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Effect of bariatric surgery on night eating syndrome: A retrospective study

Bariatrik cerrahinin gece yeme sendromu üzerine etkisi: Retrospektif bir çalışma

Halit Eren Taşkın[1]

Abstract

Aim: Prevalence of night eating syndrome (NES) is higher in obese people. The effect of bariatric surgery on preoperative and postoperative eating disorders of obese patients remains controversial. This study aims to determine the preoperative and postoperative NES in patients who underwent bariatric surgery and the impact of surgery on this syndrome.

Methods: The study was conducted on 29 patients who applied for bariatric surgery at a university hospital to treat morbid obesity. The questionnaire used as a data collection tool included the participants' sociodemographic characteristics, anthropometric measurements, and the Night Eating Questionnaire (NEQ) elements. Groups with and without improvement in NES status with bariatric surgery were formed, and the groups were compared according to the other parameters. The relationship between night eating disorder, demographic characteristics, and anthropometric measurements were also evaluated.

Results: Bariatric surgery was promising in the entire group, the mean preoperative body mass index in the entire group was 42.9 ± 5.56 kg/m2, and the mean postoperative 1st-year body mass index was 28.5 ± 5.98 kg/m2. When NEQ was evaluated, it was seen that 27.6% of the patients had NES before the surgery and 10.3% after the surgery. It was found that only smoking had a negative effect on the improvement in NES (p=0.045), while other parameters did not have significant effects (p>0.05).

Conclusions: It has been observed that bariatric surgery positively affects NES. Although smoking negatively affects the improvement in NES, studies with larger samples are needed to evaluate these and other parameters more effectively.

Keywords: Bariatric surgery, obesity, night eating syndrome.

Öz

Amaç: Obez kişilerde gece yeme sendromu (GYS) prevalansı daha yüksek oranda görülmektedir. Obez hastaların ameliyat öncesi ve sonrası yeme bozuklukları üzerine bariatrik cerrahinin etkisi tartışmalıdır. Bu çalışmanın amacı, obezite cerrahisi geçiren hastalarda ameliyat öncesi ve sonrası GYS görülme oranın ve ameliyatın bu sendroma etkisini belirlemektir.

Yöntemler: Çalışma bir üniversite hastanesine morbid obezite cerrahi tedavisi için başvuran 29 hasta üzerinde yapıldı. Veri toplama aracı olarak kullanılan ankette, katılımcıların sosyodemografik özellikleri, antropometrik ölçümleri ve Gece Yeme Anketi (GYA) unsurlarına yer verilmiştir. Bariatrik cerrahi ile gece yeme sendromu durumunda düzelme olan ve olmayan gruplar oluşturuldu ve gruplar diğer parametrelere göre karşılaştırıldı. Ayrıca gece yeme bozukluğu ile demografik özellikler ve antropometrik ölçümler arasındaki ilişkinin değerlendirildi.

Bulgular: Demografik veriler incelendiğinde bariatrik cerrahinin yeterli kilo kaybını sağladığı görüldü. Preoperatif ortalama vücut kitle indeksi 42,9 ± 5,56 kg/m2 ve 1 yıl sonra ortalama vücut kitle indeksi 28,5 ± 5,98 kg/m2 olarak saptandı. GYA'i değerlendirildiğinde hastaların %27,6'sının ameliyat öncesi, %10,3'ünün ameliyat sonrası GYS yaşadığı görüldü. Sadece sigara içmenin GYS'deki iyileşme üzerinde olumsuz bir etkisi olduğu (p=0,045), diğer parametrelerin ise anlamlı bir etkisi olmadığı (p>0,05) bulundu.

Sonuç: Bariatrik cerrahinin GYS üzerine olumlu etkileri olduğu gözlemlenmiştir. Sigara içmek GYS'deki iyileşmeyi olumsuz etkilese de, bu ve diğer parametrelerin daha etkin değerlendirilmesi için daha büyük örneklemli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Bariatrik cerrahi, obezite, gece yeme sendromu.

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Introduction

The World Health Organization (WHO) reports that obesity will be the most significant health problem of the 21st century. The prevalence of obesity is increasing in adults, children, and adolescents in our country. While many genetic, physiological, behavioral, sociocultural, and environmental physio-pathological factors lead to the development of obesity; also cultural, behavioral, and environmental factors (energy-intensive diet, large portions, physical inactivity, sedentary lifestyle) eating disorders accelerate the development of obesity [1].

The necessary treatment for obesity is lifestyle change and diet. However, pharmacotherapy or bariatric surgery is applied in patients who cannot achieve targeted weight loss. Bariatric surgery is currently the only treatment offering high and long-term weight loss [1, 2]. Significant improvement is observed with bariatric surgery in diseases such as obesity-related type 2 diabetes, hypertension, dyslipidemia, obstructive sleep apnea, renal dysfunction, and depression [3]. A multidisciplinary team for appropriate patient selection, adequate preoperative (pre-op) evaluation, and appropriate postoperative (post-op) follow-up are vital for reaching success in bariatric surgery [1]. Before and after bariatric surgery, eating behavior plays a crucial role in postoperative outcomes [4, 5]. Eating disorders and problematic eating behavior, which are more common in bariatric surgery patients compared to the non-obese population, may have adverse effects on post-op bariatric surgery outcomes [6].

Eating disorders start with insufficient or excessive food intake and cause permanent changes in eating attitudes and behavior [7]. The most frequent eating disorders among the patients who are candidates for bariatric surgery can be listed as; binge eating disorder, night eating syndrome, emotional eating, and frequent snacking or grazing during the day. Moreover, although it has not yet been included in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5), food addiction also appears in studies carried out [6, 8, 9]. The literature indicates that binge eating disorder is observed in 4-45%, grazing in 20-60%, night eating syndrome in 42%, emotional eating in 38-59%, and food addiction in 36.8% of bariatric surgery candidates [8, 10, 11]. The performance of a psychological evaluation before the bariatric surgery for the patients and providing post-op support through psychological follow-up for the patients with a diagnosed eating disorder are among the factors that will lead the patient to success after the surgery [6, 12].

Night Eating Syndrome (NES) was first described by Stunkard in 1955 as a disorder in treatment-resistant obesity patients characterized by morning anorexia, evening hyperphagia, and insomnia [13]. NES is described as the presence of morning anorexia, excessive evening eating due to omitting breakfast or eating sparingly in breakfast, at least having 25% of total daily energy after the evening meal, and the occurrence of this case at least two times per week. It has been included in DSM-5 as other eating disorders and has been reported to be associated with conscious episodes of an evening or nighttime hyperphagia and emotional stress [10, 14]. In night eating syndrome, the patient is fully aware of what is eaten when he or she wakes up at night and eats. In contrast, an entirely different illness in sleep eating disorder, the individuals wake up at night and eat. However, they are not aware of this situation and have no memory of the next day. While the prevalence of night-eating syndrome in the general population varies between 1.1% and 1.5%, this prevalence is reported as 6-16% in obese individuals. Postoperative studies indicate that 6-8% of patients experience night-eating syndrome after surgery [15, 16].

This study aims to show the rate of NES before and after bariatric surgery and how bariatric surgery affects this disorder in short-term follow-up. Also, demographic parameters and daily habits of the patients (alcohol consumption, smoking) were questioned, and any relationship regarding NES development was noted.

Material and methods

Study

This study was conducted per the principles of the Declaration of Helsinki, 2008, with patients who applied for bariatric surgery and underwent subsequent surgery at a University Hospital in Istanbul. The local ethical committee approved the study (21.05.2020/05-218614). The study was conducted by obtaining informed consent voluntarily from patients between December 2019 and May 2021. As the study's criteria, interviews were conducted with 42 patients aged 18-65 years and with no hearing impairment. The study was completed with 29 participants and was included in the statistical analysis. Patients who could not comply with one-year follow-up protocol and patients who had revisional surgery due to weight regain and complications were excluded from the study.

Variables

As a data collection tool, the sociodemographic characteristics (age, gender, educational status, marital status), anthropometric measurements (height, weight, BMI), and finally, the Night Eating Questionnaire (NEQ) of the participants were used. The Night Eating Questionnaire was first developed by Allison et al. [17] in 2008 to evaluate the scanning and symptom severity. Turkish validity and reliability study was conducted by Atasoy et al. [18] in 2014. The Cronbach's alpha coefficient was found to be 0.69. NEQ is currently the most widely used criterion. The current version is in a 5-point Likert type and consists of 14 items, with a cut-off score of 25 [17, 18].

The patients were divided into two groups according to the effects of bariatric surgery on NES. Those with NES scores >25 in the preoperative period, but <25 in the postoperative 1st year and <25 in both periods, were included in Group 1 (improvement in NES), and those with >25 scores in the postoperative 1st year were included in Group 2 (no improvement in NES). Groups were compared according to sociodemographic characteristics and anthropometric measurements. Correlation analysis was then performed to examine the factors affecting improvement in NES.

Statistical Analysis

The research is of a scanning model and descriptive. Data collected quantitatively were evaluated with IBM SPSS Statistics 25.0. The significant difference between variables was analyzed using the Mann-Whitney U test for non-parametric data and the Chi-square test for parametric data. Pearson's Correlation Analysis was also used to evaluate the parameters affecting the improvement in NES after bariatric surgery. A p-value less than 0.05 was regarded as statistical significance.

Results

Among the 29 patients included in the study, 24.1% (n = 7) were male, 75.9% (n = 22) were female. The mean age was 41.52±9.52 (24-62) years. In terms of education level, 65.5% (n=19) of the patients were university or high school graduates, and 34.5% (n=10) were primary or secondary school graduates. Additionally, 72.4% (n = 21) of them were married and 27.6% (n = 8) of them were single. These parametric did not show significant differences between groups (p>0.05). When smoking and alcohol use were evaluated, 37.9% of the patients smoked, and 17.2% used alcohol. It was determined that all patients in the group with no improvement in NES (group 2) were smokers, and statistical significance was observed between smoking status and groups (p=0.045) (Table 1). Furthermore, no significant difference was determined between the groups in terms of the number of daily main meals, the number of daily snacks, nutritionist support status, and psychological support status (p>0.05) (Table 1).

When the anthropometric values of the patients were examined, it was observed that the mean height was 165 ± 9.9 cm, preoperative mean weight of the patients was found 118 ± 21.4 kg, mean postoperative 1st-year weight was found 77.7 ± 16.2 kg. The mean preoperative BMI was 42.9 ± 5.56 kg/m^2. The mean postoperative 1st-year BMI was 28.5 ± 5.98 kg/m^2, and the excess BMI loss percentage (%EBMIL) was %86,89. No significant results were detected in comparing groups according to these anthropometric parameters. (p>0.05) (Table 1).

The rate of the night eating syndrome, which was 27.5% (Group 1, n = 8) before the surgery, decreased to 10.3% (Group 2, n = 3) after the surgery. Moreover, it was observed that six patients recovered after surgery, there was no change in the results of two patients, and night eating syndrome developed in one patient.

In the Pearson Correlation Analysis, which we used to examine the effects of the parameters on the improvement in NES, it was found that there was a significant negative correlation between smoking and improvement in NES and no correlation with other parameters (p=0.019) (Table 2).

Table 1. Comparison of the groups according to the sociodemographic and anthropometric parameters.

