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Araştırma Makalesi – Research Paper

CLINICAL FEATURES OF OUR PATIENTS WITH SPONTANEOUS INTRAMURAL INTESTINAL HEMATOMA AND THE USE OF DIRECT ORAL ANTICOAGULANTS IN THE MAINTENANCE THERAPY

SPONTAN İNTRAMURAL İNTESTİNAL HEMATOMLU HASTALARIMIZIN KLİNİK ÖZELLİKLERİ VE İDAME TEDAVİSİNDE DİREKT ORAL ANTİKOAGULANLARIN KULLANIMI

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Özet

Spontan intramural intestinal hematomlar (SIIH), antikoagulan tedavi alan hastalarda nadir görülen bir komplikasyondur ve genellikle warfarin kullanımına sekonder olarak ortaya çıkar. Çalışmamızda, SIIH olgularının klinik karakteristikleri ve tedavi yaklaşımları incelenecektir. Ayrıca çalışmamız, literatürde ilk kez idame tedavisi olarak warfarin yerine direkt oral antikoagulan (DOAC)'lara çevrilmiş SIIH hastalarının uzun dönem takiplerini de paylaşacaktır. 2015-2020 yıllarında warfarin kullanımına bağlı SIIH tanısıyla yatan 21 hastanın verisi retrospektif olarak incelendi. Çalışmaya alınan hastaların yaş ortalaması 67.6±12.0 (range: 45-90) olup, 9'u kadın 12'si erkek idi. Hastaların tümü çeşitli hastalıklar için warfarin kullanmakta idi. En sık başvuru yakınması karın ağrısı iken, tüm hastaların fizik muayenesinde karında hassasiyet saptandı. Hastaların hepsinde başvuru anında INR değeri terapotik değerlerin üstünde olup, 14 hastada anemi saptanmıştır. Abdomen bilgisayarlı tomografi (BT) hastaların hepsinde SIIH tanısı koymada yardımcı olmuştur. 18 hasta konservatif olarak tedavi edilirken, 3 hastaya operasyon uygulandı. Opere edilen hastalardan birinde postoperatif pulmoner emboli gelişimine bağlı mortalite gelişmiştir. 7 (35%) hastanın taburculuk sonrası tedavisine warfarin ile devam edilmiş iken, 13 (65%) hastanın tedavisi DOAC ilaçlar ile değiştirilmiştir. Warfarin kullanan hastaların takip süresi ortalama 22.1±18.2 ay (range: 8-61) iken, DOAC kullanan hastalarınki 26.4±19.3 (range: 6-55) aydır. Takipte her iki grupta da SIIH nüksü görülmedi. Oral antikoagulan kullanan ve özellikle de INR değerleri (seviyeleri) yükselmiş karın ağrılı hastalarda, SIIH ayırıcı tanılar arasında düşünülmelidir. SIIH'lerin tedavisinde öncelikle medikal tedavi seçenekleri denenmeli ancak hemodinamisi bozulan, akut karın bulguları olan ya da ayırıcı tanısı yapılamayan hastalarda ise operasyondan kaçınılmamalıdır. Ayrıca seçilmiş hasta gruplarında SIIH sonrası idame tedavisinde DOAC ilaçlar warfarin'e bir alternatif olarak düşünülebilir.

Anahtar Kelimeler: Antikoagulan, direkt oral antikoagulan, ince bağırsak

Abstract

Spontaneous intramural intestinal hematoma (SIIH) is a rare complication in patients receiving anticoagulant therapy and usually occurs secondary to warfarin use. In our study, the clinical characteristics and treatment approaches of SIIH cases will be examined. In addition, our study will share the long-term follow-up's of SIIH patients who have been shifted to direct oral anticoagulants (DOACs) instead of warfarin as a maintenance treatment for the first time in the literature. The data of 21 patients with a diagnosis of SIIH associated with warfarin use between 2015 and 2020 were retrospectively analyzed. The average age of the patients included in the study was 67.6 ± 12.0 (range: 45-90), 9 of them were female and 12 were male. All of the patients were using warfarin for various diseases. While the most common complaint was abdominal pain, in the physical examination of all patients, abdominal tenderness was detected. In all patients, the INR value was above the therapeutic values at the time of arrival at hospital, and 14 patients had anemia. Abdominal computed tomography (CT) helped diagnose SIIH in all patients. While 18 patients were treated conservatively, 3 patients were operated. One of the operated patients died due to the postoperative pulmonary embolism. While 7 (35%) patients continued with warfarin after discharge, 13 (65%) patients were replaced with DOAC medications. While the mean follow-up period of patients using warfarin is 22.1 ± 18.2 months (range: 8-61), those using DOAC is 26.4 ± 19.3 (range: 6-55) months. During follow-up, no recurrence of SIIH was observed in either group. In patients using oral anticoagulants, and especially with abdominal pain and elevated INR values, SIIH should be considered among the differential diagnoses. In the treatment of SIIH, firstly, medical treatment options should be tried, but the operation should not be avoided in patients with hemodynamic impairment, acute abdominal findings, or patients who cannot be diagnosed differentially. In addition, DOAC drugs may be considered as an alternative to warfarin in maintenance therapy after SIIH in selected patient groups.

