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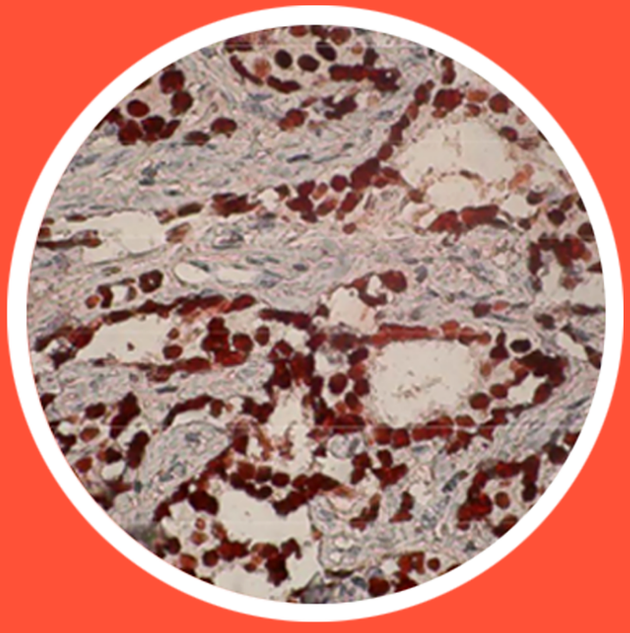

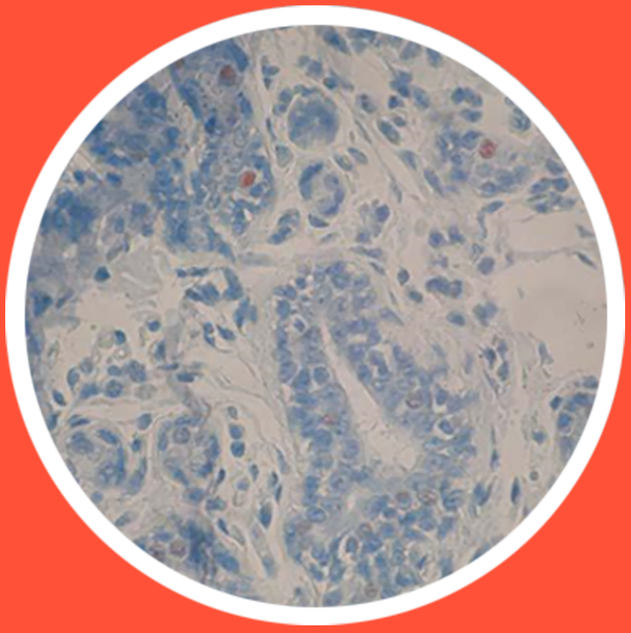

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The European Research Journal

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Original Articles

The European Research Journal 2021;7(1):1-11 Original Article

DOI: 10.18621/eurj.573519 *Applied Psychology*

A non-randomized study investigating the effectiveness of cognitive reframing in socially disconnected widows

Victor Moses

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ABSTRACT

Objectives: Socially disconnected widows usually live a lonely and depressing life with anxiety and low self-worth. Many have contemplated suicide and others have become a victim of suicide already. Evolving an intervention to provide succor to them to take control of their lives may help a great deal. This paper presents the results of a nonrandomized study assessing the potency of cognitive reframing (CR) in reducing social disconnectedness (SD) among the widows.

Methods: The pre- and post-data was collected from a non-randomized sample of 41 widows in the treatment group and 45 in the waitlist control group. The mean age of the participants was 41.383 ± 6.730 [95% CI = 39.940–42.940] (min. = 25 - max. = 56) years. The cognitive reframing administered spanned for eight weeks.

Results: Analysis of the data collected suggests that cognitive reframing is significantly effective in reducing socially disconnected behavior among the widows in the study. The social disconnected behavior among the widows reduced by 40.95% compared to 8.29% observed in the waitlist control group.

Conclusions: The CR technique may be helpful in reducing social disconnectedness in widows. However, further study may be required in a randomized sample to enhance generalization.

Keywords: Social disconnectedness, widows, cognitive reframing

A widow is a woman whose spouse has died. Losing a spouse to death through natural or man-made tragedy only brings pains, forcing many women into unprepared widowhood. All over the world, there are an estimated 258 million widows, with over 115 million living in poverty [1]. In Nigeria, male adult mortality increased from 25.98 in 1970 to 31.92 deaths per 100 male population aged 15-60 in 2015. The average annual death rate for adult male in Nigeria is 2.38% as of 2015 [2]. When a husband dies, typically, the world of a woman falls apart, and she has to dwell in a cruel world, full of misery and shame and abuses for the rest of her life. It brings a lot of negative impact on the health and well being of widows[3, 4]. Widowhood has been described as one of the most stressful events in life [5, 6]. The literature demonstrates that widowhood in old age is a dreaded phase of life due to its influence on health and well being [6-8].The plight of widows is one of the most important, yet under-reported issues facing the world today. For many women, becoming a widow does not just mean the heartache of losing a husband, but often losing everything else altogether. Through no fault of theirs, widows suffer stigma, violence, sometimes, as in parts of sub-Saharan Africa, being forced to "cleanse" herself by having sexual intercourse with a relative or a stranger or forced to marry the deceased relative [9]. Across the world, gender inequality remains the norm,

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and women have continued to encounter discriminatory practices as a result of religious and cultural practices [10]. In some parts of Africa and Nigeria, in particular, women are still treated as minors and sometimes as second-class citizens who are only to be seen and not to be heard [11, 12]. The unjust treatment faced by widows has made many to suffer from various serious mental and physical health challenges.

as a social relationship is a fundamental and vital component of human life and has important impacts on health, many widows continue to suffer from social disconnectedness, which is associated with a wide variety of adverse health outcomes [13-15]. Specifically, the term "social disconnectedness" is not a diagnosis for a specific psychiatric disorder, but a phenomenon of social isolation and the pathology of introverted behavior. The former refers to the condition of staying in one's own house to avoid relationships with others, the latter means pathology due to some psychiatric disorders or personality of introversion [16]. It is also viewed as an individual's subjective experience of a lack of satisfying human relationships, usually accompanied by a negative feeling, causing distress to an individual. Socially disconnected people often experience a subjective sense of inner emptiness or hollowness, with feelings of separation or isolation from the world, and a woman grieving over the loss of her husband is not an exemption [17, 18]. Although social support may buffer the effects of loneliness, mental problems such as depression, insomnia, and hallucinations of the dead, continue to live many widows in trouble. Widows arguably have lower levels of social support in Nigeria than married individuals do. One of the major effects of widowhood is poverty and emotional trauma. Many Nigerian widows are pauperized by those. Upon the death of a husband, widows may be completely dispossessed and chased off [19]. Widowhood among the women is simply a life of deprivation and it can have far-reaching consequences for mental well-being. In order to promote mental and general well-being and to alleviate loneliness and social disconnectedness among widows, intervention programs must be developed to improve existing or develop new relationships such as friendships [20-22].

Much research has been carried out examining the effectiveness of cognitive reframing (CR) in treating several mental problems [23-25]. CR is a psychological intervention that has to do with helping a client to identify and then dispute irrational or maladaptive thoughts. It's used to help clients to look at his condition from a slightly different perspective.The CR has proven to be an effective behavioral intervention used in modifying various psychological problems. Therefore, if this intervention could be used to assess the extent to which it can decrease socially disconnected behavior among the widows, it will be beneficial. Hawton *et al*. [26] suggested that practices could target people at risk of social disconnectedness, as individuals need to be identified early with interventions before the deterioration of their health or quality of life occurs. This study, therefore, used an on randomized method to investigate the effectiveness of cognitive reframing in socially disconnected widows in Nigeria.

METHODS

Research Design

The research is a quasi-experimental study involving two-group pre-test/posttest design (Fig.1) [27, 28]. Using two groups in an experiment is helpful because it helps the researcher to assess the effectiveness of an intervention by comparing before and after the outcome of participants in both groups [29]. Usually, the intervention is considered effective when participants' outcome scores improve compared to baseline across the two groups [30].

Participants

The study population involves widows in Kaduna metropolis who had a high score on the Social disconnected ness Questionnaire. In the study area, there is no published report about the exact number of widows by local authorities. Widows, however, constitute a large proportion of all women. A 2015 world report estimate, shows the population of widows in Nigeria was put at over two million, 2,145,605 [1]. Van Voorhis and Morgan [31] and De Winter [32]

GRP A	01	X	02
GRP B	03		04

Fig.1. Proposed research design for the study (Interpretation: 01 = Pretest, X = Intervention, and 02 = Posttest).

recommended using a small sample size to ensure adequate attention to the participants and eliminate rowdiness and likelihood of attrition. In this study, sixty-four participants were used for the experimental and waitlist control group respectively. After the eight-week intervention, the study recorded a 35.93% and 29.68% attrition rate in both the treatment and waitlist control group. The final analysis was done with 41 participants in the treatment group and 45 in the control group. The following flowchart shows the sample size of the study and the sample recruitment procedure (Fig. 2).

Ethical Consideration

Participation in this research was voluntary. Only widows identified with the social disconnectedness behavior and have agreed to participate after signing a consent form, took part in the study. The consent form as attached to the questionnaire reads: "The essence of the study has been explained to me, and I have been given the opportunity to ask questions about this research. I understand the aims, duration of the intervention and have agreed to participate. I was also assured of the confidentiality of any information I gave. I understand that my participation is voluntary, so I can withdraw from the study at any time."

At the end of the study, the waitlist control group was introduced to the treatment and was given handout on how to use it at home [9].

Treatment Credibility

Two items from the Treatment Evaluation Questionnaire [33] were used to assess treatment credibility, and these items were completed at post-treatment. These items were chosen because they appeared less likely to be affected by treatment success or failure, though it remained possible that treatment response biased these findings [34]. Participants reported whether they felt the treatment was logical and reasonable and whether they would recommend the intervention to a friend with a similar problem. The items were measured on a Likert scale ranging from 0 (strongly disagree) to 5 (not sure) to 10 (strongly agree) [9].

Outcome Measure

The social disconnectedness questionnaire developed by Russell [35] was used to assess social disconnectedness among participants during the pretreatment and post-treatment phases. The Social isolation questionnaire includes 20 questions used to assess how lonely the respondent feels. Each question

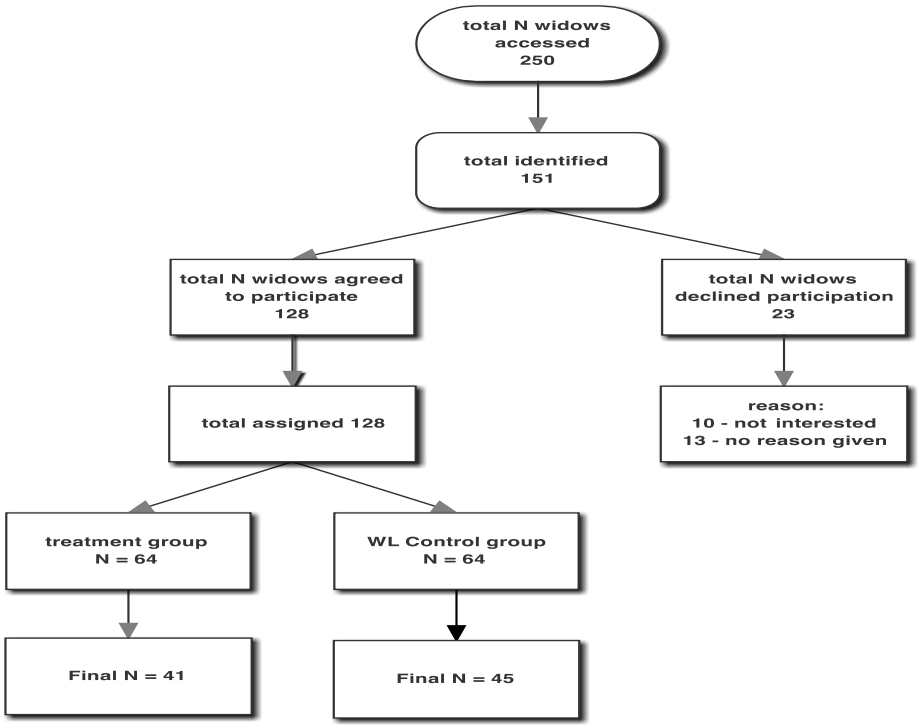

Fig.2. The sample size of the study.

Table 1. Brief explanation of CR intervention for widows

Sessions	Cognitive Reframing	Description
Session One	Introduction and pretest/intake	At this stage, the researcher introduces self to the participants, explain the essence of the study, sought for the consent and administer baseline test using SDQ
Session Two	Identifying the upsetting situation	During this session, participants were given CCD to fill. The essence was to identify upsetting thoughts.
Session Three	Recording negative feelings	The researcher along with the participants record identified upsetting/negative feelings
Session Four	Record and Analyze these thoughts	At this stage, the researcher works with the participants to analyze in order to identify prevalence negative and unbalance thoughts that need to be countered
Session Five	Construct realistic and balanced thoughts	The participants were guided to countering negative and unbalance thoughts to a more realistic thought
Session six	Continuation of session five	Same as session five
Session Seven	Evaluation of the reframing process	During this stage, participants were given a checklist of cognitive distortion (CCD) developed by Burns[42]to assess whether they have adopted a more realistic and balance thoughts
Session Eight	Posttest/termination	The SDQ was administered for the last time to examine if changes have occurred after the intervention. The sessions also terminate here

begins with the statement "How often do you feel" followed by a positive or negative description of social interactions with others. The respondent is asked to indicate the frequency he/she feels that way (never = 1, rarely = 2, sometimes = 3, always = 4) for each question. The instrument is suitable for respondents between the ages of 18 and above. Items 1, 5, 6, 9, 10, 15, 16, 19, and 20 were scored in reverse. All scores were summed together with higher scores indicating greater degrees of isolation or disconnectedness [35]. The instrument was divided into sections. The first section was made up of demographic characteristics of the respondents (age, personal income, years of widowhood, number of children, and source of financial assistance), while the second section consists of statements used to assess the dependent variable (social disconnectedness). The social disconnectedness questionnaire produced a satisfactory reliability index and consistency, and it is one of the most commonly used instrument to assess social isolation behavior. The scale has an internal consistency of .89 to .94 and test-retest of .73 [35]. It has been used successfully in several countries of different cultures [36-38].

Intervention

The data collection procedure was discussed in three phases; pretreatment phase, treatment phase, and post-treatment phase (Table 1).

Pretreatment Phase (week 1)

During week 1, the researcher introduced himself to the volunteered research participants. The participants received a briefing on the essence of the study and filled consent form approving their voluntary participation in the study. We (researcher and two assistants) administered some questionnaire, which we used to measure widows' level of social disconnectedness. We used the data collected at this stage to serve as the pretest data and bases for inclusion to the study. Participants were directed on how to fill the instruments and after that, advance

arrangements were made concerning further meetings [27].

Treatment Phase (week 2-7)

The treatment group received cognitive reframing (CR) from week 2-7. Twelve noon every Saturday was scheduled as the meeting time. The cognitive reframing used in this study were those guided by the work of Greenberger and Westbrook [39], Brosan and Hogan [40], and Gilbert [41]. The procedures were used with some modification to suit the need of the problem under investigation. Other researchers have used the techniques and procedures and they have shown to be effective in reducing mental health-related behavior problems. But there appears to be a dearth of researches using the technique in treating social disconnectedness among widows.

Statistical Analysis

The data collected were statistically analyzed with JMP ver. 13.2., computer software. The analysis was done using the Analysis of Covariance to test for treatment effects. ANCOVA is usually suitable when two or more groups are subjected to pre-test and post-test while the pre-test is treated as a covariate to 'control' for initial differences existing between the groups. Prior to testing the treatment effects, however, a test of assumption of homogeneity of regression slope was carried out. This analysis was done using an unequal number of participants from the experimental and control group due to attrition [27]. A 35.9% and 23.4% attrition rate was recorded for the treatment group and waitlist control group respectively. A .05 standard of statistical significance for the decision was used in testing the treatment effect.

RESULTS

Table 2 showed that there is no significant difference between treatment and control group in term of educational attainment, $\chi^2 = 6.316$, $p = 0.097$. The outcome indicates that 19.5% of the participants in the treatment group had no formal education as compared to the control group with only 4.4%. There were 17 (41.5%) of the participants in the experimental group who reported to have primary education compared to 22 (48%) in the control group. Additionally, 12 (29.3%) in the treatment had secondary education compared to a higher 19 (42.2%) in the waitlist control group. Only 4 participants representing 9.8% of the total sample in the treatment group reached the tertiary level of education unlike 2 participants representing 4.4% in the control group.

About family size, having to do with the number of children, data analysis indicates that 10 (24.4%) of the participants in the treatment group reported having 1-3 children compared to 5 (11.1%) participants in the control group. Over 41% in the treatment group reported having 4-6 kids compared to 33 (73.3%) in

Table 2. A comparative descriptive statistic of the respondents by Group

Group	Description	Levels				Statistic	
	Education	No formal Education	Primary Education	Secondary Education	Tertiary Education	Chi^2	*p* value
1		8 (19.5%)	17 (41.5%)	12[29.3%]	4 (9.8%)	6.316	0.097
2		2 (4.4%)	22 (48.9%)	19[42.2%]	2 (4.4%)		
	Number of Children	1-3	4-6	7+			
1		10 (24.4%)	17 (41.4%)	14 (34.1%)		8.953	**0.011***
2		5 (11.1%)	33 (73.3%)	7 (15.6%)			
	Employment status	Employed	Unemployed				
1		15[36.6%]	26[63.4%]			0.100	0.752
2		15[33.3%]	30[66.7%]				

1 = Treatment Group (n = 41), 2 = WL Control Group (n = 45)

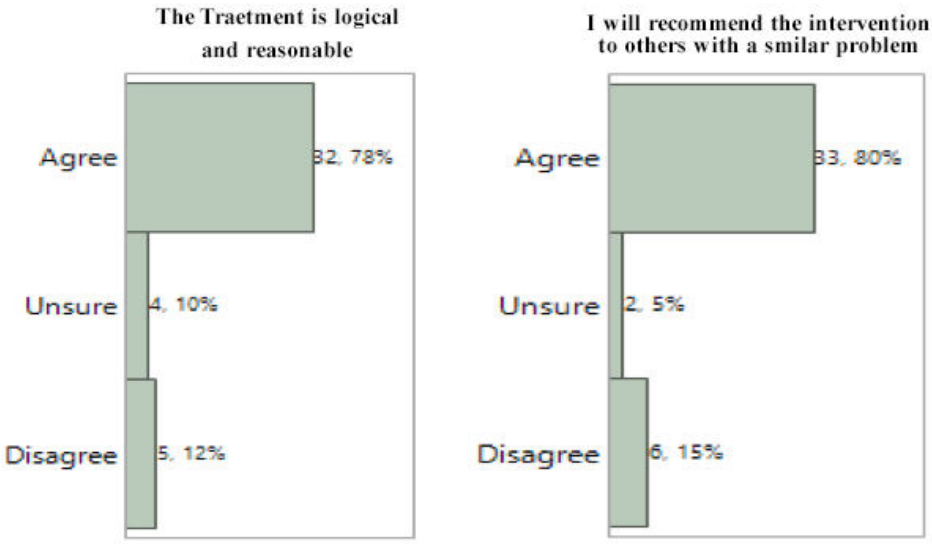

Fig.3. Analysis of responses on treatment credibility (n = 41).

the control group. The data analysis also reveals that 14 (34.1%) participants reported having 7 and above number of children in the experimental group compared to 15.6% in the control group. Largely, the result reveals a significant difference exists in the number of children between the experimental and control group, $\chi^2 = 8.953$, $p = 0.011$. There is no significant difference in the rate of employment between participants in the treatment group and the waitlist control group, $\chi^2 = 0.100$, $p = 0.752$.

An assessment of the treatment credibility shows that there is a significant difference in the participant's response on whether the treatment is logical and reasonable, $\chi 2 = 36.926$, $p < 0.001$. About 78% agreed the treatment is logical and reasonable as against 10% and 12% who are unsure and disagreed, respectively (Fig. 3). In addition, 80% agreed they would recommend the intervention to others with a similar problem while 15% disagreed, with only 5% being unsure. The difference in responses on recommendation is significant, $\chi 2 = 41.609$, $p < 0.001$. Fig. 4 is the analysis of covariance (ANCOVA) assumption test, which entails that the relationship between the covariate and dependent variable for each

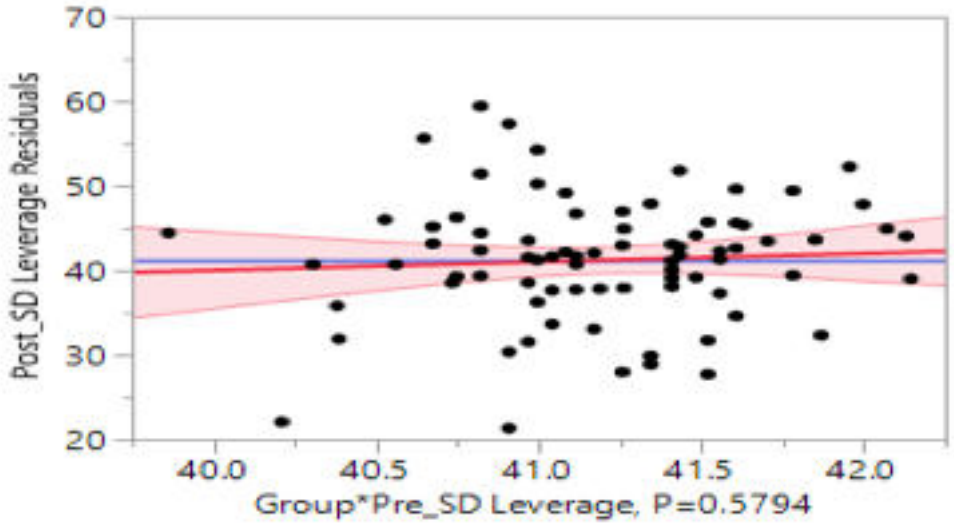

Fig.4. Leverage Plot for Pre_SD*Group testing the homogeneity of regression slope assumption.

Table 3. Test of Lack of Fit for the model

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F	Max RSq
Lack of Fit	36	2151.7927	59.7720	1.2053	0.2728	0.8106
Pure Error	46	2281.2500	49.5924			
Total Error	82	4433.0427				

of the groups is the same. Usually, similar slopes on the regression line for each group indicate this. Unequal slopes would indicate that there is an interaction between the covariate and the treatment. If there is an interaction then the results of ANCOVA could be deceptive [44, 45]. In this case, the interaction is not significant, F (1,82) = 0.310, p = 0.579, hence supporting the appropriateness of ANCOVA.

Table 3 is the lack of a fit report, which is the result of the effectiveness of cognitive reframing for widows. The essence of the test was to observe if the model fit the data collected appropriately. The lack of error analysis return sin significant outcome, F = 0.2728, p = 0.8106. This suggests that the model fits the data pretty well.

Table 4 showed the mean response and standard errors of participants' social disconnectedness before

Table 4. Pre and post-Least Sq Mean response of treatment Group and WL Control Group

Level	Group	Least Sq Mean	Std Error	Lower95%	Upper 95%
Pre_SD	Treatment Group	53.122	0.870	51.391	54.853
	WL Control Group	54.689	0.831	53.036	56.341
Post_SD	Treatment Group	31.366	1.139	29.099	33.632
	WL Control Group	50.155	1.087	47.992	52.318

Table 5. Analysis of variance showing model effects for groups

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Model	2	7595.855	3797.93	70.8412	**< 0.0001***
Error	83	4449.784	53.61		
C. Total	85	12045.640			

Summary of Fit: RSquare = 0.631; RSquare Adj = 0.622; Root Mean Square Error = 7.322; Mean of Response = 41.197; N = 86

and after the self-monitoring intervention. Mean pre-cognitive reframing of social disconnectedness among treatment group was 53.122 ± 0.870; 95% CI = 51.391-54.853, but after the intervention, mean social disconnectedness reduced to 31.366 ± 1.139; 95% CI = 29.099-33.632. The outcome showed a 40.95% remission in social disconnectedness behavior among the treated patient. The waitlist control group, on the other hand, had a mean social disconnectedness of 54.689 ± 0.831; 95% CI = 53.036-56.341 at the pre-intervention stage, but at the end of the study, WL control group mean response reduced to 50.155 ± 1.087; 95% CI = 47.992-52.318, implying a remission of only 8.29% after eight weeks.

Table 5 is the analysis of the covariance estimate, which was used to determine the overall treatment effects of group on social disconnectedness. The result revealed that overall, there is a significant effect of group F (2, 83) = 70.8412, p < 0.0001; RMSE = 7.322, suggesting that the two groups (experimental and wait-list control group) vary significantly in their response due to cognitive reframing administered. The outcome also reveals that the overall model was found to explain 63.1% variance.

Table 6. Expanded estimates nominal factors expanded to all levels [treatment vs wait-list control]

Term	Estimate	Std Error	t Ratio	Prob > |t|	Lower 95%	Upper 95%
Intercept	45.669	7.766	5.88	< .0001*	30.222	61.115
Pre_SD	-0.091	0.143	-0.64	0.5270	-0.376	0.194
Group [Treatment Group]	-9.466	0.798	-11.86	< .0001*	-11.054	-7.878
Group [WL Control Group]	9.466	0.798	11.86	< .0001*	7.878	11.054

Table 6 is an expanded estimates nominal factors expanded to all levels. It indicates that pretreatment outcome did not significantly influence the outcome of the study, β = -0.091 [95% CI = -0.376- 0.194], t = -0.64, p = 0.5270. The treatment was significantly effective for the widows in the treatment group, β = -9.466 [95%CI = -11.054- -7.878], t = -11.86, p < 0.0001 when compared to widows in the wait-list control group, β = 9.466 [95%CI = 7.878- 11.054], t = 11.86, p < 0.0001. Subjectsin the intervention group reporteda higher reduction in their social disconnectedness behavior than did those in the wait-list control group. To have a graphical view of the variance in the effects of the intervention after eight weeks, a leverage plot for the group was presented (see Fig. 5).

DISCUSSION

There is a dearth in empirical research providing evidence of CR in decreasing socially disconnected behavior among widows. This attempted to examine if eight intervention using CR would be beneficial to widows who are socially disconnected. The result revealed that there is a significant decrease in social disconnectedness among widows after the intervention. The widows reported about 40.95% reduction when compared to their pre-test outcome. The reduction is significantly better than that of the waitlist control group who reported 8.29% decrease. Several results reported by previous studies corroborated the outcome of this study. In a study aimed to explore the feasibility and efficacy of a

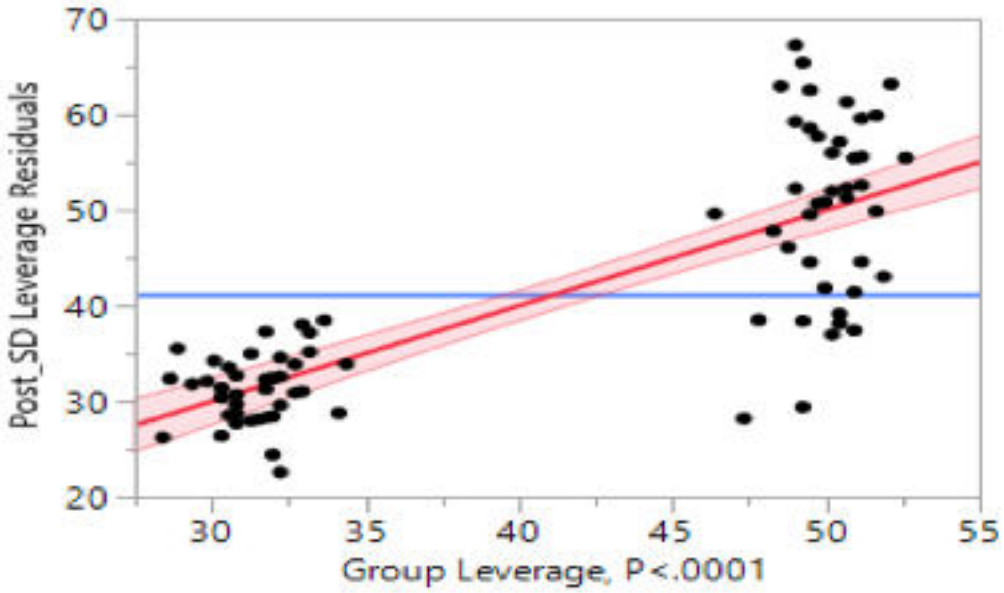

Fig.5. A leverage plot for group responsiveness to CR.

manualized cognitive restructuring program for treating adolescents suffering from posttraumatic stress disorder (PTSD), Rosenberg, Jankowski, Fortuna, Rosenberg, and Mueser [43] reported that after weekly intervention for 12–16 weeks, there were statistically significant improvements in PTSD and depression. Treatment gains were maintained at 3-month follow-up. Preliminary results suggest the feasibility of implementing a manualized cognitive restructuring program to treat PTSD in adolescents. Completers rated themselves as improved and satisfied at post-treatment and 3-month follow-up. Feedback from referring clinicians also indicated high satisfaction. In addition, Dublin [44] compared the effectiveness of Cognitive Restructuring versus Cognitive Defusion for Claustrophobic Anxiety and Avoidance. The result corroborates this outcome of this study as it shows that participants in the cognitive restructuring and cognitive defusion intervention conditions reported a significantly greater reduction in subjective anxiety at post-intervention assessment compared to those in the wait-list condition. Other findings reported that CBT for social anxiety disorder evidenced a medium to large effect size at immediate post-treatment as compared to control or waitlist treatments, with significant maintenance and even improvement of gains at follow-up [45]. Further, exposure, cognitive restructuring, social skills training, and both group/individual formats were equally efficacious [46], with superior performance over psychopharmacology in the long term [47].

Limitations

This present study has several limitations, though. Firstly, the study relied on self-reported measures of social disconnectedness instead of objective measure. Secondly, other physical and mental health problems not included or taken care of in this study may create asymmetries in widows' social relationship and limit their abilities and desires to develop and maintain healthy social relationships. Thirdly, the study only questioned the participant's level of education, number of children and employment status. Other socio demographic features like the number of siblings, the degree of closeness with siblings, the existence of close friends, the time of loss of a spouse, the number of years of widowhood, may all be related to losing reaction. The age of a widow partly accounts for some of the health disparities among widows [48]. Therefore, the fact that these variables were not looked at is a limitation of this study. Fourthly, using individual rather than group intervention may produce a better outcome as each participant would be given adequate attention. Fifthly, the used of a non-randomized method in selecting the study sample may hinder the generalization of the findings of this study. Based on these limitations, therefore, causal connections implied by the findings of this study should be interpreted and taken with caution. It is hoped that further research would refine these concepts, address the study limitations to reveal causal mechanisms and help researchers and policymakers to better understand the health risks of social disconnectedness among widows and the application of a behavioral method to help widows to take back their lives [9].

CONCLUSION

The research presents an opportunity toward searching the relative effects of cognitive reframing on social disconnectedness among widows. The eight weeks group intervention method used in the study sample (widows) has suggested a successfully reduced socially disconnected behavior among widows by 40.95% compared to 8.29% for the waitlist control group. The treatment was reported as credible as 78% viewed it as logical and reasonable while 80% would recommend it to a friend or others with a similar problem. This study outcome may provide insight into the area of grieve support and encourage a healthy adjustment to widowhood.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Efficacy and safety of single high-dose versus double high-dose intracoronary bolus tirofiban in patients with ST-segment elevation myocardial infarction

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ABSTRACT

Objectives: We evaluated the efficacy and safety of single high-dose versus double high-dose intracoronary bolus tirofiban in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Methods: A total of 80 patients, who were admitted to our clinic and underwent primary PCI, were included in this observational cohort study. The patients were divided into the single high-dose group (n = 40) and the double high-dose group (n = 40) according to the intracoronary bolus tirofiban regime. The primary endpoint was assumed as the incidence of major adverse cardiac event (s) (MACE) defined as all-cause mortality and repeat coronary revascularization (target vessel revascularization [TVR]) at 30 days. MACE and bleeding events were evaluated at 7 and 30 days.

Results: The primary endpoint was not significantly different between the single and the double high-dose groups (40.0% vs. 17.5%, $p = 0.994$). However, a significantly lower 30-day TVR rate was observed in the double high-dose group (27.5% vs. 7.5%, $p = 0.019$). No significant difference was observed in terms of 30-day all-cause mortality between the two groups (12.5% vs. 10.0%, $p = 0.712$). Major bleeding events were not observed in any group. Multivariate logistic regression analysis demonstrated that CRUSADE score (Hazard ratio [HR]: 5.721; 95% CI: 2.036 to 16.073, $p = 0.001$) and platelet count (HR: 1.009; 95% CI: 1.000 to 1.018, $p = 0.048$) were the independent predictors of bleeding at 7 days.

Conclusions: Double high-dose intracoronary bolus tirofiban in STEMI patients undergoing primary PCI was associated with significantly lower 30-day TVR rates without an increase in bleeding events. However, it did not significantly affect MACE and all-cause mortality rates.

Keywords: high-dose, glycoprotein IIb/IIIa receptor inhibitor, tirofiban, ST-segment elevation myocardial infarction, efficacy, safety

ST-segment elevation myocardial infarction (STEMI) is a potentially life-threatening condition, which usuallyoccurs as a result ofa vulnerable coronary plaque rupture and thrombus formation, andconsequently leads to an acute reduction inmyocardial blood flowand subsequentmyocardial necrosis.However, Itsometimesmanifests as sudden cardiac arrest due to ischemia-induced tachyarrhythmia. It is noteworthy that the incidence of STEMI is declining [1, 2], possibly due to the reduction in smoking, the aging

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of the population, and the prevalent use of statin therapy. Similar trends have been suggested for sudden cardiac arrest. Primary percutaneous coronary intervention (PCI) is the preferred approach for early restoration of myocardial blood flow in the infarct-related artery in patients with STEMI [3]. In addition, a combination of anti-ischemic, antiplatelet and antithrombotic therapies is indispensable.

Tirofiban is a highly selective anda short-acting platelet glycoprotein (GP) IIb/IIIa receptor inhibitor,which inhibits platelet aggregation by blocking the combination of fibrinogen and GP IIb/IIIa and consequently prevents myocardial ischemia caused by coronary thrombosis [4, 5]. Regarding tirofiban dosage, unlike the trials of low-dose bolus regimens [6-9], recent studies involving the high-dose bolus regimen support its efficacy in patients with STEMI undergoing primary PCI [10-12]. These results may translate to clinical benefit while not significantly increasing bleeding complications.Not only the optimal doses but also the ideal route of administration of GP IIb/IIIa receptor inhibitors has also been actively investigated [13, 14]. A previous study demonstrated that the standard intravenous tirofiban bolus plus infusion strategy was not superior to an intracoronary tirofiban bolus-only strategy with respect to improvement of microvascular perfusion after primary PCI [15]. In this study, we aimed to evaluate the efficacy and safety of single high-dose versus double high-dose intracoronary bolus tirofiban in STEMI patients undergoing primary PCI.

METHODS

Study Population and Design

This single-center, observational cohort study included a total of 80 patients, who were diagnosed with STEMI and underwent primary PCI within 12 h of the onset of symptoms at our cardiology clinic between January 2016 and June 2016. All patients meeting the inclusion criteria were included into the study consecutively. İnformed written consent was obtained from all patients. Data of the patients were obtained from file archives and catheter laboratory records.