		Group 1 (n=26)	Group 2 (n=3)	p
Age (year) †		41.65±9.81	40.33±8.08	0.774
Gender ‡	Male	6 (23)	1 (33)	1.000
	Female	20 (77)	2 (67)	
Marital status ‡	Single	18 (69)	3 (100)	0.540
	Married	8 (31)	0 (0)	
Education level ‡	Primary-secondary school	10 (39)	0 (0)	0.532
	High school-university	16 (61)	3 (100)	
Smoking ‡		8 (31)	3 (100)	**0.045**
Alcohol ‡		5 (19)	0 (0)	1.000
Number of daily main meals ‡	<3	11 (42)	2 (67)	0.573
	≥3	15 (58)	1 (33)	
Number of daily snacks ‡	<3	14 (54)	2 (67)	1.000
	≥3	12 (46)	1 (33)	
Nutritionist support ‡		17 (65)	2 (67)	1.000
Psychological support ‡		4 (15)	0 (0)	1.000
Height (m) †		1.65±0.10	1.63±0.07	0.857
Preoperative weight (kg)		120.19±22.16	106.33±8.14	0.151
Preoperative BMI (kg/m^2)		43.52±5.72	39.79±3.92	0.283
Postoperative 1st-year weight (kg)		77.27±13.93	75.67±12.22	0.914
Postoperative 1st year BMI (kg/m^2)		28.11±4.79	28.42±5.88	1.000
Postoperative 1st-year EBMIL (%)		87.43±30.02	82.25±3.54	0.943

†: mean ± standard deviation, ‡: n (%), BMI: Body mass index, EBMIL: excess body mass index loss.

Table 2. The effects of different parameters on the improvement of NES.

	Improvement in Night eating syndrome	
	Pearson Correlation Coefficient (r)	p
Sex	0.073	0.707
Age	0.043	0.825
Marital status	0.21	0.275
Education level	0.054	0.78
Smoking status	**-0.435**	**0.019**
Alcohol use	0.155	0.422
Number of daily main meals	0.149	0.44
Number of daily snacks	0.079	0.686
Nutritionist support	-0.008	0.966
Psychological support	0.136	0.482
Height	0.069	0.723
Preoperative weight	0.2	0.299
Preoperative body mass index	0.205	0.285
Postoperative 1st-year weight	0.037	0.851
Postoperative 1st-year body mass index	-0.02	0.919

Discussion

Bariatric surgery is recognized as the most effective treatment for obesity and, in general, results in the improvement or resolution of the medical and psychosocial comorbidities associated with morbid obesity. However, studies show that bariatric surgery candidates are likely to present with eating disorders and problematic eating behavior. These problems may persist or develop after bariatric surgery, and even psychological disorders that did not exist before may also occur [19, 20]. The prevalence of eating disorders and problematic eating behavior in bariatric surgery patients suggests that this situation may significantly impact the outcomes of bariatric surgery [14].

Among the 29 patients included in the present study, 75.9% were female, 24.1% were male, and regarding their education levels, 48.3% were high school graduates, and 27.6% were primary school graduates. In research evaluating the eating disorders in individuals who underwent bariatric surgery, it was reported that the education levels of 215 patients (82% female, 18% male) were high school or lower level with a ratio of 45.2%. Therefore, the gender ratios and education levels in the two studies show similarities [21]. Other studies examining the eating disorders show parallelism with this study, and it was seen that most of the participants were women [22, 23]. Although female gender is predominant in our study and many of the studies, there has been no gender impact on NES development before or after bariatric surgery. However, a comparative larger prospective cohort is necessary to justify this fact.

The patients' marital status and daily habits can be another contributing factor for various eating disorders. In a study conducted in Spain that included 31 individuals with a history of bariatric surgery, it was concluded that 61% of the participants were married, 39% were single, 38.2% of the participants were smoking, and 40.0% were using alcohol. The results of this study on alcohol use were found to be higher than in our study, but other findings showed similarities [24]. In another study performed on college students, it was found that smoking was not a contributory factor for NES relatively shorter sleep time and poor sleep quality were found to be contributory factors for the development of NES [25]. Compared to a study examining alcohol use in bariatric surgery, the rate of alcohol use in ours seems to be higher by 10% [26]. Our study showed that smoking had a negative effect on recovery in NES after bariatric surgery and all the patients with NES in our study were smokers. Interestingly this situation contradicts some studies in the literature. Changes in appetite caused by smoking and the resulting irregular eating habits can be reported to explain this situation.

After surgery, patients are advised to consume 3-6 meals a day, watch portion control to prevent nausea and vomiting, and take snacks [27-29]. Consuming less frequent meals and low-calorie intake during the day can contribute to NES development. When the patients' number of daily meals was examined, it was determined that 55% had three main meals a day, and 44.8% had three snacks a day. In a different study in which the nutritional quality of the patients was discussed, it is seen that 70.5% had three main meals a day, and 31.8% had three snacks a day [30]. While 62% of the patients participating in this study reported that they received dietitian support, in another study, it is seen that 74% of the participants have no contact with a dietitian [31]. We believe that continued dietitian support is of most importance for the treatment of NES and other eating disorders and to prevent weight regain after bariatric surgery.

No statistically significant difference was found between the postoperative questionnaire scores of male and female patients in the current study. Nevertheless, in a study evaluating eating behavior after surgery, there was no gender difference in the results similarly [23]. In contrast, in another study, it is reported that BMI is higher in women than in men [33].

The eating behavior of bariatric surgery candidates was examined in various studies. It was seen that between 1.9% and 41.7% of the candidates had existing NES before bariatric surgery [11]. Similarly, in another study, the prevalence of this rate varied between 8.9% and 55% [34]. These findings were in accordance with our results which show a pre-op night eating rate of 27.6%. This finding shows that careful evaluation of the patients with a dedicated dietician and psychologist is necessary before surgery.

In a study examining the effect of bariatric surgery on night eating syndrome, it is seen that the postoperative night eating questionnaire scores decreased from 14.18 ± 7.69 to 12.32 ± 7.66 and that in both studies, there was a downward trend in the postoperative night eating questionnaire scores. No statistically significant difference was found between BMI and NES in our study. The same results were also achieved by Ferreira Pinto et al.'s study [35].

The main limitation of our study was the small sample size and retrospective design. Also, comparing patients with eating disorders and NES with a control group in a longer follow-up period would lead to better and more factual findings and might clearly show the advantages of bariatric surgery in these particular groups of patients.

In conclusion, due to our findings, it was observed that there was an improvement in the incidence of night eating syndrome and questionnaire scores in patients after bariatric surgery. According to the results obtained, it is seen that evaluating the presence of eating disorders in patients undergoing bariatric surgery and raising awareness about eating disorders in patients are of importance. Moreover, smoking is an essential parameter for the improvement of NES after bariatric surgery.

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Evaluation of right ventricular function in patients with COVID-19 pneumonia after discharge with right ventricle early inflow-outflow index

COVID-19 pnömonili hastaların taburculuk sonrası sağ ventrikül fonksiyonunun sağ ventriküler erken giriş-çıkış indeksi ile ieğerlendirilmesi

Nuran Günay[1]

Abstract

Aim: The coronavirus disease 2019 (COVID-19) has been causing many cardiovascular complications. In patients with comorbidities, COVID-19 infection has a more severe course. Even with some patients who do not have comorbidities, severe infection and death may occur. In studies, many echocardiographic parameters were found to be impaired in patients with COVID-19 pneumonia. The right ventricle early inflow-outflow (RVEIO) index is a possible and indirect predictor of the severity of right ventricle dysfunction. The aim of our study is to evaluate the RVEIO index after discharge in patients with moderate-to-severe COVID-19 pneumonia without comorbidities.

Methods: The study was conducted prospectively in a single center. One month after discharge, echocardiography and biochemical tests were performed in 57 patients with moderate-to-severe COVID-19 pneumonia without comorbidities.

Results: Pulmonary artery diameter was found to be significantly larger in the severe group [1.9 (1.8-2) vs. 2 (1.9-2.1); p=0.014]. Pulmonary artery acceleration time [140.92±11.70 vs 114.58±12.03; p=0.001)] and RVOT VTI [23.48±1.96 vs 19.18±2.2; p <0.001] was significantly lower, while the RVEIO index was [2.51±0.54 vs 3.22±0.92; p<0.001] was found to be significantly higher in the severe group.

Conclusion: The long-term effects of COVID-19 infection are still unknown. Therefore, follow-up studies should be conducted. Echocardiography can be used in the follow-up of inpatients and discharged patients because of its easy accessibility and low cost. Long-term follow-up should be conducted for individuals who had a severe COVID-19 pneumonia and who do not have comorbidities. The RVEIO index may be used in the follow-ups.

Keywords: COVID-19, pneumonia, RVEIO index, right ventricle function, comorbidity.

Öz

Amaç: Koronavirüs hastalığı 2019 (COVID-19) birçok kardiyovaküler komplikasyona neden olmaktadır. Komorbiditesi olan hastalarda, COVID-19 enfeksiyonu daha ağır seyir etmektedir. Bazı hastaların komorbiditesi olmamasına rağmen, ağır enfeksiyon ve ölüm görülebilmektedir. Çalışmalarda COVID-19 pnömonili hastalarda, birçok ekokardiyografi parametresinin bozulduğu saptanmıştır. Sağ ventrikül erken giriş-çıkış (RVEIO) indeksi, sağ ventrikül disfonksiyonunun şiddetinin olası ve dolaylı bir belirtecidir. Çalışmamızın amacı, orta-ciddi COVID-19 pnömonili komorbiditesi olmayan hastalarda, taburculuk sonrası RVEIO indeksini değerlendirmektir.

Yöntemler: Çalışma tek merkezde, prospektif olarak yürütüldü. Taburculuktan bir ay sonra, komorbiditesi olmayan, 57 orta-ciddi COVID-19 pnömonili hastanın ekokardiyografisi ve biyokimyasal testleri yapıldı.

Bulgular: Pulmoner arter çapı ciddi grupta, anlamlı daha geniş saptandı [1,9 (1,8-2) ve 2 (1,9-2,1); p=0,014]. Pulmoner arter akselarasyon zamanı [140,92±11.70 ve 114,58±12,03; p=0,001)] ve RVOT VTI [23,48±1,96 ve 19,18±2,2; p <0,001] anlamlı daha düşük, RVEIO indeksi ise [2,51±0,54 ve 3,22±0,92; p<0,001] ciddi grupta anlamlı daha yüksek saptandı.

Sonuç: COVID-19 enfeksiyonunun uzun süreli etkilerini bilmiyoruz. Bu nedenle takip çalışmaları yapılmalıdır. Ekokardiyografi tetkiki kolay ulaşılabilir ve az maliyetli olması nedeniyle yatan hastalar ile taburcu edilen hastaların takiplerinde kullanılabilir. Özellikle hastalığı ciddi geçiren, komorbiditeleri olmayan bireylerin bile uzun dönem takipleri yapılmalıdır. Takiplerde RVEIO indeksi kullanılabilir.

Anahtar Kelimler: COVID-19, pnömoni, RVEIO indeksi, sağ ventrikül fonksiyonu, komorbidite.

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Introduction

Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 spread from China to the whole world in December 2019. The World Health Organization declared a pandemic in March 2020. The infection infected millions of people, causing mortality and morbidity [1, 2].

The lungs are the target organ of the virus. Asymptomatic infection in patients with COVID-19 can cause severe respiratory failure, dysfunction in other organs, primarily the heart and it can even lead to death. Mortality is higher in patients with cardiac involvement. Male gender, coronary artery disease, advanced age, hypertension, diabetes, obesity, lung disease affect mortality and morbidity. The virus can cause severe pneumonia and death in some patients, even in those who do not have comorbidity [3-5].

COVID-19 infection may cause cardiovascular complications such as myocarditis, heart failure, sudden death, acute myocardial infarction, cardiogenic shock, arrhythmia, venous thromboembolism. It causes these effects directly and indirectly [6-8]. Studies have shown that right ventricle afterload increases and right ventricle contractility decreases. It has been reported that pulmonary artery systolic pressure, tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC) and right ventricular (RV) strain are impaired and associated with mortality [9, 10].

