 (n=26)	Mean ± SD	79.6±7.4	48.6±13.3	
	Mean	80.0	45.0	
	Min.-max.	70-95	30-80	<0.01
Group 2 (n=27)	Mean	78.9±6.8	62.2±18.0	
	Median	80.0	60.0	
	Min.-max.	70-95	30-90	

* Mean ± SD: Mean±standard deviation, Min.-max.: Minimum-maximum.
**Student's t-test for dependent variables.
VAS: Visual Analogue Scale

Table 3. Comparison of the number of headache days and severity of Visual Analogue Scale pain score by age groups and treatment doses

Age group	Treatment group		Headache days before treatment	Headache days after treatment	Difference in headache days	Decrease ratio in headache days	p***
Group 1*	Group 1a (n=13)	Mean ± SD**	19.5±3.0	11.7±3.7	7.8±4.8	38.5	**<0.01**
		Mean	19.0	12.0	8.0		
		Min.-max.	15-25	5-17	(-1)-15		
	Group 1b (n=13)	Mean ± SD	19.6±3.1	12.1±3.5	7.5±4.1	37.5	**<0.01**
		Mean	19.0	13.0	9.0		
		Min.-max.	15-24	5-17	(-1)-12		
Group 2	Group 2a (n=14)	Mean ± SD	20.1±2.3	11.8±4.1	8.3±3.8	41.3	**<0.01**
		Mean	20.0	11.5	8.5		
		Min.-max.	16-25	6-21	0-14		
	Group 2b (n=13)	Mean ± SD	19.8±2.8	15.7±3.0	4.1±2.7	20.7	**<0.01**
		Mean	20.0	16.0	4.0		
		Min.-max.	16-24	9-20	0-8		
			VAS before treatment	**VAS after treatment**	**VAS difference**	**VAS decrease ratio**	
Group 1	Group 1a (n=13)	Mean ± SD	79.2±7.0	48.5±12.6	30.8±15.6	38.1	**<0.01**
		Mean	75.0	45.0	35.0		
		Min.-max.	70-90	35-75	0-55		
	Group 1b (n=13)	Mean ± SD	79.9±8.1	48.8±14.4	31.1±15.9	38.5	**<0.01**
		Mean	80.0	45.0	35.0		
		Min.-max.	70-95	30-80	0-50		
Group 2	Group 2a (n=14)	Mean ± SD	78.9±7.6	49.3±12.7	29.6±12.6	37.4	**<0.01**
		Mean	77.5	50.0	32.5		
		Min.-max.	70-95	30-75	0-50		
	Group 2b (n=13)	Mean ± SD	78.8±6.2	76.1±11.2	2.7±8.6	3.5	0.27
		Mean	80.0	80.0	0.0		
		Min.-max.	70-90	50-90	(-5)-25		

*Group 1: Patients in geriatric age group
Group 2: Patients in adult age group
Group 1a: Patients in geriatric age group that received 5 U Botulinum toxin A (BoNTA)
Group 1b: Patients in geriatric age group that received 2.5 U BoNTA
Group 2a: Patients in adult age group that received 5 U BoNTA
Group 2b: Patients in adult age group that received 2.5 U BoNTA
**Mean ± SD: Mean±standard deviation, Min.-max.: Minimum-maximum.
***Student's t-test.
VAS: Visual Analogue Scale

Discussion

In this study, three-months of follow-up results were evaluated retrospectively. In this study, the application fields are standard and the results of BoNTA application at 2.5 U and 5 U doses were examined. In the elderly population, BoNTA was administered in 2.5 U and 5 U doses in a single session in CM patients. These two doses were found to be effective in reducing the number of headache days and the severity of pain in migraine after the treatment compared to the pre-treatment. In the young population, BoNTA was administered in 2.5 U and 5 U doses in a single session in CM patients. Five doses were found to be effective in decreasing the frequency of attacks and the severity of pain in migraine after the treatment compared to the pre-treatment. When the elderly and young population groups were compared, 5 of the results of BoNTA application were found to be similar in both groups. However, 2.5 U of BoNTA application results were found to be more effective in reducing the frequency and severity of attacks in migraine in the elderly population.