The patients in the groups were in accordance with the current guidelines for the indication of tirofiban. The study population was divided into two groups by sequence number; the single high-dose group (n = 40) and the double high-dose group (n = 40). Depending on the sequence number, in the single high-dose group, tirofiban 25 mcg/kg via intracoronary route within 3 min followed by 0.15 mcg/kg/min via intravenous route for up to 24 h was administered, whereas in the double high-dose group, tirofiban 25 mcg/kg was administered within3min followed by a second dose after 5 min and 0.15 mcg/kg/min via intravenous route for up to 24 hour.Other medications were administered to all the patients according to the current best clinical practice: aspirin (loading dose of 300 mg, then 100 mg qd), clopidogrel (loading dose of 600 mg, then 75 mg qd), heparin (40-70 U/kg) or low molecular weight heparin, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), β-blocker, and statin therapy.

Patients with acute/chronic infective or inflammatory disease, severe heart valve disease, severe congestive heart failure (left ventricular ejection fraction (LVEF) < 30%), chronic kidney disease (glomerular filtration rate < 90 mL/min/1.73 m2), chronic liver disease and Killip class 3-4 were not included. The Institutional Ethics Committee approved the study protocol.

Data concerning cardiovascular risk factors, including age, gender, hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HPL), and smoking status were noted. Venous blood samples to measure complete blood count, lipid panel, high-sensitivity cardiac troponin T (hs-cTnT), creatinine, and high-sensitivity C-reactive protein (hs-CRP) levels were obtained from all the patients on admission. Routine blood chemistry and lipid panel parameters were measured with a standard auto-analyzer. Blood counts were measured with a Sysmex K-1000 (Block Scientific, Bohemia, New York, USA) auto-analyzer within 5 min of sampling. Serum concentrations of hs-cTnT were measured using an Elecsys 2010 analyzer (Cobas e 411; Elecsys, Roche Diagnostics, Mannheim, Germany). Serum concentrations of hs-CRP levels were measured using an automated chemistry analyzer by a commercial kit (Abbott, Aeroset, Holliston, Minn.).

Coronary intervention procedures were performed using commercially available Siemens (Axiom Sensis XP, Berlin, Germany) and Toshiba (Infinix CSI,Tokyo,

Japan) devices viafemoral access and standard techniques. Angiographic features, including initial TIMI flow, TIMI flow after tirofiban administration, final TIMI flow after PCI, no-reflow phenomenon, initial TIMI thrombus grade, and TIMI thrombus grade after tirofiban administration were evaluated by two blinded interventional cardiologists. The diagnosis of the no-reflow phenomenon was made when post-procedural TIMI flow grade is < 3, or in the case of a TIMI flow grade of 3 when myocardial blush grade is 0 or 1, or when ST resolution within 4 h of the procedure is < 70% [16]. Coronary thrombus was graded according to the TIMI thrombus scale [17].
Patients were followed up for 30 days for major adverse cardiovascular event (s) (MACE) and target vessel revascularization (TVR). All datas were recorded and there were no missing data. The cause of deaths were all cardiac, especially ventricular arrhythmia.

Clinical Endpoints and Definitions

Data regarding clinical end points were obtained from the health information system of our institute and the national health registry. No study-specific clinical follow-up was done. The primary endpoint was defined as the incidence of MACE defined as all-cause mortality and repeat coronary revascularization (target vessel revascularization [TVR]) at 30 days. TVR was defined as any revascularization procedure for stent thrombosis or in-stent restenosis, including bypass surgery, involving the initially treated artery. MACEs were evaluated at 7 and 30 days.Major bleeding was defined as an intracranial bleeding or a decrease in the hemoglobin concentration of 5 g/dL or more or a decrease in hematocrit of 15% or more. The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the American College of Cardiology / American Heart Association guidelines) score to stratify baseline risk of major bleeding was calculated. Bleeding was considered minor if the hemoglobin concentration decreased by < 5 g/dL or the hematocrit decreased by < 15% [18]. Bleeding events were evaluated at 7 and 30 days.

Statistical Analysis

Data analyses were performed using SPSS statistical software package version 20.0 (Chicago, IL, USA). Continuous variables were expressed as mean±standard deviation and median and interquartile range as appropriate. Categorical variables were expressed as numberand percentage. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Comparison of continuous variables between groups was performed using the Independent-Samples T test and the Mann–Whitney U test as appropriate. Comparison of categorical variables between groups was performed using the Chi-Square test and the Fisher's Exact test as appropriate. The correlation between certain variables of the treatment groups was performed using the Spearman's rank-order correlations analysisand the Pearson product-moment correlation analysis as appropriate. All significant parameters (p <0.01) in the univariate analysis were selected for the multivariate model and forward stepwise multivariate logistic regression analysis was used to determine the independent predictors of bleeding at 7 days. The coefficient of regression and 95% confidence interval for each independent variable were calculated. The 30-day event-free survival curves were constructed using the Kaplan-Meier method and statistical differences between curves were assessed by the log-rank test. The hazard ratio for treatment comparisons was estimated using Cox proportional hazard models. A two-tailed p - value of less than 0.05 was considered as significant.

RESULTS

A total of 80 patients (57 men and 23 women; mean age: 59.4 ± 10.4 years), who were diagnosed with STEMI and underwent primary PCI were included. The patients were divided into the single high-dose group (n = 40) and the double high-dose group (n = 40) regarding tirofiban dose. Baseline characteristics of the patients were similar in the two groups except in terms of gender and serum creatinine levels (Table 1).

Angiographic and procedural characteristics of the patients were similar in the two groups except in terms of the initial TIMI flow, TIMI flow after tirofiban administration and stent length (Table 2). Regarding the initial TIMI flow, proportions of patients with grade 0, 1, 2, and 3 in the single high-dose group were

Table 1. Baseline characteristics of the patients

Variable	Single high-dose group (n = 40)	Double high-dose group (n = 40)	*p*[a] value
Age (years)	59.2 ± 9.7	59.7 ± 11.2	0.807
Gender, (male), n (%)	24 (60.0)	33 (82.5)	**0.026**
HT, n (%)	11 (27.5)	14 (35.0)	0.605
DM, n (%)	6 (15.0)	7 (17.5)	0.501
HPL, n (%)	9 (22.5)	10 (25.0)	0.523
Current smoker, n (%)	10 (25.0)	12 (30.0)	0.766
CAD, n (%)	4 (10.0)	4 (10.0)	-[b]
CABG, n (%)	2 (5.0)	0 (0.0)	0.423
COLD, n (%)	1 (2.5)	1 (2.5)	-[b]
Hemoglobin (g/dL)	13.0 ± 2.1	13.1 ± 2.2	0.679
WBC, $\times 10^3$/uL	11.9 ± 4.9 10.25 (8.8-14.6)	11.0 ± 4.5 9.5 (8.2-14.5)	0.285
Hematocrit (%)	39.6 ± 6.0	41.0 ± 5.2	0.284
Platelet count, $\times 10^3$/uL	285.6 ± 74.6 269 (230.5-336.8)	287.3 ± 85.0 277 (222-321)	0.992
Creatinine (mg/dL)	0.8 ± 0.3 0.8 (0.6-1.0)	0.9 ± 0.3 0.9 (0.8-1.1)	**0.010**
Triglyceride (mg/dL)	202.5 ± 120.6 200 (96-266.8)	208.5 ± 111.7 212 (92-279)	0.573
Total cholesterol (mg/dL)	213.1 ± 58.4 209.5 (174.3-245.3)	205.0 ± 42.6 202 (184-237)	0.456
HDL cholesterol (mg/dL)	36.5 ± 7.9 33 (30-43)	39.1 ± 10.7 39 (32-44)	0.296
LDL cholesterol (mg/dL)	148.8 ± 55.2 138 (127.3-158.5)	143.4 ± 27.6 145 (128-160)	0.627
hs-CRP (mg/dL)	2.3 ± 2.9 1.8 (0.4-3.4)	2.5 ± 2.2 1.6 (0.8-3.7)	0.324
hs-cTnT (ng/mL)	3.1 ± 3.1 2.2 (0.76-4.2)	3.1 ± 3.3 1.7 (0.75-4)	0.722
LV ejection fraction (%)	46.1 ± 11.7	48.5 ± 7.0	0.261
CRUSADE risk category, n (%)			
Very low (score ≤ 20)	6 (15.0)	8 (20.0)	
Low (score 21-30)	11 (27.5)	14 (35.0)	
Moderate (score 31-40)	14 (35.0)	8 (20.0)	0.359
High (score 41-50)	8 (20.0)	6 (15.0)	
Very high (> 50)	1 (2.5)	4 (10.0)	
Cardiovascular drugs, n (%)			
Clopidogrel	40 (100.0)	40 (100.0)	-[b]
Aspirin	40 (100.0)	40 (100.0)	-[b]
β blocker	38 (95.0)	37 (92.5)	0.228
Statin	40 (100.0)	40 (100.0)	-[b]
ACE-I/ARB	40 (100.0)	40 (100.0)	-[b]

Data are presented as number (percentage) or mean ± standard deviation or median (interquartile range). HT = Hypertension, DM = Diabetes mellitus, HPL = Hyperlipidemia, CAD = Coronary artery disease, CABG = Coronary artery bypass grafting, COLD = Chronic obstructive lung disease, WBC = White blood cell, HDL = High-density lipoprotein, LDL = Low-density lipoprotein, hs-CRP = High-sensitivity C-reactive protein, hs-cTnT = High-sensitivity cardiac troponin T, LV = Left ventricle, CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines, ACEI = Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker

[a]Independent-Samples T test, Chi-Square test, Mann-Whitney U test.

[b]No statistics are computed becasue the variable is a constant.

Table 2. Angiographic and procedural characteristics

Variable	Single high-dose group (n = 40)	Double high-dose group (n = 40)	*p*[a] value
Culprit vessel, n (%)			
LAD	15 (37.5)	20 (50.0)	
LCx	9 (22.5)	8 (20.0)	
RCA	13 (32.5)	11 (27.5)	
IM	2 (5.0)	1 (2.5)	
SVG	1 (2.5)	0 (0.0)	
One vessel disease, n (%)	24(60.0)	21 (52.5)	0.423
Multi-vessel disesase, n (%)	16(40.0)	19 (47.5)	0.374
Mean ischemic time (min)	56	61	0.459
Killip class 1	21	18	0.562
Killip class 2	19	22	0.378
Balloon pre-dilatation, n (%)	24 (60.0)	27 (67.5)	0.485
Balloon post-dilatation, n (%)	17 (42.5)	9 (22.5)	0.056
No-Reflow, n (%)	29 (72.5)	25 (62.5)	0.363
Thrombus aspiration, n (%)	11 (27.5)	11 (27.5)	-[b]
Initial TIMI flow, n (%)			
Grade 0	12 (30.0)	16 (40.0)	
Grade 1	16 (40.0)	10 (25.0)	
Grade 2	12 (30.0)	12 (30.0)	
Grade 3	0 (0.0)	2 (5.0)	
TIMI flow after Tirofiban, n (%)			
Grade 0	8 (20.0)	6 (15.0)	
Grade 1	13 (32.5)	8(20.0)	
Grade 2	14 (35.0)	17(22.5)	
Grade 3	5 (12.5)	9 (22.5)	
Final TIMI flow after PCI, n (%)			
Grade 0	4 (10.0)	2(5.0)	
Grade 1	11 (27.5)	8 (27.5)	
Grade 2	14 (35.0)	16 (40.0)	
Grade 3	11 (27.5)	14 (35.0)	
Stent diameter (mm)	3.0 ± 0.5 3.0 (2.75-3)	3.0 ± 0.4 3.0 (2.75-3)	0.682
Stent length (mm)	24.9 ± 8.6 24 (18-28)	21.2 ± 10.2 19 (16-24)	0.005
Stent type, n (%)			
DES	30 (75.0)	27 (67.5)	0.459
BMS	10 (25.0)	13 (32.5)	
Initial TIMI thrombus grade, n (%)			
Grade 1	5 (12.5)	4 (10.0)	
Grade 2	22 (55.0)	18 (45.0)	
Grade 3	12 (30.0 %)	12 (30.0)	
Grade 4	1 (2.5)	5 (12.5)	
Grade 5	0 (0.0)	1 (2.5)	
TIMI thrombus grade after Tirofiban, n (%)			
Grade 1	11 (27.5)	14 (35.0)	
Grade 2	18 (45.0)	14 (45.0)	
Grade 3	10 (25.0)	8 (20.0)	
Grade 4	1 (2.5)	4 (10.0)	
Grade 5	0 (0.0)	0 (0.0)	

Data are presented as number (percentage) or mean ± standard deviation or median (interquartile range). LAD = Left anterior descending artery, LCx = Left circumflex artery, RCA = Right coronary artery, IM = Intermediate artery, SVG = Saphenous vein graft, MI = Myocardial Infarction, DES = Drug-eluting stent, BMS = Bare-metal stent, TIMI = Thrombolysis In Myocardial Infarction, PCI = Percutaneous coronary intervention

[a]Chi-Square test, Mann-Whitney U test.

[b]No statistics are computed becasue the variable is a constant

Table 3. Clinical events at 7 and 30 days

	Single high-dose group (n = 40)	Double high-dose group (n = 40)	HR (95% CI)	*p*[a] value
MACE at 7 days, n (%)				
TVR	6 (15.0)	3 (7.5)	0.387 (0.077-1.938)	0.206
Death	2 (5.0)	2 (5.0)	0.296 (0.027-3.274)	0.291
Total	8 (20.0)	5 (12.5)	0.478 (0.124-1.729)	0.195
MACE at 30 days, n (%)				
TVR	11 (27.5)	3 (7.5)	0.186 (0.037-0.945)	**0.019**
Death	5 (12.5)	4 (10.0)	0.756 (0.171-3.342)	0.712
Total	16 (40.0)	7 (17.5)	0.997 (0.381-2.605)	0.994

Data are presented as number (percentage). HR = Hazard ratio, CI = Confidence interval, MACE = Major adverse cardiac event(s), TVR = Target vessel revascularization.

[a]Log-Rank test.

30.0%, 40.0%, 30.0% and 0.0%, respectively, and in the double high-dose group they were 40.0%, 25.0%, 30.0% and 5.0%, respectively. Nevertheless, the proportion of patients with TIMI flow grade 2 after tirofiban administration was higher in the double high-dose group than in the single high-dose group. In addition, it is noteworthy that there wasmorepatients with TIMI flow grade 0-1-2 (noreflow) in the single high-dose group after tirofiban administration. Moreover, shorter stentswere deployed in the double high-dose group than in the single high-dose group ($p = 0.005$).

According to the Kaplan-Meier analysis, the primary endpoint was not significantly different

Table 4. Bleeding events at 7 and 30 days

	Single high-dose group (n = 40)	Double high-dose group (n = 40)	*p*[a] value
Bleeding at 7 days, n (%)			
Minor	5 (12.5)	5 (12.5)	-[b]
Major	0 (0.0)	0 (0.0)	-[b]
Bleeding at 30 days, n (%)			
Minor	9 (22.5)	6 (15.0)	0.390
Major	0(0.0)	0 (0.0)	-[b]

Data are presented as number (percentage).

[a]Chi-Square test.

[b]No statistics are computed becasue the variable is a constant.

between the two groups (single high-dose group: n = 16 (40.0%) vs. double high-dose group: n = 7 (17.5%); hazard ratio (HR): 0.997 (95% confidence interval [CI]: 0.381 to 2.605); log-rank test p = 0.994. However, analysis of the two main components of MACE revealed a significantly lower 30-day TVR rate in the double high-dose group (single high-dose group: n = 11 [27.5%] vs. double high-dose group: n = 3 [7.5%]; HR: 0.186 [95% CI: 0.037 to 0.945]; log-rank test p = 0.019) and a similar 30-day all-cause mortality rate in the two groups (single high-dose group: n = 5 [12.5%] vs. double high-dose group: n = 4 [10.0%]; HR: 0.756 [95% CI: 0.171 to 3.342]; log-rank test p = 0.712). Clinical events at 7 and 30 days are shown in Table 3.

There was no major bleeding in both groups. Minor bleeding occurred in 12.5% of the patients in each group at 7-day. Bleeding events at 7 and 30 days are shown in table 4. Forward stepwise multivariate logistic regression analysis demonstrated that CRUSADE score (HR: 5.721; 95% CI: 2.036 to 16.073, p = 0.001) and platelet count (HR: 1.009; 95% CI: 1.000 to 1.018, p = 0.048) were the independent predictors of bleeding at 7 days (Table 5).

Table 5. Independent predictors of bleeding at 7 days

	Univariate Model		Multivariate Model		
	Correlation coefficient	*p* value	HR	95% CI	*p* value
Age	0.332	**0.003**	-	-	-
CRUSADE score	0.484	**< 0.001**	5.721	2.036-16.073	**0.001**
Plasma hemoglobin level	-0.220	0.052	-	-	-
Platelet count	0.192	0.090	1.009	1.000-1.018	**0.048**
Serum creatinine level	0.271	**0.016**	-	-	-

HR = Hazard ratio, CI = Confidence interval, CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines

DISCUSSION

The substantial finding of our study is that, administration of double high-dose intracoronary bolus tirofiban in STEMI patients undergoing primary PCI, in addition to aspirin, heparin, and high-dose clopidogrel, wasassociated with lower 30-day TVR rates without leading to a significant increase in minor or major bleeding.However, it did not significantly affect MACE and all-cause mortality rates. Unlike the trials involved low-dose bolus regimens [6-9], studies involving the high-dose bolus regimen of tirofiban support its efficacy and safety in patients with STEMI undergoing primary PCI [10-12]. To the best of our knowledge, this is the first study in the literature comparing the efficacy and safety of the single high-dose versus double high-dose intracoronary bolus tirofiban in patients undergoing primary PCI.

Despite the considerable progress that has been made recently regarding the treatment of STEMI, including modern antithrombotic therapy, thrombus aspiration, and drug-eluting stents, questions have been raised concerning the potential benefit of GP IIb/IIIa receptor inhibitor in this setting. Several studies have demonstrated that despite these treatments events associated with thrombotic occlusion during or after PCI may still occur in 4-12.8% of the patients, and in high-risk patients, these events occur more often [19, 20]. Tirofibanis a potent, competitive and inhibitor GP IIb/IIIawith a high specificity and affinity for the GP IIb/IIIa receptor [21]. It is a small and nonpeptide tyrosine derivative that dissociates from the GP IIb/IIIa receptor relatively rapidly, with a half-life of 2-4 hours, and its action is therefore reversed within hours after the completion of the infusion [22]. Such reversibility may have significant implications with regard to bleeding, particularly in patients who are considered for

emergent cardiacsurgery.

The utility of tirofiban in patients with STEMI has been investigated in several trials [6, 10, 11, 23-25]. These studies have evaluated both the 10 mcg/kg bolus and the high-dose bolus regimens. Administration of GP IIb/IIIa receptor inhibitors for bail-out therapy where there is an angiographic evidence of massive thrombus, slow or no-reflow or a thrombotic complication in patients with STEMI is a class IIa indication according to the diary guideline of the European Society of Cardiology [26]. Large studies show that in the real-world practice, GP IIb/IIIa receptor inhibitors are approximately given to 25-30% of patients with STEMI, often for bail-out situations [27, 28]. However, they should not be always restricted to patients with complications after PCI, even in the setting when high-dose clopidogrel isalready given in advance of PCI because the maximum antiplatelet effect of 600 mg clopidogrel is achieved only after 2-4 h. Recent studies suggest that the high-bolus dose of tirofiban results in optimum platelet aggregation in most patients very early after PCI [23, 29]. Early administration of GP IIb/IIIa receptor inhibitors has actually attributed to the improvement in post-procedural myocardial perfusion and reduction in clinical outcomes, including death and cardiogenic shock [30, 31].

The results of several studiesinvolving early administration of tirofiban in patients undergoing primary PCI utilizing the 10 mcg/kg bolus regimen have suggested potential benefitsregardingthe restoration ofblood flow in the infarct-related artery and myocardial perfusion, although no improvement was found in clinical outcomes [6-8, 32].The On-TIME 2 trial [11], was the first study to determine the benefits of pre-hospital administration of tirofiban utilizing high-dose bolus regimen in addition to dual antiplatelet therapy measured by ST-segment deviation resolution. In this study, mean residual ST deviation before PCI and 1 h after PCI was significantly lower in patients pretreated with high-bolus dose tirofiban than in those given placebo. Although, the rate of major bleeding did not differ significantly between the two groups. In addition, the results of 30-day follow-up demonstrated a significant benefit favoring tirofiban regarding the combined incidence of death, recurrent myocardial infarction, urgent TVR or thrombotic bailout. Moreover, further analysis suggested a relationship between the level of residual ST-segment deviation and mortality. Thus, On-TIME 2 trial has demonstrated a benefit of high-dose bolus regimen of tirofiban over placebo with respect to clinical outcomes. Indeed the results of our study concerning TIMI flow before PCI and TVR rates at 30 days favoring not only the high-dose bolus regimen of tirofiban but also highlighting the potential benefits of double high-dose bolus regimen, without an increase in bleeding events.

In our study, triple antiplatelet therapy, with double high-dose bolus regimen of tirofiban, high-dose clopidogrel (600 mg) and aspirin pretreatment was not associated with an increased risk of major bleeding. This finding might be related to a very careful heparin-dose protocol at our catheterization laboratory where we only give extra heparin during complex PCI procedures which exceed 1 hour in duration. Furthermore, low-molecular-weight heparin was directly discouraged after completion of the tirofiban infusion except for patients with atrial fibrillation and prosthetic heart valve with an international normalized ratio less than 2.

Agents inhibiting platelet functions would be associated with an increased risk of bleeding. As it is well known, bleeding complications in patients undergoing PCI have been associated with an increased morbidity and mortality [33]. Therefore, preventing excessive bleeding is critical. Although it has been suggested that early initiation of a GP IIb/IIIa receptor inhibitor in patients with acute coronary syndrome may lead to an increase in bleeding [34], this was not observed in either the On-TIME 1 or the On-TIME 2 trials. Nevertheless, the results of On-TIME 2 trial revealed that there was no excess in major bleeding, even in patients receiving pre-hospital high-dose bolus tirofiban in addition to high-dose clopidogrel.

In our study, the rate of target vessel revascularization (TVR) at 30 days looks very high (27.5%) in the single high-dose group, because noreflow was more in single high-dose group, stent length was longer in single high-dose group. We attribute the difference in the value of TVR to these reasons.

Limitations

Our study has limitations that warrant

consideration. First, this was a single-center observational study with a small number of patients. A multi-center study involving more patients could have more significant results and data. Second, our results may not apply to patients with renal insufficiency since they were not included.

CONCLUSION

Double high-dose intracoronary bolus tirofiban regimen in STEMI patients undergoing primary PCIwas associated withsignificantly lower 30-day TVR rates without an increase in bleeding events. However, it did not significantly affect MACE and all-cause mortality rates.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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A modified basket catheter technique with semi-rigid ureterorenoscopy in the prevention of migration of proximal ureteral stones

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ABSTRACT

Objectives: Although proximal ureteral stones are common, some difficulties are encountered in semi-rigid ureterorenoscopy (URS) treatment, especially as a result of stone migration to the kidney. In this paper, we present a different use of a basket catheter for the treatment of proximal ureteral stones.

Methods: Between September 2016 and January 2019, 101 patients over 18 years of age detected to have a maximum 15-mm proximal ureteral stone were retrospectively evaluated, and 93 patients fulfilling the criteria were included in the study. Semi-rigid URS and a modified basket catheter were used together in 44 patients while no auxiliary equipment was utilized for the remaining 49 patients. In the study group, a 3F zero-tip basket catheter was disintegrated and positioned in a way to capture and retrieve the stone from the semi-rigid ureterorenoscope.

Results: No difference was found between the two groups in terms of age, body mass index, gender, and stone characteristics. The duration of operation was shorter in the basket catheter group ($p < 0.001$). The rates of stone migration, requirement to switch to flexible ureterorenoscopy (FURS), and double J-stent (JJ-stent) placement were significantly higher in the control group ($p < 0.005$). There were no significant differences between the two groups concerning operation success and complications ($p = 0.068$ and $p = 0.772$, respectively).

Conclusions: The modified basket catheter technique with semi-rigid URS was successful in preventing the migration of proximal ureteral stones. This method can be considered as an alternative in cases where FURS is not available.

Keywords: Basket catheter technique, proximal ureteral stones, semi-rigid ureterorenoscopy

Ureteral stones are one of the most common urological problems, with treatment options varying according to the location, size and composition of the stone, patient preference, experience of the surgeon, and availability of auxiliary equipment [1]. During treatment with a semi-rigid ureterorenoscopy (URS), the proximal location of the stone both reduces treatment success and increases complication rates [2]. Therefore, the use of flexible URS (FURS) is recommended for the surgical treatment of proximal ureteral and renal pelvic stones [1]. The retrograde migration of stones to the kidney is reported to vary between 3 and 15% for distal ureteral stones [3, 4], but this rate can reach 60% for stones located in the proximal ureter [5-7]. The treatment of stones that have migrated to the kidney require additional procedures,

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repetition of surgery, and JJ stent applications, which increase the morbidity rates and treatment cost.

In order to increase the success of the procedure and prevent stone migration, many mechanic devices (wire-balloon) and gels have been developed and provided successful results when placed in the proximal part of the stone. Stone baskets, such as LithoCatch®, Parachute® and Escape®, as well as vacuum device Lithovac®, balloon basket Parachute®, and Stone Cone®, PercSys Accordion® and NTrap® that form a barrier in the proximal of the stone are among mechanical tools designed to prevent stone migration [8-16]. In addition, BackStop® gel is a temporary congestion-forming substance in the heat-sensitive proximal of the stone to prevent migration [17].

With these developments, the relatively high cost of auxiliary equipment has led to the search for a cheaper and more effective method due to the limited health budget. In the current study, we aimed to present a different use of a basket catheter to prevent migration of proximal ureteral stones.

METHODS

After obtaining the approval of the university's Ethics Committee, 101 patients older than 18 years of age detected to have a proximal ureteral stone with a maximum diameter of 15 mm between September 2016 and January 2019 were retrospectively evaluated. Patients with congenital anomalies, accompanying renal stones or multiple ureteral stones were excluded from the study. Stone could not be reached in three patients due to the kinking of the proximal ureter. JJ stents were implanted in two of these patients and percutaneous nephrolithotomy (PNL) was performed in the last patient. Five patients were found to have pyonephrosis, of whom two were treated with a percutaneous nephrostomy catheter and three received a JJ stent. The patients who underwent PNL, nephrostomy and JJ stent were also excluded from the study.

The age, gender, body mass index (BMI) and comorbid disease history of the patients were recorded. In addition, hemogram, blood urea nitrogen, creatinine and urinalysis tests were conducted preoperatively. Stone localization was determined by computerized tomography (CT). The largest diameter of the stone was recorded and the stone volume was calculated as mm2 by multiplying the length and width measured on CT. URS was scheduled for patients that did not pass the stone through conservative treatment, those resistant to extracorporeal shock wave lithotripsy (ESWL)with non effective ESWL, and those for whom surgery was preferred due to severe pain and hydronephrosis.

Semi-rigid URS was performed in 93 patients (41 female, 52 male), who met the study criteria. A modified basket catheter was used in combination with URS in 44 patients, while the remaining 49 patients underwent URS without auxiliary equipment. A ureteral stricture that prevented the passage of URS in the distal of the stone was detected in six patients in the control group and four patients in the study group. In these patients, balloon dilation was performed under fluoroscopic control and the operation was continued.

In the control group, no auxiliary equipment was used to prevent stone migration. In the study group, a 3F zero-tip basket catheter (Baycare, Bayrak Medikal, Turkey,) was reconfigured and positioned in a way to capture and retrieve the stone from the ureterorenoscope (Karl Storz 9-11F, Tuttlingen, Germany) (Figs. 1 and 2). Then, ureterorenoscope was taken out and a laser lithotripter was introduced through the ureterorenoscope adjacent to the basket catheter to fragment the stone (Fig. 3). When this procedure was completed, the basket was removed from the ureter and used in the same configuration for stone retrieval from the URS. During stone extraction, if there was anything that blocked passage in any section of the ureter, the ureterorenoscope was taken out and the stone fragmentation process was repeated using the lithotripter running adjacent to the basket catheter (Fig. 4). The detached basket catheter technique was implemented by two surgeons with similar experience. A laser fiber of 365-µm in thickness was used in all patients. Stone fragmentation was performed at a laser frequency of 5 Hz and power of 1.5 Joules. The two groups were compared in terms of stone migration, peroperative requirement of switching to FURS, intraoperative and postoperative complications, JJ stent placement, operation time and success, postoperative ESWL, and second surgery requirement. The operation success was assessed at the postoperative third week using Kidney-Ureter-Bladder (KUB) X-ray in

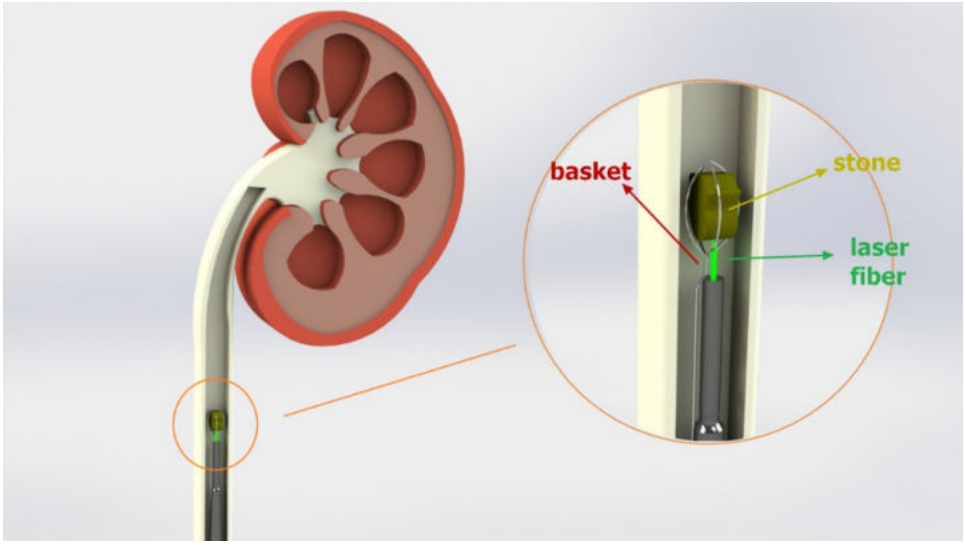

Fig 1. Schematic view of the use of the modified basket catheter.

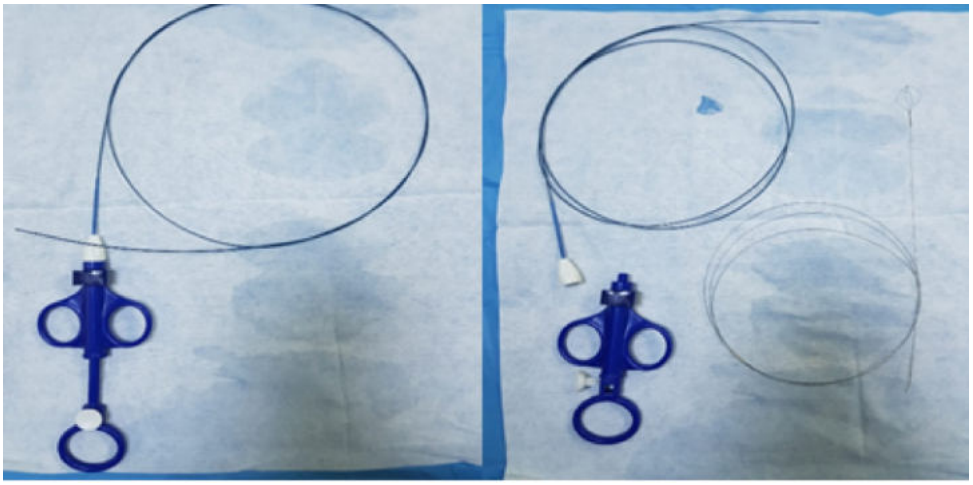

Fig 2. Normal and modified configuration of the basket catheter.

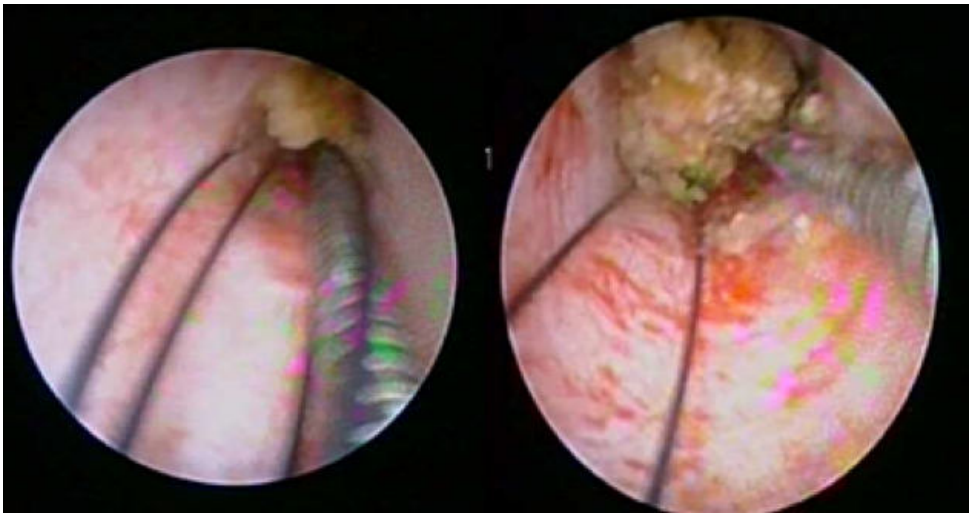

Fig 3. Engagement of the stone by the modified basket catheter.

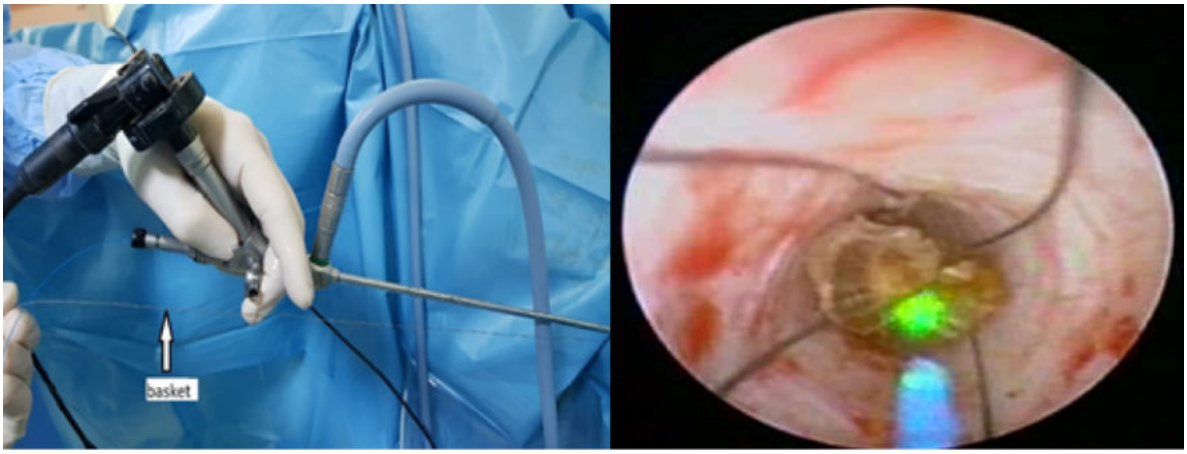

Fig 1. Schematic view of the use of the modified basket catheter.

opaque stones and ultrasonography and non-contrast CT in non-opaque stones.