Keywords: Anticoagulant, direct oral anticoagulant drug, small intestine

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1. INTRODUCTION

Today, anticoagulant drugs are frequently used for the treatment or prevention of cardiovascular diseases. While these drugs reduce thromboembolic risks by reducing the tendency of blood to clot, they can also cause bleeding due to these effects (Mekaj YH et al., 2015, p.967, Millogo GRC et al., 2018, p.1). Oral anticoagulant (OAC) drugs cause bleeding in 5-48% of patients, especially in connection with long usage times, and approximately 2-4% of these bleeding occur in the gastrointestinal system (GIS) (Levine MN et al., 2004, p. 287). Spontaneous intramural intestinal hematoma (SIIH) is a rare complication in patients receiving anticoagulant and / or antiplatelet therapy, and its annual incidence has been calculated to be 0.003% (Kang EA et al., 2019, p.135). Since SIIH can be seen anywhere in the GIS from duodenum to the rectum (Kang EA et al., 2019, p.135, Yu WH et al., 2018, p.1, Vecchio R et al., 2019, p.16), the patient's clinic may vary depending on where the hematoma has developed and the degree of complication hematoma caused. Although the most common finding in SIIH is abdominal pain, this finding is non-specific for SIIH. In addition, the fact that SIIH is very rarely seen and its clinic is variable, causes difficulties in the differential diagnosis of abdominal pain etiology and may cause unnecessary laparatomies (Costa BP et al., 2000, p.151). However, when this disease is recognized early, it usually responds to medical treatment without the need for surgery.

SIIHs occur most frequently due to the use of warfarin, a vitamin K antagonist (Kang EA et al., 2019, p.135). While only vitamin K antagonists (VKAs) have been used as oral anticoagulants for a long time in the treatment and prevention of cardiovascular diseases (Gómez-Outes A et al., 2012, p.83), new direct acting OAC drugs (DOAC) have been used in the treatment and / or prevention of various diseases in the last ten years. Compared to VKAs, DOACs show more predictable anticoagulant responses and make fewer bleeding complications (Mekaj YH et al., 2015, p.967, Baker CL et al., 2019, p.1, Cowell RP, 2014, p.529, Steffel J et al., 2018, p.1330). In addition, they are as effective as VKAs in the prevention and treatment of venous tromboembolism and in the prevention of stroke and systemic embolism (Mekaj YH et al., 2015, p.967). However, despite all these advantages, these drugs also have bleeding enhancing effects. However, in a review by Kang et al., it was reported that DOAC was not used in any of the SIIH cases presented in the literature (Kang EA et al., 2019, p.135). In addition, there is not enough information in the literature about changing the treatment of these patients from VKAs to DOAC treatment (Mekaj YH et al., p. 2015, p.967, Acar N et al., 2019, p.653, Demirli Atıcı S et al., 2019, p.295, Kones O et al., 2013, p.58, Tseng CY., 2010, p.937, Yoldas et al., 2013, p.72), and only in the study of Kang et al (Kang EA et al., 2019, p.135), it was stated that the treatment of two patients was replaced with DOAC.

In our study, the clinical characteristics and treatment approaches of SIIH cases will be examined. In addition, for the first time in the literature, our study will share the long-term follow-up of SIIH patients, whose maintenance therapy has been shifted to DOACs instead of

warfarin. According to the results of our study, DOAC drugs can be considered as an alternative to warfarin in the maintenance treatment of patients with SIIH.

