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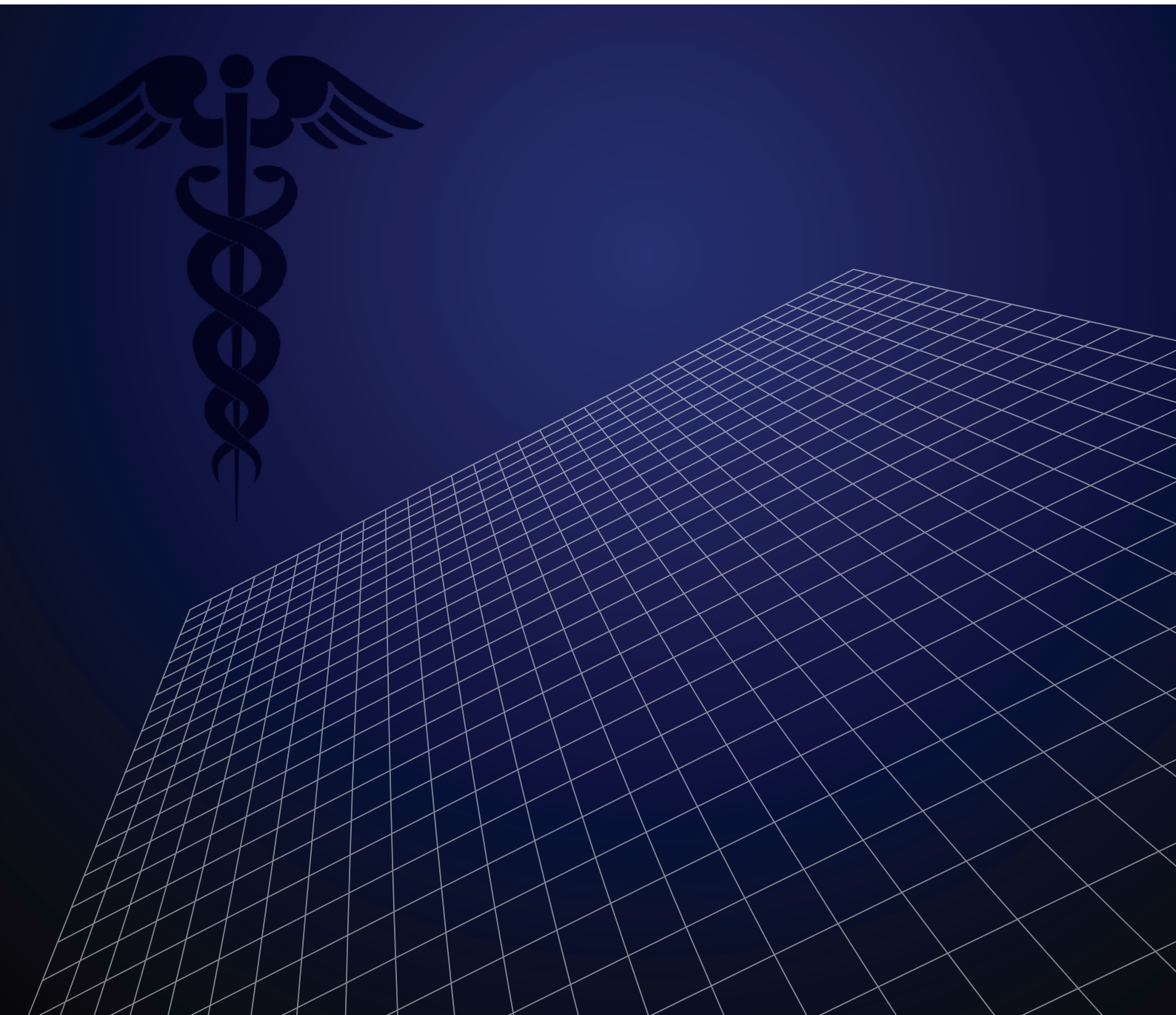

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Original Article

The effect of desmopressin and tranexamic acid on blood product use and postoperative bleeding after emergent isolated coronary artery bypass grafting (CABG) surgery

Desmopresin ve traneksamik asitin acil izole koroner arter bypass greftleme (KABG) ameliyatında kan ürünü kullanımına ve postoperatif kanama üzerine etkisi

Naim Boran TUMER[1], Atike Tekeli KUNT[2], Serdar GUNAYDIN[1], Kanat OZISIK[1], Orhan Eren GUNERTEM[3], Ali Baran BUDAK[4], Seyhan BABAROGLU[1], Onur KARAHASANOGLU[1]

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Abstract

Aim: Bleeding is a major problem in cardiac surgery, and results in a high risk of allogeneic blood transfusion associated with increased morbidity and mortality. In recent years, studies in the literature reported that desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) reduces the blood loss after surgical interventions. The aim of the present study is to analyze the effect of desmopressin and tranexamic acid on blood product use and postoperative bleeding in patients that were pretreated with P2Y12 inhibitors by cardiologists and undergone emergent coronary artery bypass grafting (CABG) surgery.

Material and Methods: The prospectively collected data of 62 adult patients who underwent emergent isolated CABG surgery and pretreated with P2Y12 inhibitors by cardiologists were retrospectively reviewed. The perioperative data of the patients included their demographic data, laboratory findings, the amount of blood loss from chest tubes, the amount of blood product use, need of re-thoracotomy, morbidity and mortality. The patient population was divided into two groups: **Group I:** Patients that received tranexamic acid and DDAVP perioperatively (n=26); and Group II: Patients that received only tranexamic acid perioperatively (n=36).