BoNTA treatment is a promising treatment for CM. BoNTA is one of the most commonly used methods in CM. The efficacy of BoNTA for migraine and primary headache treatment was found

Table 4. Comparison of group 1 and group 2 patients receiving Botulinum toxin A treatment according to treatment doses

		Groups	Mean	SD**	p***
Receiving 5 U treatment	Headache days before treatment	Group 1*	19.54	3.017	
		Group 2	20.07	2.336	0.61
	Headache days after treatment	Group 1	11.69	3.683	
		Group 2	11.79	4.061	0.95
	VAS before treatment	Group 1	79.23	7.026	0.92
		Group 2	78.93	7.641	
	VAS after treatment	Group 1	48.46	12.647	0.87
		Group 2	49.29	12.688	
Receiving 2.5 U treatment	Headache days before treatment	Group 1	19.62	3.150	0.84
		Group 2	19.85	2.853	
	Headache days after treatment	Group 1	12.08	3.546	**0.01**
		Group 2	15.69	3.172	
	VAS before treatment	Group 1	79.92	8.067	0.70
		Group 2	78.85	6.176	
	VAS after treatment	Group 1	48.85	14.456	**<0.01**
		Group 2	76.15	11.209	

* Group 1: Patients with geriatric age
Group 2: Patients with adult age
**SD: Standard deviation.
***Student's t-test.
VAS: Visual Analogue Scale

to be different in recent studies. The application techniques and criteria for determining the areas of use are not clear. In recent studies, the importance of BoNTA treatment in many painful conditions such as migraine and primary headache has been emphasized and treatment strategies for head and neck region have been tried to be developed. In a study by Silberstein, 25 U and 75 U BoNTA were used as a preventive treatment for 123 migraine patients aged 18-65 years. Both 25 U and 75 U BoNTA were found to be effective in treatment. Side effects were more common in patients receiving 75 U BoNTA. BoNTA is an exocytotic inhibitor. Although the mechanism is not fully known, it has been reported to inhibit pain pathways through the sensory system (12).

In clinical trials of PREEMPT (10), BoNTA was found to be effective and reliable in reducing the frequency of headache in the treatment of CM prophylaxis. Analysis of the data collected from the PREEMPT 1 and 2 clinical studies also showed a positive effect on headache severity. In these studies, 155 U of BoNTAs were applied to 31 points in the head and neck region. In some patients, BoNTA was applied to 39 anatomical sites according to the pain follow-up strategy. Unlike our study, BoNTA applications were performed with certain cycles. Patients were not evaluated according to age factor. In addition, high doses of BoNTA were administered.

In the multicenter open-label COMPEL study (11), a total of 155 U of BoNTAs were applied to 31 fixed points, similar to the PREEMPT study. 9 sessions were performed every 12 weeks and 108 weeks treatment period data were examined. The aim of this study was to evaluate the long-term efficacy and safety of BoNTA in adults with CM. As a result of the study, it was found that the frequency of headache decreased significantly. After each session, the side effects were evaluated, and it was found that the side effects decreased with increasing number of sessions. In this study, the elderly population was not examined separately. In addition, the efficacy of lower dose BoNTA administration was evaluated so we used different doses and injection sides (not as the same as PREEMPT study) according to our clinic experience.

The present study has some limitations; we evaluated patients retrospectively, which may lead to the possibility of selection bias. The study population was small in four groups, and the follow-up period of the patients in this study was 3 months, and this was a relatively short period.

Conclusion

As a result of our study, 5 U of BoNTA applications to standard muscles in the treatment of CM were found to be an effective treatment method in both young and old population. At the end of the study, it was found that treatment efficacy of BoNTA was superior (to the standard muscles) to 2.5 U of application at the younger population. The efficacy of lower doses of BoNTA treatment in CM was found to be effective in elderly population.

In addition, no serious side effects were observed during the injections, which would lead to the termination of the study. This demonstrates the safety and tolerability of BoNTA applications in the preventive treatment of CM.