Statistical Analysis

The data were analyzed using SPSS version 25.0 (SPSS®, IL, USA). Normally distributed data were presented as mean ± standard deviation (SD). Student's t-test was employed for continuous variables, and chi-square and Fisher's exact tests for categorical variables. $p < 0.05$ was considered statistically significant.

RESULTS

The mean age of the patients was 48.2 ± 15.9 years and the mean stone length was 10.7 ± 2.1 mm. No difference was found between the two groups in terms of age, BMI, gender, and stone characteristics (Table 1). The mean operative time was 49.5 ± 10.1, and the duration of operation was shorter in the basket catheter group ($p < 0.001$). The rates of stone migration, requirement of FURS and JJ-stent placement were significantly higher in the control group ($p < 0.005$). No significant difference was found between the two groups concerning operation success and complications ($p = 0.068$ and $p = 0.772$, respectively) (Table 2).

Stone migration to the kidney was observed in five patients in the study group during surgery. In three of these patients, the stone was not visualized in the proximal ureter at first insertion (considered to be due to the irrigation fluid causing stone migration to the kidney), whereas for the two remaining cases, the stone migrated during the procedure. In two of the three patients whose stone was not visualized at first insertion and one of the two patients with peroperative stone migration, the stone was captured using the basket catheter in the renal pelvis and pulled into the proximal ureter; then, stone fragmentation was applied. It was necessary to switch to FURS in two patients in the study group. In the control group, the

Table 1. Comparison of the demographic and stone characteristics of the patients

	Basket catheter group	Control group	*p* value
Age (years)	45.16 ± 13.9	51.02 ± 17.2	0.077
BMI (kg/m^2)	25.7 ± 3.5	24.8 ±3.2	0.233
Gender (F/M)	21/23	20/29	0.503
Stone side (right/left)	19/25	26/23	0.341
Stone width (mm)	11.02 ± 2.7	10.43 ± 1.32	0.191
Stone volume (mm^2)	100.9 ± 49.8	91.18 ± 22.04	0.238

BMI = body mass index

stone was not visualized in two patients at first insertion, and stone migration occurred in 25 further patients during surgery, making the total 27. It was seen that in 13 of the 27 patients, the stone was fragmented; thus, a JJ stent was implanted and the procedure was terminated. For the remaining 14 patients, FURS was utilized. Mild mucosal injury and hematuria occurred in two patients in the study group. In the control group, three patients had hematuria and four patients had mild mucosal injury that did not require termination of the operation. In the postoperative period, urinary tract infection developed in four patients in the study group and three patients in the control group. None of the patients had a ureteral stricture. The postoperative complications were evaluated according to the Modified Clavien (MC) classification (Table 2).

DISCUSSION

When the ureteral stones are classified according to their localization, those located in the proximal ureter have higher migration and complication rates and lower operative success compared to those in the mid-distal ureter [2, 18]. The type of energy used in the fragmentation of the stone also affects migration and the success of the operation [19-21]. Stone-Cone is one of the tools devised to prevent stone migration and it is recommended for use in the treatment of ureteral stones due to significantly reducing the possibility of stone migration [8, 20]. However, although this device increases the operation success, it cannot be effectively used in the retrieval of fragmented stones. In addition, Stone-Cone is more effective in dilated stones of 7-10 mm in diameter. If the dilatation in the proximal of the stone is more than 10 mm, the effect of the device is reduced. In the current study, since we used a modified configuration of a basket catheter to engage the stone, proximal ureter dilatation was not important. Considering that the inner diameter of the basket is 15 mm, it can be used to prevent the migration of stones of this size. A further study to compare Stone-Cone and the modified basket catheter in the prevention of stone migration can provide clearer data.

Table 2. Comparison of the study and control groups in terms of the operation outcomes and complications

	Basket catheter group	Control group	*p* value
Stone migration, n (%)			
First insertion	3 (6.9%)	2 (4.08%)	
During procedure	2 (4.5%)	25 (51.02%)	
Total	5 (11.4%)	27 (55.1%)	**< 0.001**
Use of FURS, n (%)	2 (5.5%)	14 (28.6%)	**0.002**
Complete stone-free rate, n (%)	36 (81.8%)	30 (61.2%)	
Residual fragments, n (%)			
≤ 3mm	6 (13.6%)	11 (22.4%)	0.068
> 3mm	2 (4.5%)	8 (16.3%)	
JJ stent requirement (n)	28 (63.6%)	43 (87.8%)	**0.006**
Operation time (min)	42.27±7.54	56.1±7.24	**< 0.001**
Complications, n (%)			
MC1	6 (13.6%)	7 (14.3%)	
MC2	5 (11.4%)	8 (16.3%)	0.772
Postoperative ESWL, n (%)	1 (2.3%)	5 (10.2)	0.207
Second surgery, n (%)	1 (2.3%)	3 (6.1%)	0.619

FURS = flexible ureterorenoscopy, JJ = Double j, MC = modified Clavien classification, ESWL = extracorporeal shock wave lithotripsy

The basket catheter is primarily designed for the removal of stone fragments from the ureter. In case of any entrapment occurring during the procedure, basket catheter can be disintegrated. This design allows the free release of the ureterorenoscope from the ureter. In the presented technique, the modified basket catheter was used to both prevent stone migration and retrieve residual stones after fragmentation.

In the study of Kesler *et al*. [9] concerning the Escape® basket (Boston Scientific Corp., Natick, MA, USA) and that of Kroczak *et al*. [10] investigating a basket catheter, the basket and laser were both inside the ureterorenoscope. In contrast, in the current study, the ureterorenoscope and laser were used independently from the basket catheter. The basket catheter being located adjacent to the ureterorenoscope, not inside, allows the use of a thicker laser fiber in the working channel. We also consider that this facilitates the flow of the irrigation fluid and allows the ureterorenoscope to be more easily manipulated. In his study with a small group of patients, Kesler *et al*. [9] determined the complete stone-free rate to be 100%, but he did not refer to stone localization or stone migration. In another study investigating the dual use of a basket catheter, Kroczak *et al*. [10] reported stone migration in 10 patients (14.7%), which is similar to the rate determined in the current study (five patients; 11.4%). However, the requirement of switching to FURS was lower in our study (two patients; 5.5%) compared to the study by Kroczak *et al*. [10] (19 patients; 24.1%). Lastly, our higher rate of JJ stent requirement in the control group may be due to the requirement of FURS in more patients in this group.

Since most devices that prevent stone migration cannot be used for stone extraction, the cost of surgery increases. Therefore the EAU guidelines recommends the need and use of a FURS in such cases independently of the retropulsion device.In the presented technique, the basket catheter, which is cheaper than other migration-preventing equipment, not only reduced the possibility of stone migration but also helped to retrieve stone fragments from the ureter, reducing the total cost of surgery.

One of the drawbacks of using a basket catheter to prevent stone migration is that the laser damages the wires of the basket. In the current study, we had to use a second basket in five patients because the laser cut the single wire of the basket. However, this did not harm any of the patients and the basket was successfully removed as a whole. Our complication rates in both groups were similar to those reported in previous studies [23, 24], and we did not observe any major complication.

We consider that the lack of a statistically significant difference between the two groups in terms of operative success was due to the continuation of surgery by switching to the use of FURS in cases of stone migration in the control group. This may also be one of the reasons for the longer duration of operation in the control group. Although we have access to FURS, it is an expensive device with a limited lifetime; therefore, we suggest that using semi-rigid URS as a safe and effective method for the treatment proximal ureter stones and switching to the use of FURS in cases where necessary will reduce the cost of surgery without compromising patient safety.

Limitations

The limitations of our study include the retrospective nature and non-randomized design. Furthermore, not all the patients underwent CT in the postoperative follow-up, with ultrasonography and KUB X-ray being used in some cases. This may be regarded as another limitation considering that CT follow-up after stone surgery has been shown to be superior in showing residual fragments [25]. Randomized controlled prospective studies with other migration-preventing devices are needed to better demonstrate the efficacy of the presented method.

CONCLUSION

In conclusion, the modified basket catheter technique is effective in preventing the migration of proximal ureter stones when applied with semi-rigid URS. This method can be used as an alternative when FURS is not available or resources are limited and FURS is reserved for more complicated cases requiring longer-term treatment.

Conflict of interest

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The European Research Journal 2021;7(1):29-31 Original Article

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Is the fear of malignancy in large adrenal masses realistic?

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ABSTRACT

Objectives: Adrenal masses are more frequently detected in autopsy series in recent years and are more frequently detected in clinical practice due to the development of radiological examinations. After the detection of an adrenal mass, the first two important questions come to mind. Does the mass hormonally active (functionally) or not active (non-functional), and this mass is a benign formation or is it malignant? The answer to these two questions is the obligatory questions that clinicians must answer in order to make an operation decision. The decision of operation in non-functioning adrenal masses is directly proportional to the mass's neoplastic potential. If a preoperative histopathological diagnosis is not available; this potential is predicted by the size of the mass in radiological imaging. It is shown that the malignancy rate in adrenal masses is higher in lesions 6 cm and above. In this study, we aimed to determine whether the rate of malignancy is really high in histopathological examination as a result of adrenalectomy operations performed in our clinic between the years of 2010-2012.

Methods: Fourteen women and 4 men with 6 cm or higher adrenal masses patients which performed adrenalectomy by Eskişehir Osmangazi University Faculty of Medicine Department of General Surgery between 2010-2012 were included in this study. The results of the final histopathological analysis were classified retrospectively.

Results: The rate of malignancy in adrenal masses of 6 cm or more supported by the literature was found to be high in our clinical series.

Conclusions: As a result of our clinical retrospective study, we think that the extent of the formation in the related gland is highly effective and significant in making an operation decision before adrenalectomy.

Keywords: Adrenal, mass, surgery

Adrenal glands are located upper side of both kidneys, which plays an important role of water and electrolyte balance in body metabolism. It is the main organ in the body's stress response due to hormones it secretes. Although the incidence of adrenal masses is increasing in autopsy series, their incidence reaches peak levels in the fifth decades. Although many adrenal masses do not cause clinical symptoms and do not cause any health problems, adrenal gland-borne diseases have mainly high clinical value such as Cushing, Conn, Addison, Pheochromocytoma, and have long-term follow-up. Adrenal masses that have been detected during radiological examinations for another reason and which are not known before are called adrenal insidentilomas [1]. In order for this definition to gain value, the patient should not be aware of the presence of an adrenal disease and the patient should not be followed for oncological reasons. In recent years, the incidence of adrenal insidentilomas has increased with the development of radiological examinations and equipment. When any adrenal mass is encountered, two important questions come to mind. The first

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is whether this mass is hormoneally active (functional-nonfunctional), and the second is whether this mass is malignant or benign. These benign and malign lesions include adenomas, myolipomas, ganglioneuromas, pheochromocytoma, cysts, hematomas, adrenocortical cancers and metastases. Cancers among these causes of incidentiloma have a significant mortality rate. Therefore, it is critical to establish the presence of malignancy. The feature of the mass which is thought to increase the prevalence of malignancy in adrenal masses revealed by the studies, stands out as 'dimension'. This rate is 2% in tumors less than 4 cm, 6% in 4-6 cm, and 20% in masses over 6 cm [2]. In this study, we tried to show the realism of malignancy rate in these masses of 6 cm or more in adrenalectomies performed in our clinic for 2 years.

METHODS

Between January 2010 and December 2012, we included 18 cases of adrenal insidentiloma of 6 cm and over performed by Eskişehir Osmangazi University general surgery department. There was no previous history of malignancy or history of the adrenal gland. Insidentilomas detected in each patient after tomography or abdominal pain for the patients who applied to our clinic. Fourteen patients were female and 4 were male and the mean age was 50 ± 2 years. A detailed medical history was obtained from all patients before the surgery and detailed physical examinations were performed. Serum cortisol, aldosterone, dehydroepiandrostenedione sulfate levels, free cortisol, vanilla mandelic acid, metanephrine levels in the urine were studied in patients with a known pre-operative adrenal-derived hormone active disease required for routine blood count and biochemical parameters. Upper abdominal computed tomography was performed in all patients. Some patients (n = 8) received support from dynamic adrenal computed tomography.

RESULTS

When the histopathological results of 18 adrenalectomy cases included in the study were evaluated; there were 8 adrenal adenomas, 4 adrenal cysts, 1 lymphangioma, 1 hemangioma, 2 adrenal carcinoma and two adrenal oncocytic tumors (Table 1). Four (22.2%) of 18 adrenalectomy cases had malignant potential. Under these data, a malignancy rate of 22.2% was observed in patients who were operated due to an adrenal mass of 6 cm or more. When the literature was examined, it was observed that the rate of frightening malignancy up to 20% was realistic in the masses of 6 cm and above and that this rate was present in our clinical practice. In the evaluation of the difference between the two ratios, two ratio tests were performed and no difference was found ($p = 0.815$).

Table 1. The histopathological results of 18 adrenalectomy cases

Diagnosis	Number (n)	Percent (%)
Adenoma	8	44.4
Cyst	4	22.2
Carcinoma	2	11.1
Oncocytic tumor	2	11.1
Hemangioma	1	5.55
Lymphangioma	1	5.55

DISCUSSION

In recent years, with the development of radiological techniques, an increase in the incidence of adrenal masses and an increasing number of operations for these masses are striking. Adrenal insidentiloma is a condition that is detected during screening for other reasons in patients who have unknown adrenal origin disease and who are not followed-up for any oncologic process [3]. Although the ratio of adrenal masses is 1.2-1.3 for gender (Female/Male), the mean age group is between 5 and 6 decades. In our study, the patient portfolio was found to be compatible with the age of occurrence, but inconsistent with respect to the ratio of men and women (14 females-4 males, mean age: 50 ± 2 years) [4].

Adrenal masses are usually in benign behavior (94%) and hormonal inactive (90%) and most of them do not show clinical findings. It has also been shown that approximately 80% of these masses are smaller than 2 cm in size. However, when any adrenal mass is encountered, there are two critical questions that must be answered before the operation decision. The first of these; whether the mass is hormonal active or not.

Second, the question is whether this mass is benign or malignant. If there is a suspicious histopathological examination before the operation, this option will lead to the operation. If the mass is hormonal active, the operation should be decided after the necessary preparations. However, in case of a mass that does not have a hormonal inactive and histopathological verification, the decision should be made acording to the malignancy potential of the mass [5]. Based on the available information, the only parameter available to evaluate the malignancy potential of an hormonal inactive adrenal mass is the size of the parameter. It is thought that as the size of an adrenal mass increases, the potential of malignancy increases. While the malignancy rate is 2% for masses smaller than 4 cm masses, 6% in the masses between 4-6 cm and 20% in the masses larger than 6 cm [6].

The most commonly used method for imaging adrenal masses is abdominal computed tomography (CT). Ultrasonography and magnetic resonance imaging (MRI) are also frequently used imaging methods. We preferred CT as the imaging method in all of our cases. Fine needle aspiration biopsy (FNAB) may be used in the evaluation of insidentilomas in some centers. However, false negative rates and complications may occur in approximately 40% of these cases [7]. There is no standard surgical procedure for adrenal masses, but laparoscopic adrenalectomy is a minimally invasive surgical technique. Laparoscopy is the gold standard in the surgical treatment of benign adrenal masses. Laparoscopy and open surgery should be decided by considering the relationship of the mass with the surrounding tissues, the surgeon's experience and additional internal diseases [8].

Many surgeons do not recommend surgical procedures for non-functional adrenal masses of 4 cm or less, considering the low malignancy rate [9]. Some authors recommend surgery for masses of 3 cm and over, while others recommend surgery for masses of 6 cm and over, while Linos et al. [10] argue that each patient should undergo adrenalectomy.

CONCLUSION

In our study, the rate of approximately 22% seen in tumors 6 cm and over was similar to the 20% risk of malignancy in the current literature. The data obtained from the detailed examination also support the low malignancy rates of tumors 4 cm or less. We selected 4 cm as the limit for our clinical evaluation of patients with adrenal mass. Radiologically close follow-up in smaller masses; In the masses of 4 cm and above, we are in favor of making an operation decision.

Conflict of interest

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The European Research Journal 2021;7(1):32-37 Original Article

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Effect of amino acid infusion on perioperative thermoregulation in newborn surgery

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ABSTRACT

Objectives: Decreased drug metabolism, coagulation disorders, wound infections, and cardiac arrhythmias are the most important and well-known results of intraoperative hypothermia. Perioperative amino acid infusion is known to prevent intraoperative hypothermia during general anesthesia in adults. In this study, we aimed to demonstrate the effect of perioperative amino acid infusion on the prevention of hypothermia during general anesthesia in newborn surgery.

Methods: Twenty surgical newborns, aged 1-30 days, were enrolled in this prospective randomized controlled study. Newborns were assigned randomly into two groups: the amino acid/dextrose (AAD) group and the dextrose (D) group. The core temperatures of the newborns were measured from the distal esophagus in the first minute of the induction once and every fifteen minutes thereafter. The core body temperature changes in each group during the operation and the differences between the two groups were analyzed.

Results: The surgical operations in each group were similar. The mean operating room temperatures of AAD and D groups were 25.4 ± 0.2°C and 25.3 ± 0.3°C, respectively. There were no significant differences in the general characteristics of the two groups. The mean core temperatures began to decrease after the induction of anesthesia in both groups and continued to decrease during the course of the surgery. There was no significant difference between the two groups.

Conclusions: Hypothermia develops in all neonates when surgical time exceeds one hour, even in warmer ambient temperatures. Although it seems effective in adults, amino acid-induced thermoregulation does not seem effective in newborns during general anesthesia.

Keywords: Amino-acid, anesthesia, hypothermia, newborn, thermoregulation

Decreased metabolic rate and impaired thermoregulation during general anesthesia cause significant undesirable effects, even in adults [1, 2]. Newborns, having a larger surface area and less subcutaneous fatty tissue covering central structures, are more susceptible to these inadvertent effects. Decreased drug metabolism, coagulation disorders, wound infections, and cardiac arrhythmias are the most important and well-known results [3, 4].

Core body temperature has to be kept at a constant level (37°C) in each environment for the continuation of metabolic functions [2]. Peripheral arteriovenous shunts, sweating, shivering, and non-shivering heat generation constitute important intervention mechanisms in conscious individuals [3]. General anesthesia and surgery are frequently accompanied by hypother-

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mia related to the impairment of thermoregulation and synchronous reduction of vasoconstriction thresholds and shivering [1]. Body heat is redistributed from the core to the periphery shortly after induction of anesthesia and results in a decrease in core temperature. The course is followed by heat loss exceeding metabolic heat production.

Patients can be intensively warmed or simply kept warm either by elevating the ambient temperature or by the use of extracorporeal devices such as forced-air warming blowers and infusion fluid warming devices during general anesthesia [3, 5]. As a different approach, perioperative amino acid infusion is known to prevent intraoperative hypothermia during general anesthesia in adults [6-11].

Due to the high amount of brown adipose tissue, non-shivering thermogenesis is used in preference to shivering in newborns[1, 12-14]. Despite all compensatory mechanisms, newborns have a limited capacity for thermoregulation and are prone to hypothermia. Although there are several studies about amino acid-induced thermoregulation in adults, there is no study in newborns and infants related to the subject. In this study, we aimed to demonstrate the effect of perioperative amino acid infusion on the prevention of hypothermia during general anesthesia in surgical newborns.

METHODS

The study protocols were reviewed and approved by the ethics committee of İstanbul University, İstanbul School of Medicine. All parents were informed about the study before giving their consent to participate. Twenty surgical newborns, aged 1-30 days, were enrolled in this prospective, randomized controlled study. Newborns with fever, sepsis, and those undergoing surgical procedures shorter than 60 min were not included in the study.

Newborns were randomly divided into two groups: the amino acid and dextrose 10% infusion group (AAD) and the 10% dextrose only infusion group (D). Amino acid (TrophAmine® 6%, B. Braun Hessen, Germany) solution was given at a rate of 1g/kg-1 24 h-1 and dextrose 10% solution was given at a rate 100 mL kg-1 24h-1 before and during the operation.

No premedication was given before surgery. The ambient operating room temperature was maintained near 25°C. All newborns received general anesthesia with sevoflurane and air O2.Tracheal intubation was facilitated with rocuronium. Ventilation was controlled and adjusted to keep end-tidal CO2 at 4.6-5.2 kPa (35-40 mm Hg). All newborns were placed on warm gel pads, which were placed on a constant electrical heating pad that was adjusted to 37°C (KanMedOperatherm 202; KanMed AB, Bromma, Sweden). A heat and moistureexchanger was connected to the tracheal tube connector in all newborns. The head, legs, and arms were covered by warm cotton.

The age, sex, weight, hemoglobin concentration, primary pathology, preoperative infusion time, duration of anesthesia, the initial core temperature of the newborns, and the ambient operating room temperature were recorded. The core temperatures of the newborns were measured from the distal esophagus in the first minute of the induction once and every fifteen minutes thereafter. Thermocouple probes (Ellab YRY-T, Ellab, Hillerod, Denmark) were connected to the Mennen Horizon XL monitor (Mennen Medical Ltd., Rehovot, Israel).

Statistical Analysis

The core body temperature changes in each group during surgery and the differences between the two groups were analyzed. Statistical analysis was performed using the SPSS 11 package program. Descriptive data are expressed as mean ± standard deviation and number (%). Continuous variables are given as mean ± standard deviation and categorical variables as percentage (%). Independent group comparisons were made using Student's t-test when parametric test assumptions were provided. The Mann-Whitney U test was used when parametric test assumptions were not provided. The Chi-square test was used to determine categorical variables. *P* values < 0.05 were considered statistically significant.

RESULTS

A total of 20 surgical newborns were enrolled in the study. The diagnoses of the newborns are shown in Table 1. The surgical operations in each group were

Table 1. Diagnosis of the patients

Dextrose (D) group	Amino acid and dextrose (AAD) group
Midgut volvulus	Gastric perforation
Congenital diaphragmatic hernia	Pyloric atresia
Congenital diaphragmatic hernia	Duodenal atresia
Duodenal atresia	Midgut volvulus
Malrotation	Volvulus and internal hernia
Pyloric stenosis	Gastric perforation
Pyloric stenosis	Ileal atresia
Necrotizing enterocolitis	Congenital diaphragmatic hernia
Malrotation	Meconium ileus
Intraabdominal cystic mass	Pyloric stenosis

similar. Operating room temperatures were constant within the limit of ±0.5°C for each group during the course of surgery. The mean operating room temperatures of the AAD and D groups were 25.4 ± 0.2°C and 25.3 ± 0.3°C, respectively.

Table 2 illustrates the perioperative data for the two groups. There were no significant differences in the general characteristics of the two groups. The preoperative infusion times in the AAD and D groups were 14.7 ± 4.9 hours and 15.1 ± 6.3 hours, respectively.

The mean core temperatures began to decrease after the induction of anesthesia in both groups and continued to decrease during the course of surgery (Fig. 1). Although the mean core temperatures in the AAD group were higher than in the D group during the entire surgical period, there was no significant difference between the two groups except at the 45th and 90th minutes of the operation (Table 3).

Table 2. General characteristics of two groups

	AAD	D	*p* value
Female	6	4	-
Age (day)	9.8 ± 9.1	10.7 ± 12.3	0.185
Weight (gram)	3037 ± 204	2800 ± 702	0.319
Hemoglobin (gr/dl)	14.00 ± 0.89	14.27 ± 2.7	0.710
Body Temperature (˚C)	36.5 ± 0.1	36.4 ± 0.2	0.200
AmbientTemperature (˚C)	25.4 ± 0.2	25.3 ± 0.3	0.545
Infusion Time (preop) (h)	14.7 ± 4.9	15.1 ± 6.3	0.877

AAD = amino acid/dextrose group, D = dextrose group

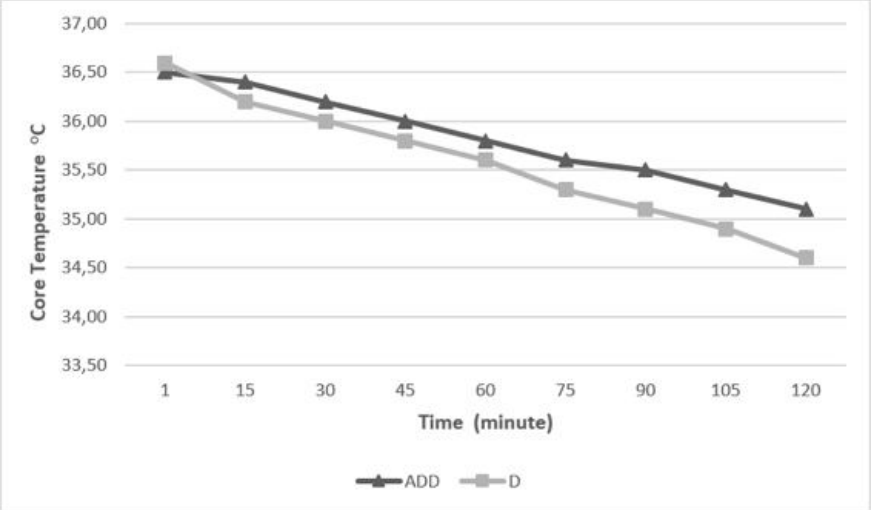

Fig. 1. Core body temperature changes in both groups.

Table 3. Measured core temperatures and differences

Time (min.)	AAD	D	*p* value
1.	36.50 ± 0.14	36.60 ± 0.13	0.103
15	36.4 ± 0.19	36.2 ± 0.19	0.083
30	36.2 ± 0.21	36 ± 0.18	0.132
45	36.0 ± 0.2	35.8 ± 0.2	**0.018***
60	35.8 ± 0.3	35.6 ± 0.2	0.138
75	35.6 ± 0.4	35.3 ± 0.3	0.180
90	35.5 ± 0.4	35.1 ± 0.2	**0.043***
105	35.3 ± 0.5	34.9 ± 0.3	0.128
120	35.1 ± 0.7	34.6 ± 0.2	0.185

AAD = amino acid/dextrose group, D = dextrose group, *$P < 0.05$

DISCUSSION

General anesthesia impairs thermoregulation and causes mild hypothermia in surgical patients. Anesthesiologists and surgeons use various approaches and combinations to keep patients normothermic. Unfortunately, it has not yet been possible to solve the problem completely. However, there is one additional internal warming method that has been known since the 1990s: amino acid-induced thermoregulation. Amino acids infused in the body stimulate both protein synthesis and breakdown and also increase blood flow, especially in extrasplanchic tissue [15].

All reactions require larger amounts of energy compared with glucose or lipid metabolism, leading to accumulating heat in the body [11]. After Sellden *et al*. reported that amino acid infusion prevented perioperative hypothermia during anesthesia without any additional sympathoadrenal activity and shortened hospital stay [6, 15, 16], Kasai *et al*. [8] reported perioperative amino acids maintained core temperature and were useful in preventing hypothermia not only during general anesthesia but also during spinal anesthesia. A contribution to the subject also came from Nakajima *et al*. [10]; amino acid infusion increased both metabolic rates and resting core temperature, but they also produced a synchronous increase in all major autonomic thermoregulatory defense thresholds at the same time.

Non-shivering thermogenesis (activation of brown fat by an uncoupling protein, thermogenin) is used in preference to shivering in infants and in small mammals [1, 12, 14]. It is thought that because of their high amounts of brown adipose tissue and their high potential for non-shivering thermogenesis, newborns should be able to produce more heat to compensate for heat loss in general anesthesia, but this is not the case. Newborns, like adults, are unable to respond to intraoperative hypothermia because inhibition of non-shivering thermogenesis occurs during general anesthesia [17-19]. In these circumstances, it might be considered that perioperative infusion of amino acids would increase heat formation via potentiation of non-shivering thermogenesis. However, the results of the current study do not support this hypothesis. Although the mean temperature of the AAD group was higher during anesthesia, the difference was not statistically significant.

Limitations

First, the operating room temperature could only be adjusted to about 22-23°C instead of 25°C, so a further decrease in body core temperature might have led to an increase in the thermogenic effect of amino acids. On the other hand, this could be more realistic because most of the time the operating room temperature was around 21-22°C. Although the optimal delivery room temperature is recommended to be 25-28°C, it is also a fact that 25°C is an uncomfortable temperature for all operating room staff [20].

Second, we could have given an amino acid solution without dextrose during the surgery because glucose supplementation inhibits endogenous glucose production and stimulates insulin secretion to a greater

extent than the administration of amino acids alone in adults. Moreover, intraoperative exogenous glucose suppresses protein catabolism and gluconeogenesis. Therefore, excessive glucose administration may disturb amino acid-mediated thermogenesis [21]. According to Fujita *et al*. [22], intraoperative amino acid infusion without glucose administration appears to be more effective for body temperature maintenance in patients undergoing colorectal surgery. However, we thought that it would be inappropriate to give amino acid solutions alone in newborns who are prone to hypoglycemia in long surgical procedures.

Third, there may be a linear relationship between the amount of amino acids and the thermogenic effect. Some groups given different amount of amino acids could be added.

In addition, cold ambient room temperature (below 23°C) can significantly interfere with the maintenance of core temperature in newborns and infants during anesthesia. However, neonates cannot maintain their core temperature, even in warmer operating room temperatures [5]. Despite taking all necessary precautions, as mentioned previously, we observed mild hypothermia in both groups during surgery. Hypothermia developed in all newborns when surgical time exceeded one hour, even though the operating room temperature was around 25°C.

CONCLUSION

Hypothermia develops in all neonates when surgical time exceeds one hour, even in warmer ambient temperature. Although it seems effective in adults, amino acid- induced thermoregulation does not seem effective in newborns during general anesthesia. This effect may be dose-dependent. Studies with more groups and different amino acid doses are needed.

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All procedures performed in studies involving human participants were accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Both authors were working in Istanbul University during the study.

Authors' Contributions

Conception and design: M.O, F.T.S; Data analysis interpretation: M.O, F.T.S; Manuscript writing and revision: M.O, F.T.S

Conflict of interest

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Investigation of the effect of chemotherapy on cytomegalovirus reactivity in patients with solid organ tumors

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ABSTRACT

Objectives: Chemotherapy induces an immunosuppressive state in patients with solid organ tumors. Cytomegalovirus (CMV) reactivation as a result of immunosuppression causes a severe clinical manifestation. However, in this group, CMV infections developing due to reactivation were not adequately discussed in the literature. The aims of this study were to determine the incidence of CMV reactivation after chemotherapy, to evaluate the contribution of chemotherapy to reactivation, to determine the incidence of asymptomatic and symptomatic infections and to investigate the results of the treatment.

Methods: A total of 93 patients with solid tumors were included in the study. Weekly blood samples were collected from the patients for three weeks before and after chemotherapy. Quantitative analysis of DNA was detected using CMV PCR kit (GeneProof CMV PCR kit, Bruno, Czech Republic). Diagnosis and treatment of patients were retrospectively reviewed.

Results: Of the patients, 65.6% were female and 34.4% were male. The mean age was 55 ± 12 years. The most common cancer types among the patients were breast cancer in 45.2%, lung cancer in 15.1%, and colon cancer in 12.9%. The mean leukocyte count of the patients was 7,647/mm3. CMV DNA was not detected in any patient. According to this result, none of the patients had CMV reactivation after chemotherapy.

Conclusions: In this study including patients with solid organ tumors with mild to moderate level of immunosuppression CMV DNA was not detected in any patient. Based on this finding no standard prophylaxis was required for CMV in this group of patients.

Keywords: Cytomegalovirus, solid organ tumor, chemotherapy

Cytomegalovirus (CMV) is the largest human herpes virus (HHV-5) that can remain latent in the body after acute infection. This virus can infect people of any age, which does not show seasonal or epidemic features for transmission. It causes widespread viral infection all over the world. It can be transmitted eas-

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ily from person to person. After the primary infection, the virus may remain latent and persistent in a wide variety of areas such as defense and epithelial cells. Infected individuals are an important source of virus scattering for a long time [1, 2].

In the United States and other developed countries, seroprevalence is 50%, while in developing countries this rate can reach 100% [3, 4]. In high-risk groups, seroprevalence can exceed 90%. CMV infection can be caused by CMV transmission (primary infection) and activation (reactivation) of latent infection due to immunosuppressive therapy. The primary infection is more benign and is seen more common in young ages. In addition to congenital infections, CMV reactivation may develop as a result of immunosuppressive treatment, usually in the period following solid organ, bone marrow or hematopoietic stem cell transplantation. CMV reactivation can present with severe clinical manifestations and the spectrum and severity vary according to the patient's serological status and the immunosuppressive treatment regimen selected. In particular, in oncology patients, chemotherapy and immunosuppressive CMV infection cause high morbidity and mortality [5]. The mortality of CMV infection which is reactivated in immunosuppressive patients is high [2, 6]. Therefore, when there are risk factors and clinical findings are suggestive of CMV infection in patients receiving chemotherapy, CMV reactivation should be considered and treatment should be applied accordingly [2, 7].

Chemotherapy-induced immunosuppression may also occur in patients with chemotherapy. However, in this group, risk of CMV reactivation was not clarified [8]. The aim of this study was to investigate the incidence of CMV reactivation after chemotherapy for solid tumors, to evaluate the contribution of chemotherapy to reactivation, to determine the incidence of asymptomatic and symptomatic infections.

METHODS

This prospective cross-sectional study was approved by the local ethics committee. Signed informed consent forms were taken from each participant.

Patients and Tests

A total of 93 patients with solid tumors were included in the study. The patients were seropositive for CMV (CMV IgG-positive). Blood samples were taken at baseline and then weekly during the chemotherapy and three weeks after chemotherapy were collected for CMV DNA study. DNA was isolated from the samples using the Hibrigen DNA isolation kit (GeneProof, Bruno, Czech Republic). Quantitative CMV DNA was detected using CMV PCR kit (GeneProof CMV PCR kit, Bruno, Czech Republic) in Rotor-Gene Q Real-time PCR instrument (Qiagen, Hilden, Germany). Blood count was studied every other that during the study. The leukocyte, lymphocyte and neutrophil values of the patients were analyzed using a particle-enhanced turbidimetric inhibition immunoassay method with Architect c8000 (Abbott Laboratories, Abbott Park, IL, USA) auto-analyzer. Other demographic data, diagnoses and treatments of the patients were retrospectively reviewed.

Statistical Analysis

Descriptive statistics were used to define the mean, standard deviation, minimum, median and maximum variables. Statistical significance level $p < 0.05$ was considered significant. The analyses were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; 2013).

RESULTS

Of the patients, 65.6% were female and 34.4% were male. The mean age was 55 ± 12 years. The most common types of cancer among the patients were breast cancer in 45.2%, lung cancer in 15.1%, and colon cancer in 12.9%. The distribution and types of cancer and drugs used in the chemotherapy types are given in Table 1.

Distant metastases were detected in 29 (31.2%) patients. A total of 54 (58.1%) patients had a history of chronic disease other than malignancy, such as hypertension, chronic obstructive pulmonary disease, diabetes mellitus, hypothyroidism, and cerebrovascular accident. Sixty-seven (72%) patients underwent surgery and 13 (14.1%) patients underwent radiotherapy. Twelve (12.9%) patients had a permanent catheter

Table 1. Distribution of solid tumor patients and the drugs used

Diagnosis	n	%	Used chemotherapeutics
Breast cancer	42	45.2	5-fluorouracil (5-FU) based, Taxane-based, Anthracycline based
Lung cancer	14	15.1	Platinum-based, Taxane-based
Colon cancer	17	18.3	5-FU based, Platinum-based
Gastric cancer	4	4.3	5-FU based, Platinum-based
Cholangiocarcinoma	3	3.2	Platinum-based, Gemcitabine based, 5-FU based
Ovarian cancer	3	3.2	Taxane-based
Pancreatic cancer	3	3.2	Platinum-based
Bass-neck tumor	2	1.1	Platinum-based
Glioma	1	1.1	Irinotecan
Larynx tumor	1	1.1	Platinum-based
Bladder cancer	1	1.1	Platinum-based
Sarcoma	1	1.1	Anthracycline based
Testicular tumor	1	1.1	Anthracycline based

(port) and none of the patients had a central venous catheter. Only three (3.2%) of the patients had steroid use. None of the patients included in the study were followed up in the intensive care unit, blood was not transfused, and total parenteral nutrition was not given. CMV DNA PCR was not positive in any patient in the study.