COVID-19 has been found to cause subclinical myocardial dysfunction even in mildly symptomatic patients [11,12]. Despite regular vaccination, the spread of the virus has not been stopped. The long-term effects of the virus are still unknown. A follow-up study of patients recovering from SARS infection has found an increased risk of cardiovascular disease [13]. For this reason, follow-up studies should be performed on patients with especially severe-critical COVID-19 infection. Echocardiography can be used in these studies because of its easy accessibility and low cost.

The RVEIO Index is a possible and indirect predictor of the severity of tricuspid regurgitation and right ventricle dysfunction in pulmonary embolism [14]. In a recent study of intensive care patients, the RVEIO index has been found to be high in severe patients [15]. Studies on the RVEIO index should be performed on discharged patients. In our study, the RVEIO index was evaluated in after-discharge echocardiograms of patients with moderate-severe COVID-19 pneumonia without comorbidities.

Material and methods

Study Population

The study was conducted prospectively in a single centre between 15 May 2020 and 30 July 2020. The clinical and radiological definition of the World Health Organization was used to diagnose patients with COVID-19 pneumonia [16]. Echocardiography and biochemical tests were performed 1 month after discharge on 31 severe and 26 moderate COVID-19 pneumonia patients without comorbidities. The COVID PCR tests of the patients were positive at admission and the PCR tests performed after discharge were negative. Patients with severe COVID-19 had one of the three criteria: I-Respiratory distress and respiratory rate greater than 30 per minute; II-Fingertip blood oxygen saturation at rest <93%; III-Partial arterial oxygen pressure (PaO2)/fraction of inspired oxygen (FiO2) <300 mmHg. Patients who did not undergo invasive mechanical ventilation were included in the study.

Patients over the age of 18 without comorbidity were included in the study. Coronary artery disease, hypertension, heart failure, left bundle branch and right block, atrial fibrillation, patients under 18 years of age, moderate-severe valve pathology, diabetes mellitus, anemia, thyroid dysfunction, chronic renal failure, pulmonary hypertension, invasive mechanical ventilation, patients with a history of pulmonary embolism, cancer, rheumatic valve disease, chronic lung disease, BMI > 30 kg/m2 and myocarditis during hospitalization, acute coronary syndrome and patients with poor echogenicity were excluded from the study.

Echocardiographic examinations

Transthoracic echocardiographies of the patients were performed and recorded with the EPIQ 7C ultrasound system (Philips Medical Systems, Andover, Massachusetts). Two independent observers analysed the images. Two-dimensional, M-mode transthoracic, tissue Doppler echocardiographies were performed in accordance with the guidelines of the American and European Society of Echocardiography [17,18]. Left ventricle end-diastolic (LVEDD) and end-systolic diameter (LVESD), interventricular septum (IVS), posterior wall (PW) and left atrium (LA) diameters were measured from the parasternal long axis. Right ventricular (RV) diastolic diameter, RV diastolic area, RV systolic area were obtained from RV-focused apical 4-chamber view. RVFAC was calculated from right ventricular area measurements. Mitral and tricuspid early diastolic and late diastolic maximal flow velocities were determined from the apical 4-chamber view using pulse wave (PW) Doppler. Left ventricular ejection fraction (LVEF) was calculated by the Teicholz method. Pulmonary artery systolic pressure was calculated from the tricuspid regurgitation jet using Bernoulli's equation. Estimated pulmonary artery systolic pressure (PAPs) was calculated by adding 5-10 mmHg to these values according to the width of the inferior vena cava. Intermittent flow spectral mode was used for tissue Doppler imaging. Systolic, early and late diastolic tissue velocities were measured by taking tissue Doppler images from the apical 4-chamber view of the mitral and tricuspid lateral annulus. TAPSEs were measured using the M mode. Pulmonary artery acceleration time was measured with PW Doppler just proximal to the pulmonary valve annulus. RV outflow velocity time interval (VTI) was traced from the pulse-wave Doppler recording at the RV outflow tract (RVOT) on the parasternal short-axis view (Figure 1). The RVEIO index was calculated using the equation described in Figure 2.

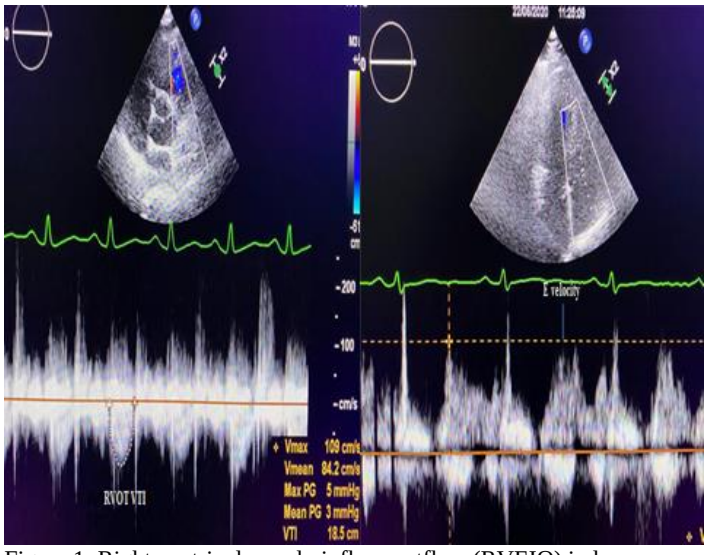

Figure 1: Right ventricular early inflow-outflow (RVEIO) index parameters.

RVEIO Index= E velocity/RVOT VTI

Figure 2: Equation of RVEIO index.

Statistical Analysis

All data was analysed using SPSS (Statistical Package for Social Sciences) software version 26.0. Student-t test was used for data showing normal distribution and Mann Whitney-U test was used for data not showing normal distribution. Paired sample-t test was used for the comparison of the parameters within the group and the chi-square test was used for the comparison of the qualitative data. Mean±standard deviation was used for descriptive parameters. The results were evaluated at the 95% confidence interval. A p value of <0.05 was accepted to indicate statistical significance.

Results

A total of 57 patients, 45 of whom were male, were included in the study. The mean age of the severe group was higher [43.26±10.31 vs. 49.29±10.86; p=0.037]. Six patients in the severe group and one patient in the moderate group were hospitalized in the intensive care unit [p=0.018]. The duration of hospital stay was longer in the severe group than in the moderate group [8.80±4.51 vs. 14.13±7.14; p=0.002]. Other clinical, demographic characteristics and laboratory findings were similar in the two groups. Table 1 shows the clinical, demographic characteristics and laboratory findings of the patients.

Table 1. Clinical, demographic and laboratory characteristics of the study population.

	Moderate Pneumonia (n=26)	Severe Pneumonia (n=31)	p value
Age, years	43.26±10.31	49.29±10.86	0.037
Gender (male), *n*	20 (76.9)	25 (80.6)	0.731
BMI, kg/m^2	27.48±2.15	27.22±2.18	0.7
Tobacco exposure, n	1 (3.8)	1 (3.2)	0.946
SBP, mmHg	118±10.32	115±8.11	0.12
DBP, mmHg	74.73±6.02	72.58±7.28	0.22
Heart Rate, beats/min	88.69±15.01	90.38±12.62	0.64
Oxygen Saturation %	98 (96-98)	97 (96-98)	0.380
ICU stay, n	1 (3.8)	6 (19.4)	0.018
Total time of stay, days	8.80±4.51	14.13±7.14	0.002
WBC	4609±732	4315±726	0.135
Lymphocyte, count	2218±746	1981±593	0.21
Hemoglobin, g/dL	14.07±1.36	13.80±1.26	0.44
Platelet, count	222538±65831	193354±72446	0.11
CRP, mg/dL	0.55±0.4	0.36±1	0.39
LDH, U/L	222±66.76	231±52.74	0.64

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, WBC: white blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase, ICU: intensive care unit.

The patients were treated according to the national COVID-19 treatment guidelines. While hydroxychloroquine, favipravir and antibiotics were included in the medical treatment, there was no intensive steroid treatment. Hydroxychloroquine was given to 8 patients, hydroxychloroquine and azithromycin to 49 patients, favipravir to 41 patients and tocilizumab to 6 patients. Only 4 of the patients received intravenous steroid therapy. All patients were given sc heparin and pulmonary embolism was not detected in any of the patients. All patients received oxygen therapy. Invasive mechanical ventilation was not applied to the patients hospitalized in the intensive care unit.

Echocardiographic data of the two groups are summarized in Table 2. The EF of both groups was within normal limits but the EF of the severe group was found to be significantly lower compared to the moderate group [65.96±2.63 vs 64.36±2.59; p=0.027]. The apicobasal length of the right atrium was significantly higher in the severe group [3.61±0.22 vs 3.78±0.27; p=0.017]. The pulmonary artery was found to be significantly larger in the severe group [1.9 (1.8-2) vs 2 (1.9-2.1); p=0.014]. Pulmonary artery acceleration time [140.92±11.70 vs 114.58±12.03; p=0.001)] and RVOT VTI [23.48±1.96 vs 19.18±2.2; p <0.001] was significantly lower. The RVEIO index was [2.51±0.54 vs 3.22±0.92; p<0.001] was significantly higher in the severe group.

Table 2. Echocardiographic characteristics of the study population.

	Moderate Pneumonia (n=26)	Severe Pneumonia (n=31)	p value
LVEDD, cm	4.85±0.28	4.85±0.33	0.985
LVESD, cm	3.0 (2.7-3.1)	3.0 (2.8-3.1)	0.534
LA, cm	3.65±0.19	3.61±0.15	0.517
IVS, cm	1.1±0.1	1.1±0.2	0.935
PW, cm	0.9±0.1	1±0.1	0.517
LVEF %	65.96±2.63	64.36±2.59	0.027
Mitral E, cm/s	77.43±11.1	73.13±16.7	0.268
Mitral A, cm/s	70.91±15.71	69.95±14.97	0.814
Mitral DT, ms	220 (211-230)	211 (201-236)	0.072
Mitral tdi E`, cm/s	14.55±3.02	16.34±13.63	0.514
Mitral tdi A`, cm/s	13.21±3.32	13.74±2.58	0.504
Mitral tdi S, cm/s	13.1±2.06	12.82±1.82	0.541
RA Mediolateral, cm	3.31±0.18	3.42±0.27	0.065
RA Apicobasal, cm	3.61±0.22	3.78±0.27	0.017
RA area, mm2	11.70±2.24	11.08±3.26	0.400
RV EDD bazal, cm	2.5 (2.47-2.6)	2.5 (2.4-2.6)	0.762
RV ED area, mm2	19.19±3.51	19.81±3.24	0.491
RV ES area, mm2	10.66±2.14	10.97±2.71	0.628
RVFAC %	45.11±7.36	42.78±7.08	0.235
TAPSE, cm	2.29±0.23	2.26±0.26	0.248
Tricuspid E, cm/s	58.77±12.81	60.61±13.01	0.593
Tricuspid A, cm/s	56.39±14.74	60.55±17.58	0.343
Tricuspid tdi E`, cm/s	14.96±2.58	14.38±3.78	0.493
Tricuspid tdi A`, cm/s	13.95 (12.2-15.67)	14.7 (12.3-17.2)	0.619
Tricuspid tdi S, cm/s	14.34±2.11	14.15±1.39	0.69
PAPs, mmHg	22.57±7.3	22.25±7.91	0.875
Pulmonary artery, cm	1.9 (1.8-2)	2 (1.9-2.1)	0.014
RVOT VTI, cm	23.48±1.96	19.18±2.22	<0.001
PAAT, ms	140.92±11.70	114.58±12.03	0.001
RVEIO index	2.51±0.54	3.22±0.92	<0.001

LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LA: left atrial, IVS: interventricular septum, PW: posterior Wall, LVEF: left ventricular ejection fraction, RA: right atrial area, RV EDD: right ventricular end-diastolic diameter, RVFAC: right ventricular fractional area change, TAPSE: tricuspid annular plane systolic excursion, tdi: tissue Doppler imaging, PAPs: systolic pulmonary artery pressure, RVOT VTI: Right ventricular outflow tract velocity time integral, PAAT: Pulmonary Artery Acceleration Time, RVEIO: right ventricle early inflow-outflow.