The efficacy of pericranial muscle BoNTA injections for the treatment of CM was found to be different in many studies. These differences may be due to the presence of different types of headache associated with CM may result from factors such as BoNTA dose, pharmacological combination, study design, method of administration, and number of applications. Prospective, randomized, double-blind, placebo-controlled, long-term studies with different doses of BoNTA, by using different head and neck muscles and recurrent injections are needed to fully demonstrate the effectiveness and potency of BoNTA applications in the treatment of CM.

Ethics

Ethics Committee Approval: This study was approved by the Liv Hospital Local Ethics Committee (protocol no: 2019/002-008).

Informed Consent: All patients underwent the procedure after obtaining written informed consent.

Peer-review: Externally peer-reviewed.

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

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A rare case of multiple fibro-folliculomas and lung cysts: Possible Birt-Hogg-Dube syndrome

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Keywords: Autosomal disease, lung cyst, folliculomas, skin lesion, renal cyst

ABSTRACT

Birt-Hogg-Dubè syndrome (BHD) is an autosomal-dominant syndrome, which is very rare to come across with in clinical practice. The disease demonstrates itself with multiple skin hamartomas, multiple fiber-folliculomas, and lung cysts with possible involvement of other organs and systems. The purpose to present this case report is to draw an attention to the possibility of BHD syndrome in patients who come to the hospital with multiple lesions and cysts of various localizations. For this purpose, we present the case report of a 75-year-old patient who presented to the clinic with multiple skin lesions on the face, abdomen and back. Multiple thin-walled cysts scattered throughout the both lungs were discovered during further investigation. The patient had the perilous medical history of hypertension and hyperlipidemia, as well as recent history of prominent cough.

Introduction

Birt-Hogg-Dubè (BHD) syndrome, also called Hornstein-Knickenberg syndrome, was first described in 1977 (1). It is a rare autosomal dominant disease that is characterized by multiple fibro-folliculomas on the skin, lung cysts that predispose to spontaneous pneumothorax, and increased risk of renal cancer (2,3). BHD syndrome is caused by loss-of-function mutation in the folliculin, also known as *FLCN* gene found on chromosome 17p12-q11.2 that encodes for the protein folliculin. Folliculin is expressed in a variety of tissues including the skin, lungs and kidneys. The prevalence of BHD is about 1/200,000 although it is believed that this has been underestimated because of the wide phenotypic interfamilial variability. Less than 300 families have been described to date in the literature and the incidence has been the same for both sexes (4).

Presentation of Case

A 75-year-old white Afro-American male with a history of smoking visited Nardone Medical Associates for the complaint of cough. The patient also had a history of hypertension and hyperlipidemia. On more detailed physical examination, the patient was found to have multiple skin lesions on the face, abdomen and back. The patient could not recall any similar findings in his first degree family members. Because of his recent complaint of cough and the smoking history, low dose computed tomography (CT) of chest was ordered. On the sixth

of June 2016, a CT of the lung without intravenous contrast revealed upper lobe predominant centrilobular and paraseptal emphysema. In addition, there were multiple thin-walled cysts scattered throughout both lungs. Calcified granulomas and perifissural lymphoid aggregates were also present. No suspicious granules were found. The CT of the chest also showed mild coronary calcification and scattered mediastinal and hilar nodes, the largest of which measured 1 cm. Limited upper abdominal view revealed renal lesion as well.

A more detailed CT of the abdomen and pelvis with contrast was ordered on June 15, 2016. The image showed multiple bilateral benign renal cysts and unhanged thin walled pulmonary cysts at the lung bases.

The imaging findings and the skin manifestations were strongly indicating BHD syndrome. The patient was referred to the dermatologist and biopsy of the skin lesions was obtained.

The biopsy results came back ambiguous, as so the pathological evaluation of the skin lesions neither proved nor denied the diagnosis.

The results of pathological evaluation of the lung nodules specimen were ambiguous regarding the presence of BHD, as well.