The mean leukocyte and neutrophil counts of the patients before the chemotherapy were 7,856/mm3 and 5,109/mm3, respectively. The nadir of leukocytes was seen on 7th day of chemotherapy, with the mean leukocyte and neutrophil counts of 6,213/mm3 and 3,928/mm3. After chemotherapy, severe leukopenia (< 500 /mm3) was not detected in 5 out of 93 patients. After 14 days, leukocyte and neutrophil counts were comparable, with a slight increase in leukocytes and a

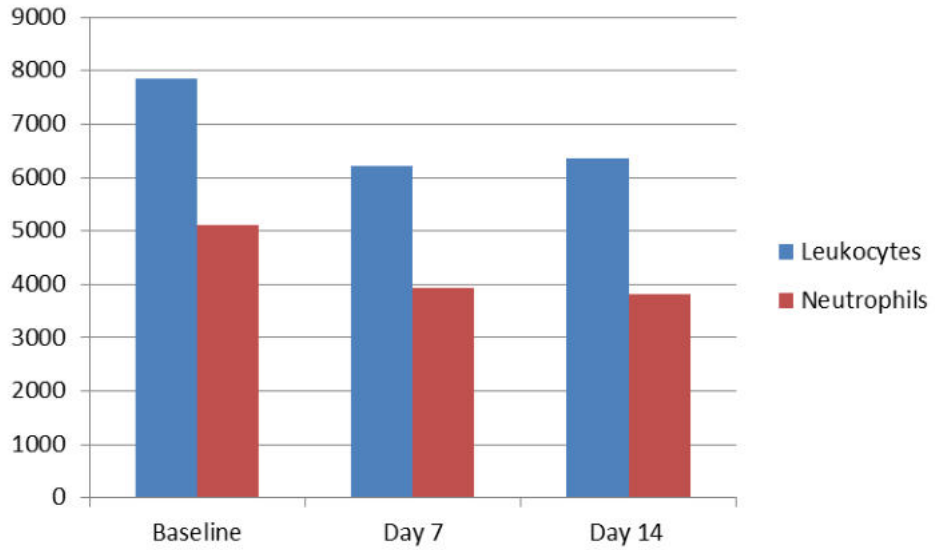

Fig. 1. Leukocyte and neutrophil count (/mm3) at baseline, 7th day and 14th day of chemotherapy.

Table 2. Cell counts of patients

Cells	Cell count (/mm^3, Mean ± SD)		
	Baseline	Day 7	Day 14
Leukocyte	7856 ± 2854	6213 ± 3336	6359 ± 3796
Neutrophils	5109 ± 2542	3928 ± 3022	3806 ± 3175
Neutrophils < 500/mm^3	0/93	5/93	0/93
Lymphocytes	1933 ± 846	1680 ± 750	1743 ± 844

SD = standard deviation

slight decrease in neutrophil counts (6,359/mm3 and 3,806/mm3, respectively) (Fig. 1, Table 2).

DISCUSSION

CMV reactivation can be life threatening in severity. Reactivation is seen as a result of immunosuppression which develops due to the decrease in lymphocytes and dysfunction of lymphocytes. Although this condition is seen mostly in transplant patients, chemotherapies used in patients with solid tumors also have reported to associate CMV reactivation [3, 5-8]. Our study is one of the few studies investigating CMV reactivation in solid tumor cases. CMV infection caused by reactivation causes fever, colitis, interstitial pneumonia, hepatitis, meningoencephalitis, radiculopathy in peripheral nerves, myelopathy, leucopenia or retinitis. This condition, which is also described as CMV syndrome, occurs in 60% of patients under the risk [6-10]. The mortality rate after infection with CMV reactivation is very high. In a study, CMV mortality was reported as 61.3% in patients with solid organ tumors. Mortality rates in these patients have been reported to be even higher than those with hematologic malignancies or who have undergone transplantation [9]. Emiroglu *et al*. [11] reported that CMV reactivation developed in a case of solid tumor with febrile neutropenia after chemotherapy. However, he was mortal after receiving CMV treatment after the seventh day. In CMV infection, mortality is reduced by accurate diagnosis and rapid treatment [7, 8, 12]. The mortality rate of infection caused by CMV reactivation in HIV patients, especially those receiving solid organ transplantation therapy, is high. This is especially important in countries where CMV seropositivity is close to 100%. Due to the immunosuppressive agents used in organ transplantation, aggressive use of immunosuppressives may cause reactivation of CMV [1, 2, 13]. When prophylaxis is not given after transplantation, it is reported that reactivation can occur in 25-30% of the patients within three months, and within six months with higher positivity [7, 8, 14]. CMV infection in HIV positive patients has also high morbidity or mortality, with association of low numbers of CD4 + T lymphocytes [2]. In HIV positive patients, infections such as retinitis, colitis, esophagitis and pneumonia due to CMV may develop. Studies have shown that CMV infection is common (between 59-100%) in HIV-infected patients [15]. This indicates that CMV reactivation will increase dramatically in cases lymphocytes cannot function or when number of lymphocytes decreases.

In our study, none of the patients with chemotherapy who were followed up with the diagnosis of solid tumor were found to have CMV reactivation. Studies evaluating CMV reactivation in patients with solid tumors are very rare. Some studies are available indicating that malignancy is not a risk factor in the development of CMV infection [16-18]. In addition, several studies showed that CMV reactivation might be due to the weakening of immunity [16]. In their study, Mera *et al*. [19]. found that CMV infection due to CMV reactivation was detected in 42% of patients with solid tumors in autopsy. In their large-scale literature review, Osawa and Singh [8] found that immunosuppression can cause CMV reactivation in 0-36% of inpatients in intensive care unit. Capria *et al*. [20]. reported that 35% of the patients with hematological malignancy had reactivation after chemotherapy with CMV infection. In a study con-

ducted by Kuo *et al*. [21] they reported that CMV infection due to reactivation was not detected in any patient with solid tumor who received chemotherapy. In other two studies, it was reported that CMV reactivation might be rare in patients with solid tumor diagnosed with chemotherapy [22, 23].

In light of the data provided, we may link the absence of CMV reactivation in our study for several reasons. As it is known, lymphocytes in the blood have an important role in preventing CMV infection. The decrease in the number of lymphocytes and mediators such as TNF and IL-1 may lead to CMV reactivation [21, 24-28]. Drugs used in chemotherapy of patients with solid tumors leads to immunosuppression and drugs reducing the number of lymphocytes in cancer patients may cause CMV reactivation [6, 21, 29]. Purine analogues, major chemotherapy drugs such as cyclosporine, high-dose steroids cause severe immunosuppression. This results in reactivation and increase in viral load in these patients [21]. None of our patients had severe neutropenia and lymphopenia. Taxane, platinum, 5-FU, gemcitabine and anthracycline-based drugs were used in patients included in our study and these drugs have the potential to cause neutropenia. However, none of these drugs have the ability to make significant lymphopenia. Based on these data another reason for the absence of CMV reactivation in our study may be the lack of chemotherapy drugs that cause severe immunosuppression. Although we have studied with a very large group, some solid tumor types might have an inadequate number of patients. However, we believe that our study may be a guide for future studies.

The change in the number of lymphocytes affects the rate of CMV reactivation. However, it is also stated that low lymphocytes do not always cause CMV reactivation. The reason for this is shown as the presence of an old immune response to CMV infection [17].

It has been reported that CMV infection due to reactivation may develop more in some solid tumor types than others [1, 25, 26]. CMV reactivation may be present in 5-75% of the hematology patients [10, 30]. In particular, CMV infection due to reactivation is reported to be higher in colon, lung and brain tumors compared to other solid tumors. CMV positivity was found in 90% of patients with these tumors [28]. In the study of Schlick *et al*. [6] two patients with pancreas cancer and one patient with breast cancer were reported to have CMV infection following chemotherapy. In our study, CMV reactivation was not observed although we had this group of patients.

Any situation that reduces the number of lymphocytes means that the most important defense mechanism against CMV is weakened. Steroids reduce the number of lymphocytes only with high doses for a long time [18]. The reason for the absence of CMV reactivation in three patients with steroid use in our study may be related to short-term and low-dose steroids disrupting cell function but not decreasing their number.

The CMV PCR test is a rapid and sensitive test that best detects the reactivation indicator in the detection of the virus [2] The immune response, which ELISA tests cannot detect, can be detected by PCR. In the study of Emiroglu *et al*. [11] PCR test detected CMV in a CMV-pp65A-negative patient with solid organ tumor. This shows that molecular detection of the virus is more sensitive and specific than immunological response-based ELISA method. This test also provides additional information as the amount of viral load will be determined by the PCR test [10, 25, 26].

CONCLUSION

CMV infection can be mortal especially in patients with immunosuppression. Prophylaxis in patients with transplantation, prolonged use of steroids and immunosuppression in patients with transplantation can prevent mortality. When CMV infection is detected in patients with chemotherapy who have hematological malignancies and solid tumors, CMV DNA detection by PCR should be performed and treatment should be given rapidly. We conclude that CMV reactivation is very rare in patients with solid organ tumors receiving chemotherapy suggests that standard prophylaxis is not required.

Conflict of interest

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Examination and clinical correlation of olfactory system disorders by an objective method Sniffin' Sticks odor test in Parkinson's disease

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ABSTRACT

Objectives: This study is aimed to investigate the frequency of olfactory dysfunction in Parkinson's Disease (PD) and its relationship with motor/non-motor symptoms and treatment in comparison to isolated olfactory dysfunction patients and healthy controls.

Methods: This study includes 40 PD patients, 37 anosmia patients and 42 healthy controls. PD patients are evaluated with PD evaluation form including; sociodemographic features, disease history, Unified Parkinson's Disease Rating Scale (UPDRS) score, and Hoehn and Yahr (H-Y) score. All patients were evaluated with cranial CT and MRI. Olfactory function was evaluated with Sniffin' Sticks Test (SST). A p value < 0.05 was considered to be statistically significant.

Results: The mean age and median disease duration of PD patients were 62.2 ± 11.9 and 4.5 years, respectively. Fifteen of them had comorbid diseases. Median UPDRS score was 19.5 (4-60) and 67.5% of subjects were H-Y Stage-1. Most frequent non-motor symptom was constipation (67.5%). Olfactory dysfunction was found in 75% of PD patients by SST. No difference was observed between PD patients with or without olfactory dysfunction regarding non-motor symptoms and dementia (p > 0.05). Patients with isolated olfactory dysfunction were significantly younger than both patients with PD and the healthy controls (p <0.001). Non-motor symptoms were not significantly different between isolated olfactory dysfunction group and healthy subjects (p > 0.05).

Conclusions: Most of the patients with PD had olfactory dysfunction, which was found not to be correlated with disease duration and stage based on the results of an objective test, namely Sniffin-Sticks odor test.This result might support the role of non-dopaminergic pathways in the etiopathogenesis of olfactory dysfunctions in PD. In clinical practice, data from further studies is required to comment on an ideal screening or diagnostic test in the olfactory system evaluation of early stage PD patients that would be repeatable and objective.

Keywords: Parkinson's disease, olfactory dysfunction, Sniffin' Sticks test, anosmia

Parkinson's disease (PD) is a progressive neurological disorder characterized by tremor, rigidity, and slowness of movements. With a lifetime risk of developing the disease of 1.5%, PD is the second most prevalent neurodegenerative disorder [1, 2]. PD is associated with progressive neuronal loss of the substantia nigra and other brain structures [1, 3]. Very few of the cases are related to mutations in; a-synuclein, leucine-rich repeat kinase-2 and glucocerebrosidase, but the most common form is still idiopathic [3].

Although the motor symptoms of PD are well defined, the non-motor features as altered smell, taste,

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vision, cardiovascular function, sleep, gastric and bowel function, salivation, sebaceous gland activity, mood, and cognition are under-recognized and ultimately undertreated [3. 4]. Non-motor symptoms can be present at all stages of disease but the frequency generally increases with progression of disease and some studies have shown that these symptoms have a major impact on the quality of life in advance of motor symptoms [5, 6].

The most remarkable non-motor feature of PD is impairment in smelling with estimates of prevalence ranging from 50% to 90% [7-9]. Olfactory dysfunction is one of the earliest manifestations of PD and although definitive neural mechanisms are still unclear, they appear a few years prior to characteristic motor symptoms. While cardinal motor symptoms are primarily caused by dopamine depletion within the nigrostriatal pathway, olfactory symptoms appear to be unaffected by dopaminergic therapy, suggesting the involvement of other neurotransmitter systems and / or extranuclear pathology. A few recent studies show brain atrophy in regions related to primary olfactory and orbitofrontal cortex in early-stage PD [10, 11].

Based on literature knowledge mentioned above, this study is aimed to investigate the frequency of olfactory dysfunction in PD and its relationship with motor/non-motor symptoms and treatment in comparison with isolated olfactory dysfunction patients and healthy controls.

METHODS

In this study, it was aimed to quantitatively evaluate the olfactory disturbance of the patients who were followed up with diagnosis of Idiopathic Parkinson's Disease (IPD) at Ankara Numune Training and Research Hospital Neurology Clinic by quantifying Sniffin' Sticks odor test and to investigate the relationship between olfactory dysfunction and motor / non-motor symptoms.

The study population is consisted of 40 IPD patients who admitted to Ankara Numune Training and Research Hospital Neurology Clinic, 37 anosmia patients from Ear, Nose and Throat (ENT) Clinic and 42 healthy controls.

Inclusion criteria were (1) having a diagnosis of PD, (2) admission to the hospital with the complaint of selective olfactory sensation loss, (3) absence of any neurological diagnosis other than PD, or excluded the cases with secondary parkinsonism.

Exclusion criteria were, (1) symptoms of non-PD parkinsonism, (2) use of any drugs that cause parkinsonism, (3) to be younger than 18 years of age and (4) to avoid participation in the study.

For the control group 42 healthy volunteer, who had no age-related illness, no parkinsonism, no drug use, no sense of smell loss, no cognitive impairment to prevent cognitive co-operation were selected.

Each patient was assigned to a standard Parkinson's disease assessment form which included; sociodemographic characteristics (age, sex, occupation, education level, socioeconomic level etc.), PD and a family history of olfactory disorder, hand dominance information, disease duration and age at onset, first symptom and localization of the disease, chronological order of symptoms, Unified Parkinson's Disease Rating Scale (UPDRS) score, Hoehn and Yahr (HY) staging and information of drugs used by patients. Other systemic diseases, smoking status and head trauma history of the patients were also recorded.

In addition, presence of non-motor symptoms other than olfactory disturbance were recorded. These symptoms were assessed according to the patient's history. Patients' ear nose and throat examinations were performed at the ENT clinic and the presence of pathological findings were recorded. All patients were evaluated with cranial CT or cranial MRI.

All the patients were evaluated and tested by the same neurologist. Mini Mental State Assessment Scale was used for objective evaluation of the cognitive status of the patients. A Mini-mental status assessment score of 24 and below were considered significant in terms of dementia [12].

The Sniffin' Sticks odor test was given to the patient and control groups to quantitatively assess the sense of smell. This test consists of 12 felt-tipped pencils with different odors and the smell is released when the cover is opened. Multiple choice testing is based on the identification of daily smells. The patient chooses the one that best describes the smell from among the 4 types shown to him. Patients can choose an option to say they do not smell any odor or that they cannot identify the smell. The cut-off value for the test was set at < 7 to be indicative of odor loss [13].

Statistical Analysis

Statistical analyses were performed using the SPSS for Windows software version 11.5. The variables were investigated using Kolmogorov Smirnov test to assess whether or not they are normally distributed and homogeneity of variances were asessed with Levene test. Descriptive analyses were presented as mean ± standard deviation or median (minimum-maximum) for numerical variables, and categorical variables were reported as number of cases (n) and percentages (%). Categorical variables were assessed by Pearson's Chi-Square, Fisher's exact or Likelihood Ratio test. Whether or not there was statistically significant correlation between disease duration, UPDRS and Hoehn-Yahr stage and smell-end result in Parkinson's disease was investigated using Spearman's Correlation test. Comparison between two groups was done with Student's t test/Mann Whitney U test and multiple groups with One-Way ANOVA/ Kruskal Wallis test. One-way ANOVA/ Kruskal Wallis tests were followed by Post Hoc Test (Tukey HSD or Conover's nonparametric multiple comparison test). A *p* - value less than 0.05 was considered to show a statistically significant result.

RESULTS

PD Features

The mean age of 40 PD patients were 62.2 ± 11.9 years, median disease duration were 4.5 years (range between 1-20 years) and 57.5% were male. Almost all

Table 1. Basic demographic and clinical characteristics of PD patients according to olfactory function

	Normal (n = 10)	Olfactory dysfunction (n = 30)	*p*-value
Age (years)	58.6 ± 13.1	63.4 ± 11.4	0.270†
Sex			0.717‡
Male	5 (50.0%)	18 (60.0%)	
Female	5 (50.0%)	12 (40.0%)	
Smoking	4 (40.0%)	12 (40.0%)	1.000‡
Family history	2 (20.0%)	4 (13.3%)	0.629‡
Disease Duration (years)	10.5 (1-20)	3 (1-15)	0.024¶
Leading symptom			0.716‡
Bradykinesia	6 (60.0%)	14 (48.3%)	
Tremor	4 (40.0%)	15 (51.7%)	
Nausea/vomiting	3 (30.0%)	7 (23.3%)	0.689‡
Postural hypotension	5 (50.0%)	15 (50.0%)	1.000$
Visual hallucinations	0 (0.0%)	8 (26.7%)	0.165‡
Wearing off	1 (10.0)	4 (13.3%)	1.000‡
On/off	1 (10.0%)	4 (13.3%)	1.000‡
Dyskinesia	3 (30.0%)	2 (6.7%)	0.089‡
UPDRS	23 (8-60)	18 (4-59)	0.315¶
Hoehn-yahr			0.962¶
Stage 1	7 (70.0%)	20 (69.0%)	
Stage 2	1 (10.0%)	4 (13.8%)	
Stage 3	1 (10.0%)	4 (13.8%)	
Stage 4	1 (10.0%)	1 (3.4%)	

†Student's t test, ‡Fisher's exact test, ¶Mann Whitney U test, $Pearson's Chi-Square test

the patients were right handed, 37.5% had at least one comorbid diseases (32.5% hypotension, 20.0% diabetes mellitus, 10.0% goiter) and 15,0% had a family history of PD. Median UPDRS score of PD patients were 19.5 (range between 4-60) and 67.5% were HY stage 1, 12.5% were HY stage 2, 12.5% were HY stage 3 and 5.0% were HY stage 4.

First symptom of PD were as follows; 27.5% left hand tremor, 12.5% gait disturbance, 10.0% bradykinesia, 7.5% right hand tremor. Distribution of symptoms added to PD were; 45.0% bradykinesia, 12.5% tremor, 10.0% left sided tremor and 5.0% falls and bradykinesia. Most common examination findings were; 12.5% bradykinesia, 12.5% tremor, 10.0% bradykinesia and bilateral tremor, 10.0% bradykinesia and hypomimia. Motor and non-motor symptoms were; 50.0% bradykinesia, 47.5% tremor, 25.0% nausea and vomiting, 50.0% postural hypotension, 20.0% visual hallucinations, 12.5% wearing off, 12.5% on/off and 12.5% dyskinesia. Treatment given to patients were; 45.0 L-dopa/Benserazide, 40.0 pramipexole, 37.5 rasajilin and 35.0 L-dopa/Carbidopa/Entacapone combination.

Sniffin' Sticks Odor Test

With the olfactory system examination, 10 (47.5%) patients had positive results but 30 (75.0%) patients had positive test results according to Sniffin' Sticks odor test.

Sniffin' Sticks odor test scores of PD and isolated anosmia patients were significantly higher than those of the healthy controls ($p < 0.001$) but similar results were obtained for PD and isolated anosmia patients ($p = 0.21$).

There was no positive correlation between disease duration (r=0.28, $p = 0.07$), UPDRS score (r=0.08, $p = 0.61$), HY stage (r=0.02, $p = 0.89$) and level of odor test within the PD group. (Table 1).

Comparison Between PD Patients with and without Olfactory Dysfunction

There was no statistically significant difference between the groups with or without olfactory dysfunction in terms of age, gender, smoking and family history of Parkinson disease, motor symptoms, nausea and vomiting, postural hypotension, visual hallucinations, wearing off, on/off and dyskinesia, but median

Table 2. Comparison between non-motor symptoms of PD patients according to smoking

	No smoking (n = 24)	Smoking (n = 16)	*p*-value
Nausea	5 (20.8%)	6 (37.5%)	0.295†
Constipation	17 (70.8%)	10 (62.5%)	0.581‡
Sialorrhea	8 (33.3%)	6 (37.5%)	0.787‡
Orthostatic	12 (50.0%)	8 (0.0%)	1.000‡
Urogenital	8 (33.3%)	8 (50.0%)	0.292‡
Incontinence	6 (25.0%)	7 (43.8%)	0.215‡
Sexual	7 (29.2%)	8 (50.0%)	0.182‡
Depression	7 (29.2%)	5 (31.3%)	1.000†
Confusion	3 (12.5%)	1 (6.3%)	0.638†
Dementia	4 (16.7%)	2 (12.5%)	1.000†
Psychosis	1 (4.2%)	0 (0.0%)	1.000†
Sleep arrest	7 (29.2%)	7 (43.8%)	0.343‡
REM	1 (4.2%)	1 (6.3%)	1.000†
Restless Leg	2 (8.3%)	0 (0.0%)	0.508†
Periodic leg	1 (4.2%)	0 (0.0%)	1.000†
Olfactory abnormality	13 (54.2%)	6 (37.5%)	0.301‡
Abnormal Sensation	3 (12.5%)	7 (43.8%)	0.059†

†Fisher's exact test, ‡Pearson's Chi-square test

disease duration was significantly lower in PD patients with olfactory dysfunction ($p = 0.024$). PD patients were also evaluated by their smoking status and no statistically significant difference was found between motor and non-motor symptoms and smoking status (Table 2). There was also no difference between olfactory dysfunction in PD patients, according to taking dopaminergic treatment or not ($p = 0.604$).

Comparisons Between Isolated Anosmia and Control Group

Anosmia patients' mean age was lower than PD and control groups ($p < 0.001$). Groups were similar with regard to sex and hand dominance ($p > 0.05$) (Table 3).

Mean Body Mass Index (BMI) values were similar within groups. Median MMT score was significantly lower in the PD group ($p = 0.03$). There were no statistically significant differences with regard to smoking, head trauma history and PD family history between groups ($p > 0.05$). A family history of anosmia was more frequent within the anosmia group than healthy controls ($p < 0.001$). Abnormal brain MRI's were significantly less frequent within anosmia group than PD ($p = 0.03$). There was statistically significant difference between groups regarding abnormal findings at ear ($p = 0.03$), head/neck ($p < 0.001$) examinations (Table 4).

With regard to non-motor features; constipation, sialorrhea, orthostatic hypotension, urogenital and sexual symptoms were more frequent in PD patients group than isolated anosmia patients and healthy control group ($p < 0.05$) (Table 5). Groups were similar

Table 3. Demographic characteristics of groups

	Control (n = 42)	Anosmia (n = 37)	PD (n = 40)	*p*-value
Age (years)	61.8 ± 10.3	50.3 ± 16.4	62.2 ± 11.9	**< 0.001**
Sex				**0.068**
Male	22 (52.4%)	12 (32.4%)	23 (57.5%)	
Female	20 (47.6%)	25 (67.6%)	17 (42.5%)	
Hand dominance				0.526
Right	40 (95.2%)	34 (91.9%)	39 (97.5%)	
Left	2 (4.8%)	3 (8.1%)	1 (2.5%)	

Table 4. Basic clinical characteristics of cases according to groups

	Control (n = 42)	Anosmia (n = 37)	PD (n = 40)	*p*-value
BMI (kg/m^2)	27.6 ± 4.4	27.8 ± 4.5	28.0 ± 4.7	0.933
Mini mental test	27 (10-30)	27 (18-30)	26 (15-29)	39
Smoking	20 (47.6%)	13 (35.1%)	16 (40.0%)	0.522
Head trauma	5 (11.9%)	6 (16.2%)	4 (10.0%)	0.704
PD family history	1 (2.4%)	2 (5.4%)	6 (15.0%)	0.084
Abnormal neurological finding	2 (4.8%)	-	39 (97.5%)	< 0.001
Family history of anosmia	-	7 (18.9%)	4 (10.0%)	3
Abnormality in brain MRI	18 (54.5%)	9 (40.9%)	26 (74.3%)	36
Head and neck problem	14 (33.3%)	27 (73.0%)	26 (65.0%)	< 0.001
Ear problem	1 (2.4%)	4 (10.8%)	-	35
Throat problem	-	-	1 (2.5%)	0.414

Table 5. Distribution of non-motor symptoms within groups

	Control (n = 42)	Anosmia (n=37)	PD (n=40)	*p*- value
Non-motor findings				
Nausea	1 (2.4%)	4 (10.8%)	11 (27.5%)	**0.003**
Constipation	8 (19.0%)	8 (21.6%)	27 (67.5%)	**< 0.001**
Sialorrhea	-	1 (2.7%)	14 (35.0%)	**< 0.001**
Autonomic dysfunction				
Orthostatic	4 (9.5%)	4 (10.8%)	20 (50.0%)	**< 0.001**
Urogenital	3 (7.1%)	5 (13.5%)	16 (40.0%)	**< 0.001**
Urinary incontinence	9 (21.4%)	4 (10.8%)	13 (32.5%)	0.071
Sexual	-	1 (2.7%)	15 (37.5%)	**< 0.001**
Psychiatric				
Depression	5 (11.9%)	10 (27.0%)	12 (30.0%)	0.111
Confusion	2 (4.8%)	1 (2.7%)	4 (10.0%)	0.375
Dementia	1 (2.4%)	-	6 (15.0%)	**0.007**
Psychosis	-	-	1 (2.5%)	0.333
Sleep problems				
Sleep disruption	4 (9.5%)	2 (5.4%)	14 (35.0%)	**< 0.001**
REM Behaviour Disorder	-	1 (2.7%)	2 (5.0%)	0.231
Restless legs	-	-	2 (5.0%)	0.109
Periodic Leg Movement	-	-	1 (2.5%)	0.333
Sensory findings				
Olfactory deficit	-	37 (100.0%)	19 (47.5%)	**< 0.001**
Other abnormal sensory findings	-	-	10 (25.0%)	**< 0.001**

with regard to urinary incontinence, depression, confusion, psychosis ($p < 0.05$) (Table-5).

Sniffin' Sticks odor test scores were statistically significantly higher in anosmia and PD patients than controls (both $p < 0.001$) but results were similar at PD and anosmia patients ($p = 0.21$) (Fig. 1)

DISCUSSION

Olfactory dysfunction is an important nonmotor symptom of IPD that begins before the prodromal phase and before the appearance of characteristic motor symptoms and its pathogenesis is still not clear [14]. In this study, the odor disorder - which is known to be one of the early stage non-motor findings of the Parkinson's Disease - was investigated in relation to other features of the disease. An important objective in the handling of cases is to describe the fact that olfactory dysfunction is an unidentified etiopathogenesis in the early stage of the disease and that it is related to the other components of the disease to elaborate findings present in the approach to PD. In this study Sniffin' Sticks odor test is used to evaluate quantitative differences between groups and 30 (75.0%) patients had positive test results, but test results were similar at PD and anosmia patients ($p = 0.21$).

An objective assessment of olfactory disturbance is a valuable method of allowing patients to obtain scientific and descriptive records without being limited to complaints about olfactory impairment. Therefore, it has been found that qualitative investigation of olfactory deficit has no place in patients' diagnosis of Parkinson and non-Parkinsonian odor disorders [15].

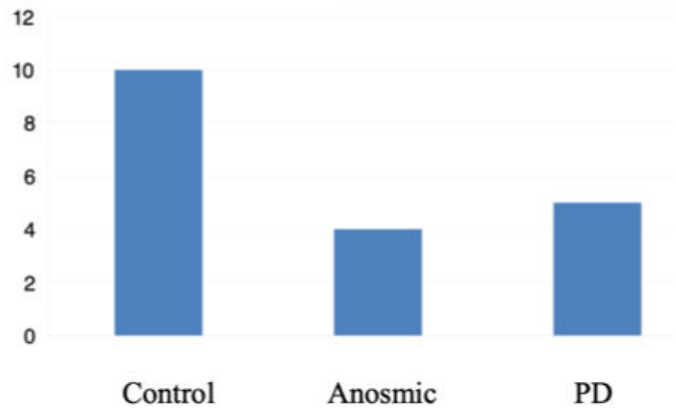

Fig. 1. Sniffin Stick odor test scores.

PD patients with impaired olfactory function had a shorter disease duration but there was no difference between the groups in terms of UPDRS scores and HY staging. On the other hand, it was determined that the olfactory disturbance was not related to motor and non-motor symptoms [8]. Similar to our results, studies showed no correlation between odor impairment and progression of motor symptoms. This result suggests that the olfactory disturbance seen early in the course of Parkinson's disease is a key finding of the disease, and the etiopathogenic mechanism might be different from the known classical mechanisms. There is a need for further screening and pathological studies of this uninformed system.

Smoking and non-smoking PD patients were similar in terms of motor and non-motor symptoms. Contradictory to our work, in one study, the odor test performances of the non-smoker group were higher than both the smoker healthy controls and the smoker and non-smoker Parkinson group [16]. In this study, according to ear and neck examinations, pathological findings were higher in the isolated anosmia group than in PD patients. This difference is thought to be significant in the etiopathology of smell loss belonging to the selective odor loss group independent of the Parkinson's disease pathogenesis.

The presence of studies demonstrating that olfactory dysfunction in Parkinson's patients results from changes in the central nervous system primarily and independently of olfactory epithelium damage [17]. Dementia was more frequent in the PD group than in anosmia patients ($p = 0.007$), but there was no difference between olfactory disorder group in PD patients ($p = 0.026$).

In a study of morphometric Magnetic Resonance detection of gray matter atrophy in the right parietal cortex, also known as primer olfactory area in Parkinson's patients, it has been shown that olfactory disturbance in Parkinson's patients is associated with gray matter atrophy [18]. In our study, percentage of patients with dementia did not differ between PD patients with and without olfactory dysfunction. However, assessment of cognitive functions with test batteries more detailed and sensitive than MMSE might have allowed for a difference between groups.

CONCLUSION

In our study, the quantitative analysis of the olfactory deficits using the Sniffin-Sticks odor test further detected odor deficit in one fourth of the patients, in addition to the subjective questioning. In clinical practice, there is a need for additional data to be obtained from studies conducted based on advanced imaging methods that include more patient groups to comment on an ideal screening or diagnostic test that can be performed which is repeatable and objective in the early stages of Parkinson's disease.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

The study was approved by the Local Ethics Committee (Ankara Numune Training and Research Hospital, Ankara, Turkey with Ref: 2014-834). Informed consent statement was provided by patients.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Comparison of the etiological causes in patients under and/or over the age of 65 admitted to the emergency department with non-traumatic chest pain

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ABSTRACT

Objectives: One of the most common reasons for admission to the emergency department is chest pain. The clinical presentation of chest pain is quite wide. The study aimed to compare the diagnoses of patients under and/or over the age of 65 admitted to the emergency department with non-traumatic chest pain.

Methods: A thousand patients admitted to the emergency department with non-traumatic chest pain between 15.10.2014 and 15.07. 2015 were included in the study. Patients were divided into two groups according to age group as < 65 years old and ≥ 65 years old. Age, gender, the type of admission, comorbidities, accompanying symptoms, diagnosis, outcome and hospitalization were recorded.

Results: Five hundred eighteen males and 482 females were included in the study. Eight hundred nineteen patients were between the ages of 18 to 64. The most common accompanying symptom was dyspnea in both age groups. Hypertension was the most common concomitant disease in the 18-64 year age group while coronary artery disease was the most common diseasein the 65 and over age group.

Conclusions: Non-cardiac chest pain is more common in the young population admitted to the emergency department while life-threatening chest pain is more common in the population over the age of 65.

Keywords: Chest pain, emergency department, acute coronary syndrome, coronary artery disease

One of the most common reasons for admission to the emergency department is chest pain. It is a common clinical symptom that may be due to various causes such as acute myocardial infarction (AMI) or a benign cause such as thoracic muscle pain [1, 2]. Chest pain is one of the reasons that cause anxiety in patients and therefore causes frequent admissions to the emergency department. Anamnesis and physical examination are very important in chest pain. With a good anamnesis and physical examination, patients-don'tundergo unnecessary procedures, so the time of diagnosis for the disease is shortened. Thus, mortality and morbidity rates can also be significantly reduced [3, 4].

Demographic characteristics, vital signs, examination findings, and physiological changes associated

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with aging are important in determining the causes of chest pain. The causes of chest pain are affected by many factors. One of the most important of these factors is age. The causes of chest pain differ in patients according to age (Above and under 65 years of age). Although patients under the age of 65 are admitted to the emergency department more frequently with chest pain, life-threatening chest pain is less common in those patients. Patients older than 65 are less commonly admitted to the emergency department with chest pain, but these patients have more serious diagnoses. Aging physiology leads to atypical signs and symptoms, pharmacodynamic changes, decrease in functional reserve, and social problems. This makes it difficult to determine the cause of chest pain in elderly patients in an emergency department. For this reason, it is often necessary to take anamnesis from the relatives of the patientwho knowhim very well.

The study aimed to compare the diagnoses of the patients underand/or over the age of 65 admitted to the emergency service with non-traumatic chest pain.

METHODS

Patients who were admitted to Bursa Yüksek İhtisas Training and Research Hospital Emergency Department with non-traumatic chest pain between 15.10.2014 and 15.07. 2015 were included in the study. Ethics committee approval was obtained for the study. Patients under the age of 18 and patients that exposed to trauma were excluded from the study.The study was a prospective study. A thousand patients were included. The data was recorded to the study form by the emergency medical assistant who evaluated the patients. The patients' names and surnames, date of admissions to the emergency department, hospital protocols, age, gender, the type ofadmissions, accompanying diseases, accompanying symptoms, diagnoses, outcomes, and hospitalizations were recorded in the study form.

Patients were divided into two groups according to age group as < 65 years and ≥ 65 years. Chest pains were divided into three groups as the chest wall-induced, pleuritic and visceral chest pain. Costochondritis, xifodynia, fibromyalgia were included in the chest wall-induced chest pain. Pulmonary embolism, pneumonia, spontaneous pneumothorax, pericarditis, and pleurisy were included in the pleuritic chest pain group. Typical effort angina, atypical angina, acute myocardial infarction, aortic dissection, esophageal reflux, and peptic ulcus were included in the visceral type chest pain group.

The types of admission were divided into two as outpatient or 112 (Emergency call number in Turkey). The methods of termination were hospitalization, discharge, referral, exitus in the emergency department and refusal of treatment. In our study, gender, ways of admission, comorbidities, accompanying symptoms, diagnoses and terminations were compared according to age groups.

Statistical Analysis

SPSS 21.0 software was used for statistical analysis of the data. Mean, standard deviation, median, lowest and highest frequency and ratio values were used in descriptive statistics of the data. The chi-square test was used to analyze qualitative data.