2. MATERIAL AND METHOD

The data of the patients hospitalized in the general surgery clinic of University of Health Sciences İzmir Tepecik Training and Research Hospital with SIIH due to warfarin use in from January 2015 to January 2020 were retrospectively extracted from their files. 21 patients were included in the study. The patients were examined in terms of age, sex, comorbidity, symptoms and findings on arrival at hospital, laboratory and imaging results, treatment approaches and length of hospital stay. In addition, complications and follow-up periods of patients due to the use of warfarin or DOAC (apixaban, edoxaban, rivaroxaban and dabigatran) after discharge were recorded.

All patients were treated by hospitalization. OAC use and enteral intake were stopped during hospitalization. High INR levels were tried to be reduced by giving fresh-frozen plasma (FFP) and vitamin K to all patients. Red blood cell (RBC) transfusion was performed in patients with low hemoglobin values, major bleeding or symptomatic anemia and patients to be operated. Hemoglobin and INR levels were measured daily. When INR values regressed to therapeutic values, low molecular weight heparin was initiated to the patients. Prophylactic antibiotics were not given to nonoperated patients due to SIIH.

Surgical treatment option was applied to patients with acute abdominal findings, heavy prolonged bleeding or differential diagnosis difficulties. Diagnostic laparotomy was applied to these patients and they were treated according to the findings in the operation. The operated patients were taken to the postoperative intensive care unit and taken to the clinic after hemodynamic stabilization. Nasogastric tubes of the patients were taken in the early period. For oral intake, early feeding was provided without waiting for the gas and stool output, and low-rate enteral solutions were given to the patients whose intubation continued. Preoperative single dose prophylactic antibiotics were applied to the patients who had surgery. During the surgery, whenever a contaminated or dirty wound was encountered, or if the patient had additional foci of infection, the treatment was followed with appropriate antibiotics.

Patients whose treatment was completed and discharged due to SIIH were evaluated by the branches dealing with primary disease in terms of continued use of OAC (eg, patients with atrial fibrillation or coronary artery were evaluated by cardiology, those with cerebrovascular disease by neurology). Provision of appropriate therapeutic drug levels was followed up by the physicians providing OAC treatment in the outpatient clinic settings. The patients were followed up at short intervals (every 2-3 months) at first, and then annually in the general surgical outpatient clinic due to the risk of complications and relapse related to SIIH. Approval from the institutional research ethics board was obtained (decision number 2020/8-7). For the analysis SPSS V.17 software was used. Mean ± standard deviation and percentage and frequency values are reported for the variables.

Ethical Statement

Ethics committee approval was received for this study from the Ethics Committee of University of Health Sciences Tepecik Training and Research Hospital. (Decision number: 2020/8-7)

3. RESULTS

The average age of the patients included in the study was 67.6 ± 12.0 (range: 45-90), 9 were female and 12 were male. Nineteen patients were referred to us from the emergency department and 2 patients from other services for consultation. The most common complaint of patients was abdominal pain (n = 21). In addition, 1 patient had upper and 2 patients had lower gastrointestinal (GI) bleeding and 2 patients had bowel obstruction. While tenderness was found in the abdominal examination of all patients, only 4 patients were found to have a localized tenderness to a single quadrant (patients' complaints at the time of arrival at hospital and examination findings were summarized in table 1). Patients were using warfarin for various cardiological, cerebrovascular or hematological diseases. The most common indications for use of OAC were coronary artery disease and atrial fibrillation (AF) (Table 2).

Table-1. Patients' complaints at the time of arrival at hospital and examination findings (n =21, 100%)

Complaints	**(n; %)**	**Signs**	**(n; %)**
Abdominal pain	21; 100	Abdominal tenderness	21; 100
Vomiting	9; 42.9	Only one quadrant tenderness	4; 19.0
Anorexia	13; 61.9	Rebound tenderness	3; 14.3
Hematemesis	1; 4.7	Abdominal distension	4; 19.0
Hematochezia	2; 9.5	Anemia	14; 66.6
Constipation	2; 9.5	Ecchymosis	0; 0

Table-2. Indications for Warfarin Sodium in all patients (n = 21, 100%)

Indications	**n; %**
CHD	12; 52.2
AF	8; 34.8
CVA	2; 8.7
Hematological disease	2; 8.7
DVT	2; 8.7
Cardiac valve replacement	2; 8.7
Pulmonary embolism	1; 4.3

CHD, Coronary heart disease; AF, atrial fibrilation; CVA; Cerebrovascular accident; DVT, deep venous thrombosis.