Although the clinical presentation of the patient was strongly indicating the presence of a rare autosomal-dominant disease, the diagnosis was not proved diagnostically based on a genetic testing for the detection of mutation in *FLCN* gene.

Discussion

BHD syndrome is a multi-organ, autosomal dominant disorder and was initially described as a dermatologic syndrome. The classic triad present on the skin consists of hamartomas of the hair follicles (fibrofolliculomas), which is the most characteristic clinical finding, tumors of the hair disc (trichodiscomas) and skin tags (acrohondrons). Skin changes typically appear in the third to fourth decades of life. These cutaneous, benign tumors are multiple, skin colored, dome shaped and are more prevalent on face, neck and upper trunk (5,6). Mutations that cause premature protein termination in the *FLCN* gene and are the cause of the BHD syndrome are also associated with lung cysts, spontaneous pneumothorax, and renal cancer (4). Pulmonary involvement is present in more than 80% of patients with BHD that manifests as multiple bilateral cysts that increase the risk of recurrent spontaneous pneumothorax 50 times compared to healthy individuals. The median age of pneumothorax is estimated to be around the age of 38 years (3,7,8). The distinguishable feature between BHD syndrome and other known cystic lung diseases is the presence of cysts predominantly in the lower lung, which vary in size and shape (9,10).

Renal cancer occurs at a mean age of 50.7 years although other cases report an earlier onset (3). The risk for renal malignancies in affected individuals is 7 times more compared to those not affected (8,11). Renal cell carcinoma (RCC) appears to be multiple with bilateral lesions presenting in the surrounding parenchyma. The histology of those lesions that are related to BHD syndrome is similar to chromophobe RCC. This is a differentiating factor between BHD syndrome and other syndromes with renal involvement, e.g Von Hippel-Lindau disease that presents with renal tumors of clear histology (12). Involvement of other organs has been suspected to be associated with BHD, such as parathyroid adenomas, angiolipomas, lipomas, parotid oncocytoma (13), colon cancer, and breast cancer but these presentations may be incidental or associated with other syndromes (12,14).

Given the life threatening complications of BHD syndrome, early detection and diagnosis of the disease are important. Menko et al. (2) proposed diagnostic criteria for BHD syndrome.

Major criteria consist of:

- At least five fibrofolliculomas, at least one of which is confirmed histologically and,

- FLCN mutation.

While minor criteria are:

- Multiple bilateral cysts on the base of the lungs,

- A first degree relative with BHDS and,

- Renal cancer of early onset -<50 y/o (15).

Patients with BHD are at increased risk for renal neoplasia and may benefit from periodic surveillance. Similarly, family members should be screened and offered genetic counseling. BHD syndrome is a rare disorder and may be under-recognized because of the great variability in clinical expression (2).

Ethics

Informed Consent: The patient gave an informed consent to publish the case report without revealing his identity, which was followed.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Inflammatory fibroid polyp: A case report with review of the literature

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Keywords: Inflammatory fibroid polyp, stomach, Vanek's polyp, case report

ABSTRACT

Inflammatory fibroid polyps (IFPs) are rare benign mesenchymal neoplasms that occur anywhere in the gastrointestinal tract but most commonly in the stomach and small intestine. Here, in this study, we reported a case of IFP in gastric antrum in an Iranian woman in Western Iran. The report included a 59-year-old woman with a chief complaint of dyspepsia. The upper endoscopy revealed "gastric antrum polyp" and the previous pathology report was "adenomatous polyp (tubular adenoma) with low-grade dysplasia". In conclusion, IFP is a benign submucosal lesion occurring more frequently in 6th or 7th decade of life, which is rarely associated with adenocarcinoma or adenoma and is been treated by local excision.