RESULTS

A thousand patients admitted to the emergency department with chest pain were included in the study. Five hundred eighteen males and 482 females were included in the study. Eight hındred nineteen patients were between the ages of 18 to 64 (Table 1).

Five hundred and seventy-six patients (57.6%) had accompanying symptoms. The most common accompanying symptom was dyspnea in both age groups. In the study, 581 (70.9%) of the patients in the 18-64 age group did not have any comorbidities, whereas 138 (79.0%) in the 65 years and older group had comorbidities. Hypertension was the most common comorbidity in the 18-64 age group and

Table 1. Comparison of age groups and genders

	18-64 years old	≥ 65 years old	*p* value*
Gender, n (%)			
Female	408 (49.8%)	74 (40.9%)	**0.030**
Male	411 (50.2%)	107 (59.1%)	**0.030**

Data are shown as n (%). *The chi-square test

Table 2. Comparison of accompanying symptoms and comorbidities according to age groups

	18-64 years old	≥ 65 years old	*p* value*
Accompanying symptoms, n (%)			
No	381 (46.5%)	43 (23.8%)	**< 0.001**
Yes	438 (53.5%)	138 (76.2%)	
Dyspnoea	113 (13.8%)	57 (31.5%)	
Malaise	59 (7.2%)	17 (9.4%)	
Tachycardia	61 (7.4%)	7 (3.9%)	
Cough	51 (6.2%)	12 (6.6%)	
Nausea	45 (5.5%)	13 (7.2%)	
Other	109 (13.3%)	32 (17.6%)	
Comorbidities, n (%)			
No	581 (70.9%)	38 (21.0%)	**< 0.001**
Yes	238 (29.1%)	143 (79.0%)	
Hypertension	70 (8.5%)	38 (21.0%)	
Coronary Artery Disease	54 (6.6%)	45 (24.9%)	
Diabetes	50 (6.1%)	27 (14.9%)	
COPD	10 (1.2%)	11 (6.1%)	
Asthma	10 (1.2%)	2 (1.1%)	
Psychiatric Diseases	16 (2.0%)	0 (0.0%)	
Other	28 (3.5%)	20 (11.0%)	

Data are shown as n (%). *Chi-square test. COPD = Chronic obstructive pulmonary disease

coronary artery diseasewas the most common comorbidity in the 65 and older age group (Table 2).

Visceral pain was the most common cause of pain in both age groups. It was found that 62.3% in the 18-64 age group and 77.9% in the patients over 65 had visceral pain. In the evaluation of acute chest pain type, atypical angina was found 29.5% in the 18-64 age group and AMI was found as 31.5% in the group over 65. The discharge rate was 84.7% in the 18-64 age group, while the discharge rate was found to be 51.4% over 65 (Table 3).

Although the group over 65 were grouped as 65-74, 75-84 and over 85, there was no statistically significant difference between the groups in terms of gender, type of hospital admission, comorbidities, cause of pain and the final status. (Table 4).

DISCUSSION

Chest pain is a common symptom that affects 20 to 40% of the general population throughout their lifetime [5]. It is estimated that the prevalence of chest pain in adults in the United States is 7.8 million cases annually, which accounts for 5.4% of all emergency visits throughout the country [6, 7]. In England and Wales, annual emergency service visits were reported to be 15 million and chest painaccounted for 2.4% of these visits [8].

In the hospital where the study was conducted, the emergency room visits were around 360 thousand cases annually and the prevalence of chest pain was 0.37%. These rates were found to be less than the studies in the literature. The reason for that may be the presence of cardiology and chest diseases branch hospitals in a very close location to our hospital.

In a study, it was reported that 20-50% of the patients with chest pain were hospitalized and only 2-5% of these patients were diagnosed with the acute coronary syndrome (ACS) [9, 10]. In our study, 20% of the patient population was treated as inpatients. When we look at the subgroups, the hospitalization

Table 3. Comparison of the types of chest pain according to age groups and distribution of end-forms of patients with age groups

	18-64 years old	≥ 65 years old	*p* value*
Diagnosis, n (%)			**< 0.001**
Chest Wall Pain	236 (28.8%)	15 (8.3%)	
Pleuritic Pain	73 (8.9%)	25 (13.8%)	
Visceral Pain	510 (62.3%)	141 (77.9%	
Types of Acute Chest Pain			
Atypical angina	242 (29.5%)	44 (24.3%)	
Fibromyalgia	209 (25.5%)	11 (6.1%)	
Acute myocardial infarction	70 (8.5%)	57 (31.5%)	
Psychogenic causes	101 (12.3%)	4 (2.2%)	
Pneumonia	57 (7.0%)	20 (11.0%)	
Esophageal reflux	47 (5.7%)	11 (6.1%)	
Typical exertional angina	32 (3.9%)	17 (9.4%)	
Xiphodynia	24 (2.9%)	2 (1.1%)	
Peptic ulcus	12 (1.5%)	4 (2.2%)	
Pneumothorax	11 (1.3%)	0 (0.0%)	
Costochondritis	4 (0.5%)	2 (1.1%)	
Pleurisy	3 (0.4%)	2 (1.1%)	
Pulmonary embolism	2 (0.2%)	3 (1.7%)	
Aortic dissection	3 (0.4%)	1 (0.6%)	
Aortic aneurysm	1 (0.1%)	1 (0.6%)	
GIT perforation	1 (0.1%)	0 (0.0%)	
Pancreatitis	0 (0.0%)	1 (0.6%)	
Upper GIT bleeding	0 (0.0%)	1 (0.6%)	
Result			**< 0.001**
Discharged	694 (84.7%)	93 (51.4%)	
Treatment Rejection	6 (0.7%)	5 (2.8%)	
Exitus	0 (0.0%)	2 (1.1%)	
Hospitalization	119 (14.5%)	81 (44.8%)	
Coronary ICU Referral	81 (9.8%)	59 (32.6%)	
Cardiology Hospitalization	17 (2.2%)	10 (5.6%)	
Chest Surgery Hospitalization	10 (1.2%)	0 (0.0%)	
Chest Diseases Hospitalization	4 (0.5%)	7 (3.8%)	
Internal Medicine Hospitalization	2 (0.2%)	3 (1.6%)	
Cardiovascular ICU Referral	3 (0.4%)	0 (0.0%)	
General Surgery Hospitalization	1 (0.1%)	1 (0.6%)	
Intensive Care Unit Referral	1 (0.1%)	1 (0.6%)	

Data are shown as n (%). *Chi-square test. GIT = Gastrointestinal tract, ICU = Intensive care unit

Table 4. Comparison of gender, type of hospital admission, comorbidities, accompanying symptoms, diagnosis and results according to age groups

	65-74 years	75-84 years	≥ 85 years	*p* value*
Gender				0.706
Female	38 (43.7%)	28 (39.4%)	8 (34.8%)	
Male	49 (56.3%)	43 (60.6%)	15 (65.2%)	
Type of Admission				0.887
112	15 (17.2%)	12 (19.9%)	3 (13.0%)	
Outpatient	72 (82.8%)	59 (83.1%)	20 (87.0%)	
Comorbidities				0.451
Yes	16 (18.4%)	15 (21.1%)	7 (30.4%)	
No	71 (81.6%)	56 (78.9%)	16 (30.4%)	
Accompanying Symptom				0.591
No	23 (26.4%)	14 (19.7%)	6 (26.1%)	
Yes	64 (73.6%)	57 (80.3%)	17 (73.9%)	
Diagnosis				0.378
Chest Wall Pain	9 (10.3%)	4 (5.6%)	2 (8.7%)	
Pleuritic Pain	8 (9.2%)	12 (16.9%)	5 (21.7%)	
Visceral Pain	70 (80.5%)	55 (77.5%)	16 (69.6%)	
Result				0.776
Discharged	46 (52.9%)	38 (53.5%)	9 (39.1%)	
Treatment Rejection	1 (1.1%)	2 (2.8%)	2 (8.7%)	
Exitus	1 (1.1%)	1 (1.4%)	0 (0.0%)	
Hospitalization	39 (44.8%)	30 (42.3)	12 (52.2%)	

Data are shown as n (%). *Chi-square test

rate was found to be 14.5% in the population under 65 years of age and 44.8% in the group over 65 years of age.The most frequent reason for hospitalization in the group under and/or over 65 years of age was due to the cardiac origin. The overall ACS rate of these patients was 12.7%. When we look at the literature, our current hospitalization rates are similar, but we have a higher rate of ACS. If we examine the causes of this situation, it was thought that the patients did not comply with hypertension (HT), hyperlipidemia, and Diabetes Mellitus (DM) treatments and did not have enough information about their health. It was thought that there was a moderate inverse relationship between the development level of the society and the incidence of ACS.

In a study conducted in our country regarding the age groups of patients with chest pain, it was observed that the age group under 65 years was higher. In this study conducted by Coşkun *et al*. [11], 76.4% of the patients were under 65 years of age while 23.6% were over 65 years of age. In a study by Madsen *et al*. [12], it was found that 21.6% of the patients admitted to the emergency department with chest pain were patients over 65 years old while 78.4% were patients under 65 years old. In our study, 81.9% of the patients were under the age of 65 and 18.1% were over the age of 65, which was consistent with the literature. As seen in these studies, the majority of the patients admitted to the emergency department with chest pain are patients under 65. That the individuals in the patient group under 65 years of age are socially active and they work actively can cause acute pain such as non-specific myalgia. Because of the high life expectancy and increasing health literacy in the population under 65 years of age, patients pay attention to their complaints and apply to the emergency department.

However, the clinical presentation is more prominent in patients with chest pain such as ACS. Pain localization is more specific in these patients as neuropathy is undeveloped or negligible. Because of the development of autonomic neuropathy and diabetic neuropathy in the group over 65 years, these patients apply to the emergency department less or later. Atypical findings are more common in the clinical presentation of these patients. In addition, the presence of comorbiditiesor previous ACS in patients over 65 years of age may mask patients' acute symptoms.This may reduce or delay the patient and patient relatives' paying attention to the condition. For instance, in a patient with chronic obstructive pulmonary disease (COPD), sudden onset dyspnea is perceived as COPD exacerbation by the patient and relatives, sometimes even by the clinician and the possibility of pulmonary embolism or acute heart failure may be missed. This delays the application and sometimes results in mortality. Elderly patients have difficulty in expressing themselves because of impaired cognitive functions. For this reason, the anamnesis that we recieve from the relatives of the elderly patients who know them is very important.

Advanced age is one of the causes of poor prognosis for ACS. Mortality in ACS increases by 70% with a 10-year increase in age [13]. Although elderly people are at high risk and therefore constitute the group of patients who will benefit most from intensive treatment, they are treated with lower intensity and conservative methods in practice. ACC/AHA is defined as an especially high risk group > 75 years in the ACS treatment guidelines [14, 15].

In our study, the mortality rate was higher in the group over 65 years than in the group under 65 years. The mortality rate in patients with chest pain over 65 years is 1.1%. When we look at the overall rate of our study, it was seen that the mortality rate was low compared to the general patient group. This rate is thought to be low due to the success of early diagnosis and treatment.

In a study conducted by Coşkun *et al*. [11], it was reported that the most common accompanying disease in patients admitted to the emergency department with chest pain was HT (33.3%), the second was Coronary Artery Disease (CAD) (26.8%) and the third was DM (13.6%). In our study, the most common accompanyingdisease was HT (10-8%), the second was CAD (9.9%) and the third was DM (7.7%), which was consistent with the studies conducted in our country.

In a study conducted on the symptoms accompanying chest pain, it was found that 9.2% of patients had nausea-vomiting, 9.2% had back pain, 9.2% had syncope, and 9.2% had shortness of breath [16]. The most common concomitant symptom was dyspnea in both age groups in our study. The reason for this might be that chest pain often causes shortness of breath.

I n our study, it was observed that the discharge rate of patients with chest pain under 65 was higher (84.7%), whereas discharge rate was lower in the group over 65 years of age, but the hospitalization (44.8%) or referral (29.3%) rate was higher. It can be concluded from those findings that there is a more serious diagnosis in patients with chest pain over 65 and they should receive inpatient treatment.

Mortality and morbidity are higher in patients over 65 years of age as a result of changes in cardiovascular system and decrease in compensation mechanisms with age. Therefore, although the discharge rate is lower in the group over 65 years, the rate of referral to another institution for hospitalization or further treatment is higher.

CONCLUSION

In conclusion, it is seen that the demographic characteristics, vital signs, examination findings and physiological changes associated with aging are important in determining the causes of chest pain. Nowadays, with the increasing population, it is thought that the number of admissions of elderly patients to the emergency services will increase. Therefore physiological changes in these patients should be well known and these patients should beevaluated more carefully in terms of vital signs, additional symptoms and accompanying diseases.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2021;7(1):59-65 Original Article

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Early-term results of early coronary artery bypass graft surgery in patients undergoing primary percutaneous coronary intervention due to acute coronary syndrome

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ABSTRACT

Objectives: This study aimed to investigate the early results of the patients presented with acute coronary syndrome (ACS) who underwent coronary artery bypass grafting (CABG) after percutaneous coronary intervention (PCI) to the culprit lesion.

Methods: Patients who underwent CABG between January 2011 and January 2014 were enrolled and divided into two groups. Group 1 (102 patients) was consist of the patients who were hospitalized with ACS and underwent CABG after a previous PCI. Group 2 (107 patients) was consisting of the patients who underwent elective CABG operation after elective coronary angiography.

Results: There was no statistically significant difference between the groups in terms of demographic features and preoperative risk factors. Preoperative use of angiotensin-converting enzyme inhibitor and levosimendan were significantly higher in group 1 compared to group 2. (95 (93.1%) vs. 89 (83.1%), $p = 0.027$). The operative variables were similar between two groups whereas the postoperative blood drainage amounts were significantly higher in group 1 than group 2 (546.3 ± 172 cc vs. 424.2 ± 185 cc, respectively, $p < 0.001$). The blood product usage was significantly higher in group 1 than in group 2 (3.3 ± 1.8 units vs.1.7 ± 0.9 units, respectively, $p < 0.001$).

Conclusions: Early CABG operation after ACS is a safely applicable process with acceptable mortality and complication rates.

Keywords: Early CABG operation after ACS is a safely applicable process with acceptable mortality and complication rates.

Cardiovascular Diseases (CVDs) are the most common cause of mortality in developed countries as it is the expected case to be valid in developing countries in the future [1]. Coronary artery disease (CAD) is the most common form of cardiovascular diseases which is associated with high mortality and morbidity all over the world. Ischemic heart disease may clinically manifests as silent ischemia, stable angina pectoris, unstable angina pectoris, myocardial infarction (MI), heart failure, or sudden cardiac death. Acute coronary syndrome (ACS) is the name of a group of diseases that show different clinical manifes-

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tations in the course of coronary artery disease but entirely have a common pathophysiological mechanism [2]. The primary goal of the treatment in this clinical presentation, which manifests in a broad clinical spectrum ranging from unstable angina to ST elevation myocardial infarction (MI), is to eliminate acute obstruction in the coronary circulation by thrombolytic therapy, emergent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) surgery. In this study, the patients presented with ACS who underwent PCI for the culprit lesion were examined. The patients who were scheduled to undergo CABG for coronary artery stenosis after PCI were compared with those who were scheduled to undergo elective CABG only. The aim of this study was to compare early (30 days) postoperative outcomes including mortality, morbidity and relevant factors between the two groups.

METHODS

Patients

This study was approved by the Medical Research Ethics Committee of our hospital. The data of 209 patients who were included in the study between January 2011 and January 2014 in our cardiovascular surgery department were retrospectively analyzed. According to the diagnostic and treatment protocol for ACS in our hospital, Coronary angiography (CAG) is scheduled within the first six hours after the onset of chest pain in patients presented with ACS. In our study, PCI was performed for the responsible coronary lesions detected by CAG, and then the patients underwent CABG surgery because of extensive coronary lesions other than the culprit lesion. The patients who were scheduled to undergo CABG-only in the early period were also enrolled. In the same period, the patients who were scheduled to undergo elective CABG-only after elective CAG were also reviewed. Another patient group was randomly selected from the patients who had undergone CABG and included in the study as the control group. The 30-day postoperative mortality and morbidity data and the factors related to morbidity and mortality were investigated using the digital medical files of the patients. In this study, a total of 102 patients presented with ACS and had undergone CABG after PCI were classified as Group 1; in the same period, 107 patients who underwent elective CABG-only after elective CAG were classified as Group 2. The demographic characteristics, past medical history, perioperative data, and early postoperative mortality and morbidity outcomes were examined. The left ventricular function of all patients was evaluated by transthoracic echocardiography on the day before the surgery. As a clinical protocol, 87 (85.3%) patients underwent CABG when preoperative troponin I level was below 3 ng/ml after MI. In this group, although they were hemodynamically stable, 15 (14.7%) patients underwent CABG within the first three days due to a critical coronary artery lesion [severe left main coronary artery stenosis or severe proximal left anterior descending artery (LAD) stenosis] and ongoing angina despite optimal medical treatment after MI.After the first antiaggregant treatment given after PCI procedure, the antiaggregant treatment was terminated. If the stent was placed on the culprit lesion, clopidegrol (75 mg 1×1) was started on the second postoperative day. Patients with a history of previous CABG operation, those who required additional surgery other than CABG, and who needed emergency surgery due to hemodynamic instability were excluded from the study.

Statistical Analysis

SPSS 16.0 program was used for the analysis of the data. Categorical variables were expressed as number (%) and continuous variables were expressed as the mean ± standard deviation. The Fisher's Exact Test, Pearson's Chi-Square test, independent-samples t-test, and Mann-Whitney U test were used for the relevant analyses. A p value of <0.05 was considered as statistically significant.

RESULTS

In Group 1, there were a total of 102 patients (71 men and 31 women) with a mean age of 60.2 ± 9.0 years. In Group 2, there were a total of 107 patients (77 men and 30 women) with a mean age of 61.2 ± 10.6 years. The preoperative variables of the patients in the two groups are shown in Table 1. The mean waiting time for the surgery was 9.7 ±4.6 days in the patients who were admitted with ACS. All patients had undergone CABG between 1 to 21 days after hospi-

Table 1. Preoperative characteristics of thepatients

	Group 1 (n = 102)	Group 2 (n = 107)	*p* value
Age (years)	60.2 ± 9.0	61.2 ± 9.0	0.489
DM	49 (48%)	41 (38.3%)	0.156
HT	84 (82.3%)	82 (76.6%)	0.307
HL	68 (66.6%)	66 (61.6%)	0.453
Smoking	74 (72.5%)	74 (69.1%)	0.590
COPD	26 (25.4%)	21 (19.6%)	0.310
Beta blocker use	93 (91.1%)	88 (82.2%)	0.058
ACEI use	95 (93.1%)	89 (83.1%)	**0.027**
Levosimendan use	21 (20.5%)	11 (10.2%)	**0.039**
EF (%)	44.7 ± 9.7	46.5 ± 9.3	0.169

Data are shown as mean ± standard deviation or n (%). ACEI = Angiotensin-converting enzyme inhibitor, DM = Diabetes Mellitus, HT = Hypertension, HL = Hyperlipidemia, COPD = Chronic Obstructive Pulmonary Disease, EF = Ejection Fraction

talization. There was no statistically significant difference between the two groups in terms of DM, HT, HL, smoking, and chronic obstructive pulmonary disease. The percentage of the patients using oral ACE inhibitors preoperatively was quite close in the two groups, but the difference was statistically significant [95 (93.1%) vs. 89 (83.1%), respectively; $p = 0.027$]. The number of patients taking intravenous levosimendan in the preoperative period was higher in Group 1 than in Group 2 [21 (20.5%) vs. 11 (10.2%), respectively; $p = 0.039$].

The variables that were evaluated during the surgery in the two groups are shown in Table 2. The variables such as the number of grafts used in CABG, cross-clamping time, perfusion time, and LIMA usage among the perioperative data were compared between the groups. The LIMA graft was frequently used in both groups and there was no statistically significant difference between the two groups regarding LIMA use [97 (95%) and 97 (90.6%), respectively; $p = 0.213$]. There was no statistically significant difference between the two groups in terms of cross-clamping times [67.1 ± 27.2 min vs. 69.6 ± 27 min, respectively; $p = 0.498$], perfusion times [91.8 ± 36 min vs. 90.8 ± 33.4 min, respectively; p = 0.843] and the number of grafts used in CABG [3.3 ± 1 vs. 3.3 ± 0.9, respectively; $p = 0.901$].

The patients were monitored in terms of early surgical complications and certain parameters in the intensive care unit until the discharge. The amount of drainage in the first 24 hours postoperatively was found to be 546.1 ± 173 cc in Group 1 and 424.2 ± 185.6 cc in Group 2 ($p < 0.001$). Parallel to this, the amount of blood products used in the first 48 hours postoperatively was 3.3 ± 1.8 units in Group 1 and 1.7 ± 0.9 units in Group 2 ($p < 0.001$). The number of pa-

Table 2. Peroperativedatas of the patients

	Group 1 (n = 102)	Group 2 (n = 107)	*p* value
Number of the grafts	3.3 ± 1	3.3 ± 0.9	0.901
Cross-clamp time (min)	67.1 ± 27.2	69.6 ± 27	0.498
Perfusion time (min)	91.8 ± 36	90.8 ± 33.4	0.843
LIMA use	97 (95%)	97 (90.6%)	0.213

Data are shown as mean ± standard deviation or n (%). LIMA = Left internal mammary artery

Table 3. Postoperative datas of the patients

	Group 1 (n = 102)	Group 2 (n = 107)	*p* value
Time to extubation (hours)	12.6 ± 6	12.5 ± 12.5	0.932
Drainage (cc)	546.3 ± 172	424.2 ± 185	**< 0.001**
Blood transfusion (unit:300 cc)	3.3 ± 1.8	1.7 ± 0.9	**< 0.001**
IABP use	22 (21.5%)	13 (12.1%)	0.068
Pacemaker use	7 (6.8%)	4 (3.7%)	0.312
Atrial fibrillation	27 (26.4%)	19 (17.7%)	0.129
Infection	17 (16.6%)	11 (10.2%)	0.175
ICU stay (days)	3.3 ± 2.4	2.4 ± 1.4	**0.002**
Hospital mortality	5 (4.9%)	4 (3.7%)	0.470

Data are shown as mean ± standard deviation or n (%).ICU = Intensive care unit, IABP = Intraaortic balloon pump

tients requiring intra-aortic balloon pump (IABP) support in the postoperative period was higher in Group 1 than in Group 2, but the difference was not statistically significant between the two groups [22 (21.5%) vs. 13 (12.1%), respectively; $p = 0.068$]. IABP support was used in the management of pump failure following cardiopulmonary bypass, and low cardiac output syndrome in both groups (Table 3).

In the overall study population, mortality was observed in 9 (4.3%) patients. Three patients died due to low cardiac output and one patient died due to multi-organ failure in Group 1; while two patients died due to multi-organ failure and 3 patients died due to sepsis in Group 2. There was no significant difference between the two groups in terms of in-hospital mortality rate [5 (4.9%) and 4 (3.7%), respectively; $p = 0.470$].

DISCUSSION

In this study, we demonstrated that CABG can be performed in the early period with acceptable morbidity and mortality rates after PCI applied to the responsible coronary lesion in patients presented with ACS.

The acute coronary syndrome is the acute deterioration of underlying coronary artery disease by atherothrombotic occlusion of epicardial coronary arteries which leads to significant rates of mortality and morbidity. Successful interventional treatments have been developed over time for this acute devastating disease and significant improvements in in-hospital and long-term mortality rates have been achieved [2-5]. When ACS is diagnosed, treatment modality should be determined and the appropriate process for the required revascularization method should be initiated. Considering the coronary anatomy, the general condition of the patient and the interventional capability of the center, PCI or CABG should be decided for revascularization of the responsible coronary lesion or lesions. Recently, PCI has become the first choice treatment in the setting of ACS which results in satisfactory outcomes [5]. By the introduction of new devices and technical improvement in PCI procedures have allowed satisfying revascularization of lesions in epicardial coronary arteries and have significantly increased the availability of the procedure even in complex lesions. However, PCI can be inadequate to open target vessels in some cases such as left main coronary artery diseaseand multi-vessel disease or depending on the skill and experience of the cardiologist who performs the procedure. Under these circumstances, CABG becomes the preferred revascularization method. Along with the developments in invasive cardiology, it is possible to determine the limits of operability criteria, which is an important problem in cardiac diseases. In the previous studies till today, the precise indications for PCI and CABG have been determined. However, there are still debates on some lesions and patient characteristics. "Intervention-free life expectancy" and "event-free life expectancy" rather than the survival rates of patients after the procedure have become essential in determining indications [6].

Although both procedures can be performed in ACS, the choice and timing of the revascularization method are still controversial. In randomized studies, it has been emphasized that immediately identifying the patients who will benefit from early surgical revascularization is important [7]. According to coronary lesions viewed by CAG, medical treatment of the patients is initiated after the decision for the choice of revascularization method (PCI or CABG). Five large randomized studies (RITA, GABI, CABRI, EAST, and BARI) have compared outcomes of the patients with multivessel disease after PCI and CABG. These studies concluded almost the same results. Both revascularization methods have similar risks of death and nonfatal myocardial infarction. However, patients treated with CABG were less likely to suffer from angina and to take anti-anginal drugs in the postoperative period. Further revascularization intervention was needed more frequently in patients who were treated with PCI. Moreover, it has been clearly shown in the BARI study that surgical method was superior to PCI in the management of diabetic patients with multi-vessel CAD.

We designed our study for the patients who were presented with ACS and underwent PCI for the culprit coronary lesion and then underwent elective isolated CABG for the other lesions in the early postoperative period. As a control group, we randomly selected the patients with stable CAD who underwent elective isolated CABG after elective CAG in the same time period in our hospital. Hemodynamically unstable patients were not included in our study. Coronary artery by-pass grafting was performed on an average of 9.7 ± 4.6 days in ACS patients. There was no significant difference between the two groups in terms of mortality. In a study including 12,227 patients between 2000 and 2012, Potluri *et al*. [7] have shown that there was a significant reduction in all-cause mortality in patients who underwent primary angioplasty after ACS and then who underwent CABG due to appropriate indications. The mortality rate of this study is very close to our mortality outcome. The general decline in mortality rate was emphasized overall ACS patients who had undergone CABG thereafter, especially in the group underwent CABG after PCI.

In our study, there was no statistically significant difference between the two groups in terms of the preoperative variables, demographic characteristics and concomitant diseases. Among the preoperative variables, there was a statistically significant between the two groups regarding the medical treatments used in the preoperative period. There was a statistically significant difference between the two groups in terms of the use of oral ACE inhibitors and the use of intravenous levosimendan before the surgery. The use of oral ACE inhibitor was higher in Group 1. ACE inhibitors have the proven benefits such as increasing survival in ACS patients, reducing ventricular remodeling, having anti-atherogenic effect, and reducing the risk of death due to CAD [8-14]. In our study, we think that the use of oral ACE inhibitor was higher in Group 1 because of these reasons. In our hospital, the patients presented with ACS are treated with oral beta-blockers and oral ACE inhibitors routinely if there is no contraindication. Both drugs have been proven in terms of efficacy, so included in our routine clinical practice [15, 16]. The treatment protocol of our center can explain the difference between the study groups regarding medications used.

Similarly, another preoperative medication that was statistically significantly different between the two study groups was the percentage of patients received intravenous levosimendan. Myocardial dysfunction develops frequently in acute and subacute periods after ACS. Early revascularization results in early reperfusion in infarct- or ischemia-related artery and a rapid improvement in ventricular function usually occurs after thrombolysis. However, if transmural injury and/or microvascular obstruction occurs, especially in the anterior wall after NSTEMI or STEMI, the pump failure accompanied with pathologic remodeling and clinical signs and symptoms of heart failure may complicate the acute phase and can result in chronic heart failure. Before CABG, especially in the period after ACS, the situations such as the development of left ventricular dysfunction in echocardiography may be encountered which represent increased risk of morbidity and mortality after CPB. In these cases, preoperative levosimendan infusion would be beneficial in preventing increased mortality due to left ventricular dysfunction during and after cardiac surgery [17-19]. The fact that this treatment protocol, which was used significantly higher in Group 1, was applied for the medical treatment of the left ventricular dysfunction occurring after ACS would also explain the statistically significant difference between the two groups. In our postoperative data, although it is not

statistically significant, greater use of IABP in Group 1 may explain that the increase in preoperative use of levosimendan was related to the intention to ameliorate the left ventricular dysfunction.

In the postoperative period, there was no statistically significant difference between the two groups in terms of the time spent on mechanical ventilation, the development of heart rhythm problems, infections, and the length of stay in the intensive care unit. However, in the postoperative period, there was a statistically significant difference between the two groups in terms of the amount of blood in drainage systems and the amount of blood and blood products used. Although the increased drainage in Group 1 did not require re-exploration for surgical revision of the bleeding, it became important with the increased need for blood and blood products. In addition to the mechanical approach to vascular pathology in the treatment of ACS, there are also medical treatment options to increase and maintain the blood flow and prevent re-stenosis after revascularization. Various drug groups such as thrombolytics, antithrombotics and anticoagulants have taken place in the treatment. These treatments, which are part of the treatment of ACS, bring the risk of bleeding problems together [20]. In the ACUITY study by Ben-Gal *et al*., after CABG was performed in patients with ACS and stable angina pectoris, the patients' mid- and long-term results have been examined. In this study, the authors mentioned that bleeding problems were experienced in the ACS group in the postoperative period due to antithrombotic and anticoagulant therapy used in the treatment of 1ACS preoperatively [21]. In our study, we obtained similar results and there was no reoperation need for bleeding revision, which suggest that this treatment protocol is suitable and its implementation prior to CABG does not create essential problems in the postoperative period.

Limitations

This study is a retrospective study carried out in two homogeneous groups of patients. Our results may have been affected by our treatment methods. Relatively small number of patients is also a limitation of the study. The surgical interventions had been performed by different surgeons which. make the standardization difficult. Our patients were analyzed for in-hospital mortality and morbidity. For this reason, its mid-term and long-term results could not be assessed. In addition, patients with hemodynamic instability after myocardial infarction were excluded. The patients were operated at least 24 hours after myocardial infarction. Therefore, the data of this critical group of patients were not included in the comparisons between the study groups. On the other hand, this situation made it possible to increase the homogenization of the groups and prevented the critical preoperative condition to affect the results of the study.

CONCLUSION

According to our results, the use of preoperative levosimendan infusion and the need for postoperative IABP support were higher in the patients who were admitted with ACS and had undergone CABG-only compared to the group that underwent elective CABG-only. This finding has reinforced the depressive effect of ACS on left ventricular functions. Nevertheless, there was no significant difference in mortality rates between the two groups. It may be thought that the increased need for medical practice and IABP support as well as the length of stay in the intensive care unit increase the treatment costs. However, there is no previous comparative study on this topic. Based on the results of our study and the previous studies, we believe that CABG can be safely and successfully performed in the early period with acceptable morbidity and mortality rates in ACS patients who underwent PCI for the culprit lesion and who have an indication for CABG surgery due to the remainder lesions.

Declaration of authorship

All authors have directly participated in the planning, execution, analysis or reporting of this research paper. All authors have read and approved the final version of the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Estrogen receptor expression in normal breast epithelium in invasive ductal carcinoma

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ABSTRACT

Objectives: Invasive ductal carcinomas (IDCs) are the most important group of malignant breast tumors and constitute 75-80% of breast carcinomas. While IDCs often present with ductal carcinoma in situ (DCIS), they sometimes include a low level of DCIS or they do not include any accompanying DCIS at all. We planned this study to compare estrogen receptor (ER) expression levels in normal mammary epithelium in IDCs with extensive DCIS (Group I) and IDCs without DCIS (Group II).

Methods: Eighty IDC cases selected from among samples that were analyzed in our pathology laboratory. The cases were assessed retrospectively in light of immunohistochemical analysis results and pathology reports. Evaluation of immunohistochemistry: ER positivity in IDC was defined with a nuclear staining of more than 10% of cancer cells regardless of intensity of staining. Presence of cells showing nuclear staining for normal breast epithelium was classified in 4 groups according to their quantity and intensity. These were: 0-None: No staining was observed, 1-Single: One or two positive cells, 2-Dispersed: Dispersed positive cells surrounded by negative cells, 3-Adjoined: 10 or more positive cells contacting each other.

Results: Statistically no significant difference was found between Group I and Group II in terms of ER expression. Group I were more prevalent in younger and in the premenopausal period than Group II.

Conclusions: According to our study, there was no difference between Group I and Group II in terms of ER expression. But the significantly presence Group I in more young people and in premenopausal women suggests that these carcinomas develop due to high estrogen levels and that Group II develop independently than estrogen. This suggests that these groups may have different carcinogenesis and etiologies. We therefore think that this first study on IDCs with extensive DCIS and IDCs without DCIS should be supported by new research studies.

Keywords: Estrogen reseptor, breast epithelium, invasive ductal carcinoma, ductal carcinoma in situ

Breast cancer is the second most prevalent type of cancer throughout the world and it is the fifth most common cause of death-related to cancer [1]. Several researchers believe that breast carcinogenesis is a multi-step process [2], yet the etiologic mechanisms of breast carcinogenesis are not yet completely understood.

Histologically, estrogen receptor (ER) is expressed in approximately 4-15% of normal human mammary epithelial cells (HMEC) [3, 4]. ER has a key role in

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progression of early breast lesions towards breast cancer [5]. Moreover, ER is an admitted factor of prognosis and prediction for breast cancer [6]. More than 50 % of malignant neoplasms coming from breast gland epithelium are ER+ [7]. It is also reported that estradiol causes breast cancer formation with its both ER dependent and genotoxic ER – free effects [8]. Another study suggests that breast cancers of gene expression patterns ER+ and ER- can originate from different stem cells and ER- breast cancers develop independently from estrogen [9, 10]. All this information and additional research performed in the past fifty years show that estrogen and ERs have important roles in breast carcinogenesis [11, 12].

Invasive ductal carcinomas (IDCs) are the most important group of malignant breast tumors and constitute 75-80% of breast carcinomas [13, 14]. While IDCs often present with ductal carcinoma in situ (DCIS), they sometimes include a low level of DCIS or they do not include any accompanying DCIS at all. If there exists a DCIS in or around the IDC that constitutes at least 25% of the neoplasm, this is called IDC including extensive DCIS. When invasive ductal carcinomas are accompanied by DCIS, there is a significant association between histological degrees of IDC and DCIS components [15]. This hypothesis is supported by genetic studies showing similar patterns of loss of heterozygosity (LOH) in both invasive and DCIS components of the same tumor [16]. ER expression in breast tissue is higher in the epithelium showing proliferative changes around the carcinoma [17]. A positive correlation of ER levels is also reported between tumor and benign tissue neighboring the tumor [18].

The rate of ER positive cells in premenopausal women is between 4% and 15% depending on the phase of menstrual cycles. These cells are dispersed one by one and they are surrounded by ER negative cells [2, 19, 20]. The number of ER positive cells increases with advanced age [21].

We planned this study to compare ER expression levels in normal mammary epithelium around carcinomas in women with IDC with extensive DCIS (a rate of 30% and above) (Group I) and without DCIS (a rate of 5% and less) (Group II). Moreover, we analyzed the association between the two groups in terms of parameters such as age, menopausal status, tumor diameter, number of tumor foci, Nottingham histological grade, ER in carcinoma, progesterone receptor (PR) and C-erb-B2 expression status, lymph node metastasis status and also status of these parameters in all IDCs.

METHODS

Ethics committee approval for the study was obtained from the clinical research ethics committee of our institution. A total of 80 IDC cases selected from among breast mastectomy samples that were analyzed in our pathology laboratory were assessed. Forty-two of these were Group I and 38 were Group II. The cases were assessed retrospectively in light of immunohistochemical analysis results, pathology reports and information gathered from interrogations through telephone conversations.