International normalized ratio (INR) levels of all patients were above the therapeutic values, and the mean was 10.1 ± 2.3 (range: 6.3-14.3). Anemia was detected in 14 patients and the mean of hemoglobin (Hg) values was 11.7 ± 2.0 (range: 6.45-15.4) mg / dl. Laboratory parameters of the patients are summarized in Table 3. The patients were given an average of 2.6 ± 1.0 units of fresh frozen plasma (FFP) (range: 2-5) and 0.5 ± 0.8 units of RBC. INR regressed to the therapeutic level in an average of 2.3 ± 1.4 days.

Table 3; Patients' clinical laboratory parameters

Patient No.	Age	Sex	WBC	Hb	Htc	Platelet	INR	BUN	Creatinin
1	70	F	9.300	12.2	37.3	212.000	12.3	25.6	0.8
2	58	M	14.800	13	40.3	168.000	7.22	21.9	0.9
3	69	M	10.200	10.3	41.7	220.000	13.6	40.6	1
4	50	F	8.800	13.9	40	294.000	8.18	10.2	0.6
5	80	F	15.400	9.6	28.5	266.000	6.88	36.9	1.6
6	70	F	9.700	10.4	31	234.000	10.86	22.9	1.2
7	57	M	20.400	15.4	46.4	234.000	10.62	11.6	0.7
8	45	M	10.800	14.4	43.5	290.000	11.35	9.3	0.9
9	75	M	14.700	11.1	32.8	285.000	14.33	36	1.2
10	80	M	11.900	12.5	37.1	235.000	6.36	17.7	1.1
11	79	M	12.600	10.9	33.7	207.000	12.83	63.5	3.7
12	68	M	12.900	15.1	44.3	241.000	10.99	42.0	1.6
13	51	F	16.000	11.1	34.8	365.000	10.49	44.8	1.4
14	84	M	9.700	10.9	33.4	244.000	10.54	31.7	1.7
15	73	M	12.100	14.1	42.5	219.000	8.72	15.8	1.1
16	52	M	11.400	10.4	31.6	217.000	11.7	31.7	1.2
17	62	M	28.600	6.45	20	205.000	10.3	61.2	3.9
18	69	F	12.400	12.8	39.4	309.000	9.6	18.7	1
19	66	F	17.700	11.7	33.4	265.000	11.97	16.3	1.1
20	90	F	12.700	10.4	31.9	317.000	12.23	27.1	0.7
21	72	F	10.500	11.1	32	214.000	6.5	14.5	0.8

Table-4. Findings on ultrasound and computerized tomography screening of patients with spontaneous intramural hematomas of the gastrointestinal tract

Imaging modality	Finding	No. (%)
Plain abdominal radyography	Not performed	17 (81)
	No pathology detected	5 (23.8)
Ultrasound	Not performed	5 (23.8)
	No pathology detected	7 (33.3)
	Intra-abdominal minimal fluid	3 (14.3)
	Intra-abdominal severe fluid	2 (9.5)
	Wall thickening	7 (33.3)
Computerized tomography	Intra-abdominal minimal fluid	6 (23.8)
	Intra-abdominal severe fluid	2 (9.5)
	Wall thickening (with location)	
	Jejenum	10 (47.6)
	Ileum	10 (47.6)
	Sigmoid colon	1 (4.7)

While all patients underwent abdominal computed tomography (CT) examination, 16 (76.2%) patients underwent abdominal ultrasound (US). Abdomen X-Ray was performed in 5 (19%) patients, but no specific finding was found in any of them. For the 7 (43.7%) of 16 patients who had undergone ultrasound, the examination was normal, and 7 patients had intestinal wall thickening, 1 patient had intestinal mesentery inflammation and 5 patients had intra-abdominal fluid. CT examination revealed intestinal wall thickening (n = 21) in one or more segments in all patients, and intra-abdominal fluid in 8 patients. Two patients with diffuse fluid were operated. The patients underwent bowel resection and anastamosis. Due to an enlarged hematoma in the anastomosis of a patient who underwent resection and intestinal resection due to ileal hematoma, anastomosis was disrupted and the area with hematoma was excised, and anastomosis was repeated after careful hemostasis.

While the mean hospitalization time of patients were 7.3 ± 3.6 days (range: 3-17), the average length of hospitalization of the 9 patients that had to be followed in the intensive care unit were 3.9 ± 2.2 days (range: 2-8). Mortality developed in one of the patients due to post-operative pulmonary embolism. While treatment of 7 (35%) patients was continued with warfarin, treatment of 13 (65%) patients was replaced with DOAC drugs (apixaban, edoxaban, rivaroxaban and dabigatran). The mean follow-up period of patients using warfarin were 22.1 ± 18.2 months (range: 8-61), while patients using DOAC were 26.4 ± 19.3 (range: 6-55) months. No recurrence of SIIH was observed in either group at follow-up.