Discussion

Our study consisted of patients without comorbidities who were hospitalized for moderate-severe COVID-19 pneumonia in the first wave of the pandemic. In echocardiography performed one month after discharge, we found the RVEIO index to be significantly higher in the severe group than the moderate group. We argue that this parameter can be used especially in the follow-up of patients who had severe or critical COVID-19 pneumonia.

SARS-CoV-2 causes RV damage by increasing RV afterlode and decreasing RV contractility due to acute respiratory distress syndrome, pulmonary vascular thrombosis, direct viral myocardial damage, hypoxia, inflammatory response and autoimmune damage [19].

The right ventricle is more prone to disruption than the left ventricle. Studies have shown that decreased RV longitudinal strain (LS) is a strong predictor of mortality in patients with COVID-19 despite having normal LV EF [20, 21].

Studies in hospitalized and discharged patients have shown an increase in pulmonary artery pressure, decrease in TAPSE and RVFAC, decrease in tricuspid tdi S and deterioration in left and right ventricle strain parameters [20-22]. Therefore, studies showing right ventricle dysfunction and looking at the RVEIO index should be performed on discharged patients.

In a 12-year follow-up study of patients with SARS infection, cardiovascular problems were found in 44%, impaired glucose metabolism in 60% and dysregulated lipid metabolism in 68% [13]. In SARS-CoV-2 virus, we may see these complications in more patients in the coming years, as it resembles SARS virus and spreads more rapidly. In addition, in community-acquired pneumonia, the risk of active cardiovascular disease has been found to be increased several years after hospitalization [23,24].

It is known that viral infections can lead to pulmonary hypertension [25, 26]. Studies have shown that the pulmonary vascular effects of COVID-19 infection resemble the pathology of pulmonary hypertension [27,28]. In COVID-19 pneumonia, unlike other pneumonias, vascular thickening has been detected [29–32]. Therefore, patients with COVID-19 pneumonia may develop more pulmonary hypertension over time unlike other viral infections.

Karagodin et al. [33] found that the echocardiographic parameters of the patients in the first wave of the pandemic were significantly more abnormal than those of the patients in the second wave. LV and RV global LS, RV free wall strain, RV basal diameter were statistically found to be significantly lower in patients in the first wave compared to the patients in the second wave and RV basal diameter was statistically higher. They commented that the reason for this is the effect of new treatment methods and the increasing awareness of COVID-19 patients. Our patients were also treated with the treatment protocol in the first wave of the pandemic and did not receive intensive steroids.

The RVEIO index is a new parameter that has proved to be useful in determining the severity of tricuspid regurgitation and evaluating RV dysfunction in pulmonary embolism [14, 15]. The main cause of RV failure in COVID-19 pneumonia is tho ught to be an increase in pulmonary vascular resistance (PVR). The increase in RA pressure in response to increased PVR causes an increase in E-wave velocity on echocardiography. The reduction in RVOT VTI is the result of impaired RV systolic function due to increased PVR. RVEIO index is calculated from these two parameters. Parameters indicating RV dysfunction may not deteriorate simultaneously. RV functions can be maintained despite an increase in RV afterload up to a critical threshold. An increase in the RVEIO index may indicate RV adaptation at this stage. Kahyaoğlu et al. [15] showed that the RVEIO index can provide information about the severity of pneumonia in patients hospitalized in the intensive care unit due to COVID-19. They found an increase in the RVEIO index in the severe patient group compared to the non-serious group [15]. In our study, we found the RVEIO index to be significantly higher in the severe group one month after discharge than in the moderate group.

In the study of Mostafavi et al., it was stated that the RVEIO index in hospitalized patients was not an index showing RV dysfunction and mortality in patients with COVID-19 [34]. In BJ Kimura's article, Kahyaoglu's study was criticized while the necessity of conducting studies on the RVEIO index was highlighted [35]. Our study is a follow-up study that has shown that the RVEIO index can be used especially in the controls of patients with severe-critical COVID-19 pneumonia.

Despite all the precautions taken, COVID-19 infection continues to infect millions of people around the world. It appears that some patients have been infected with COVID-19 several times even if they have more than one vaccine. In follow-up studies, subclinical myocardial dysfunction has been shown even in patients with mild infection. With the cumulative effect of recurrent infections, further damage may occur to the heart of patients. In studies, disturbances were detected in strain echocardiography of patients. In our country, strain echocardiography program is not available in every clinic. Therefore, we can use echocardiographic parameters such as the RVEIO index in the follow-up of patients.

As the limitations of the study, since most of the hospitalized patients with COVID-19 pneumonia had comorbidities, the number of patients in our study was small. If the number of patients were greater, statistically more significant results could be obtained. Most of the patients did not have baseline echocardiograms. If they had baseline echocardiograms, we could compare it to echocardiograms done one month after discharge.

In conclusion, since the long-term effects of COVID-19 infection are unknown, follow-up studies are essential. In particular, even patients who had serious or critical COVID-19 infection but do not have comorbidities should be checked for a long time at certain periods. Echocardiography, an easily accessible and noninvasive imaging method, can be used in these controls. We think that the RVEIO index will be useful in the follow-up of patients.

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Efficacy of colchicine treatment in COVID-19 patients: A case-control study

COVID-19 hastalarında kolşisin tedavisinin etkinliği: Bir vaka-kontrol çalışması

Ahmet Doğan[1], Taliha Karakök[2], Yakup Gezer[3]

Abstract

Aim: Various clinical studies have been conducted on many alternative options in treating COVID-19 since the beginning of the pandemic process. This study aimed to investigate the effectiveness of colchicine treatment in patients hospitalized in clinical wards due to COVID-19.

Methods: The study was retrospectively planned between October 2020 and October 2021. A total of 110 cases who received colchicine + standard treatment (favipiravir + corticosteroid + anticoagulant + symptomatic treatment) were included in the study group. The control group included randomly selected 220 patients who received only standard treatment. All cases' demographic characteristics, features of antibiotic and corticosteroid treatment, comorbidities, and clinical courses were recorded. Patients who received treatment for less than three days due to COVID-19, patients aged >95 years and <18 years, and those transferred to the clinical wards from the intensive care unit were excluded from the study. The groups were compared regarding treatment failure, including the number of intensive care unit admissions and mortality due to COVID-19 infection.

Results: While the mean age was 59.4 years in the study group, it was 65.0 years in the control group (p=0.001). The most common coexisting disease was hypertension (63%). There were significant differences between the groups in the proportions of antibiotic use (p=0.002) and high-dose corticosteroid use (p=0.004). The values of white blood cell count (p=0.003), urea (p=0.029), D-dimer (p=0.021), creatine kinase-myocardial band (p=0.003) and troponin (p<0.001) were statistically different. There was no difference in terms of intensive care unit admission (p=0.174), the mortality rate (p=1.000), and treatment failure (p=0.505).

Conclusions: According to the results of our study, colchicine treatment does not affect the prognosis of COVID-19 patients. There is a need for prospective studies investigating the role of colchicine treatment in COVID-19 infections.

Keywords: COVID-19 virus infection, colchicine, mortality rate, intensive care.

Öz

Amaç: Pandemi sürecinin başlangıcından bu yana COVID-19 enfeksiyonu tedavisinde birçok alternatif seçenek üzerinde çeşitli klinik çalışmalar yapılmıştır. Çalışmanın amacı, COVID-19 nedeniyle hastaneye yatırılan ve yataklı serviste takip edilen hastalarda kolşisin tedavisinin etkinliğini araştırmaktır.

Yöntemler: Çalışma Ekim 2020 – Ekim 2021 tarihleri arasında retrospektif olarak planlandı. Çalışma grubuna kolşisin + standart tedavi (favipiravir + kortikosteroid + antikoagülan + semptomatik tedavi) alan 110 vaka, kontrol grubuna ise sadece standart tedavi alan 220 vaka rastgele dahil edildi. Tüm olguların demografik özellikleri, antibiyotik ve kortikosteroid kullanımı, komorbidite durumları ve klinik seyirleri kaydedildi. COVID-19 nedeniyle üç günden az tedavi görenler, 95 yaş üstü ve 18 yaş altı hastalar ve yoğun bakım ünitesinden servise alınan hastalar çalışma dışı bırakıldı. Gruplar yoğun bakım ünitesine yatış ve mortalite olarak tanımlanan COVID-19 enfeksiyonu tedavi başarısızlığı açısından karşılaştırıldı.

Bulgular: Yaş ortalaması olgu grubunda 59,4 yıl ve kontrol grubunda 65,0 yıl idi (p=0,001). En sık görülen komorbidite durumu hipertansiyon (%63) idi. İki grup arasında antibiyotik (p=0,002) ve yüksek doz kortikosteroid kullanımı (p=0,004) açısından anlamlı farklılıklar vardı. Lökosit sayısı (p=0,003), üre (p=0,029), D-dimer (p=0,021), kreatin kinaz-MB (p=0,003) ve troponin (p<0,001) değerlerinde istatistiksel anlamlı farklılıklar tespit edildi. Ancak yoğun bakım ünitesine yatış (p=0,174) ve ölüm oranı (p=1,000) ve bu iki klinik durum birlikte değerlendirildiğinde tedavi başarısızlığı (p=0,505) iki grup arasında fark izlenmedi.

Sonuç: Çalışmamızın sonuçlarına göre kolşisin tedavisinin COVID-19 hastalarının prognozu üzerine etkisi yoktur. COVID-19 enfeksiyonu tedavisinde kolşisin tedavisinin tedavisinin rolünü araştıran prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: COVID-19 virüs enfeksiyonu, kolşisin, mortalite oranı, yoğun bakım.

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Introduction

Coronavirus Disease 19 (COVID-19) continues to spread rapidly worldwide. The pandemic process has directed clinicians to use traditional and new drugs for managing the disease. For the treatment and prophylaxis of the disease, many are being tested worldwide. Although treatment protocols have been developed in most countries to reduce the disease's mortality, no drugs or natural compounds have been found for prevention and treatment. Treatment strategies focusing on reducing the immune system's excessive activation have come to the fore in the search for effective COVID-19 management [1].

It is aimed to prevent complications that develop during the natural course of COVID-19 disease, including acute respiratory distress syndrome, cardiovascular involvement, renal damage, multi-organ failure with anti-inflammatory treatments [2, 3]. In this context, it has been suggested that colchicine may be an alternative option in the treatment of COVID-19 together with other drugs with anti-inflammatory properties [4, 5].

Colchicine is an ancient drug that has long been used to treat familial Mediterranean fever, Behcet's Disease, gout, pericarditis, and some viral infections [4, 6]. In the treatment of COVID-19, colchicine may act through different inflammatory pathways, such as inhibition of neutrophil adhesion, chemotaxis, and migration, inhibition of inflammasome, reduction of the production of superoxide ions, reduction of the production of inflammatory cytokines [4]. In randomized controlled experimental studies, the benefit of colchicine treatment in the treatment of COVID-19 has been demonstrated [7-9].

The study aimed to retrospectively investigate the effectiveness of colchicine treatment in patients hospitalized and followed up due to COVID-19 infection.

Material and methods

Study

The study was retrospectively planned between October 2020 and October 2021 at the Clinic of Infectious Diseases and Clinical Microbiology, Fatsa State Hospital in Ordu, Turkey. The local ethical committee approved the study (Ordu University, Clinical Research Ethics Committee, 2021/230). The study was conducted in compliance with Good Clinical Practice requirements and the Declaration of Helsinki. An informed consent form from patients could not be obtained since it was a retrospective study and no health care intervention was planned on patients.