The samples were paraffin-embedded blocks obtained from pathologic samples of 80 female patients (Group I 42 female patients and group II 38 female patients) who underwent mastectomy or breast protective surgical treatment in our hospital. In routine standard sampling, 3 samplings were performed on average from the tumor tissue.

The samples were fixed in 10% neutral buffered formalin for 24-48 hours and were embedded in paraffin. In each case, a sufficient tumor sample and a block including normal breast tissue around the tumor were selected. Dako EnVision+kit (DakoCytomation,

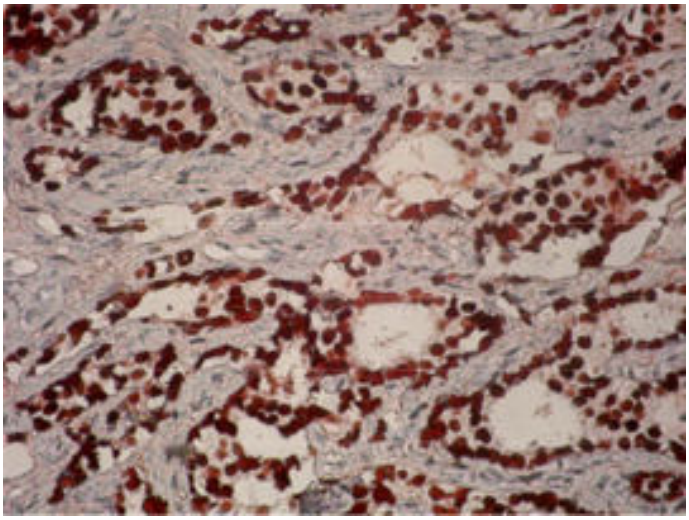

Fig. 1. Estrogen receptor positivity in invasive ductal carcinoma.

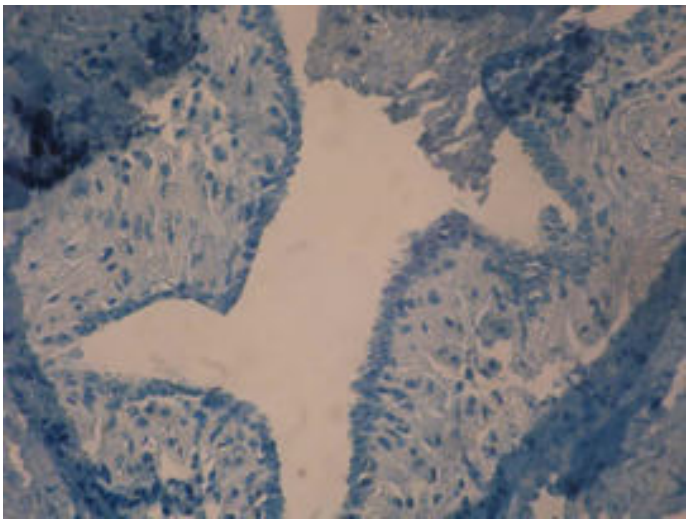

Fig. 2. Estrogen receptor expression pattern group 0: No staining is observed in normal breast ductus epithelium.

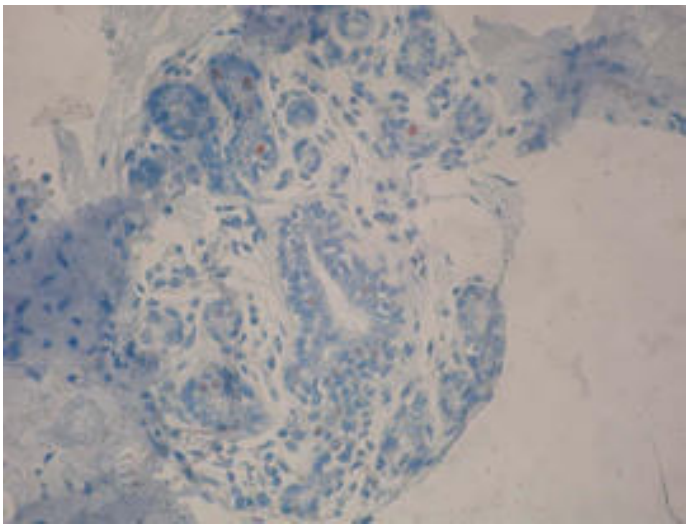

Fig. 3. Estrogen receptor expression pattern group 1: Ductus epithelium cells are observed with one or two stained cells in normal breast ductus epithelium.

Glostrup, Denmark) was used manually following the manufacturer's instructions. Preparations were deparaffinized in xylene and rehydrated gradually in ethanol/water mixture series. Antigen retrieval process was applied to preparations, which were heated in a water bath of 95-99 C for 40 minutes in "target retrieval solution high pH (Dakocytomation)". After 20 minutes of cooling, sections were processed with primary antibody for 30 minutes following exposure to 3% hydrogen peroxide for 5 minutes at room temperature. Monoclonal mouse anti-human ER (clone 1d5; Dakocytomation) antibody was used at 1/50 dilution.

Evaluation of immunohistochemistry: ER positivity in IDC was defined with a nuclear staining of more than 10% of cancer cells regardless of intensity of staining (Fig. 1). Presence of cells showing nuclear staining for normal breast epithelium was classified in 4 groups according to their quantity and intensity. These were: 0-None: No staining was observed (Fig. 2), 1-Single: One or two positive cells (Fig. 3), 2-Dispersed: Dispersed positive cells surrounded by negative cells (Fig. 4), 3-Adjoined: 10 or more positive cells contacting each other (Fig. 5) [22].

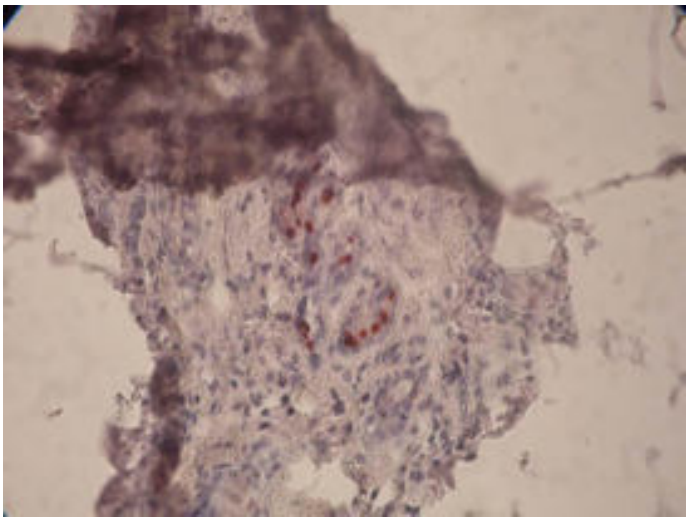

Fig. 4. Estrogen receptor expression pattern group 2: There is linear or dispersed cellular staining consisting of less than 10 cells adjoined to each other in normal breast ductus epithelium.

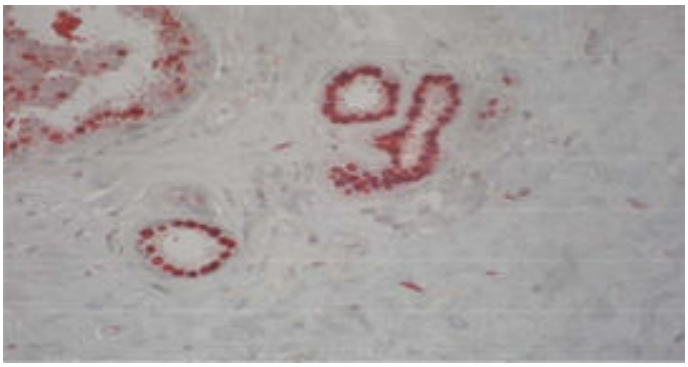

Fig. 4. Estrogen receptor expression pattern group 3: There is adjoining linear staining consisting of more than 10 cells in normal breast ductus epithelium.

Table 1. Relation between negative and positive distribution of ER expression pattern groups 0, 1, 2, 3 in normal breast epithelium around the carcinoma

		ER Pt. NME 0	ER Pt. NME 1	ER Pt. NME 2	ER Pt. NME 3	*p* value
ER in IDC	Negative	8 (100.0%)	5 (29.4%)	10 (30.3%)	6 (31.6%)	χ^2:14.7
	Positive	0 (0.0%)	12 (70.6%)	23 (69.7%)	13 (68.4%)	0.002

ER = Estrogen receptor, Pt = pattern, NME = normal mammary epithelium, IDC = invasive ductal carcinoma

Statistical Analysis

In this study, statistical analyses were performed with NCSS 2007 package software. Besides descriptive statistical methods (mean, standard deviation) for assessment of data, Kruskal Wallis (KW) test was used for multiplex group comparisons, Dunn's multiple comparison test was used for sub-group comparisons, Mann-Whitney (MW) U test was used for comparison of double groups and Chi-square test was used for comparison of qualitative data. The results were assessed at a level of significance of $p < 0.05$.

RESULTS

Statistically no significant difference was found between Group I and Group II in terms of ER expression in normal breast epithelium around the carcinoma. Statistically no significant difference was found between Group I and Group II in terms of expression pattern in normal breast epithelium around the carcinoma (0, 1, 2 and 3), tumor diameter, metastatic lymph node quantity, metastatic lymph node involvement phase, total Nottingham Histological Score and Nottingham histological grade.

In invasive ductal carcinomas, statistically a significant difference was observed between expression pattern groups (0, 1, 2 and 3) of ER in normal breast epithelium around the carcinoma and expression of ER in the carcinoma ($p = 0.002$) (Table 1). There was a parallelism between ER expression in normal breast epithelium around IDC and ER expression in IDC.

There were 42 cases in Group I and 38 cases in Group II. Ages of these cases were between 27 and 84 (mean age: 55.88 years). Mean age in Group I was 52.45 ± 13.31 years, and mean age in Group II was 59.68 ± 14.83 years, and statistically there was a significant difference between the mean ages of the groups (MW=564, p = 0.025). Group I cases were more prevalent in younger ages than group II cases.

A significant difference was observed between distribution of menopause status of cases of the two groups ($p = 0.002$) (Table 2). While group I were more prevalent in the premenopausal period, group II were more prevalent in the postmenopausal period. Approximately 54.8% of group I were in the premenopausal period and this rate was 21.1% of group II.

In invasive ductal carcinomas, postmenopausal presence was significantly lower in the ER expression pattern group 0 compared to ER expression pattern groups 1, 2 and 3 ($p = 0.018$) (Table 3). While the number of cases showing ER expression in normal breast epithelium around IDC were much more for postmenopausal, cases without ER expression were usually premenopausal cases.

Statistically, a significant difference was found between distribution of ER expression pattern groups in normal breast epithelium around the carcinoma in invasive ductal carcinomas and the arithmetic mean of metastatic lymph node quantity ($p = 0.041$).

Table 2. Distribution of premenopausal / postmenopausal status of Group I and II cases

Menopause Status	Group I n (%)	Group II n (%)	*p* value
Premenopausal	23 (54.8%)	8 (21.1%)	χ^2:9.55
Postmenopausal	19 (45.2%)	30 (78.9%)	0.002

Table 3. The relationship between the expression pattern groups 0, 1, 2 and 3 of ER in normal breast epithelium around the carcinoma and the menopausal status

Menopause Status	ER Pt. NME 0	ER Pt. NME 1	ER Pt. NME 2	ER Pt. NME 3	*p value*
Premenopausal	7 (87.5%)	4 (23.5%)	14 (38.9%)	6 (31.6%)	**χ^2:10**
Postmenopausal	1 (12.5%)	13 (76.5%)	22 (61.1%)	13 (68.4%)	**0.018**

ER = Estrogen receptor, Pt = pattern, NME = normal mammary epithelium

Table 4. Relation between distribution of ER expression pattern in normal breast epithelium around the carcinoma and the arithmetic mean of metastatic lymph node quantity

	ER Pt. NME 0	ER Pt. NME 1	ER Pt. NME 2	ER Pt. NME 3	KW	*p* value
Metastatic lymph node quantity	6 ± 0.01	11.14 ± 9.53	4.19 ± 3.1	4.36 ± 4.74	6.48	**0.041**

ER = Estrogen receptor, Pt = pattern, NME = normal mammary epithelium, KW = Kruskal-Wallis test

However, when Dunn's multiple comparison test was applied, metastatic lymph node quantity of group 1 of ER expression pattern in normal breast epithelium around the carcinoma (slightly positive) was significantly higher than the number of metastatic lymph nodes of pattern groups 2 and 3 (medium and highly positive) ($p = 0.034$, $p = 0.046$). Statistically, no significant difference was observed between the other pattern groups ($p > 0.05$) (Table 4 and 5). Much more lymph node metastasis occurs in cases with a slightly lower level of ER expression (Pattern group 1) in normal breast epithelium around IDC compared to the cases with medium and high levels of ER expression (Pattern groups 2 and 3).

Table 5. Relation between distribution of ER expression pattern in normal breast epithelium around the carcinoma and the arithmetic mean of metastatic lymph node quantity

Dunn's Multiple Comparison Test	Metastatic Lymph Node Quantity
ER Pt. NME 0 / ER Pt. NME 1	0.631
ER Pt. NME 0 / ER Pt. NME 2	0.969
ER Pt. NME 0 / ER Pt. NME 3	0.978
ER Pt. NME 1 / ER Pt. NME 2	**0.034**
ER Pt. NME 1 / ER Pt. NME 3	**0.046**
ER Pt. NME 2 / ER Pt. NME 3	0.998

ER = Estrogen receptor, Pt = pattern, NME = normal mammary epithelium

In invasive ductal carcinomas, statistically no significant difference was observed between the ER expression pattern groups (0, 1, 2 and 3) in normal breast epithelium around the carcinoma and tumor diameter, age, Nottingham histological grade total score, Nottingham histological grade, metastatic lymph node involvement phase, PR in carcinoma, C-erb-B2 expression and focality.

DISCUSSION

In our study, the ER expression level in surrounding breast ductus epithelium did not show a difference between the group I and group II. We could not find any significant difference between these two groups in terms of other variables (such as lymph node metastasis, tumor diameter, multifocality, histological score, PR in IDC and C-erb-B2 positivity). Similar to our study, Ahmed *et al*. [19] did not detect a significant difference in their study of 100 consecutive cases between groups with and without extensive DCIS in

terms of tumor size, histological grade, nodal status, pathologic phase, ER and PR expression. Also in the study of Stuart *et al*. [23], no direct correlation was detected in case groups with extensive DCIS fields with multifocality or other parameters. On the other hand, Fisher *et al*. [24] showed that the most significant difference was the increase of multicentricity in cases with extensive DCIS.

According to our study, the relation between ER expression pattern (pattern groups 0, 1, 2 and 3) in normal ductus epithelium around the carcinoma in IDCs and negativity and positivity of ER in the carcinoma was statistically significant. In expression pattern group 0, positivity of ER in the carcinoma was not observed. Moreover, ER positivity in the carcinoma was observed at a rate of 69.5% on average in ER expression pattern groups 1, 2 and 3 in normal breast epithelium around the carcinoma. Positivity of ER in normal breast epithelium around the carcinoma in IDCs was detected in 90% of the cases (72 of 80 cases). Like our study, Umekita *et al*. [22], who compared ER expression in surrounding breast tissue and ER expression in the tumor, found this rate to be 99% (217 of 220 cases). In contrast to our study, Yang *et al*. [25] found ER expression levels in the terminal ductal lobular unit in ER positive tumors to be significantly low. Whereas in our study, ER negativity was not detected at all in normal breast epithelium in positive IDCs, and low ER positivity was at a rate of 25%, medium level ER positivity was 48% and high level of ER positivity was 27% (Table 1).

Statistically, no significant difference was observed between ER expression pattern groups distribution in normal breast epithelium around invasive ductal carcinomas and the arithmetic mean of ages of the cases. In addition, it is remarkable that the mean age of the cases increased as the ER expression increased in surrounding normal breast epithelium. In particular, while the mean age of cases without ER expression or cases with low level of expression was 45, the mean age of cases with high level of ER expression was 60. Kumar *et al*. [26] measured ER expression levels in tumor and normal breast epithelium surrounding the tumor with enzyme immunoassay and compared them with age. In parallel with our findings, while tumor ER levels increased with age, no change was seen in ER levels in normal breast epithelium around the tumor in different age groups. Barnes *et al*. [27] observed in their study that the rate of ER positive cells slightly increased with age in ordinary ductal hyperplasia. In addition to this, in all atypical ductal hyperplasia (ADH), lobular carcinoma in situ and DCIS cases, a high level of ER positivity (Pattern group 3) was observed in most of the lesions. However, this relation between ER positive cell quantity and age was lost with these lesions. This situation, in one sense, shows the autonomy of proliferation of ER expression or cells expressing receptor. This hypothesis is based on deterioration of configuration of ER positive cell quantity or receptor expression in the ADH phase, which starts abnormal expression of cyclins and other cell cycle proteins. These results suggest a hypothesis that can explain the lack of a significant relation between age and expression patterns of ER in normal breast ductus epithelium around IDC in our study. Woolcott *et al*. [28], in parallel with our findings, used breast excisional biopsies taken for diagnostic purposes as a control group in their research. While there was a significant relation between age and ER levels in nonneoplastic tissue in groups of breast cancer cases and the control group, they could not detect a relation between age and ER levels in case groups. In another study, Giani *et al*. [29], in parallel with our findings, determined that the mean age of ER positive women was higher than ER negative women. Throughout society, besides a significant positive relation between ER positivity and age, there is a tendency towards ER positivity in postmenopausal women rather than premenopausal women. The results of Rochman *et al*. [30] and Ellinidi *et al*. [31] are in parallel with each other and show great similarity with our findings. They indicate that in primary breast cancers, there is a positive relation between age of the patients and increasing incidence of ER positive tumors.

In our study, statistically no significant difference was observed between the two groups in terms of positive and negative distribution of ER in carcinomas. Likewise, in the study of Xuefeng *et al*. [32], no difference was detected between these two groups. The positive correlation in this case is the relation between DCIS and the invasive component accompanying DCIS, and both in situ and invasive components have the same positive and negative rate. The only important difference is that staining density

and extent of ER in the in situ component is much more than in the invasive component.

CONCLUSION

We performed the first study to investigate ER expression between group I and group II. According to our study, there was no difference between group I and group II in terms of ER expression in carcinoma and in normal breast ductus epithelium around the carcinoma. But there was a significant difference between group I and group II in terms of mean age and menopause status of cases. The significantly presence of group I cases in more young people and in premenopausal women suggests that these carcinomas develop due to high estrogen levels and that group II cases develop independently than estrogen. This suggests that these groups may have different carcinogenesis and etiologies. We therefore think that this first study on group I cases and group II cases should be supported by new research studies.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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How to perform surgical planning for hemodialysis access? Routine preoperative doppler ultrasound mapping

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ABSTRACT

Objectives: The aim of the study was to evaluate the effect of routine preoperative Doppler ultrasound mapping on surgical planning in patients having hemodialysis fistulas.

Methods: Patients with arteriovenous fistulas (AVF) or arteriovenous grafts (AVG) were retrospectively reviewed between June 2010 and July 2017. Physical findings, preoperative Doppler ultrasound and postoperative findings of 1924 patients were reviewed.

Results: Fistula maturation rate was 82%. The average duration of patency of the first fistula was 19 months (3-38 months) and the duration for a previous fistula operation history was 11 months (1-14 months). Patency rate after 6 months was 78%. Mean maturation times for AVF and AVG were 70 and 28 days, respectively. Doppler ultrasound findings affected operation plans of surgeons in 227 of 908 (25%) first time fistula operation patients, and in 569 of 1016 (56%) patients with previous history of fistula surgery. Review of two groups revealed that Doppler ultrasound affected 41% (796/1924) of fistula planning of surgery for hemodialysis.

Conclusions: We suggest that preoperative Doppler ultrasound should be routinely performed in patients undergoing fistulation for hemodialysis. Furthermore, a vascular radiologist and a vascular surgeon should decide the surgical plan together.

Keywords: arteriovenous fistulas, arteriovenous grafts, Doppler ultrasound, hemodialysis

An arteriovenous fistula (AVF) has become the gold standard modality for hemodialysis because of its long patency, good durability and low infection risk [1]. It has been suggested that Doppler ultrasound (DUS) should be performed after clinical examination and before AVF surgery. By this way, AVF failure rate can be reduced and negative surgeries can be avoided [2, 3].

At our institution DUS is routinely performed before hemodialysis fistulation in all patients. In this study we aimed to evaluate the effect of routine preoperative DUS mapping on surgical planning.

METHODS

Data Collection

Patients having AVF or arteriovenous grafts (AVG) were retrospectively reviewed between June 2010 and July 2017 in our hospital. All of patients were examined before hemodialysis fistulation by one of two experienced vascular surgeons. Consultations by a cardiologist, pulmonologist, anesthesiologist, and/or studies accepting Doppler ultrasound were also included. The surgeon noted the first preoperative plan into patient folders after the physical examination. The

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vascular radiologist and vascular surgeon made their decision on the final preoperative plan according to DUS examination. In some circumstances, the other vascular surgeon also evaluated the patient and the result was stated as a "council decision" in the folder. Initial and final plans in the patient folder were compared. "Doppler ultrasound affected surgery" group was composed of patients whose surgical plans were made following Doppler ultrasound due to reasons such as obesity, edema, or multiple surgical operations.

Patients with inadequate data for the study or who were evaluated with radiological modalities like venography (except Doppler ultrasound) were excluded from the study.

Preoperative Doppler Ultrasound

Preoperative DUS was performed to all patients prior to fistula surgery for hemodialysis in our hospital.

Upper extremity DUS examinations were made with a GE LOGIQ P7 ultrasound system having 6-12 MHz probe, in a silent, adjusted heat and light level, and comfortable room. The patient sat against the radiologist with arms protracted forward in a comfortable position.

Arterial examination included longitudinal and transvers scanning of subclavian, axillary, brachial, ulnar and radial arteries. Morphologic parameters such as tracks of the vessels, diameter, wall thickness, changes in the vessel wall, obstructive vessel lesions, and hemodynamic changes were evaluated (Fig. 1).

Venous examination included longitudinal and transverse scanning of superficial and deep veins of the arm (between wrist and distal of the subclavian vein). Parameters evaluated were venous wall thickness, wall structure, flexibility, diameter, track, existence of collateral vessel, and deepness. In case of thin veins, a tourniquet was applied to the brachial region, and this was stated at the report (Figs. 2 and 3). In addition, narrowing of central veins was prevented by using Valsalva maneuver during spectral sampling from the axillary and subclavian levels. If the spectral sampling results were suspicious, venography was made.

Preoperative Planning

Snuff box AVF, radiocephalic AVF (low, medium, high), brachiocephalic AVF, mobilized basilic vein AVF, ulnabasilic AVF, radiobasilic AVG, brachiocephalic AVG, brachiobasilic AVG, brachiobrachial AVG and brachioaxillary AVG for hemodialysis is made in our unit. The aim was to carry out AVF to the non-dominant arm and the distal part of the arm. If it wasn't suitable for AVF, the dominant arm was used. AVG was performed if no suitable vessel was present for AVF. Patients with history of several fistula operations undergone hybrid fistulas.

The ultimate goal was an artery wider than 1.6 mm and flow greater than 50 ml/min (Fig. 1). Veins with thin and smooth walls, anechoic lumen, and the ones which were completely compressible were accepted as normal (Figs 2 and 3). Aimed criteria for veins were a diameter wider than 1.6 mm, depth for the skin less than 1 cm, normal structure vein with an 8-10 cm straight section.

Statistical Analysis

Data obtained from files of patients were evaluated from aspects of planning, after physical examinations, and the last planning was done after DUS and fistula maturations. Patients were separated into two groups as ones that were operated for the first time and others that were operated previously. Each group was also analyzed for similarities and differences after physical examination planning data and DUS planning data. The effect of DUS on the preferred surgical plan was investigated.

RESULTS

A total of 2,133 fistula operations for hemodialysis were made in our hospital between June 2010 and July

Table 1. Demographic parameters of patients

Age (year)	14-82 (mean:58)
Sex	
Male	1.022
Female	902
Hypertension	543
Diabetes mellitus	432
Cardiovascular diseases	522
Smoking	652

Table 2. Distribution of fistula types

Type of Fistula	First Time Fistula	Multipl Time Fistula	Total
Snuff box AVF	47	3	50
Radiocephalic AVF	468	240	708
Brachiocephalic AVF	295	423	718
Mobilized basilic vein AVF	11	24	35
Ulnar-basilic AVF	5	12	17
Radiobasilic AVG	5	5	10
Brachiocephalic AVG	11	45	56
Brachiobasilic AVG	61	224	285
Brachioaxillar AVG	5	40	45
Total	908	1.016	1.924

AVF = Arteriovenous fistula, AVG =: arteriovenous grafts

2017. Demographic data of the patients are shown in Table 1. Two hundred nine patients who did not meet inclusion criteria were excluded. Distribution of fistula types based on the first time operation and previous fistula operation history are shown in Table 2.

Fistula maturation rate was 82%. The average time patency for the first fistula was 19 months (3-38), and the time of previous fistula operation history was 11 months (1-14). The rate of completeness after 6 months was 78%. The mean maturation time was 70 days for AVF and 28 days for prosthetic AVG in the study group.

DUS affected operation plans of the surgeon in 227 (25%) of the 908 first time fistula operation patients, and 569 (56%) of the 1016 patients with previous history of fistula surgery (Fig. 3). The effect of Doppler ultrasound on the planning of the fistula surgery for hemodialysis was 41% (796/1924) when the average of two groups was investigated.

DISCUSSION

Success of AVF procedure affects hemodialysis directly and may have a significant impact on patients. Traditionally, surgeons decide the type of AVF accord-

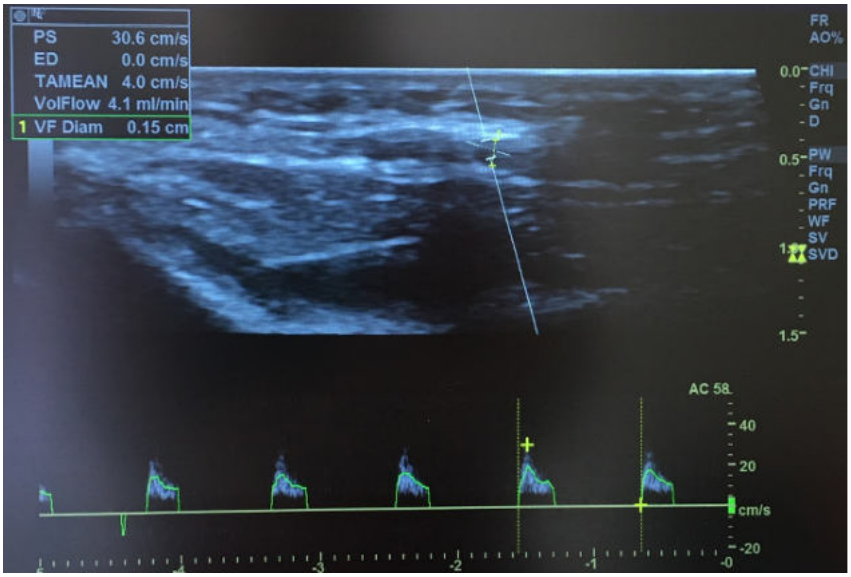

Fig. 1. Extensive calcific atherosclerotic changes are observed in the radial artery wall. Diameter of radial artery is 1.5 mm, flow velocity 4.1 ml/min, flow pattern monophasic.

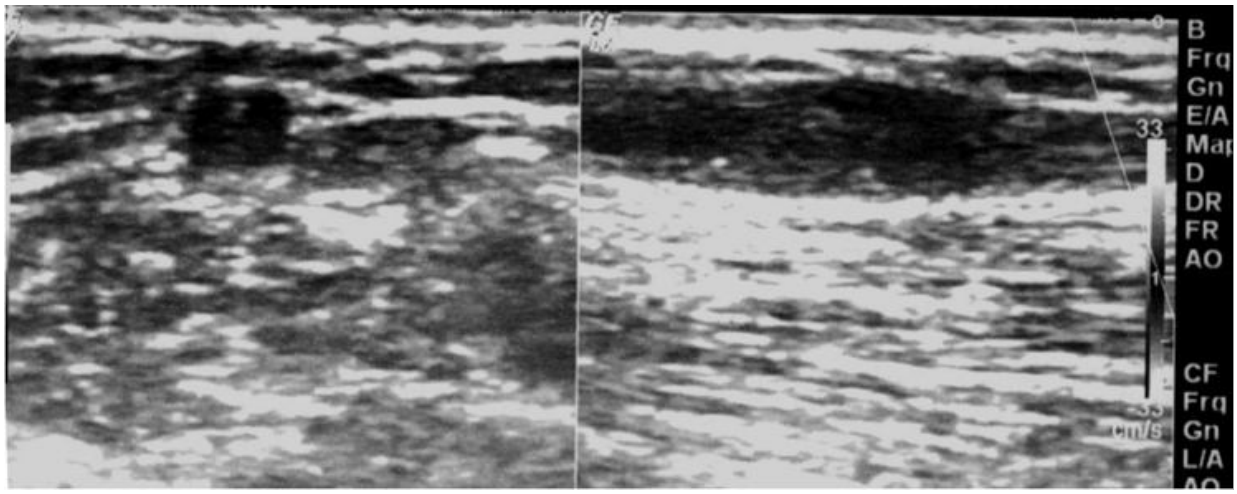

Fig. 2. **Axial and sagittal views of the subacute period thrombus in the cephalic vein. Recently, the patient has a history of intracath insertion from this localization.**

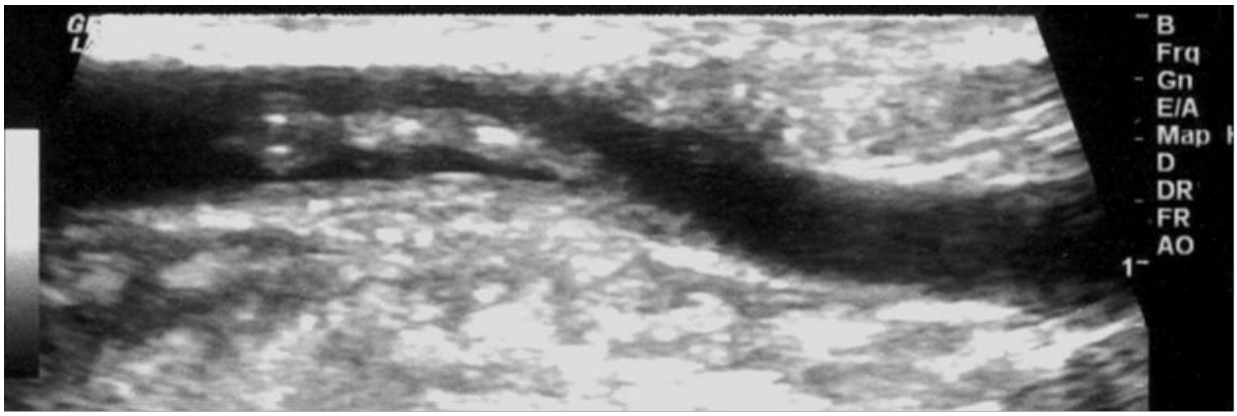

Fig. 3. **Axial views of the cronic period thrombus in the cephalic vein.**

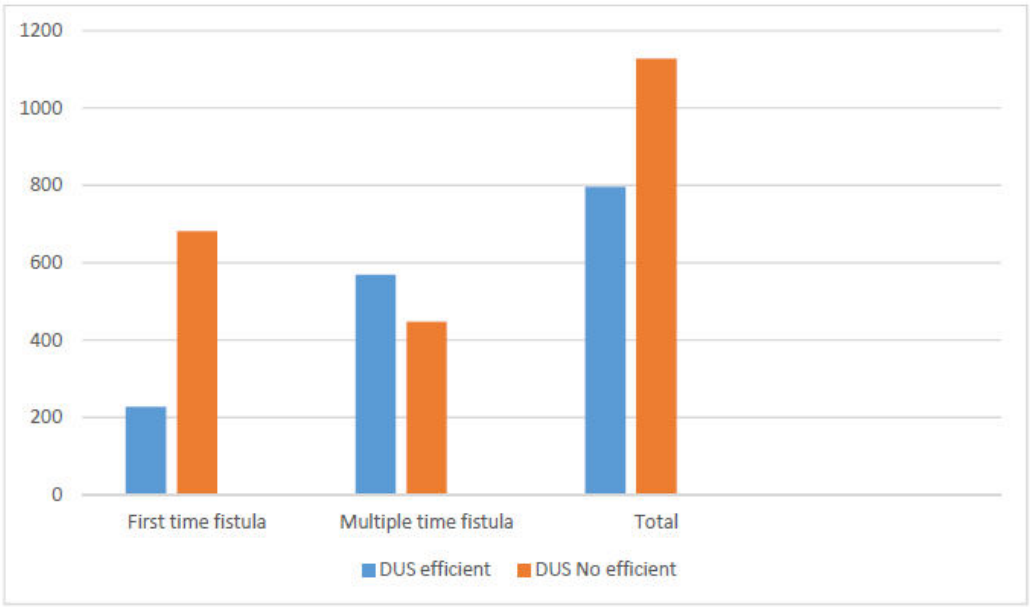

Fig. 4. **The effect of Doppler ultrasound on the planning of the fistula surgery for hemodialysis. DUS = Doppler ultrasound**

ing to clinical examination. However, physical examination may not be adequate to decide the AVF type due to conditions of patients like previous fistula surgery, medical comorbidities, etc. This necessitates need of additional examination methods to identify suitable veins [4].

Recently, interest on advantages of ultrasound has increased. It is a noninvasive, safe, and effective method and duplex scanning helps surgeons to improve AVF maturation rates by establishing morphologic and functional parameters or characteristics of vessels [3]. Disadvantages of routine preoperative DUS for hemodialysis fistula are inexperienced vascular radiologists and increased burden on the radiology unit.

Guidelines of the Kidney Diseases Outcomes Quality Initiative recommend routine ultrasound for mapping in all AVF patients while acknowledging the track of Level 1 supportive evidence [5]. Disease Outcomes Quality Initiative guidelines and European Best Practice Guidelines suggest routine use of preoperative ultrasound examination based on level 2 evidence [6]. However, there is no standard accepted DUS mapping routine [7].

It has been stated in a recent meta-analysis study that clinical examination is not sufficient alone for AVF planning and preoperative DUS decreases rates of negative exploration and early AVF failure [4]. In another recently published study, it was shown that the maturation rate was 77.3% for Doppler ultrasound and 56.8% ($p = 0.008$) for non-Doppler ultrasound when patients evaluated by physical examination and by DUS compared [8]. In our study, the maturation rate was 82% and the 6 month completeness rate was 78%.

Silva *et al*. [9] postulated in their study that routine preoperative DUS scanning increased the rate of native AVF in their practice from 14% to 63%. Ferring *et al*. [10] described that routine preoperative DUS scanning is superior to the use of DUS for the selected patients. Smith *et al*. [11] reported in their study, with 39 patients, that routine preoperative DUS for fistula operation for hemodialysis caused a 30% change planning of surgery. This ratio was 41% in our study. On the other hand, this ratio was 25% for patients undergoing fistula operation for the first time and a 56% higher rate was found in patients with previous history of fistula operation.

Limitations

Limitations of our study was being a single centered study, where one vascular radiologist and two vascular surgeons having experience for working together. We suggest that further studies in different centers will be helpful.