4. DISCUSSION

This study retrospectively examined the clinical features and prognosis of 21 patients with SIIH who were treated in a tertiary reference hospital. As far as we can see in the literature, our study is the first in which post-discharge maintenance therapy is performed by using new generation OACs and long-term follow-up is given in patients who developed SIIH due to warfarin use.

Although SIIHs can be seen in diseases that cause bleeding diathesis, leukemia, pancreatic diseases, liver failure, and autoimmune diseases such as lupus, the main reason in the etiology is the use of OAC drugs (Kang EA et al., 2019, p.135). Among OAC drugs, Warfarin causes SIIH complications most frequently (Kang EA et al., 2019, p.135, Acar N et al., 2019, p.653, Yoldas T et al., 2013, p.72). Warfarin is often used in the prevention or treatment of cardiovascular diseases. All of the patients in our study had at least one cardiovascular disease and all had been using warfarin during the development of SIIH. When the literature is analyzed, it is seen that the mean age of the patients who developed SIIH was determined at an advanced age in accordance with our study (Kang EA et al., 2019, p.135, Acar N et al., 2019, p.653, Tseng CY et al., 2010, p.937). On arrival at hospital, the most common complaint of patients with SIIH is abdominal pain, as in our study. Since SIIHs occur frequently in the small intestine, the localization of pain may vary depending on the segment of the intestine (Yu W-H et al., 2018, p.1). It can be said that the abdominal pain of the patients in our study is not generally localized to a certain area and therefore there is no characteristic abdominal pain pattern specific to SIIH. Also, if hematoma obstruction causes necrosis or perforation, ileus or hollow organ perforations are considered at the forefront in the differential diagnosis of abdominal pain, which leads to difficulty in differential diagnosis. Therefore, SIIH should be considered in differential diagnoses in every patient who uses OAC and especially with increased INR values.

When the laboratory tests were examined, it was found that the INR values of all patients were well above the therapeutic values. Anemia was detected in 14 patients, and a total of 7 patients were given RBC upon the suggestion of symptomatic anemia or preoperative anesthesia. Although 2 patients' urea and creatinine values were found to be very high, it decreased to normal values after appropriate fluid treatment. Although two of our patients had mitral valve replacement (MVR), FFP and vitamin K were given to all our patients in order to

lower their INR values. The American College of Cardiology / American Heart Association (ACC / AHA) guidelines do not routinely recommend the use of high doses of vitamin K in patients with MVR, as it can cause valve thrombosis and thromboembolism. However, it is said that FFP can be used with low-dose vitamin K for bleeding control (Panduranga P et al., 2012, p.54). In our study, two patients with MVR without active bleeding were given vitamin K in the emergency room. Although a thromboembolic event has not developed in these two patients, it is necessary to avoid high-dose vitamin K replacement in patients with MVR.

Coagulation factor concentrate was given to a patient with an INR value> 10 in the emergency department, and then treatment of this patient was continued with FFP and vitamin K. Concentrated coagulation factors II, VII, IX and X are included in this drug, and it corrects INR levels faster than FFP (Saccullo G et al., 2017, p.277). However, studies have shown that this drug is superior to FFP only if it is administered in the early period of life-threatening bleeding conditions, and no significant relationship between INR reduction and clinical improvement has been found.

Although imaging methods such as abdomen X-Ray, US or CT are used in the evaluation of abdominal pain (Acar N et al., 2019, p.653, Demirli Atıcı S et al., 2019, p.295), it is not recommended for routine use since abdomen X-Ray has low sensitivity in showing common causes of abdominal pain (Ahn SH et al., 2002, p.159). For this reason, we have not requested routine abdomen X-Ray for a long time in our routine practice. Therefore, only 5 (81%) of our SIIH patients were asked for abdomen X-Ray, but no specific finding was found in any of them. While US determines the intramural intestinal hematoma findings with 71.4% sensitivity, this rate reaches 80% in CT, and when two images are used together, it can be diagnostic at up to 100% (Polat C et al., 2003, p.208). In our study, approximately one-third of US patients had no pathology, whereas in the remaining patients, wall thickening and / or free fluid was detected in the intestines.