Introduction

Inflammatory fibroid polyp (IFP) or Vanek's polyp is a rare polyp, the etiology of which is not fully understood (1). IFP can arise everywhere in the gastrointestinal tract but is described more frequently in the gastric antrum (2). Its incidence rate is extremely low, from 0.1% to 2% (3). IFPs may be seen at any age but mainly in the fifties to sixties (2). Gastric IFPs are usually asymptomatic or present with nonspecific symptoms (4). The endoscopic investigation only shows nonspecific submucosal polyp (5). Macroscopically, the tumor size is from 0.2 to 4.2 cm with a mean size of 1.7 cm (6). Microscopically, the lesions are located in submucosa and composed of spindle and inflammatory cells. Spindle cells are whorled around vasculature with onion skin pattern. Inflammation contains many eosinophils. The background is fibromyxoid and atypia is none with rare mitoses if any (6,7). The spindle cells are immunoreactive for the cluster of designation (CD) 34 and negative for CD117 and also smooth muscle actin (SMA) staining is variable (6,8). Recent data show that the spindle cells express platelet-derived growth factor receptor alpha (PDGFRA). This activating mutation is seen in the majority of IFP cases. Therefore, IFP represents true benign mesenchymal tumors of the gastrointestinal tract (9). Although it is rarely associated with adenocarcinoma or adenoma, local excision is usually curative (10). This study reported a case of IFP in gastric antrum in an Iranian woman in Western Iran.

Presentation of Case

A 59-year-old woman was admitted to the department of gastroenterology on July 26th, 2018 with a chief complaint of dyspepsia lasting for 2 years. There was no significant past

medical history or drug history. The physical examination was unremarkable. The lab data such as complete blood count, thyroid function tests, biochemistry, and coagulative function analysis were normal. The patient underwent upper gastrointestinal endoscopy on 28th August, which was reported as "antral polyp" (M: 1.5×1×0.5 cm) and the pathology was reported as "Adenomatous Polyp (tubular adenoma) with low-grade dysplasia". The second endoscopy was done on 6th October, reporting an "antral polyp" (M: 1×0.5×0.5 cm) and the pathology was reported as IFP. Grossly the specimen consisted of multiple grayish-tan fragments measuring 1×0.5×0.5 cm. Microscopic examination on the 21th showed "Submucosal lesion of loose edematous stroma that composed of spindle stromal cells with thin-walled blood vessels and "onion skin" arrangement around vessels and Inflammatory infiltration rich in eosinophils, with no atypia and mitotic activity", which was compatible with the diagnosis of IFP (Figure 1). The immunohistochemistry (IHC) staining of CD34 was positive, whereas CD117, cytokeratin, and SMA were negative in favor of the diagnosis (Figure 2). The treatment process was thoroughly explained to the patient, and written informed consent was obtained prior to the onset of treatment. Moreover, the patient was informed about reporting the case and consented to the publication of photographs and radiographs.

Discussion

IFP is a rare, usually solitary, sessile or pedunculated submucosal polyp, which was proposed by Helwig and Ranier as "inflammatory fibroid polyp" in 1953 (8). It was initially reported by Vanek (7) in 1949, as it is clinically called Vanek's tumor, and histologically was called "gastric submucosal granuloma with eosinophilic infiltration" (11). We reported a case of IPF of gastric antrum in a 59-year-old woman with two-year dyspepsia without a significant past medical history. This tumor is more prevalent in middle-aged females, with the mean age in 60s (2,12). It occurs anywhere in gastrointestinal tract but most commonly in stomach, and it constitutes 2% of all gastric polyps. It usually arises in antrum (70%) adjacent to pyloric sphincter, followed by the small and large bowel (25%), gallbladder (1%), esophagus (1%), duodenum (1%), anal canal (1%), and appendix (2). Although exact pathogenesis is unknown, one study suggested a familial basis, referred to as Devon polyposis (13). Clinical symptoms and endoscopic appearances are usually nonspecific (14). IFPs are submucosal with an average diameter of 1.7 cm, most lesions are smaller than 3 cm. Microscopically, it is a submucosal lesion with an abrupt demarcation of the muscularis propria and is characterized by a vascular and fibroblastic proliferation (often in a whorl-like arrangement around blood vessels) and a polymorphic inflammatory response, dominated by eosinophils in an edematous background (6,7,14). The differential diagnosis includes eosinophilic gastroenteritis, gastrointestinal stromal tumor, inflammatory pseudotumor, hemangioendothelioma, and hemangiopericytoma (2,14). In IHC staining, stromal cells are positive for PDGFR, CD34, vimentin, fascin, CD35, cyclin D1, and calponin and negative for CD117 (14). Although it is rarely associated with adenocarcinoma or adenoma, local excision is usually curative, and no endoscopic surveillance is required after the histological diagnosis is confirmed. However, Mori et al. (10) emphasized that association between IFP and adenoma or adenocarcinoma was possible and they showed this in 6 cases. Mucientes et al. (15) stated that only 7 cases were on the literature for association of IFP and gastric carcinoma and they reported another case of early gastric carcinoma underlying IFP. Association between IFP and adenoma or carcinoma is limited to case reports. Whether this association is an incidental finding or not needs to be clarified by further studies.