CONCLUSION

CONCLUSION

We conclude that performing DUS routinely in the preoperative period is important especially in patients with previous fistula operation history. We recommend that patients fistulated for hemodialysis, should be subjected to preoperative DUS a vascular radiologist and vascular surgeon should decide surgical planning together.

Conflict of interest

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The European Research Journal 2021;7(1):80-87 Original Article

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Outcomes of surgical practice on tubo-ovarian abscess in an academic hospital

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ABSTRACT

Objectives: We aimed to analyseour experience in the surgical management of tubo-ovarian abscess at a tertiary hospital.

Methods: Data from patients who underwent laparoscopy or laparotomyfor treatment of tubo-ovarian abscess were retrospectively analyzed. The clinical and surgical outcomes of patients with tubo-ovarian abscess were compared according to the applied surgical approach.

Results: The mean largest diameter of the abscess in the laparoscopy and laparotomy groups were similar (p = 0.520). The mean day for total antibiotic use was significantly shorter in the laparoscopy group (10.00 ± 4.37 day vs 17.91 ± 6.59 day; p = 0.002). All cases in the laparotomy group needed to change the antibiotic regimen, but it was needed only in 28.58% of patients in the laparoscopy group. However, preoperative fever and pulse rate was significantly higher in laparotomy group than in the laparoscopy group (p = 0.004, p = 0.014; respectively). There was no statistical difference in terms of applied surgical procedure betweenthetwo groups. The most applied surgical procedure was abscess drainage in both of the groups (71.42%, 90.90%; respectively). The median operation time in patients with laparoscopy was statistically shorter than in patients with laparotomy (65.50 [58-93] minutes vs 84 [74-90] minutes, p = 0.048). In comparison of postoperative complications between two groups, there was no statistically significant difference. We observed statistically significant declination in white blood cell count and C-reactive protein values at the postoperative 7th day in all patients (p < 0.001and p < 0.001, respectively).

Conclusions: In terms of surgical approach for tubo-ovarian abscess, laparoscopy is more effective than laparotomy for shorter duration of postoperative antibiotic use, operation time and length of hospital stay.

Keywords: Laparoscopy, laparotomy, pelvic inflammatory disease, surgical approach, tubo-ovarian abscess

Tubo-ovarian abscess (TOA) is a complex infectious adnexial mass affecting the fallopian tubes and ovaries. It usually comes across as a sequelae of pelvic inflammatory disease (PID). Common clinical signs are adnexial mass, high fever, foul-smelling discharge, lower abdominal pain and high leukocyte counts. In addition, clinical presentations may vary. If the abscess ruptures, it can be life-threatening because of sepsis. Therefore, hospitalization is recommended to begin treatment immediately after the diagnosis of TOA [1-3].

In cases which developed TOA, an underlying PID is often found, but it is not a must. In recent years, new management schemes created by Centers for Disease Control and Prevention (CDC) in the investigation and treatment of sexually transmitted diseases have re-

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duced the incidence of TOA to 2.3% in patients with a history of PID [4]. However, patients with TOA still face serious complications such as chronic pelvic pain, deterioration of pelvic anatomy, risk of future ectopic pregnancy, infertility and recurrent PID.

Today, 70% of patients with TOA can be treated conservatively with improvements in broad spectrum antibiotics, imaging methods and drainage techniques [5, 6]. If an unruptured TOA is detected, treatment with intravenous antibiotics may be initiated. However, 31% of these patients may require surgical intervention due to medical treatment failure. Although the classical initial treatment is antibiotic therapy, surgery may be required if rupture occurs or antibiotic treatment fails.

Today, surgical procedures such as abscess drainage, salpingectomy, salpingo-oophorectomy and hysterectomy can be performed with laparoscopy or laparotomy in patients who require surgery due to TOA. In addition, percutaneous drainage can be performed by the help of interventional radiology [7]. But there is no consensus on what is the optimal surgical treatment for the TOA. In this research, we aimed to investigate patients who treated surgically due to TOA in our clinic in terms of surgical approach.

METHODS

This study was conducted from May 2016 to May 2020. Ethical approval was obtained from the ethics committee for clinical research of Mugla Sitki Kocman University, School of Medicine, Mugla, Turkey. Data from patients who treated surgically for TOA were retrospectively analyzed. The diagnosis of TOA was established in patients who met the PID criteria in accordance with CDC criteria [8]. We extracted patients who underwent laparoscopy or laparotomy as inclusion criteria. Exclusion criterias were as follows; lack of medical records, malignancy suspicion or malignancy diagnosis. The essential data were retrieved from the patient files and hospital database records.

During this period, 30 patients treated surgically for TOA due to medical treatment failure by our experienced surgical team. Data from 4 (endometrial cancer (1), ovarian cancer (3)) patients with malignancy were excluded from the study. One patient with lack of hospital records was also excluded. A total of 14 patients with laparoscopy and 11 patients with laparotomy were included. The characteristic features of patients such as age, gravida, parity, weight, height, BMI (body mass index), any history related to normal parturition, caesarean and/or abortion, menopausal status, comorbidities (diabetes, hypertension), smoking, intrauterine device use, surgical approach (laparoscopy/laparotomy), surgical procedure (drainage/salpingectomy/salpingo-oophorectomy/hysterectomy), operation time, postoperative complications (bladder, ureter and bowel injury, postoperative ileus and venous thromboembolism), largest abscess diameter, vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, and fever), preoperative and postoperative first and seventh day levels of biochemical parameters (hemoglobin, hematocrit, white blood cell count (WBC), platelet count and C-reactive protein), abscess culture (positivity/negativity), transfusion need (erythrocyte suspension), duration of preoperative and postoperative antibiotic treatment, and need of antibiotic regimen change were obtained from the hospital database.

The scheme of antibiotic treatment in cases diagnosed with TOA during the whole study length was identical and was followed in all patients. Medical treatment failure is defined as not to respond antibiotics within 48 or 72 hours after admission, progressive increase in C-reactive protein, increasing fever and sign/symptoms of abscess rupture [9]. In cases of medical treatment failure, the surgery was performed either by laparoscopy or laparotomy. During the entire research length, our default surgical approach for patients who failed medical treatment was laparoscopy. Laparotomy was performed in selected patients with a history of multiple abdominal opertaions and deep pelvic endometriosis.

It has been checked that, all the blood samples taken from patients both 24 hours preoperatively and,1st and 7th day postoperatively (hemoglobin, hematocrit, platelet, WBC count and C-reactive protein). The calculation parameters are in g/dL, %, ×103/μL, ×103/μL and mg/L, respectively.

The patients were grouped into the laparoscopy group (n = 14) and the laparotomy group (n = 11). Demographical features of patients were described. Preoperative and postoperative surgical outcomes were compared and analyzed. Abscess diameter were determined according to transvaginal/transabdominal ultra-

sonography scan, abdominal computed tomography and magnetic resonance imaging examination (if performed) records as the biggest diameter of the measurement.

Statistical Analysis

The collected data were analyzed by using SPSS software, version 23. The data were expressed as the mean±SD and range for continuous or discrete variables, and categorical variables were reported as frequency and percentage. The significance of differences between the groups was determined using Independent samplesT-test (for normally distributed data) and Mann-Whitney U test (for non-normally distributed data). The Friedman's test, an alternative to the single factor variance analysis, was used for the not normally distributed data.All statistical comparisons were considered significant at a *p* value of less than 0.05.

RESULTS

The characteristics of the two groups of patients are documented in Table 1. No differences in demographic variables and comorbidities appeared, and the average age of women in the two groups was similar (laparoscopy: 42.57 ± 9.04 vs laparotomy:42.09 ± 13.98; $p = 0.918$). A total 21.42% of the laparoscopy group and 27.27% of the laparotomy group had a history of caesarean section ($p = 0.582$). Prior abort history was present in 42.85% of the laparoscopy group and 45.45% of the laparotomy group ($p = 0.903$). There was no significant difference in the rates of smoking and intrauterine device usage between the groups.

The clinical and surgical outcomes of the two groups were compared and are reported in Table 2. The mean largest diameter of the abscess in the laparoscopy and laparotomy groups were similar (6.09 ± 1.93 cmvs 6.99 ± 4.74 cm, $p = 0.520$). It was 6.48 ± 3,40 cm in all patients who underwent surgery. The mean day for antibiotic use was 3.07 ± 2.76 days in laparoscopy group, preoperatively and it was 3.82 ± 4.26 days in laparotomy group ($p = 0.601$). The mean day for total antibiotic use was statistically significantly shorter in the laparoscopy group (10.00 ± 4.37day vs 17.91 ± 6.59 day; $p = 0.002$). Four patients (28.58%) in laparoscopy group and 7 patients (63.63%) in the laparotomy group were needed trans-

Table 1. Demographic characteristics of the study population

Variable	Laparoscopy (n = 14)	Laparotomy (n = 11)	Total (n = 25)	*p* value
Age (years)	42.57 ± 9.04	42.09 ± 13.98	42.36 ± 11.21	0.918*
Weight (kg)	74.14 ± 10.83	83.18 ± 25.44	78.12 ± 18.82	0.241*
Height (cm)	163.42 ± 6.46	166.09 ± 4.20	164.60 ± 5.64	0.250*
BMI (kg/m^2)	28.51 (25.08-31.16)	29.76 (26.03-31.64)	28.72 (25.71-31.18)	0.584¥
Gravidity (n)	2.86 ± 1.95	2.27 ± 1.67	2.60 ± 1.83	0.439*
Parity (n)	2.07 ± 1.14	1.45 ± 1.63	1.80 ± 1.38	0.278*
NSVD (n)	2 (0-3)	2 (0-3)	1 (0-3)	0.075¥
Prior C/S, n(%)	3 (21.42)	3 (27.27)	6 (24)	0.582¥
Prior Abortus, n (%)	6 (42.85)	5 (45.45)	11 (44)	0.903¥
Smoking, n (%)	5 (35.71)	3 (27.27)	8 (32)	0.660¥
IUD use, n (%)	7 (50)	3 (27.27)	10 (40)	0.259¥
Diabetes, n (%)	3 (21.42)	2 (18.18)	5 (20)	0.844¥
Hypertension, n (%)	4 (28.57)	3(27.27)	7 (28)	0.944¥

Data are shown as mean±SD* or median (25^{th}-75^{th})¥ or n (%). BMI = Body mass index, NSVD = Normal spontaneous vaginal delivery, C/S = Cesarean section, IUD = Intrauterine device

*Independent sample t-test; ¥Man-withney U test, Statistically significance: $p < 0.05$

Table 2. Clinical and surgical characteristics of the study population

Variable	Laparoscopy (n = 14)	Laparotomy (n = 11)	Total (n = 25)	*p* value
Abscess size (cm)	6.09 ± 1.93	6.99 ± 4.74	6.48 ± 3,40	0.520*
Preop AR (day) (n)	3.07 ± 2.76	3.82 ± 4.26	3.40 ± 3.44	0.601*
Total AR (day) (n)	10.00 ± 4.37	17.91 ± 6.59	13.48 ± 6.67	**0.002***
Transfusion need, n (%)	4 (28.58)	7 (63.63)	11 (44%)	0.086¥
(+) Culture, n (%)	3 (21.42)	5 (45.45)	8 (32)	0.210¥
Change in AR, n (%)	4 (28.58)	11 (100)	15 (60)	**0.001¥**
SBP (mm/Hg)	110 (102-130)	110 (90-120)	110 (95-125)	0.558¥
DBP (mm/Hg)	66.5 (60-72.5)	70 (60-80)	68 (60-75)	0.795¥
Pulse (beat/min)	84.71 ± 7.63	92.64 ± 7.08	88.20 ± 8.28	**0.014***
Fever (^{0}C)	36.55 (36.4-36.72)	37.3 (36.8-38.5)	36.7 (36.4-37.35)	**0.004¥**
Drainage, n (%)	10 (71.42)	10 (90.90)	20 (80)	0.244¥
Salpingectomy, n (%)	6 (42.85)	3 (27.27)	9 (36)	0.441¥
SO, n (%)	6 (42.85)	5 (45.45)	11 (44)	0.902¥
Hysterectomy, n (%)	3 (21.42)	2 (18.18)	5 (20)	0.848¥
Operation time (minute)	65.50 (58-93)	84 (74-90)	75 (64-89)	**0.048¥**
Bladder injury, n (%)	0	1 (9.1)	1 (4)	0.259¥
Bowel injury, n (%)	0	0	0	
Ureter injury, n (%)	0	1 (9.1)	1 (4)	0.259¥
Ileus, n (%)	0	0	0	
Wound infection, n (%)	0	2 (18.18)	2 (18.18)	0.103¥
VTE, n (%)	0	0	0	

Data are shown as mean ± SD* or median (25^{th}-75^{th})¥ or n (%). LOHS = Length of hospital stay, AR = Antibiotic regimen, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, SO = Salpingo-oophorectomy, VTE = Venous thromboembolism

*Independent sample t-test; ¥Man-withney U test; Statistically significance: $p < 0.05$

fusion requirement. Three of 14 patients (21.42%) in laparoscopy group and five of 11 patients (45.45%) in the laparotomy group had abscess culture positivity. All cases in the laparotomy group needed to change in antibiotic regimen, but only 28.58% of patients in the laparoscopy group needed antibiotic change. In terms of preoperative vital signs, SBP and DBP were recorded similar in either group. However, preoperative fever and pulse rate were statistically significantly higher in laparotomy group than in the laparoscopy group ($p = 0.004$; $p = 0.014$, respectively).

There was no statistical difference in terms of applied surgical procedure between two groups. In the laparoscopy group, 10 patients underwent drainage, 6 patients underwent salpingectomy, 6 patients underwent salpingo-oophorectomy and 3 patients underwent hysterectomy procedures. In the laparotomy group, 10 patients underwent drainage, 3 patients underwent salpingectomy, 5 patients underwent salpingo-oophorectomy and 2 patients underwent hysterectomy.

The median operation time in patients with laparoscopy was statistically shorter than in patients with laparotomy (65.50 [58-93] minutes vs 84 [74-90] minutes, $p = 0.048$). It was 75 [64-89] minutes in all patients who underwent surgery.

In comparison of postoperative complications between two groups, there was no statistically significant

difference. No cases of postoperative complications, such as bladder injury, ureter injury, postoperative ileus, bowel injury, venous thromboembolism or wound infection, were recorded in the laparoscopy group. However, postoperative bladder injury in one patient (9.1 %), ureter injury in one patient (9.1 %) and postoperative wound infection in two patients (18.18 %) in the laparotomy group were recorded.
When we checked the hemoglobin, hematocrit and platelet counts in all surgical patients, there was no statistical difference between preoperative, postoperative 1st and 7th day values. However, we observed statistically significant decline in WBC count and C-reactive values at the postoperative 7th day in all patients ($p < 0.001$and $p < 0.001$, respectively) (Table 3).

In the laparotomy group, the operation was started laparoscopically in three patients but converted to laparotomy due to dense adhesions. The rate of conversion to laparotomy in cases initiated by laparoscopy was 21.43 %.

Of the 25 surgically treated patients, 4 of them had history of an intervention with in last three months of TOA formation (hysterosalpingography (1), therapeutic curettage (1), endometriosis operation (1) and caesarean section (1)). Pathology reports of 2 patients were proven as uterine abscess. Moreover, TOA was developed in the basement of endometriosis in two patients.

DISCUSSION

The present updated clinical guidelines suggest that medical management is offered as the first-line treatment approach for TOAs in hemodynamically stable patients with abscess size < 9 cm and no signs or symptoms of abscess rupture [4]. In our clinic, the initial treatment for hospitalized TOA patients is started with medical treatment in accordance with the newly updated clinical guidelines, and laparoscopy or laparotomy is performed in cases of antibiotic failure. Since interventional radiological methods are not activelyperformed in our hospital, we do not have such experience in this regard. In this study, we documented and compared the findings of patients who underwent surgery for TOA in our clinic. The main result of our study was that although there was no difference in abscess size in both groups, the duration of antibiotic use and antibiotic regimen change in hospital stay period were significantly lower in laparoscopy group than in laparotomy group. Moreover, postoperative 7th day-WBC count and C-reactive protein values in all patients decreased significantly and it was observed that antibiotic attendance was important especially during the first 7 days of postoperative period.

The most important procedure recommended in patients with antibiotic failure is abscess drainage or removing the abscess focus. Here, the age of patient

Table 3. Preoperative, postoperative 1st and 7th day biochemical parameters of all patients

Variable	Preop mean ± SD (min-max)	Postop 1st day mean ± SD (min-max)	Postop 7th day mean ± SD (min-max)	*P* value
Hemoglobin (g/dL)	10.90 ± 1.52 (8.2-13.8)	9.98 ± 1.32 (7.5-12.5)	10.52 ± 1.16 (8.9-13)	0.227
Hematocrit (%)	33.12 ± 3.99 (26.60-40.90)	30.62 ± 4.46 (21-39)	32.26 ± 3.63 (26.30-41.30)	0.053
WBC (×10^3/µL)	14.63 ± 4.49 (5.93-24.02)	13.55 ± 4.88 (5.30-24.60)	10.32 ± 5.02 (4.90-28.30)	**< 0.001***
Platelet (×10^3/µL)	348.96 ± 130.23 (171-658)	349.48 ± 102.50 (178-543)	418.40 ± 174.21 (186-892)	0.261
CRP (mg/L)	188.76 ± 126.06 (20-463)	168.80 ± 108.01 (8-372)	46.20 ± 44.82 (1-148)	**< 0.001***

Preop = Preoperative, Postop = Postoperative, SD = Standart deviation, WBC = White blood cell count
*Statistically significant difference. Friedman's Test (χ^2=39.65; $p < 0.05$)

and desire for fertility are effective in determining the type of surgery. 6% of failure rate has been reported in patients underwent only laparoscopic abscess drainage [10]. This is why aggressive surgical options can be considered especially in postmenopausal patients who have completed fertility [11]. There are some authors recommending laparoscopic approach to all patients with a desire for fertility [12]. In our clinic, we apply laparoscopy to all patients who have failed medical treatment and have a desire of fertility. We also applied salpingectomy, salpingo-oopherectomy, hysterectomy and drainage procedures to all of our patients alone or in combination. There was no difference in terms of applied surgical procedures between groups, but the most commonprocedure in both groups was abscess drainage. It is useful to emphasize that abscess drainage is an essential procedure in patients underwent surgery due to medical treatmen tfailure.

Patients received infertility treatment was related with higher incidence of surgical intervention and complicated clinical course, as evidenced by a shorter time interval from admission to surgery, higher rates of antibiotic failure, higher conversion rate from laparoscopy to laparotomy, increased pre- and postoperative complications rate, and a longer length of hospital stay [1]. In our study, there was a patient who received treatment for infertility. TOA was developed on the 15th day after hysterossalpingography application. The patient's surgery was started with laparoscopy but turned into laparotomy, and antibiotic regimen was needed to change twice. The clinical course of this patient was really more complicated and the duration of treatment took longer than other patients. Therefore, we can say that close follow-up of patients with a history of fertility treatment or prior interventional procedures is important for early diagnosis and treatment by means of TOA development.

Farid *et al* [13] reported in their study with 26 TOA cases underwent surgery that the average diameter of the TOA was found to be 7.85 cm [13]. In this group of patients, duration of hospitalization, inpatient antibiotic use and outpatient antibiotic use were 6.77 days, 5.71 days and 11.2 days, respectively. They concluded that in selected patients, concurrent abscess drainage may represent the most optimal treatment choice for patients who have WBC count greater than 16K and abscess size greater than 5.18 cm at initial admission. The mean largest TOA diameter of all our surgical patients was 6.48 cm and the total duration of in patient antibiotic use was 13.46 days. In our country, there are many effective intravenous forms of antibiotics, but oral forms of these effective antibiotics do not exist or are difficult to reach. Therefore, many of TOA patients complete their 7-or 14-day treatment schemes in hospital. Long duration of inpatient antibiotic use in our study has been related with this condition.

In the literature, there are some data reported that medical treatment failure was related with fever and varying degrees of abscess size (5.18 cm, 5.7 cm, 6 cm, 7 cm, 8 cm) [13-17]. It is also stated that these patients may be offered drainage as an initial treatment. In our study, the mean diameter of abscesses in both groups was found to be consistent with the literature. It is noteworthy that fever and pulse rate values of patients with laparotomy were significantly higher in preoperative period compared to patients with laparoscopy. In our analysis, the duration of antibiotic use in the laparotomy group was longer in the postoperative period than in the laparoscopy group. Moreover, all patients in the laparotomy group needed alteration in postoperative antibiotic regimen and this rate was significantly lower in laparoscopy applied patients. The impact of surgical approach on systemic inflammation is more in patients who underwent laparatomy than laparoscopy [18]. Moreover, Jacobi *et al*. [19] showed that inflammatory response was significantly higher in the laparotomy group compared to laparoscopy group. According to our data, lower systemic inflammatory response in laparoscopy may have positively affected the duration of postoperative antibiotic usage in laparoscopy applied patients. In fact, the higher systemic inflammatory response in the laparotomy group may have contributed to the alteration in antibiotic regimen during the postoperative period. Hence, laparoscopic approach with sufficient experience seems to be preferable to laparotomy in selected patients in TOA surgery.

There are some authors reported that pelvic malignancy can be found simultaneously with TOA [20]. So the investigation of concomitant pelvic malignancies such as the endometrium, ovary or cervix is very important in the presence of TOA, especially during the postmenopausal period. In their study, Yagur *et al*. [20] and Protopas *et al*. [21] detected pelvic malig-

nancy in 1/22 and 8/17 of postmenopausal TOA patients concomitantly, respectively. In our study, one endometrial and three ovarian cancer cases were detected in postmenopausal TOA patients concomitantly. Although these cases were not included in our study, we want to emphasize here that it is very important to evaluate all organs in clockwise direction when exploring the pelvic cavity either by laparoscopy or laparotomy to aviod missed diagnosis of any pelvic malignancy in patients with TOA, especiallly in postmenopausal patients.

Güngördük *et al*. [22] stated in their study that surgical complications increase when the size of the abscess exceeds 7 cm in size. In their study, 63.15% of their cases were performed by laparotomy. We did not observe a correlation between abscess size and postoperative complications. In our study, although there was no statisticals ignificant difference between the two groups in terms of postoperative complications, all postoperative complications detected were belong to the laparotomy group. Here, it can be thought that the better visualization provided by laparoscopy during surgery may prevent postoperative complications.

Limitations

The strength of this study is that TOA diagnosis proven by histopathologically because all patients underwent surgery. Conversely, the retrospective design and limited number of patients to make subgroup analysis for surgical interventions are limitations of this study.

CONCLUSION

In conclusion, we evaluated the surgical approaches in cases with TOA in our clinic. Laparascopy should be the first choice of surgical approach in order not to lenghten the hospital stay, operation time and to maintain the initial antibiotic regimen.

Conflict of interest

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The European Research Journal 2021;7(1):88-92 Original Article

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The outcomes of external dacryocystorhinostomy with bi-canalicular silicone knot started in the lacrimal sac without suturing posterior flap

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ABSTRACT

Objectives: During external dacryocystorhinostomy (DSR) - Bicanalicular silicone tube implantation (BSTI), it is aimed to utilize the mechanical pressure effect due to the initiation of silicone knotting inside the lacrimal sac and evaluate the effectiveness of this modified technique in which the sac and nasal mucosa posterior flaps are not sutured.

Methods: Sixty-six patients between the ages of 8-57 years who were admitted to Kartal Lütfi Kırdar Training and Research Hospital and Somalia Mogadishu Recep Tayyip Erdogan Training and Research Hospital Eye Diseases outpatient clinic with irrigation and lacrimal secretion complaints between January 1, 2010 and December 31, 2019 were included in the study. In these patients with lacrimal stenosis, external dacryocystorhinostomy (DSR) and Bicanalicular silicone tube implantation surgery method were applied.

Results: A total of 66 patients, 3 males (4.5%) and 63 females (95.5%), were included in this study. The mean age of the patients was 45 (8-57) years. It was determined that 4 of the patients who were followed up for an average of 16 months developed atrophic mucosa due to chronic rhinitis, and 6 developed nasolacrimal ductus obstruction due to excessive wound healing due to young age.

Conclusions: When the comfort and complications it provides are evaluated together, this technique emerges as a preferred method.

Keywords: External dacryocystorhinostomy, bicanalicular silicone knot, posterior flap

The tear drainage system covers the part between the punctums and the place where the naso-lacrimal canal opens to the nose. Tears flow into the nasal mucosa thanks to the lacrimal pump system. Any blockage at any point in this system will prevent tear flow, and tears will accumulate in the conjunctiva and reveal a condition called epiphora.

The surgical intervention to be performed according to the location of the obstruction varies, and the surgical methods related to the tear drainage system

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are as follows: (1) Dacryocystorhinostomy, (2) Dacryocystorhinostomy + bicanalicular silicone tube (DSR + BST), (3) Canaliculodacryocystorhinostomy, (4) Conjunctivodacryocystorhinostomy, (5) Conjunctivorinostomy, and (6) Conjunctivodacryocystotomy. While the first two methods to be preferred in nasolacrimal sac and nasolacrimal canal obstructions are "bicanalicular silicone tube implantation with dacryocystorhinostomy", one of the other methods can be applied in case of a blockage in the canals extending from the punctal to the sac. The most preferred methods are Conjunctivodacryocystorhinostomy (CDSR) and Conjunctivorinostomy (CR). These two methods provide the flow of tears by creating a passage from the conjunctiva directly to the nasal cavity with the help of silicone and Peyrex tubes.

Failure to open the bone and/or mucosa window sufficiently and the closure of the osteotomy site in endonasal DCR surgeries are seen as an important problem [1-3], and in this respect, External DCR remains a successful and reliable method in nasolacrimal canal occlusion compared to other techniques. High success has been reported in many published case series [4, 5]. However, it can be considered as a medium-length and difficult surgery. The most difficult and time consuming stage for surgeons is the stage in which flaps are formed and sutured. At the same time, the excessive bleeding that develops during the preparation of the nasal mucosa flaps makes the operation area difficult to see. Some variations have been introduced to this stage in order to shorten the operation time and reduce bleeding, and the use of only anterior flaps has been a frequently tried method [6-9].

In our study, it is aimed to benefit from the mechanical compression effect due to the initiation of silicone knotting in the tear sac during Bicanalicular silicone tube implantation (BSTI) and to evaluate the effectiveness of external dacryocystorhinostomy (DCR) operation in which the sac and nasal mucosa posterior flaps are not sutured.

METHODS

Sixty-six patients between the ages of 8-57 who presented with the complaints of irrigation and lacrimal secretion to the Kartal Lütfi Kırdar Training and Research Hospital Research Hospital and Somalia Mogadishu Recep Tayyip Erdoğan Training and Research Hospital ophthalmology outpatient clinic between January 1, 2010 and December 31, 2019 were included in the study. Ethics committee approval was obtained for our study (20.02.1019/5549-614).

Surgical Technique

After the eye area was wiped with Baticon, local infiltrative anesthesia was performed. A tampon impregnated with Pantocaine and Adrenaline was placed through the nose half an hour before the operation to reduce bleeding. Lacrimal, nasociliary and infraorbital local anesthesia was applied with jetocaine (Lidocaine HCL). The tear sac and nasal mucosa were exposed as in classical DCR (Fig. 1a and 1b). The bone window was opened to be 1×1.5 cm. H-shaped incisions were modified so that the posterior flap in the tear sac and the anterior flap in the nasal mucosa were quite long. After the BSTI was

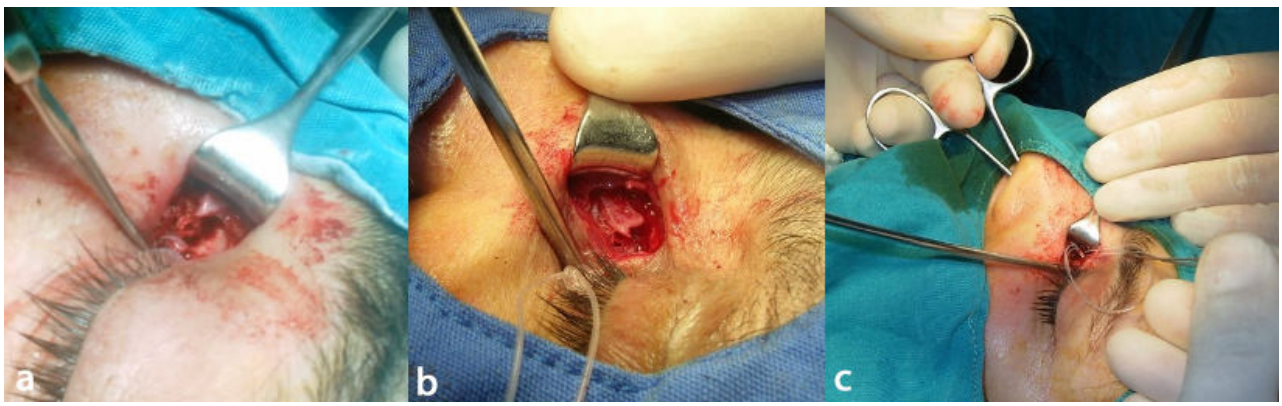

Fig. 1. Surgical stages. (a) lacrimal sac and nose exposure, (b) lacrimal sac and nasal mucosa suturing, and (c) taking silicone into the nose.

performed, the ends of the bicanalicular silicone tube were knotted 10-15 times starting from the pouch and extended into the nose. The tear sac and nasal mucosa anterior flaps were sutured with 6/0 Vicryl (Fig. 1b and 1c). After the deep tissues and skin were covered, bleeding was controlled and systemic antibiotics, anti-inflammatory, analgesic, topical antibiotics and steroid eye drops were recommended for 10 days after surgery. The patients were reminded to avoid excessive straining and blowing for at least 2 weeks, and they were asked to come to the control examinations on the postoperative 1st day, 1st week, 1st, 6th and 12th months and then once a year. Antibiotic lavage was applied when exudate was detected around the tube in the samples of the cases. The case records were reviewed retrospectively.

Statistical Analysis

Continuous variables were shown as average ± standard deviation, while categorical variables were expressed as frequency and percentage.

RESULTS

A total of 66 patients, 3 males (4.5%), 63 females (95.5%) were included in this study. The mean age of the patients was 45 years (8-57 years) and the mean follow-up period was 16 (4-48) months. Silicone tubes were removed at an average of 7 months. Follow-up examinations were performed on the 1st day, 1st week, 1st, 6th and 12th months following the surgery and once a year. According to the last examination findings of the patients, the passage was found to be obstructed in 10 (15.1%) patients. While failure was due to nasal mucosa disorder in 4 patients; In 6 patients, it was found that it developed due to nasolacrimal obstruction due to excessive wound healing (Table 1).

Table 1. Clinical and demographic findings of the cases

Findings	Data
Gender, n (%)	
Female	63 (95.5)
Male	3(4.5)
Mean age (years) (range)	45 (8-57)
Follow up time (months) (range)	16 (4-48)
Operation failure rate, n (%)	10 (15.1)
Atrophic mucosa (n = 4)	
Excessive wound healing (n = 6)	

DISCUSSION

BSTI is an application that increases the success rates in external DCR surgeries. Suturing the posterior flaps is a very difficult and time-consuming procedure. In this study, the technique of flap incision was changed, leaving the lacrimal sac posterior flap long, and the silicon tubes knotted were pushed towards the nasal mucosa by mechanical effect. In addition, the long anterior flap of the nasal mucosa was sutured with the anterior wall of the lacrimal sac to create a wide space towards the nose. With this method, it was planned to shorten the operation time and increase the success rate of the operation. In our study, only the anterior flaps were sutured and the posterior flaps were left without suturing.

Suturing the posterior flaps is an uncommon method in terms of difficulty of application and prolonging the duration of the surgery. According to previous studies on this subject, the variations that can be applied to flaps can be grouped under four main headings: 1) creation of only anterior flap, 2) creation of anterior flap and excision of the posterior flap, 3) creation of anterior and posterior flap, and 4) No flap creation [8]. Also, there are three procedures that can be performed for the posterior flap during external DCR: 1. Excision, 2. Leaving without intervention, and 3. Shaping and suturing directly to the nasal mucosa. In a study where DSR was applied with only anterior flaps, the patients were divided into two groups; in the first group, large anterior flaps were created and sutured without creating any posterior flaps, in the second group, after anterior and posterior flaps were created, the posterior flaps were excised and the anterior flaps were combined [10].

While a success rate of 90% was observed in the first group, this rate was 85% in the second group [11]. Baldeschi *et al*. [12] stated that the adhesions formed by the anterior flaps in the deep tissues are one of the most common reasons for the failure of the surgery, to prevent adhesions after creating and combining large

and free flaps in the nasal mucosa and lacrimal sac, they sutured the flaps to the orbicular muscle in order to remove the flaps from the deep tissues and to increase the opening of the canal. They applied this new technique they reported on 45 patients and reported a 100% success rate.In another study where they investigated the effect of the lengths of the non-milked mucosa margins on the success of external DCR and compared three different methods; in the first group, they made only a vertical incision on the pouch while creating a single large anterior flap in the nasal mucosa and sutured the posterior and anterior edges separately,in the second group, they created anterior and posterior flaps in the nasal mucosa and sac and sutured them separately, in the third group, while creating as large anterior flaps as possible in the sac and nasal mucosa, they did not form the posterior flaps and only left the posterior edges while suturing the anterior flaps. Baldeschi *et al*. [13] found no difference in the success of the surgery between the methods they applied by creating flaps of different shapes and sizes. Becker [14] predicted that granulation tissue created by continuous tear flow would prevent obstruction, and reported 90% success in the external DCR method applied without creating a flap by modifying the Kasper technique on 50 patients.

There is no consensus among oculoplastic surgeons regarding the application of silicon tube with DSR. While some surgeons reported that silicone tube application should only be applied in problematic situations [15]. Some surgeons apply it in all lacrimal drainage system obstructions. Rosen *et al*. [16] reported a success rate of 91.3% in 253 patients who applied silicon tube with external DCR, emphasized that the tube was well tolerated postoperatively and that the complications that occur were rare and benign. Sodhi *et al*. [17] applied external DCR with bicanalicular silicone tube implantation to 25 patients with chronic dacryocystitis and problems with a low chance of success in terms of DCR and reported a 76% chance of success. Doğan *et al*. [18] found a success rate of 85.7% in the retrospective examination of 70 patients who applied bicanalicular silicone tube with the Kinosian method after four years. Köksal *et al*. [15] reported a success rate of 80.5% in 61 patients who performed external lacrimal surgery with silicone tube implantation.

We also applied silicone tube implantation to all of our cases in order to benefit from the compression effect of the silicone tube and to increase our chances of success in this surgical technique where we released the posterior flaps. It has also been reported that silicone tube implantation eases the surgery and facilitates post-op follow-up in cases of excessive bleeding during surgery and nasal mucosal tears [15]. Although the modification made in our study facilitated the application of the technique and shortened the operation time, it was found that the success rate was not much different from the classical External DCR (BSTI) methods.Atrophic mucosa due to chronic rhinitis in 4 of the unsuccessful cases, nasolacrimal duct occlusion due to excessive wound healing due to young age in 6 cases were detected.It was observed that the failure rates and reasons were compatible with similar studies in the literature [19, 20].

Limitations

The application of the technique in a wide age range is one of the limitations of our study, since the wound healing is not similar in different age groups and the possibility of atrophic mucosa is higher as the age progresses.