Patients

Patients aged >18 years and <95 years, hospitalized in the COVID-19 clinical wards and diagnosed with COVID-19 by SARS COV2 Polymerase Chain Reaction studied from nasopharyngeal swab samples were included. Patients who were hospitalized less than three days due to COVID-19, aged >95 years and <18 years, treated in the intensive care unit (ICU), and transferred to the clinical wards from the ICU were excluded from the study. One hundred ten patients received colchicine (0.5 mg twice per day) + other treatment modalities according to the COVID-19 Guideline of Turkey Ministry of Health (favipiravir + corticosteroid + anticoagulant + symptomatic treatment) were added to the study group. With a 1:2 ratio, 220 patients treated with other than colchicine were randomly selected for the control group. Demographic data, colchicine use, duration and dosage of colchicine treatment, comorbid conditions, antibiotic and corticosteroid use, COVID-19 vaccine status, laboratory parameters, length of hospital stay, admission to the ICU, and mortality characteristics of all patients were recorded. Clinical improvement in the patients' follow-up was considered treatment success, and admission to the intensive care unit or mortality was considered a treatment failure. The patient's medical records were obtained by scanning our hospital's automation system.

Statistical Analysis

The data in the study were obtained retrospectively from the hospital automation system and uploaded to the IBM SPSS v.26 package program. Mean (± standard deviation) and min-max values were given for quantitative variables, and number (percentage) values were given for qualitative variables. Chi-square test for categorical variables and Man-Whitney U test for non-normally distributed independent quantitative data were analyzed. $P < 0.05$ was accepted as a statistical significance level.

Results

The study included 110 patients in the study group and 220 patients in the control group. The demographic characteristics of the patients, duration of hospitalization, antibiotic and corticosteroid treatment, COVID-19 vaccine status, presence of comorbid disease, ICU admission, and mortality outcomes are in Table 1. The mean duration of the colchicine treatment was 7.88±4.02 days, with a range from 3 to 29 days.

There were significant differences between age, antibiotic use, and corticosteroid dosage of the two arms. The mean age was significantly higher in the control group than the study group (p=0.001). Antibiotic use and high dosage corticosteroid treatment were significantly higher in the study group (p= 0.002 and p=0.004).

The most common coexisting disease was hypertension (63%), followed by chronic obstructive pulmonary disease and asthma (27.3%) for all patients. There was no significant difference in the proportion of comorbidities between the two groups (p=0.855).

The mean values of white blood cell count (p=0.003), urea (p=0.029), D-dimer (p=0.021), creatine kinase-myocardial band (p=0.003), and troponin (p=0.000) were statistically significantly higher in the control group than those in the study group (p<0.005) (Table 2). The mean value of neutrophil count was higher in the study group (p=0.001). In terms of other parameters, no significant difference was observed between the two groups (Table 2).

It was observed that a total of ten patients were transferred to the ICU, one (0.9%) in the study group and nine (4.1%) in the control group during the follow-up. There were four patients with mortality; three (1.4%) in the control group and one (0.9%) in the study group. The rates of treatment failure (ICU admission +mortality) were 5.45% and 1.8% in the control and study groups. Although there were more patients with treatment failure in the control group, the difference in the treatment failure rate between the groups was insignificant (p=0.505) (Table 1).

Discussion

According to our results, colchicine treatment with a dosage of 0.5 mg twice daily did not affect the treatment of COVID-19 patients. Although there were more patients with ICU admission and mortality in patients without colchicine treatment, there was no statistically significant difference between the two groups in terms of treatment failure.

Table 1. Baseline demographic and clinical characteristics of the groups.

		Control group (n=220)	Study group (n=110)	p
Age (year) †		64.95±15.92	59.37±14.78	0.001
Gender ‡	Male	106 (48.2)	59 (53.6)	0.350
	Female	114 (51.8)	51 (46.4)	
COVID-19 vaccine status ‡	Unvaccinated	22 (10)	2 (1.8)	0.781
	1 dose	7 (3.1)	8 (7.2)	
	2 doses	95 (43.2)	45 (41)	
	3 doses	25 (11.3)	13 (11.8)	
	4 doses	2 (1)	0 (0)	
	No information	69 (31.4)	42 (38.2)	
Comorbidity ‡		172 (78.9)	87 (79.1)	0.855
Antibiotic use ‡		175 (79.5)	102 (92.7)	0.002
Corticosteroid dosage ‡	<250 mg	192 (87.3)	82 (74.5)	0.004
	≥ 250 mg	28 (12.7)	28 (25.5)	
Intensive care unit admission ‡		9 (4.1)	1 (0.9)	0.174
Mortality ‡		3 (1.4)	1 (0.9)	1.000
Treatment failure ‡		12 (5.45)	2(1.8)	0.505
Length of hospital stay †		7.73±3.77	8.48±5.26	0.354

†: mean standard deviation, ‡: n (%)

Table 2. Laboratory parameters of the groups.

Laboratory parameters †	Control group (n=220)	Study group (n=110)	p
White blood cell count (10^3/µL)	8.20±3.84	7.1±3.70	0.003
Hemoglobin (g/dL)	12.63±1.88	12.97±1.66	0.152
Platelet count (10^3/µL)	213.08±85.71	200.35±75.80	0.212
Neutrophil count (10^3/µL)	6.43±3.65	6.07±7.87	0.001
Lymphocyte count (10^3/µL)	1.19±0.64	1.20±0.59	0.724
Urea (mg/dL)	43.51±24.95	37.06±20.06	0.029
Creatinine (mg/dL)	1.05±0.76	1.03±0.87	0.877
Alanine aminotransferase (U/L)	28.3±29.65	28.74±32.58	0.827
Aspartate aminotransferase (U/L)	28.3±29.65	35.63+39.51	0.240
Gamma-glutamyltransferase (U/L)	55.36±114.85	45.85±57.98	0.836
Alkaline phosphatase (U/L)	93.60±73.31	74.3±38.71	0.093
C-Reactive Protein (mg/dl)	98.66±72.91	85.41±66.02	0.136
D-dimer (ng/ml)	898.1±1195.37	614.33±849.88	0.021
Ferritin (µg/L)	483.39±592.46	342.32±286.43	0.081
Creatine kinase-MB (ng/ml)	1.94±2.17	1.27±1.12	0.003
Troponin (ng/ml)	0.14±0.31	0.08+0.13	<0.001

†: mean ± standard deviation

While there are studies suggesting that colchicine is beneficial in treating COVID-19 infection by suppressing the cytokine storm, there are also studies reported to the contrary [10-13]. In a prospective open-label randomized planned GRECCO-19 study, 105 patients who were followed up in the hospital were evaluated. Clinical deterioration was observed at a lower rate in the group receiving colchicine [7]. In another multicenter, randomized, double-blind study in which 4488 patients were evaluated, hospitalization and mortality were lower in the group receiving colchicine treatment among COVID-19 patients who were followed up without hospitalization for one month [14]. Other studies show that colchicine treatment reduces mortality in patients with COVID-19 [15,16]. However, some meta-analyses and reviews about colchicine treatment for COVID-19 do not suggest a definite benefit due to the low number of randomized controlled trials [13,15]. Our study did not find a significant impact of colchicine on treatment failure. Prospective studies with a larger sample size are needed to clarify the controversy about the prognostic effect of colchicine on COVID-19 infection.

Comorbid diseases, corticosteroid use, vaccination status, hypercoagulation, and increased risk of thrombosis are other important parameters affecting the patient prognosis in cases of COVID-19 [17-19]. In addition, the incidence of primary or secondary bacterial infections in COVID-19 cases has been reported as 0-6% to 3-8% [20,21]. For this reason, the use of appropriate antibiotics is another factor that may affect the prognosis [20]. In our study, no significant difference was observed between the two groups regarding comorbid diseases and vaccination status. Considering the higher use of high-dose corticosteroids in the case group, it can be assumed that clinicians may have used colchicine treatment for patients with a more severe course. However, some of the laboratory parameters associated with a severe course on admissions, such as D-dimer, CK-MB, and troponin, were significantly higher in the control group. Such differences might be regarded as the confounder factors while evaluating the effectiveness of colchicine.

Another factor why the results of our study differ from other studies may be the lower treatment dose and shorter treatment period. In the GRECCO-19 study, the colchicine dose was planned as 1.5 mg for the first dose and 2x0.5 mg for the maintenance treatment after one hour for three weeks [7]. In the COL-COVID study, the first dose was planned at 1.5 mg in the 48 hours, and the maintenance treatment was planned as 2x0.5 mg for 28 days [9]. In the RECOVERY study, the first dose was 1 mg, and the maintenance dose was 2x0.5 mg for ten days or until discharge [22]. Unlike these studies, no loading dose was applied to the patients in our study. It was observed that treatment was given at a dose of 2x0.5 mg starting from hospitalization. Based on the current findings, standardization has not yet been established for the dose of colchicine in the treatment of COVID-19.

The major strength of our study was that it is the first comparative case-control study in our country investigating the efficiency of colchicine in COVID-19 infection.

Limitations of this study include a small sample size. The significant differences between the two arms in terms of corticosteroid use and laboratory parameters on admission might be the confounding factors that impacted the outcomes.

In conclusion, although colchicine has been one of the preferred anti-inflammatory treatments in the treatment of COVID-19, we did not prove its efficiency in the prognosis of COVID-19 infection. Our findings showed no difference in duration of hospitalization, admission to ICU, or mortality. Studies continue with large sample sizes for colchicine treatment efficacy and dose standardization to reach a clear global treatment dose standardization. New randomized controlled trials will be beneficial to conclude a definite suggestion.

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Potential value of pleth variability index in intraoperative fluid management of geriatric patients

Geriatrik hastaların intraoperatif sıvı yönetiminde pleth değişkenlik indeksinin potansiyel değeri

Meliha Orhon Ergün[1], Seniyye Ülgen Zengin[1], Beliz Bilgili[1], Tümay Umuroğlu[1]

Abstract

Aim: This study was designed to determine the effects of pleth variability index (PVI) guided monitoring on the optimal intravascular volume replacement during hip and knee arthroplasty in geriatric patients, and whether using PVI could reduce blood transfusion and vasopressor requirements.

Methods: One-hundred geriatric patients who underwent elective hip and knee arthroplasty were included, assigned to either PVI group (volume replacement was PVI guided) or to a control group (volume replacement was based on traditional methods). Sealed envelope technique was used for randomization. Perioperative hemodynamic parameters, infusion rate of crystalloids, colloids, blood/blood products, ephedrine hydrochloride requirements and perioperative urine outputs were recorded.

Results: Crystalloid infusion rate was higher (9.5 vs. 6.8 ml/kg/h, p<0.001) and ephedrine requirement was lower (2.0% vs. 38.0%, p<0.001) in group PVI. Postoperatively, the percentage of patients with high BUN, creatinine, and lactate levels were higher among controls (p<0.001). PVI group had significantly lower mean heart rate intraoperatively.

Conclusions: Our findings suggest that intraoperative fluid replacement guided by PVI monitoring provides hemodynamic stability, preserves normal levels of BUN, creatinine, and lactate, and reduces unnecessary use of vasopressor agents in elderly surgical patients.

Keywords: Geriatric, pleth variability index, anesthesia, intraoperative fluid management, renal function.

Öz

Amaç: Bu çalışma, geriyatrik hastalarda kalça ve diz artroplastisi sırasında pleth değişkenlik indeks (PVI) monitörizasyonunun optimal intravasküler volüm replasmanı üzerindeki etkilerini ve PVI kullanımının kan transfüzyonu ve vazopressör gereksinimlerini azaltıp azaltmayacağını belirlemek için tasarlanmıştır.