CT is accepted as the gold standard in diagnosing SIIH (Acar N et al., 2019, p.653). In CT, intestinal wall thickening was observed in all our patients, minimal free liquid in 6 patients, and widespread free liquid in 2 patients. If patients with a diagnosis of SIIH are considered, if the hemodynamic status is stable and acute abdominal signs are absent, medical treatment should be tried first. In our study, 3 patients were operated on because they showed signs of acute abdomen. Segmental resection and anastomosis were performed in 2 patients with jejunal hematoma, and anterior resection and anastamosis were performed on the patient with hematoma in the sigmoid colon. In one of our patients who underwent resection due to jejunal hematoma, it was observed that an enlarged hematoma was formed in the suture line while anastamosis was performed. The anastomosis was disrupted, and after the area of hematoma was excised, a careful hemostasis was achieved and the anastomosis was renewed. This complication may be caused by the tendency to bleeding in operations performed under emergency conditions, because INR does not fall to the desired level, as well as due to technical

errors. For this reason, the surgeon performing the operation should be alert for hematomas and bleeding that may occur after resection.

An important part of SIIH cases related to the use of anticoagulants in the literature is due to warfarin. Warfarin is a vitamin K antagonist, due to its narrow therapeutic range, drug levels should be monitored, and caution should be exercised in their interactions with drugs and foods containing potassium. Non vitamin K antagonists, also known as DOACs, perform their effects directly through factor Xa (apixaban, edoxaban, and rivaroxaban) or thrombin (dabigatran). The main use of DOACs is to reduce the risk of stroke due to nonvalvular atrial fibrillation (NVAF). DOACs are more effective and safe compared to VKAs and do not require follow-up by routine laboratory testing, they have less food and drug interactions and have a rapid onset and offset of action times (Steffel J et al., 2018, p.1330).

In the last decade, while a decrease is observed in the use of warfarin in reducing the risk of stroke due to nonvalvular atrial fibrillation (NVAF), an increase in the use of DOACs is observed (Brown JD et al., 2016, p.427). However, SIIH cases related to DOAC use have not been reported in the literature yet (Kang EA et al., 2019, p.135). Although DOACs have a bleeding effect like VKAs, the fact that no SIIH cases related to DOACs have been reported in the literature, may be attributed to the less use of these drugs by physicians, possibly because they know less of these drugs and have less clinical experience, (Cowell RP, 2014, p.529). In addition, although DOACs are used in knee surgery (Cowell RP, 2014, p.529) and cancer patients (Chen H et al., 2020, p.1) to prevent thromboembolic events, the main indication for DOACs is non-valvular AF patients (Steffel J et al., 2018, p.1330). Narrow indications for use of DOACs may also be one of the reasons for the low use of these drugs. When we examined the literature, only Kang et al's study indicated that 2 patients continued their treatment after SIIH with DOACs (Kang EA et al., 2019, p.135), but we could not find any other study on this subject.

In our study, warfarin was continued in 7 (35%) patients and DOAC was started in 13 (65%) patients. Among DOACs, apixaban (n = 11/13) was used most frequently. Also in the literature, apixaban has generally been the preferred DOAC in elderly patients with excessive comorbidity, high bleeding risk and stroke risk (Baker CL et al., 2019, p.1, Deitelzweig S et al., 2017, p.1745.). The mean follow-up period of patients using warfarin and patients using DOAC was 22.1 months and 26.4 months, respectively. In the follow-up, the absence of recurrence of SIIH in both groups suggests that DOACs may be an alternative to warfarin therapy. However, in our country, DOACs are only paid back by the social security institution in patients with AF. In addition, the high cost of these drugs, lack of specific antidotes, and low clinical experience are the disadvantages of DOACs compared to VKAs. In addition, DOACs are not used in severe renal and hepatic insufficiency, in patients under 18 years of age, in pregnant women, and in patients with mechanical heart valves (Mekaj YH et al., 2015, p.967, Steffel J et al., 2018, p.1330).

5. CONCLUSION

SIIH should be considered among differential diagnoses in patients on OAC medication and especially in patients with abdominal pain with increased INR values. In the treatment of SIIH, medical treatment options should be tried first, but the operation should not be avoided in patients with haemodynamic impairment, with acute abdominal findings, or in patients whom differential diagnosis can not be made. In addition, in the discharge of patients who developed SIIH, with which anticoagulant the maintenance therapy will be continued should be decided together with the physicians controlling the primary disease. Although the number of patients in our study was rather limited, our results revealed for the first time that long-term follow-ups of DOACs was similar to warfarin in terms of recurrence of SIIH. However, prospective randomized studies are required to obtain clearer data.

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