CONCLUSION

Despite this, the results of our study; considering its advantages and complications, this method is important in terms of its emergence as an option that enables shortening the operation time and facilitating surgical maneuvers.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2021;7(1):93-99 Original Article

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Assessment of colorectal cancer awareness in patients admitted to the general surgery outpatient clinic

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ABSTRACT

Objectives: Colorectal cancer could be prevented with some basic lifestyle modifications.In this study we query the awareness of the participants about colorectal cancer who visit the general surgery outpatients clinic.
Methods: A questionnaire consisting of 13 questions was applied to the participants as well as demographic data. Differences in awareness of screening and risk factors were sub-grouped according to age, BMI, education, employment status, monthly income, marital status, status of first-degree relative colorectal cancer, smoking-alcohol use status and exercise status.
Results: The most known screening method was colonoscopy with 73.6%, while the least known screening method was sigmoidoscopy with 13.4%. Also, the best known risk factor was smoking with 67.4%, while the least known risk factor was type 2 diabetes with 29.8%. In our study, those over 45 years of age, having higher education, working, having more monthly income, having a family history of colorectal cancer and exercising regularly had more awareness about colorectal cancer screening and risk factors.
Conclusions: Our study had high levels of awareness compared to developing countries, however, awareness levels are not high enough and it is possible to increase these rates by educating the patients on cancer awareness.
Keywords: Colorectal cancer, awareness, general surgery

According to World Health Organization (WHO) data, cancer is the second most common cause of death in the world and it is estimated that it causes 9.6 million deaths in 2018 [1]. The economic burden of cancer increases with each passing day, and the economic cost of cancer in 2010 is estimated to be US $ 1.16 trillion [2].

Colorectal cancer is among the most common types of cancer worldwide. Colorectal cancer is the third most common type of cancer in both men and women. According to the data of the WHO, 694 thousand people died in 2012 due to colorectal cancer and this number increased to 862 thousand people in 2018 [1, 3].

According to the Turkish Ministry of Health Cancer Statistics, 2004-2006, the incidence rate of colorectal cancer standardized by age was 17.0 per hundred thousand people in men, 11.7 per hundred thousand people in women in Turkey [4, 5]. Although colorectal cancer screening tests are performed rou-

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tinely in our country as in many countries, however the lack of sufficient information about colorectal cancer decreases the rate of applications of these tests [6, 7].

In many studies related to colorectal cancer awareness, inadequate awareness among individuals is observed especially in middle and underdeveloped countries. These studies are usually based on random populations and a small number of them were performed on health workers [7-13]. Although the diagnosis of colorectal cancer is usually diagnosed by some clinical branches which care to gastrointestinal system such as general surgery, however we did not find any study evaluating the colorectal cancer awareness levels of patients coming to these outpatient clinics.

In this study, we aimed to determine the level of awareness of colorectal cancer and knowledge about colorectal cancer screenings in patients who applied to general surgery outpatients clinic where patients with rectal bleeding applied and colorectal cancer was most frequently diagnosed in Turkey.

METHODS

This observational study was descriptive and has cross-sectional design and it was initiated following the approval of the local human ethical committee and was conducted between May 2019 and August 2019 in patients admitted to the general surgery outpatient clinic of the three different hospital. Clinical trials registrations were performed (NCT04020614). All patients included in the study signed an informed consent form. The questionnaires were conducted with the participants by face to face question-answer method. The flow diagram of the participants is shown in Fig. 1.

Inclusion criterias were adult individuals older than 18 years and younger than 80 years who do not have a mental disorder such as Alzheimer's or mental retardation and agreeing to participate in the study, and the exclusion criteria are refusing to participate in the study, being under 18 or over 80, having known mental disability and colorectal cancer. In addition to demographic data, a questionnaire which was defined by Briant *et al*. [14] consisting of 13 questions was used to determine the level of colorectal cancer awareness level. The first 5 questions of the questionnaire relate to the level of awareness about colorectal cancer screening and the next 8 questions relate to the level of knowledge about colorectal cancer risk factors.

Differences in screening and risk factors were subgrouped and analyzed according to age, Body mass index (BMI), education, employment status, monthly income, marital status, the status of first-degree relative colorectal cancer, smoking-alcohol use status

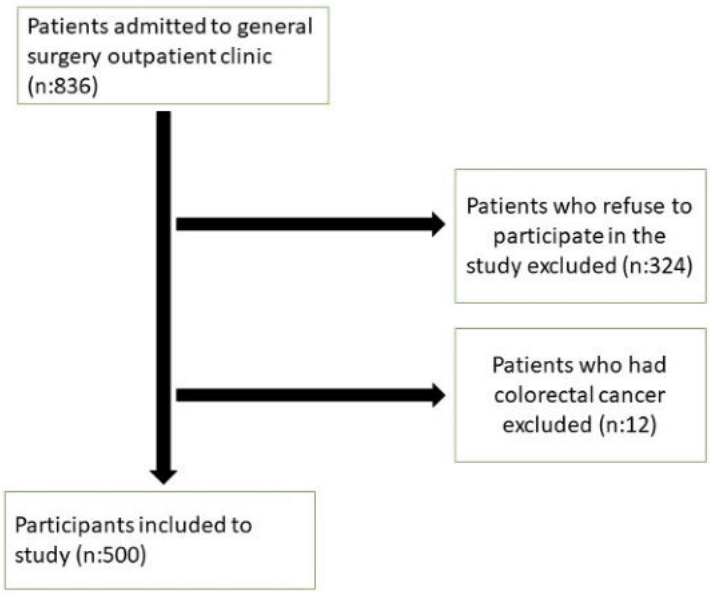

Fig. 1. Flow diagram of the participants.

and exercise status. The questions in the study were performed by asking the patients face to face and no intervention was made to the volunteers. The survey duration for each patient lasted approximately 10 minutes.

Statistical Analysis

The SPSS 22.0 (SPSS Inc., Chicago, IL, USA) computer program was used for analyzing the data. Descriptive statistics are shown in numbers (n) and percentages (%). The chi square test was used to analyze the relationship between screening and risk factors of the subgroups formed according to the demographic characteristics of the patients. A level of $p < 0.05$ was set as statistically significant.

RESULTS

The mean age of the 500 volunteers in the study was 47.07 ± 11.77 years and the female/male ratio was found to be 1.25. All the volunteers who participated in the study answered all the questions in the questionnaire and their demographic characteristics were given in Table 1.

The responses of the volunteers about colorectal cancer screening methods are given in Table 2 and the answers given to colorectal cancer risk factors are shown in Table 3. The 385 (77%) of the participants had information about any colorectal cancer screening method, colonoscopy was the most known screening method with 73.6%, while sigmoidoscopy was the least known screening method with 13.4%. Also, the best known risk factor was smoking with 67.4%, while the least known risk factor was type 2 diabetes with 29.8%.

When the awareness of screening and risk factors were evaluated separately according to the volunteer descriptive data;Young people have less knowledge about Fecal occult blood test (FOBT) than the 45 upper individuals (33.7% vs 42.8%, $p = 0.042$). Individuals over 45 years of had more information about aging which increase the risk of colorectal cancer than young people (42.8% vs 33.7%, $p = 0.042$). Individuals over 45 years of age had more information about smoking which increases the risk of colorectal cancer (71.4% vs 61.2%, $p = 0.018$). Individuals over 45 years of age were more aware

Table 1. Demographic characteristics of the participants

Characteristics	n (%)
Gender	
Female	278 (55.6)
Male	222 (44.4)
Age	
< 45 years	196 (39.2)
> 45 years	304 (60.8)
BMI	
< 25 (Normal)	162 (32.4)
25-30 (Overweight)	228 (45.6)
> 30 (Obese)	110 (22.0)
Education	
Elementary school	212 (42.4)
High school	203 (40.6)
Graduate level or higher	85 (17.0)
Working condition	
Working	204 (40.8)
Not Working	173 (34.6)
Retired	123 (24.6)
Monthly income	
Minimum wage or less	218 (43.6)
Up to ×2 of minimum wage	206 (41.2)
More than ×2 of minimum wage	76 (15.2)
Marital status	
Maried	379 (75.8)
Single	85 (17.0)
Divorsed	36 (7.2)
Family history of colorectal cancer in first degree relatives	
Yes	57 (11.4)
No	443 (88.6)
Smoking	
Yes	162 (32.4)
No	338 (67.6)
Alcohol use	
Yes	46 (9.2)
No	454 (90.8)
Regular exercise (min. 150 minutes per week)	
Yes	195 (39.0)
No	305 (61.0)

Table 2. The answers of participants about knowledge of colorectal cancer and its screening

Questions	Yes n (%)	No n (%)	No idea n (%)
Have you ever heard of colorectal cancer?	454 (90.8)	28 (5.6)	18 (3.6)
Know Fecal Occult Blood Test is available for CRC?	196 (39.2)	62 (12.4)	242 (48.4)
Know Sigmoidoscopy is available for CRC?	67 (13.4)	32 (6.4)	401 (80.2)
Know Colonoscopy is available for CRC?	368 (73.6)	25 (5.0)	107 (21.4)
Most patients can survive CRC if it is found early and removed?	294 (58.8)	38 (7.6)	168 (33.6)

CRC = Colorectal Cancer

about type 2 diabetes which increases the risk of colorectal cancer in (36.5% vs 19.4%, $p < 0.001$). Individuals over 45 years of age had more information about the fact that obesity increases the risk of colorectal cancer (68.1% vs 52.6%, $p < 0.001$). Those with normal BMI had more information about the applicability of colonoscopy as a screening method (80.9% vs 68% vs 74.5%, $p = 0.017$).

Individuals at higher education level had more information about the applicability of colonoscopy as a screening method (64.2% vs 78.8% vs 84.7%, $p < 0.001$). Individuals at higher education level had more information about the lack of vegetables and fruits in the diet that increased the risk of colorectal cancer (36.8% vs 42.4% vs 64.7%, $p < 0.001$). Individuals who have job was more aware about using sigmoidoscopy as a screening method (18.6% vs 10.4% vs 8.9%, $p = 0.016$). Working Individuals had more information about the applicability of colonoscopy as a screening method (78.9% vs 64.7% vs 77.2%, $p = 0.005$). Retired individuals were more familiar with the increased risk of type 2 diabetes for colorectal cancer (26% vs 26.6% vs 40.7%, $p = 0.010$). Individuals who have more monthly income more information about the applicability of colonoscopy as a screening method (63.3% vs 77.6% vs 81.6%, $p < 0.001$).

Individuals with more monthly income were more aware about low percentage of vegetables and fruits in the diet which increases the risk of colorectal cancer (37.2% vs 48.1% vs 51.3%, $p = 0.028$). Individuals who had more monthly income about low fiber intake

Table 3. The answers of the participants about the knowledge of the risk factors of colorectal cancer

Questions	Yes n (%)	No n (%)	No idea n (%)
Getting older increases the risk of CRC?	196 (39.2)	132 (26.4)	172 (34.4)
A diet lack of fruits and vegetables increases the risk of CRC?	219 (43.8)	112 (22.4)	169 (33.8)
A family history of colorectal cancer increases the risk of CRC?	326 (65.2)	67 (13.4)	107 (21.4)
A diet that is high in fat and low in fiber increases the risk of CRC?	293 (58.6)	45 (9.0)	162 (32.4)
Smoking increases the risk of CRC?	337 (67.4)	53 (10.6)	110 (22.0)
Having type 2 diabetes increases the risk of CRC?	149 (29.8)	70 (14.0)	281 (56.2)
Lack of physical activity increases the risk of CRC?	292 (58.4)	62 (12.4)	146 (29.2)
Being overweight or obese increases the risk of CRC?	310 (62.0)	45 (9.0)	145 (29.0)

CRC = Colorectal Cancer

and high fat intake which increase the risk of colorectal cancer (50.5% vs 63.6% vs 68.4%, p = 0.004). Individuals with more earnings per month than fatness increased the risk of colorectal cancer (54.6% vs 66% vs 72.4%, p = 0.007). Widow individuals had more information about colorectal cancer family history as a risk factor for colorectal cancer (62.5% vs 70.6% vs 80.6%, p = 0.049). Individuals with a family history of colorectal cancer had more information about the applicability of colonoscopy as a screening method (89.5% vs 71.6%, p = 0.004). Individuals with a family history of colorectal cancer had more information about the colorectal cancer family history as a risk factor for colorectal cancer (78.9% vs 63.4%, p = 0.021).

Individuals who made regular exercise had more information about the use of FOBT in colorectal cancer screening (47.2% vs 34.1%, p = 0.003). Also they were more informed about the applicability of colonoscopy as a screening method (78.5% vs 70.5%, p = 0.049). Individuals who made regular exercise were more likely to know that the lack of vegetables and fruits in the diet increases the risk of colorectal cancer (51.8% vs 38.7%, p = 0.004). Individuals who performed regular exercise were more aware about that colorectal cancer family history was a risk factor for colorectal cancer (71.8% vs 63.4%, p = 0.021). Individuals who had regular exercise were more aware about dietary fiber intake and fatty foods increases the risk of colorectal cancer (70.3% vs 51.1%, p = 0.000). Individuals who made regular exercise had more information about smoking which increases the risk of colorectal cancer (72.8% vs 63.9%, p = 0.039). Individuals performed regular exercise were more familiar with the lack of physical activity which increase the risk of colorectal cancer (69.2% vs 51.5%, p < 0.001). Also they were more aware about the obesity as a risk factor for colorectal cancer (73.3% vs 54.8%, p < 0.001).

DISCUSSION

Colorectal cancer accounts for 10% of all cancers and may develop sporadically, familially, or secondary to an inflammatory disease. Colorectal cancer is often described as a lifestyle disease and its incidence is higher in sedentary populations with a high fat and caloric intake [3]. In some studies, it has been reported that 70% of colorectal cancer can be prevented by life style changes [15].

According to the American Cancer Society colorectal cancer screening guideline, the recommended age for starting colorectal cancer screening decreased form 50 to 45 years old. It is also recommended, FOBT should be tested for every year, flexible sigmoidoscopy should be performed once in five years and colonoscopy should be performed once in ten years. That tests should be continued until at least 75 years of age [16]. In studies related to the awareness of colorectal cancer screening programs, it is seen that wareness of people about colorectal cancer screening programs vary according to the region. In a study about colorectal cancer screening from Saudi Arabia, 37.2% of the participants of this study were aware about colorectal cancer screening tests [17], whereas in a study from the United States, 96% of the participants were aware about colorectal cancer screening tests [12]. In a study from Lebanon, 55% of the participants had awareness about colorectal cancer screening methods [13]. In one such study by Tastan *et al*. [11] 90% of individuals not awared about the colorectal cancer screening programs. In another study by Baran *et al*. [18], 85.7% of women individuals did not know about colorectal cancer screening methods. In many studies, a positive relationship was seen between education level and awareness of colorectal cancer screening methods [17,19-21]. In a study that included 132 volunteers and examined colorectal cancer screening methods in individuals over the age of 50, it was observed that 10.7% of the individuals had a stool occult blood test and 9.2% had a colonoscopy [22]. In the sub-analysis of the study, it was determined that women, non-smokers participants who did not drink alcohol and made regular exercise had more stool occult blood screening tests [22]. While 90.8% of the participants in our study had heard of colorectal cancer before, 77% of them knew at least one of the colorectal cancer screening methods. However, a large proportion of volunteers have no idea about sigmoidoscopy. The probable reason for this is that a large number of volunteers do not know what sigmoidoscopy is or do not know the difference between colonoscopy and sigmoidoscopy. Our study has higher levels of awareness of screening tests compared to many other studies, and the probable

cause is that, patients admitted to our outpatient clinic with symptoms such as gastrointestinal bleeding had a chance to have information about colorectal cancer before they come to our outpatient clinic with a variety of sources. In our study, in accordance with the literature, a positive relationship was observed with the increase in the level of education on the awareness of colorectal cancer screening methods.

Considering that diet, life style and education play an important role in the prevention of colorectal cancer, knowledge of risk factors helps prevent colorectal cancer development [3, 23]. There are many studies examining the effect of risk factors on screening programs [24, 25]. In one study, it was reported that smokers participated in cancer screening programs were lesser that non-smokers and in another study, obese women were less included in colorectal cancer screening programs compared to normal weighted women [24, 25]. In a study which had measured the knowledge level of colorectal cancer with 92 volunteers which are over 55 years oldobserved that they had risk factors associated with colorectal cancer, did not have the desired level of knowledge about the disease, and did not use early diagnosis methods adequately [26]. Although our study did not examine the participation rates of patients in screening programs, however it was found that individuals over 45 years of age, higher educated, working, and earning more monthly, a family history of colorectal cancer, and those exercising regularly had a higher level of awareness about colorectal cancer screening and risk factors.

In a study on the awareness of colorectal cancer risk factors and symptoms on 371 volunteers the risk and symptoms were reported 17.2% and 31.5% respectively. In the same study, it was reported that the most known risk factors were red meat eating, smoking and intestinal diseases, and the least known risk factors were diabetes and physical exercise [13]. In one study, it was reported that obesity is more associated with colorectal cancer and other gastrointestinal cancers [26]. Baran *et al*. [18] reported that 72.4% of the participants of this study were aware about obesity as a risk factor of colorectal cancer. In our study, smoking, family history and obesity were the most well-known risk factors, while the least known risk factors were age, type 2 diabetes and poor nutrition from vegetables.

Limitations

Limitations of our study include the small number of participants and the fact that no comparative study was performed with patients who applied to any outpatient clinic except general surgery.

CONCLUSION

Our study had higher awareness rates of screening and risk factors of colorectal cancer than many developing countries, however higher levels of awareness were needed. It is understandable that these rates are higher than the literature when it is thought that the individuals who participated in the study were patients who applied to a outpatients clinic with knowledge of gastrointestinal diseases. It is possible to increase these rates by providing education to the patients on cancer awareness, improving education level and living conditions.

Conflict of interest

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Reliability of cavernous sinus sampling in management of Cushing's disease

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ABSTRACT

Objectives: The purpose of this study is to find out the accuracy of bilateral cavernous sinus sampling (CSS) for preoperative tumor lateralization within the pituitary in Cushing's disease (CD).

Methods: Sixty-five patients who had undergone transsphenoidal surgery (TSS) following CSS for CD between 2000-2016 at our institution were analyzed retrospectively. All patients underwent bilaterally CSS with corticotropin-releasing hormone (CRH) stimulation. Radiological, preoperative, and pathological findings with remission status were correlated with CSS data. The accuracy of CSS is decided according to compliance with the magnetic resonance imaging (MRI), pathology or remission after surgery of the normal MRI cases.

Results: CSS indicated the correct lateralization in 52 (80%) patients. There was the same level elevation of both sides in 3 patients who had central adenoma. Remission rate in the final follow-up was 83.87% for 65 patients. We found out the contralateral pathological side in 13 (20%) of the patients showing false lateralization. Twenty-four patients with normal MRI had a positive accuracy rate of 83%. Of those patients, with a positive accuracy of CSS sampling, 18 (90%) had a positive remission. As a result of the Kappa analysis, statistically significance and relation was found between the final diagnosis and lateralization test ($\kappa = 0.63$ $p < 0.001$).

Conclusions: Our results showed that CSS is a safe and reliable method for microadenomas which has high diagnostic accuracy (80%) in indicating the correct lateralization in CD, providing us higher remission rates in a challenging pathology.

Keywords: Cushing's disease, pituitary tumor, adrenocorticotropic hormone, cavernous sinus sampling, venous sampling

Cushing's disease is a rare disease characterized by uncontrolled release of Adrenocorticotropic hormone (ACTH) from the anterior pituitary and consequently excessive cortisol release from the adrenal gland. Diagnosis can be delayed by 2-4 years, especially in patients with mild or cyclic hypercortisolism

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[1, 2]. Biochemical tests should be performed to consolidate the diagnosis with clinical findings due to hypercortisolism. After diagnostic tests, dexametasone supression, metyrapone or corticotropin releasing hormone (CRH) stimulation test should be performed to distinguish the diagnose from ectopic corticotropin syndrome [3-5]. Although they are reliable tests, they are often inadequate to make this distinction. At this point, contrast enhanced pituitary magnetic resonance imaging (MRI) is used for the confirmation of presence or absence of a pituitary adenoma. The median size of the adenomas in Cushing's disease (CD) is 5 mm. MRI with 3 mm sections can not capture approximetely 40-50% of the adenomas smaller than this median size and reported as normal [6, 7]. When the MRI findings are uncertain or biochemical tests are inconclusive, subtotal or total removal of the pituitary gland may be performed despite the endocrine deficiency risk.

Central venous sampling is an assistive method used to localize the pathology [8, 9]. Because of false positivity risk in laboratory tests it is a key method for definitive diagnosis and lesion localization. It can be performed in the inferior petrosal sinus or cavernous sinus [10]. It is possible to obtain an almost exact result with this method. If there is a difference > 1.4 in ACTH levels between the sides in venous sampling, it is accepted that it predicts the side of the lesion in CD patients with negative MRI.

The primary objective of this study was to to find out the accuracy of bilateral CSS in preoperative tumor lateralization within the pituitary in patients with CD.

METHODS

Study Design

Our prior study with 26 patients was expanded and re-studied [11]. After the local Ethics Comittee aproval we retrospectively identified 65 consequtive patients who had undergone cavernous sinus sampling (CSS) and transsphenoidal surgery (TSS) in the department of neurosurgery, Cerrahpaşa School of Medicine, by a single surgeon (NG) between 2000 and 2016.

Participants

Patients who have endocrinological evidence of CD had diagnosed with a standard protocol by a multidisciplinary team in Istanbul University Pituitary Center. All of the patients with normal MRI or lesions smaller than 6 mm who were operated via TSS approach were evaluated. Data of patients were collected from the medical history records. Endogenous hypercortisolism was confirmed with the increased urinary free cortisol (UFC), loss of circadian rhythm and lack of suppression of cortisol after low dose dexamethasone supression tests (DST). Pituitary origin was diagnosed with the 8 mg dexamethasone test and CRH stimulation test. We included the patients with the MRI evaluations who showed up either a normal MRI or a mass smaller than 6 mm within the gland. All patients with CSS indicating central etiology underwent TSS without perioperative steroid coverage.

Remission Criteria

Remission was defined as: normalization of circadian rthym and ACTH and postoperative basal cortisol < 3.5 µg/dl; serum cortisol < 1.8 µg/dl after 1 mg dexamethasone suppression test.

Statistical Analysis

Continuous variables are reported as means ± standard deviation and categorical variables are reported as percentages. Student's t test was used for comparison of normal distributed variables and Mann-Whitney U test was used for non-normally distributed variables. Categorical variables were compared by the Chi-Square test or Fisher's exact test as appropriate. Kappa coefficient was used for a statistical measure of inter-rater reliability. A p value less than 0.05 were considered significant.

RESULTS

Demographics

Retrospective analysis of 65 patients who were diagnosed as Central Cushing's Disease showed female dominancy of 81.53%. There were 12 male patients and 53 female patients. Mean age was 38.78 years (ranging from 5-66). Four (6.15%) of the patients were under 18 years.

Preoperative MRI

All patients underwent preoperative MRI evalua-

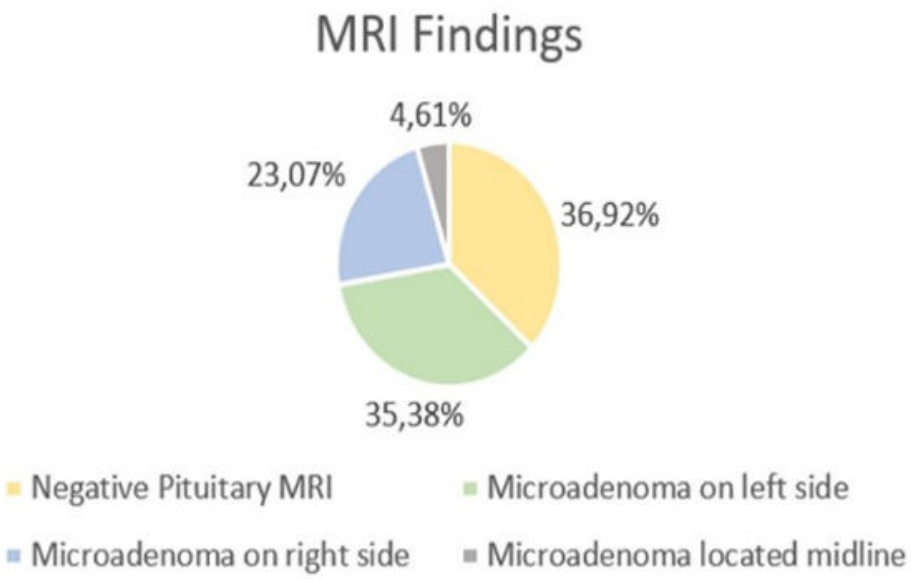

Fig. 1. Distribution of patients according to MRI findings.

tion. All of the patients showed up normal MRI or microadenoma smaller then 6mm. 24 (36.92%) of them were with normal MRI, 23 (35.38%) with left sided microadenoma, 15 (23.07%) with right sided microadenoma and 3 (4.61%) of them were central microadenoma (Fig.1).

CSS

Sixty-five patients underwent CSS under general anesthesia or sedation. Heparinization with 5000 UI bolus followed by 1000 U/h additional dose has been done. Bifemoral punction with 5F catheter, Picard (Cook) catheter to IPS (Inferior petrosal sinus) followed by 0.18 microcatheter placement to CS (cavernous sinus) by 0,16 guide. Blood samples were taken without CRH and in the 1st, 2nd, 5th and 10th minutes after CRH stimulation simultaneously from both cavernous sinüs (CS). The central / peripheral (c / p) ratio was interpreted as central if the gradient was greater than 3 with CRH stimulation and we evaluated R / L or L / R ratio as lateralization if it was great equal 1.4. A positive gradient between right and left sides was found in 62 patients ranging from 1.56 to 250 (mean: 19.37). There was 3 (4.61%) without lateralization but central to peripheral gradient (Table 1). We found accuracy of 80% (52/65) which was decided as positive if the CSS side is compatible with the MRI, pathology or remission after hemihypophysectomy of the normal MRI cases.

Thirteen patients showed false CSS lateralization. Eleven patients among this 13 false lateralization were in remission. Of the 24 patients with normal MRI, 20

Table 1. Data forpatients who underwent CSS and TSS, remission rate, accuracy

		TSS exploration findings n = 65*					
CSS ratio	No	Same side HH	Same side A	Counter A	HH+A	Final follow-up remission	Accuracy*
Right	31	8	4	3	16	27	21
Left	31	9	15	6	1	25	28
Equal	3	0	3	0	0	3	3

CSS = Cavernous sinus sampling, TSS = Transsphenoidal surgery, HH = Hemihypophysectomy, A = Adenomectomy, MRI = magnetic resonance imaging

*Accuracy decided as positive if the CSS side is compatible with the MRI, pathology or remission after hemihypophysectomy of the normal MRI cases.

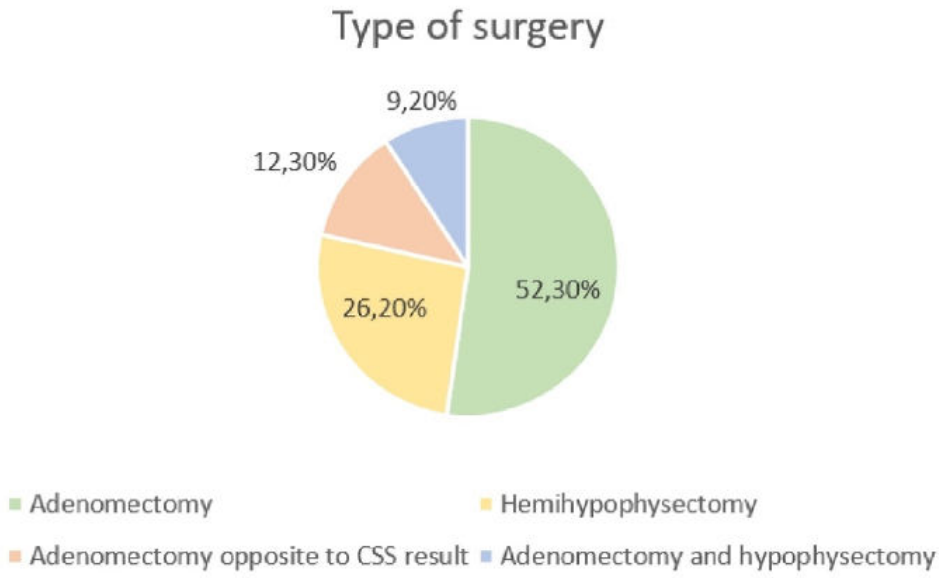

Fig. 1. **Type of surgery.**

had positive accuracy for CSS (83%). Patients with a positive accuracy of CSS sampling had a remission rate of 18/20 (90%). Tumors less than 6 mm which was verified by MRI scans had an accuracy of 31/41 (75.6%). Twenty-six of them had a positive remission in the final follow-up (83.87%).

There was only one complication of guidewire breakage during cavernous sinus sampling. The distal part of the wire had to be left but removed during the following TSS after the removal of tumor. There were no other complications.

Surgical approach and remission

We performed either endoscopic or microscopic TSS for all of the cases after CSS. We started to use endoscopic TSS since 2007 and all patients were operated endoscopically after 2007. Surgical strategy consisted of exploring the whole gland, starting from the suspected side. If the adenoma is detected, adenomectomy is performed. If not hemihypophysectomy was performed according to the CSS lateralization. There were 17 temporary diabetes insipidus and 1 permenant diabetes insipidus treated with desmopressin.

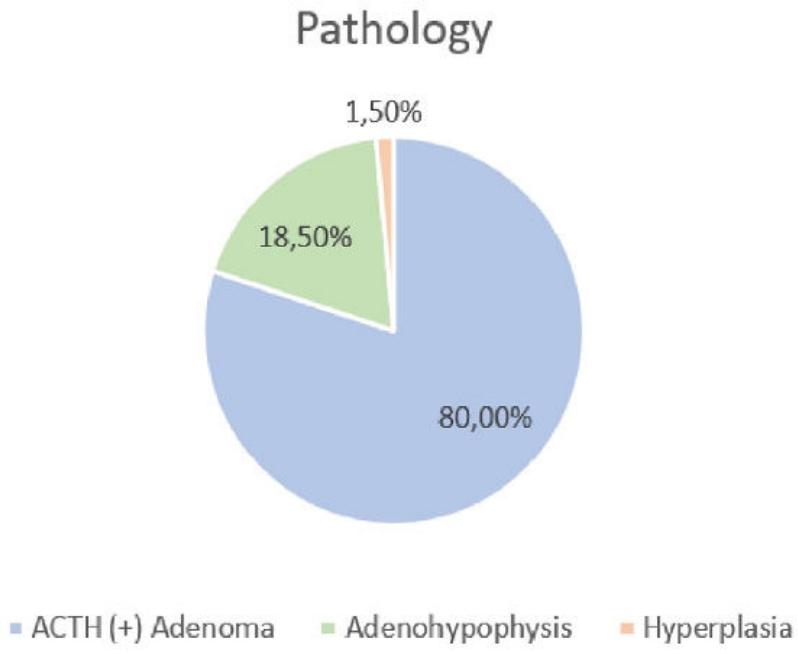

Fig. 1. **Distribution of the pathological result of the patients.**

One patient had rhinorrhea who was treated by lomber CSF drainage of 72 hours. Four patients had hypothyroidism post-operatively and 1 patient with panhypopituitarism who underwent medical treatment. One of the patients had a menenjitis treated by antibiotic treatment. There were no mortality related to our surgical procedure but 4 patients died during long-term follow-up because of complications related to CD. We had no mortality nor neurological morbidity after the surgical procedures. Patients who had remission on the final follow up was 55 (84.6%). Types of surgeries performed and pathological results of the patients are as shown in Figs. 2 and 3.

DISCUSSION

Treatment of Cushing's disease is problematic and should be treated by a multidisciplinary team and the treatment aims to improve the patients clinical manifestations with the resection of tumoral mass normalizing the hormone secretion. Despite all treatment methods, the biggest problem with these patients is the inability to achieve the desired remission rates and the recurrence of the disease. There are considerable number of CD patients with normal MRI, with empty sella, and with some suspect lesions or fullness in one side of the pituitary. Preoperative MRI identification of an adenoma has been associated with high remission rates [12]. Of course this can be linked to the advantages of knowing the enemy and dealing with it. Invisible adenomas are the adenomas that surgeons are mostly not like to operate. Endoscopic TSS may be a good option for better visualization of adenomas but most of the time it doesn't solve this suspect lesion problem completely.

In 1985 Oldfield *et al*. [13] reported the high accuracy of inferior petrosal sinus sampling (IPSS) method in differentiating the ectopic sourced Cushing's syndrome from pituitary adenomas. In time, venous sampling methods began to spread and a number of series began to be published. The common feature of the series was that the methods of venous sampling either IPSS or CSS were helpful to identify the central etiology in ACTH-dependent CD. There is however no consensus about their value of correctly locating the tumor within the pituitary [12, 14-16, 17]. The trick point is the experience of the interventional neuroradiology team. This study is not a comparison between IPSS and CSS, however it is worth to review the advantages and disadvantages of both methods (Table 2). ACTH secreting pituitary adenomas are mostly located laterally [18]. Therefore, venous sampling results are one of the most indispensable guide for surgeon's intervention. Both halves of the pituitary gland drain into the cavernous sinus of its own side, and therefore direct cavernous sinus sampling is thought to yield more accurate results about lateralization of the adenoma because of the high concentration of the ACTH levels [12, 17]. Whether it is CSS or IPSS, the placement of catheters in both is very important for the interpreting of lateralization results [19].

In our study CSS sampling had a 80% accuracy.

Teramoto *et al*. [14] reported the correct lateralization of CSS 57% to 80%. Of the 24 patients whose MRI showed no adenoma, we found correct lateralization for 20 (sensitivity 83%). Patients with a positive accuracy of CSS sampling had a remission rate of 18/20 (90%). Of the 41 patients who has an adenoma < 6 mm on their MRI, correct lateralization for 31/41 (75.6%) was found which 26 of them had a final remission in the follow-up (83.87%). Of course there are cases where CSS is also insufficient. In our study we found false CSS result for 13 patients. In this group, 4 patients with normal MRI had an contralateral ade-

Table 2. Advantages and disadvantages of CSS and IPSS

	Advantages	Disadvantages
IPSS	Easier	Frequent venous variations Not reliable for lateralization
CSS	Closer to the lesion, providing more elevated ACTH concentration in the sample	Need for experienced neuroradiologist Painful procedure requiring general anesthesia or sedation

CSS= Cavernous sinus sampling, IPSS = Inferior petrosal sinus sampling, ACTH = Adrenocorticotropic hormone

noma compared to CSS sampling side.

Incorrect (false) lateralization is a possible problem in all venous sampling methods. There may be many reasons for this undesirable situation. Mamelak *et al*. [20] emphasized that the asymmetric drainage of the inferior petrosal and cavernous sinuses was the main cause of the incorrect lateralization. Variations of the venous system, communications between cavernous sinuses and the compartmantalizations of the sinuses with fibrous septaes are the other possible reasons for this false lateralizations [17, 20, 21].

When we look at the literature, we see that our results are compatible with other studies. Correct rate of CSS sampling was reported as 82% by Burkhardt *et al*. [8], 91% by Teramoto *et al*. [14, 17] and 83% by Graham *et al*. [21]. In our institution we prefer CSS for the preoperative assessment of lateralization. It is useful to underline again that the method of sampling is determined according to the experience of the neuroradiology team. Surgery may affect the venous drainage therefore CSS may not be helpful in relapsed cases. All cases in this study were operated first time. The accuracy of the CSS in recurrent cases may be the subject of further studies.

CONCLUSION

Nowadays, adenomas are detected in smaller sizes due to the widespread use of MRI for various reasons. The biggest problem for invisible adenomas and small sized adenomas is finding adenoma during surgery or where to perform the hemihypophysectomy. Every additional information is helpful to the surgeon therefore we emphasize that performing CSS may improve the remission rates.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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