IFP occurs more frequently in middle-aged adults and is more common in the gastric antrum. The incidence is extremely

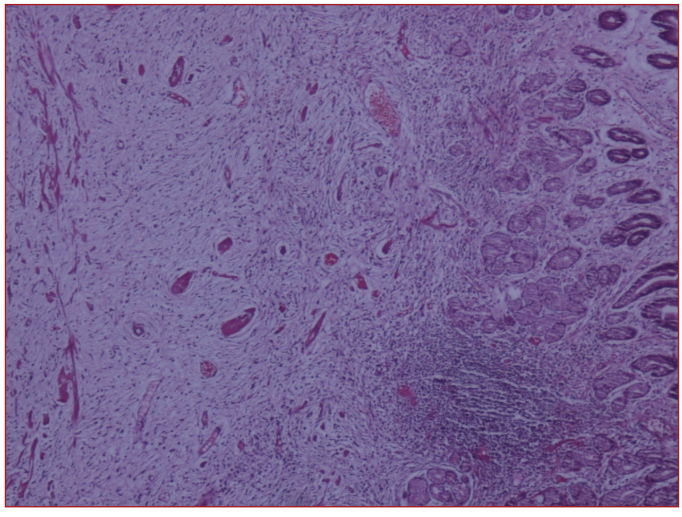

Figure 1. Spindle cells around vasculature and inflammatory cells containing eosinophils. Hematoxylin-Eosin staining (x40 magnification)

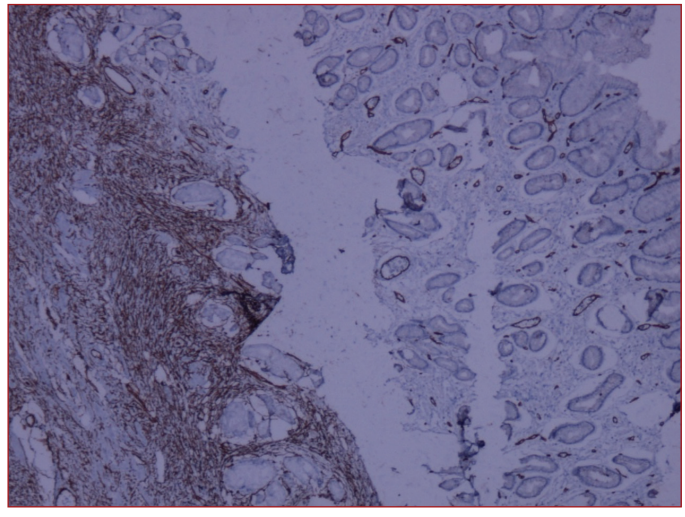

Figure 2. CD34 positive cells. Immunohistochemistry staining (x40 magnification)

low: from 0.1% to 2%. Clinical manifestations are heterogeneous and endoscopic examination reveals only the presence of a submucosal lesion. Clinical, endoscopic, and histopathologic correlation would lead to the diagnosis of IFP. The IHC staining is useful in confirmation and ruling out of the differential diagnosis. IFP is a benign lesion and is been treated by local excision.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.R., B.J., Design: M.R., B.J., Data Collection or Processing: M.R., B.J., Analysis or Interpretation: M.R., M.S., Literature Search: B.J., Writing: M.R., B.J., M.S.

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

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