Yöntemler: Elektif kalça ve diz artroplastisi uygulanan 100 geriyatrik hasta, PVI grubuna (volüm replasmanı PVI rehberliğinde yapıldı) veya kontrol grubuna (geleneksel yöntemlere dayalı volüm replasmanı yapıldı) dahil edildi. Randomizasyon kapalı zarf usulu yöntemine göre yapıldı. Perioperatif hemodinamik parametreler, kristaloidlerin, kolloidlerin, kan ve kan ürünlerinin infüzyon miktarı, efedrin hidroklorür gereksinimleri ve perioperatif idrar çıkışları kaydedildi.

Bulgular: Kristalloid transfüzyonu grup PVI'da daha yüksekti (9,5'e karşı 6,8 ml/kg/saat, p<0,001) ve efedrin gereksinimi daha düşüktü (%2,0'ye karşı %38,0, p<0,001). Ameliyat sonrası BUN, kreatinin ve laktat düzeyleri yüksek olan hastaların yüzdesi kontroller arasında daha yüksekti (p<0,001). PVI grubu, intraoperatif anlamlı olarak daha düşük ortalama kalp hızına sahipti.

Sonuç: Bulgularımız, PVI monitorizasyonu ile intraoperatif sıvı replasmanının hemodinamik stabilite sağladığını, normal BUN, kreatinin ve laktat seviyelerini koruduğunu ve geriyatrik cerrahi hastalarda gereksiz vazopressör ajan kullanımını azalttığını göstermektedir.

Anahtar Kelimeler: Geriyatrik, pleth değişkenlik indeksi, anestezi, intraoperatif sıvı yönetimi, renal fonksiyonlar.
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Introduction

Aging is closely related with the progressive structural and functional deteriorations of the body systems, predisposing elderly patients to increased risk for perioperative organ decompensation [1]. Nevertheless, organ function assessment is not always easy in this age group. Inadequate compensatory responses to fluid load or dehydration as a result of the structural and functional deteriorations, are the biologic prices of the older body systems [2,3]. Therefore, this age group deserves optimal intraoperative fluid management [4].

A number of different intraoperative fluid management protocols are being utilized for achieving optimal fluid status in this setting. One of the main approaches includes goal-directed fluid therapy (GDT). The perioperative use of GDT allows the anesthesiologists to closely monitor the patient and assists in achieving the optimal risk/benefit balance, minimizing end organ deteriorations [5]. Dynamic hemodynamic indices based on respiratory variations are used to guide intraoperative GDT [6,7]. It is already accepted that these parameters are superior to static parameters in the assessment of volume responsiveness [8].

Pleth variability index (PVI) is one of the non-invasive dynamic indices allowing continuous monitoring tool [9]. This index is derived from respiratory variations in the perfusion index (PI), providing an automatically measured numerical value [10-13]. PVI monitoring is able to predict intraoperative volume status and fluid responsiveness [14-16]. PVI can also reduce postoperative complication rate as well as the length of hospital stay and mechanical ventilation, after the intermediate-risk surgical procedures [17].

The primary aim of this study was to determine the effects of pleth-guided monitoring on the optimal intravascular volume replacement during hip and knee arthroplasty in geriatric patients, helping to reduce blood transfusion and vasopressor requirements. Secondarily, perioperative blood urine nitrogen (BUN), serum creatinine and lactate levels, as well as urine output were investigated.

Material and methods

Patients

This prospective study included 100 geriatric patients with ASA physical status II-III, aged 64 years or older, who underwent elective hip or knee joint replacement surgery. The study protocol was approved by the ethics committee of Marmara University (date, 09.2019; no, 356). All patients gave written informed consent prior to study entry. The study was conducted in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki Declaration and its later amendments. The study was registered to Australian and New Zealand Clinical Trial Registry (ANZCTR) (www.anzctr.org.au) (number, ACTRN12620000419965).

Patients with severe cardiac arrhythmias and peripheral artery disease, low ejection fraction (under 30%), pulmonary or neurologic pathology, hepatic or renal dysfunctions were excluded from the study. Patients who were decided to require invasive monitoring tools such as cardiac output or intraarterial monitors were not included in the study.

Sealed envelope technique was used for randomization. Patients were assigned to either PVI group (group PVI) in which volume replacement was guided by the aid of the PVI device monitoring or to a control group (group C) in which intraoperative fluid management was done by the standard approach of the institution based on traditional methods such as measurements of blood pressure (BP), heart rate (HR) and electrocardiogram (ECG) (Fig 1) (Fig 2).

Figure 1. Pleth variability index monitor.

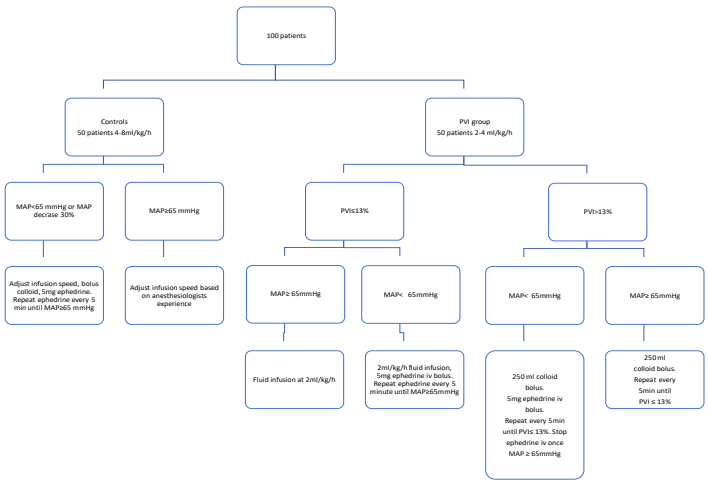

Figure 2. Intraoperative fluid management algorithm for the controls and the study group.

Study outcomes

The primary outcome was the maintenance of hemodynamic stability reducing blood transfusion and vasopressor requirements in geriatric patients in whom fluid administration was guided by the plethysmographic monitoring. Optimization of the intraoperative hemodynamic parameters, perioperative maintenance of normal levels of BUN, serum creatinine and lactate, as well as urine output were determined as the secondary outcomes.

Anesthesia management

Preoperative fasting period was strictly 8 hours in all patients. Anesthesia induction was achieved with 2 mg/kg propofol and 1μgr/kg remifentanil. Two minutes after the administration of 0.6 mg/kg rocuronium bromide the trachea was intubated, and volume-controlled ventilation was delivered. Four to 6% desflurane and 67% N2O in oxygen were used for the maintenance of anesthesia. Standard monitoring including heart rate (HR), electrocardiogram (ECG) in DII derivation, noninvasive systolic (SBP), diastolic (DBP) and mean (MAP) blood pressures, peripheral oxygen saturation (SpO2), end tidal carbon dioxide concentration, core body temperature, together with anesthetic agent analyzer to maintain a minimum alveolar concentration of 1, hourly urine output. Finger PVI (Radical 7, Masimo Pulse CO-Oximetry) monitoring was achieved in both groups, however anesthesia team was blinded to the study as well as the PVI readings in the control group. Insertion of the central venous catheter was at the discretion of the responsible anesthesiologist and the values were not taken into the account of the study. Ventilator patterns were set as follows: volume-controlled ventilation with a tidal volume of 8 ml/kg of the ideal body weight, respiratory rate and inspiratory to expiratory ratio

adjusted to restore end tidal carbon dioxide between 35-45 mmHg. SpO2 was targeted within the ranges of 96 to 100%.

Intraoperative fluid management

Individualized hemodynamic management aimed to achieve a plethysmographic variability index under 13%, and the standard management strategy aimed to maintain a mean arterial pressure above 65 mmHg during general anesthesia. MAP values under 65 mmHg or under 30% of the patient's preoperative values was defined as hypotension.

Group C

In this group, volume status of the patients was fundamentally appreciated clinically, based on hemodynamic parameters such as HR, MAP together with hourly urine output. Intraoperative fluid administration was performed with lactated ringer solution at a rate of 4-8 ml/kg/h to maintain hydration. In cases of hypotension, crystalloid solution (typically 250 mL) was administered in order to determine responses to fluid bolus. The patient is assumed to be fluid responsive if the desired level of MAP was achieved. If not, the rate of the crystalloid infusion was increased, colloid solution infusion was initiated, and ephedrine hydrochloride was applied by the recommended algorithm shown in Fig 2.

Group PVI

Fluid replacement was maintained with lactated ringer solution at 2-4 ml/kg/h, PVI measurements were used for additional requirements, targeting values lower than 13%. If PVI was higher than 13% for more than five minutes, 250 ml bolus colloid (Gelofusine®) was administered. If PVI was still higher than 13%, colloid bolus infusion was repeated until PVI was lower than 13%.

In both groups, an intravenous bolus of 5 mg ephedrine hydrochloride was given as needed to keep the mean blood pressure above 65 mmHg.

Measurements

The preoperative creatinine, BUN and lactate levels were defined as the levels obtained closest to the surgery. Postoperative values were the highest levels obtained within the 24 h after the surgery.

Hemodynamic parameters and all data in both groups were recorded by another anesthesiologist who was also blinded to the study, at 15-min intervals. In addition, pre and postoperative blood levels, perioperative use of crystalloids, colloids, blood/blood products, bleeding amounts, ephedrine hydrochloride requirements and perioperative urine outputs were recorded and compared statistically.

Statistical Analysis

For data analysis, SPSS (Statistical Package for Social Sciences) version 21 software was used. The difference in crystalloid infusion rates in a previous study was used as the reference for sample size calculation [15]. Accordingly, to detect a difference of 452 ml in the amount of crystalloid infusion, with alpha = 0.05 and 0.80 power, at least a total of 68 patients had to be included (n = 34 in each group). Normality was tested using graphical methods and hypothesis tests. Between-group comparisons of continuous variables were done using student t test for independent samples or Mann-Whitney U test, depending on data distribution. Within-group comparisons of continuous variables were done using student t test for paired samples or Wilcoxon signed-rank test, where appropriate. Pearson chi-square test or Fisher's exact test was used for between-group comparison of categorical variables. Two-way ANOVA test for repeated measurements was used to examine the differences between groups in terms of change in intraoperative variables over time. Comparison of groups at different time points was done with Mann-Whitney U test. Two-sided p values <0.05 were considered indication of statistical significance.

Results

Patients

Demographic characteristics and perioperative parameters were shown in Table 1. Patients in group PVI were older than the controls in a statistically significant manner (p=0.011), but we assumed that its clinical value was negligible. Sex distribution and weight between groups were similar.

Perioperative parameters

Intraoperatively, the rate of crystalloid infusion was higher (9.5 versus 6.8 ml/kg/h, p<0.001) and ephedrine hydrochloride requirement was lower (2.0% versus 38.0%, p<0.001) in group PVI, compared to group C (Table 1). In the preoperative period; BUN, creatinine, and lactate levels were higher in group PVI than group C, staying in normal clinical values. In the postoperative period, although all of the three parameters decreased significantly in group PVI; they increased significantly in group C, when compared to the preoperative values (p<0.001) (Table 2). Postoperatively, the percentage of the highest BUN, creatinine, and lactate levels were more common in group C (p<0.001, p<0.001, and p=0.002, respectively) (Table 1).

There was no difference between groups regarding intraoperative bleeding amount, colloid infusions requirement, erythrocyte suspension requirement, and intra and postoperative hourly urine output.

Figure 3 shows intraoperative changes in HR, MAP, PVI, and PI. The two groups differed in terms of changes in HR (p<0.001) and PVI (p<0.001), but not in terms of MAP (p=0.157) and PI (p=0.138). Group PVI had significantly lower HR and PVI values (p<0.05) except the preoperative values when compared to group C.

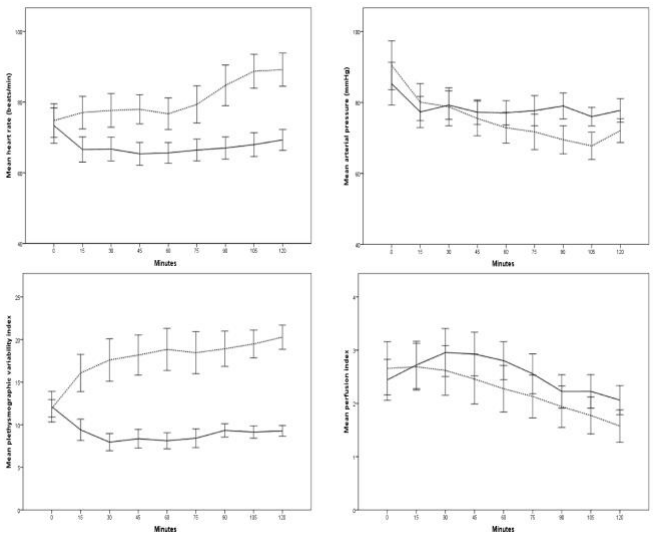

Figure 3. Changes in mean heart rate, arterial pressure, plethysmographic variability index, and perfusion index over time during the operation. Error bars indicate 95% confidence intervals. Straight lines and dotted lines indicate PIV group and controls, respectively.

Table 1. Demographic data.

	All patients (n=100)	PVI group (n=50)	Controls (n=50)	P
Demographics				
Age, years	71.9±6.7	70.3±6.3	73.5±6.8	0.011
Sex, M/F	48/52	25/25	23/27	0.689
Weight, kg	75.3±15.8	78.3±17.4	72.3±13.5	0.099
Intraoperative parameters				
Bleeding, ml	365.7±412.1	337.2±400.1	394.2±425.9	0.184
Crystalloid infusion rate, ml/kg/h	8.2±3.4	9.5±3.9	6.8±2.0	<0.001
Colloid requirement, n (%)	39 (39.0%)	23 (46.0%)	16 (32.0%)	0.151
Ephedrine requirement, n (%)	20 (20.0%)	1 (2.0%)	19 (38.0%)	<0.001
Erythrocyte suspension requirement, (Units)	0.3±0.8	0.2±0.7	0.4±0.9	0.109
Intraoperative urine output, ml/kg/h	1.7±1.1	1.6±1.1	1.8±1.1	0.292
Postoperative parameters				
Postoperative urine output, ml/kg/h	0.6±0.3	0.8±0.3	0.3±0.1	0.292
High BUN, (>23 mg/dL)	22 (22.0%)	3 (6.0%)	19 (38.0%)	<0.001
High creatinine (>1.2 mg/dL)	27 (27.0%)	1 (2.0%)	26 (52.0%)	<0.001
High lactate (>2 mmol/L)	12 (12.0%)	1 (2.0%)	11 (22.0%)	0.002

PVI, plethysmographic variability index; M, male; F, female; BUN, blood urine nitrogen. Unless otherwise stated, data presents as mean ± standard deviation.

Table 2. Changes in BUN, creatinine, and lactate levels compared to baseline.

Parameter	Timing	PVI group (n=50)	Controls (n=50)	p*
BUN, mg/dL	Preoperative	18.8±5.4	14.0±4.4	<0.001
	Postoperative	15.8±4.8	22.0±6.0	<0.001
	Difference	-3.0±4.3	8.0±5.3	<0.001
	p†	<0.001	<0.001	
Creatinine, mg/dl	Preoperative	0.9±0.2	0.7±0.2	<0.001
	Postoperative	0.8±0.3	1.2±0.3	<0.001
	Difference	-0.1±0.1	0.5±0.3	<0.001
	p†	0.004	<0.001	
Lactate, mmol/L	Preoperative	1.2±0.7	0.9±0.3	0.049
	Postoperative	1.0±0.4	1.8±0.6	<0.001
	Difference	-0.2±0.5	0.9±0.6	<0.001
	p†	0.002	<0.001	

Data presented as mean±standard deviation. * for between-group difference. † for within-group difference, postoperative versus preoperative.

Discussion

The principal finding of this study is that PVI monitoring offers a great advantage over other methods based on static parameters, in the perioperative fluid management of the elderly patients undergoing hip and knee joint replacement. The advantages include optimal volume administration with better hemodynamic stability, reduction in the use of vasopressor agents and preservation of BUN, blood creatinine and lactate levels in normal ranges.

PVI is one of the noninvasive methods in the management of fluid administration during surgery, and studies investigating its advantages are usually focused on the postoperative complications and hospital length of stay, presenting contradictory results [17]. To the best of our knowledge, no previous study has investigated the effectiveness of PVI monitoring on the intraoperative fluid management of the geriatric surgical patients. Noninvasiveness and continuity are two main attractive features of PVI monitoring offering great advantages for the vulnerable geriatric patient. Indeed, we found that PVI guided intraoperative fluid management was associated with administration of higher volumes of crystalloid solutions (9.5 versus 6.8 ml/kg/h, respectively), together with significant reductions in the administration of bolus doses of vasopressors (ephedrine hydrochloride in our study), compared to the conventional fluid therapy. This finding emphasizes the recognition of the fine line between the risk of excessive volume load or vasopressor administration in geriatric surgical patients. During hypotensive episodes of the geriatric surgical patients, the fear of administering excessive volume results in the use of excessive and unnecessary vasopressor agent, without evaluating the volume status of the patient.

In fact, many patients receive vasopressors either as intermittent boluses or infusions to counteract intraoperative hypotension not responding to fluid administration. This approach is related to the GDT algorithm in which the use of vasopressors is reasonable only when the preload is adequate [18]. It is evident that when the patient is volume under resuscitated, the end organ perfusion gets worse. This negative effect is correlated with the drug exposure time, and in our study, it is not reasonable to blame ephedrine hydrochloride for the adverse clinical conditions of the patients. Vasopressors exert their effects by elevating cardiac contractility, vascular tonus, and heart rate. The incidence of vasopressor use during surgery was investigated in other studies [8]. Although these studies were not restricted to the geriatric patients, they concluded that fluid administration guided by PVI monitoring reduced the requirement of vasopressors as a result of the recognition of intravascular volume status. The underlying physical status of the elderly is not always stabile. Therefore, the major question is that whether vasopressor administration during surgery is safe or not in volume depleted elderly patients. In fact, geriatric patients experiencing intraoperative hypotension, vasopressor use was shown to be related with postoperative hypertension, together with delirium [19]. Vasopressor use has been reported to be associated with reduced cerebral oxygen saturation that may lead to postoperative cognitive impairment [20,21]. Therefore, the patient's MAP should be high enough to prevent hypotension; but it should be kept in mind that extremely high MAP levels may lead to arrythmias, increased cardiac demand and impaired tissue perfusion. Therefore, vasopressors should only be administered after the optimization of the volume status of the geriatric patients, emphasizing the importance of PVI guided monitoring during hypotensive episodes.

Geriatric patients may already be hypovolemic intraoperatively due to prolonged perioperative fasting times and reluctance in administering fluids, potentially leading to perioperative poor organ perfusion [22]. Hypotension lasting more than 15 minutes is known to be associated with myocardial and renal injury [23]. In elderly, changes in heart rate do not always reflect changes in volume status, probably due to the blunted compensatory responses to hypovolemia. Furthermore, intraoperative tachycardia may not be manifested in response to hypovolemia due to the widespread use of beta blockers in geriatric patients [24]. In our study, beta blocker use was similar

between groups, but heart rate values were significantly higher in the control group together with normotension probably due to the administration of ephedrine. High PVI values in these patients have reflected reduced intravascular volume. Intraoperative tachycardia was known to be associated with postoperative adverse outcomes in geriatric population [24]. We assumed that the clinical triad in the control group consisted of hypovolemia, unnecessary use of vasopressors and tachycardia. The disadvantage of this triad carried the risk of the reduction of adequate perfusion to the vital organs such as heart, brain, and kidneys.

In this study, standard fluid management strategy was associated with elevated postoperative BUN, blood creatinine, and lactate levels, while fluid administration based on PVI monitoring did not cause any abnormal blood levels. Similarly, in other studies performed on non-geriatric patients it was demonstrated that fluid management under PVI guidance may reduce postoperative blood lactate levels [11,25,26]. Although they were primarily focused on the effects on the duration of hospitalization, the results of Fischer et al study offered opposite results: lactate levels were similar between PVI-guided and routine fluid management groups. Fluid loading was more frequently performed in the PVI group than in the control group, vasopressor use was similar [17]. Blood lactate level is an indirect marker of the intravascular volume status, tissue hypoxia, or organ dysfunction [27]. In our study, patients in the PVI group had high crystalloid infusion rate and low ephedrine requirements explaining preservation of normal blood lactate levels.

Preoperatively, all patients had normal BUN and blood creatinine levels. Postoperative BUN and blood creatinine levels decreased significantly in patients monitored with PVI. Contrarily, they increased in patients in whom fluid management was guided with static parameters. All patients had normal hourly urine output either in the intra and postoperative periods. Although BUN and creatinine were the known indicators of kidney function, the occurrence of postoperative renal complications may be best diagnosed by measuring glomerular filtration rate, creatinine clearance or some kidney specific markers such as Neutrophil Gelatinase-Associated Lipocalin (NGAL. Being limited to BUN and blood creatinine for the assessment of renal function was one of the major limitations of the study. Creatinine levels may be low in elderly patients due to the diminished muscle mass. Patients in the standard fluid management group had normal perioperative hourly urine output but increased BUN levels, indicating fluid deficit rather than acute kidney injury.

We did not focus on the neurologic outcomes, but none of the patients developed postoperative agitation, delirium or clinically remarkable cognitive dysfunction. The lack of intraoperative cerebral oxygen saturation monitoring and postoperative cognitive function testing stood as another limitation in the study. It was therefore not possible to say that intraoperative volume status or vasopressor use was associated with negative neurologic outcomes.

Our findings showed that PVI-guided fluid management strategy seems to offer an effective, practical, and rational approach to prevent perioperative complications associated with the administration of fluids in elderly patients undergoing hip and knee joint replacement.

In conclusion, we suggested that intraoperative fluid replacement guided by PVI monitoring provided hemodynamic stability, preserved normal levels of BUN, creatinine and lactate blood concentrations reducing unnecessary use of vasopressor agents in elderly surgical patients. We believe that these findings deserve further prospective evaluations to emphasize the effectivity and necessity of the PVI monitoring as part of GDT.

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DOI: 10.25000/acem.1050566 Olgu Sunumu / Case Report

AA amyloidosis presented with ileus by forming a mass in the small intestine: A case report

İnce bağırsakta kitle oluşturarak ileus ile kendini gösteren AA amiloidoz: Bir olgu sunumu

Meryem İlkay Eren Karanis [1], Ramazan Saygın Kerimoğlu [2], İlknur Küçükosmanoğlu [1], Nermin Keni Beğendi [3]

Abstract

Intestinal amyloidosis frequently encountered as a part of systemic amyloidosis, but rarely can be confined in the gastrointestinal tract. A 54-year-old male presented with the complaint of gas and stool discharge. Urgently segmental bowel resection was performed for ileus. Macroscopically nodular lesions, the largest at 7x3x0.7 cm in size were observed in the intestinal lumen. Microscopically; the accumulation of dense eosinophilic material that formed a mass in the submucosal area was noted. This material was positive with Crystal Violet, Congo Red and Amyloid A. Kappa and Lambda were negative. No monoclonal gammopathy, increase in serum amyloid A levels, chronic inflammatory disease, infectious disease or malignancy was determined. The case was evaluated as "intestinal AA amyloidosis". While AA amyloidosis was existent in our case, it comprised a mass lesion and caused intestinal obstruction. It is also exraordinary for AA amyloidosis to be confined in gastrointestinal tract.

Keywords: amyloidosis; intestinal amyloidosis; ileus; small intestine; intestinal mass

Öz

İntestinal amiloidoza sistemik amiloidozun bir parçası olarak sıklıkla rastlanır, ancak nadiren gastrointestinal kanalda sınırlı olabilir. 54 yaşında erkek hasta gaz ve gaita çıkaramama şikayeti ile başvurdu. İleus nedeniyle acil olarak segmental bağırsak rezeksiyonu yapıldı. Makroskopik olarak bağırsak lümeninde en büyüğü 7x3x0.7 cm boyutlarında nodüler lezyonlar gözlendi. Mikroskobik olarak; submukozal alanda kitle oluşturan yoğun eozinofilik materyal birikimi kaydedildi. Bu materyal Crystal Violet, Congo Red ve Amiloid A ile pozitifti. Kappa ve Lambda negatifti. Monoklonal gamopati, serum amiloid A düzeylerinde artış, kronik inflamatuar hastalık, enfeksiyöz hastalık veya malignite saptanmadı. Olgu "intestinal AA amiloidoz" olarak değerlendirildi. Olgumuzda AA amiloidoz mevcut iken, kitle lezyonu oluşturmuş ve intestinal obstrüksiyona neden olmuştur. AA amiloidozun gastrointestinal kanalda sınırlı olması da olağan dışıdır.

Anahtar kelimeler: amiloidoz; intestinal amiloidoz; ileus; ince bağırsak; bağırsak kitlesi

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Introduction

Amyloidosis is a rare disease group that is characteristically express extracellular fibrillar protein deposition in various tissue. Although many amyloidogenic proteins have been identified to date, amyloidosis is classified into four groups. Immunoglobulin light-chain (AL) amyloidosis (primary amyloidosis) is a plasma cell disorder and the most common type of amyloidosis. Serum amyloid A (AA) amyloidosis (secondary amyloidosis) is associated with chronic inflammatory disease, infections and malignancies. ß2-microglobulin amyloidosis is associated with dialysis and is the type of amyloidosis that seen in end-stage renal disease patients. TTR (ATTR) accumulation occurs in hereditary amyloidosis and in senile systemic amyloidosis [1, 2].

Amyloidosis can be localized or systemic. Involvement of various organs may be seen in systemic amyloidosis. Cardiac, dermal, renal and peripheral neurological involvement is common [3]. Gastrointestinal tract is also frequently involved in amyloidosis and the most commonly affected gastrointestinal site is the small intestine. Although amyloidosis is rarely seen locally in the gastrointestinal tract, it is frequently encountered as a part of systemic amyloidosis [4, 5].

The presentation in amyloidosis is variable and can vary depending on the organ involved and the degree of involvement. Amyloid can accumulate in many tissues such as muscles, vessels, nerves in the intestines. AL amyloidosis is usually accumulate in the gastrointestinal tract in submucosal area, muscularis mucosa and muscularis propria. This accumulation usually cause polypoid masses and myopathy and these patients often presented with constipation, obstruction or pseudo-obstruction. On the contrary, AA amyloidosis tends to involve the lamina propria and present with ulceration, bleeding or malabsorption [6].

Here in, we present a case of AA amyloidosis presented with ileus by forming a mass in the small intestine.

Case report

A 54-year-old male presented with the complaint of gas and stool discharge. On physical examination, the abdomen was distended, bowel sounds could not be detected, and widespread abdominal tenderness was appointed. Rectal examination revealed empty rectum and no mass was detected. Computed tomography images revealed dilatation in the stomach, duodenum and jejunum, as well as air-fluid levels in the jejunum. Dilatation was not observed in the ileum and colon. The patient was urgently operated for ileus; a mass lesion that causing obstruction in the jejunum was observed. When segmental bowel resection was performed to excise the mass, it was noteworthy that there were >100 nodular lesions in the lumen of the remaining intestinal tissue. An isoperistaltic ileoileostomy anastomosis was performed side by side from the relatively solid area. In the macroscopic examination of the 13 cm long small bowel resection material; a nodular lesion, 7x3x0.7 cm in size, covered with ulcerated mucosa was observed in the intestinal lumen. In addition, a 2.5x2x1.5 cm polypoid lesion and a nodular lesion of 3x1.5x0.5 cm in size were observed (Figure 1). Microscopically; the mucosa was ulcerated, and the accumulation of dense eosinophilic material that formed a mass in the submucosal area was noted. It was observed that the same material was deposited on the vessel walls and muscularis propria. Positive staining was determined with Crystal Violet and Congo Red stains in this material (Figure 2). While Amyloid A stain was positive immunohistochemically, Kappa and Lambda light chains were negative. The case was pathologically reported as AA amyloidosis.

Subsequent esophagogastroduodenoscopic examination revealed mild edema in the antrum, nodularity and polypoid lesions in the duodenum. No pathological findings were found in colonoscopic examination. Amyloidosis was detected in the antrum and duodenum biopsies on histopathological examination, and no amyloidosis was detected in the colon. Plasma cell increase and amyloid accumulation was not detected in the bone marrow biopsy, plasma cells were observed at a rate of 5% and these cells were found to be polyclonal. No monoclonal gammopathy was detected in the serum immunelectrophoresis study. There was no increase in serum amyloid A levels. No chronic inflammatory disease, infectious disease, Crohn's disease, familial mediterranean fever or malignancy was determined. With these findings, the case was evaluated as "intestinal AA amyloidosis".

A written consent was obtained from the patient for the publication of this case report and accompanying images.

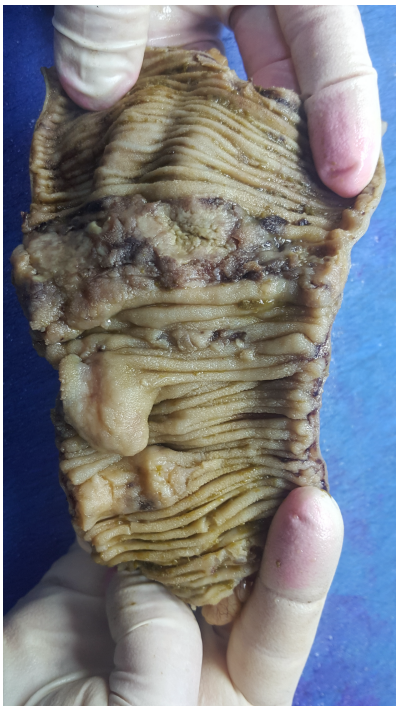

Figure 1: A nodular lesion, 7x3x0.7 cm in size, covered with ulcerated mucosa, a 2.5x2x1.5 cm polypoid lesion and a nodular lesion of 3x1.5x0.5 cm in size were observed in the small bowel lumen.

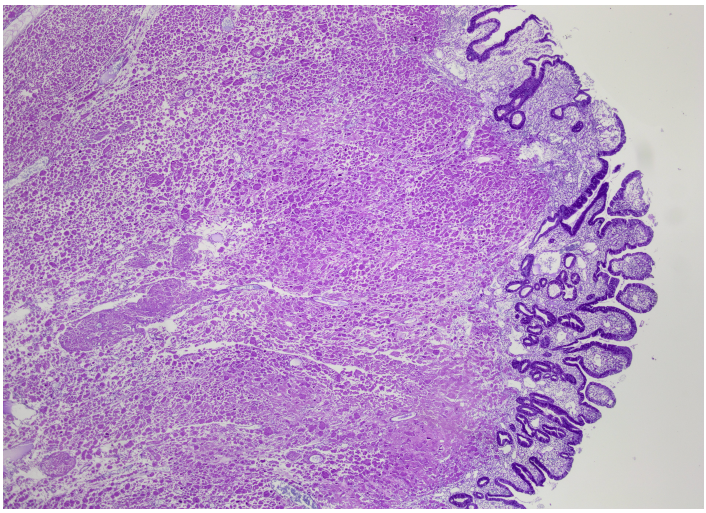

Figure 2: Accumulation of dense material that formed a mass in the submucosal area in the small bowel. Positive staining with Crystal Violet in this material. Crystal Violet x 100.

Discussion

The clinical manifestation of amyloidosis can range from asymptomatic to fatal disease. Intestinal amyloidosis can cause a wide variety of symptoms by causing both structural and functional impairment in the organ where it deposits. Symptoms are usually nonspecific and weight loss, abdominal pain, diarrhea, malabsorption, lower and upper gastrointestinal tract bleeding are common symptoms. The severity of these symptoms is related to the amount and extent of amyloid deposition [3].

Endoscopic findings are also nonspecific as well as clinical findings of intestinal amyloidosis. Erythema, granular appearance, erosion, ulceration, friability, polypoid protrusion, submucosal masses can be observed. Endoscopic findings may be normal in intestinal amyloidosis. Localized amyloidosis in the small intestine is characterized by focal amyloid deposits that form a mass and cover the entire intestinal wall. These are called amyloidomas and are seen as a polioid mass lesion or an ulcerated lesion, as in our case [7].

The diagnosis of amyloidosis is difficult and can be missed because of its rarity, nonspecific symptoms and nonspecific endoscopic findings. Although gastroenterologists and endoscopists play critical role in diagnosis of amyloidosis, histopathological demonstration is necessary for definitive diagnosis. In differentiating amyloid from other protein deposits, Congo red is the most specific stain. Crystal Violet is another histochemical stain demonstrating amyloid. Immunohistochemical Amyloid A, Lambda and Kappa stains allow us to differentiate the type of amyloidosis besides showing that the accumulation is amyloid. While amyloid A positivity indicates AA amyloidosis; Lambda or Kappa positivity supports AL amyloidosis [8].

Amyloid can accumulate in all layers and structures of the intestine and may lead to different conditions depending on the structure in which it accumulates. Deposition in the muscularis propria and myenteric plexus can lead to myopathy and neuropathy and causes atrophy, diarrhea and dysmotility. Deposition in vascular structures can lead to ischemia, infarction, ulceration and bleeding [7]. The localization and presentation of amyloid deposition in gastrointestinal tract depends on the type of amyloid. Generally in AL amyloidosis, amyloid deposition occurs in the submucosal area and in the muscularis propria; it may cause a mass lesion, present with constipation, mechanical obstruction or pseudo-obstruction. In AA amyloidosis, the accumulation is mostly seen in the lamina propria, mucosa and submucosal area in macular form and manifests with granular appearance and friability of the mucosa. AA amyloidosis often causes clinical signs of diarrhea and malabsorption [9, 10]. Although our case has AA amyloidosis; it was noteworthy that amyloid was deposited in the submucosal area, muscularis proria and vessel walls, formed a polypoid submucosal mass and presented with obstruction findings.

Treatment of AA amyloidosis is carried out by treating the underlying disease, such as autoimmune disease, infections or malignancy that causes an increase in amyloid precursors. In addition, symptomatic treatment based on alleviation of complaints may be useful in amyloidosis. Cases with malabsorption can be suplemented by nutritonsand vitamins. Surgical treatment can be applied in cases with bleeding or obstruction. Since we did not determine an underlying disease and didn't detect an increase in serum amyloid A level in our case, our patient did not receive additional treatment after surgery.

Although amyloid accumulation is common in the gastrointestinal tract as a part of systemic amyloidosis, it is rare for amyloidosis to be confined in the gastrointestinal tract [11]. Amyloidosis is a chronic disease and rarely requires immediate surgical treatment.

It is interesting that while AA amyloidosis was existent in our case, it comprised a mass lesion, caused intestinal obstruction, and required urgent surgical treatment. It is also exraordinary for AA amyloidosis to be confined in the gastrointestinal tract.

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