Results: The two groups of patients had similar characteristics at baseline. There was a statistically significant difference between Group I and II regarding postoperative blood loss from the chest tubes, re-thoracotomy, red blood cell and thrombocyte transfusions ($p<0.05$). No statistically significant differences were observed between the two groups in terms of fresh frozen plasma transfusion, inotropic support and mortality.

Conclusion: We suggest that desmopressin in addition to tranexamic acid reduces bleeding and the amount of blood product use in patients undergoing emergent isolated CABG surgery.

Keywords: CABG; desmopressin; tranexamic acid; blood management

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Öz

Amaç: Kanama kalp cerrahisinde önemli bir sorundur ve artan morbidite ve mortalite ile ilişkili yüksek allojenik kan transfüzyonu riskine yol açar. Son yıllarda, literatürdeki çalışmalar desmopresinin (1-deamino-8-D-arginin vazopressin, DDAVP) cerrahi müdahalelerden sonra kan kaybını azalttığını bildirmişlerdir. Bu çalışmanın amacı, kardiyologlar tarafından P2Y12 inhibitörleri ile tedavi edilen ve acil koroner arter baypas greftleme (KABG) ameliyatı geçiren hastalarda desmopressin ve traneksamik asidin kan ürünü kullanımı ve postoperatif kanama üzerindeki etkisini analiz etmektir.

Gereç ve Yöntemler: Acil izole KABG ameliyatı geçiren ve öncesinde P2Y12 inhibitörleri ile tedavi edilmiş 62 erişkin hastanın prospektif olarak toplanan verileri retrospektif olarak incelendi. Hastaların perioperatif verileri birlikte demografik verileri, laboratuvar bulguları, göğüs tüplerinden kan kaybı miktarı, kan ürünü kullanım miktarı, yeniden torakotomi ihtiyacı, morbidite ve mortalite sonuçları değerlendirildi. Hasta popülasyonu iki gruba ayrıldı: Grup I: Perioperatif traneksamik asit ve DDAVP alan hastalar (n=26); ve Grup II: Perioperatif olarak sadece traneksamik asit alan hastalar (n=36).

Bulgular: İki hasta grubu başlangıçta benzer özelliklere sahipti. Grup I ve II arasında göğüs tüplerinden postoperatif kan kaybı, yeniden torakotomi, alyuvar ve trombosit transfüzyonları açısından istatistiksel olarak anlamlı fark vardı ($p < 0.05$). İki grup arasında taze donmuş plazma transfüzyonu, inotropik destek ve mortalite açısından istatistiksel olarak anlamlı bir fark gözlenmemiştir.

Sonuç: Acil izole KABG ameliyatı geçirenlerde traneksamik asitle birlikte desmopresin kullanımının perioperatif/postoperatif kanamayı ve kan ürünü kullanımını azalttığını düşünüyoruz.

Anahtar kelimeler: KABG; desmopressin; traneksamik asit; kan yönetimi

Introduction

Perioperative bleeding is a major problem in cardiac surgery. The underlying mechanism of bleeding is multifactorial and can be due to surgical or nonsurgical factors in general.[1] Non-surgical factors include acidosis, hypothermia, effect of heparin and mainly hemostatic abnormalities.[1,2] Perioperative bleeding results in a high risk of allogeneic blood transfusions and consequent increase in morbidity, mortality and costs.[3] Although a common issue in cardiac surgery, perioperative bleeding had no standardized definition until Dyke et al.[4] made a universal definition (Universal Definition of Perioperative Bleeding, UDPB in adult cardiac surgery). They classified perioperative bleeding into five groups as Class 0 being insignificant bleeding, and Class 4 being massive bleeding based on postoperative chest tube output, transfusion of packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate, use of factor concentrates, use of recombinant activated factor, surgical re-exploration and delayed sternal closure (Table 1). The authors suggest that UDPB would standardize the nomenclature of perioperative bleeding in adult cardiac surgery. They also stated that moderate and above bleeding classes (Class 2-4) were significantly related with increased mortality.[4] It is well known that emergent status of cardiac surgery is associated with increased risk of perioperative bleeding and also with increased re-exploration risk.[5] Emergent cardiac surgical patients are mostly premedicated with a second-generation P2Y12 antagonist (ticagrelor/prasugrel) by cardiologists as these drugs are reported to decrease the risk of thrombotic complications in acute coronary syndrome. However, the risk of bleeding complications increases with these new second-generation antithrombotic agents.[6] Many pharmacological agents are studied to overcome non-surgical causes of perioperative bleeding in cardiac surgery. One of them is tranexamic acid (TA), it is a synthetic lysine analogue that interferes with the binding of plasminogen to fibrin. It is the most commonly used anti-fibrinolytic agent in cardiac surgery and its use is recommended both by STS/SCA and European blood conservation guidelines as Class IA.[6,7] It is reported that TA use in cardiac surgery resulted in a reduced transfusion of blood components and a lower incidence of postoperative mortality or morbidity.[8,9]

Table 1. Bleeding categories according to the UDPB in adult cardiac surgery (4)

Bleeding Definition	Postoperativechesttube-bloodlosswithin 12 hours (mL)	PRBC (units)	FFP (units)	PLT (units)	Cryoprecipitate	PCCs	rFVIIa	Reexploration/tamponade	Delayedsternalclosure
Class 0 (insignificant)	<600	0*	0	0	No	No	No	No	No
Class 1 (mild)	601-800	1	0	0	No	No	No	No	No
Class 2 (moderate)	801-1000	2-4	2-4	Yes	Yes	Yes	No	No	No
Class 3 (severe)	1001-2000	5-10	5-10	N/A	N/A	N/A	No	Yes	Yes
Class 4 (massive)	>2000	>10	>10	N/A	N/A	N/A	Yes	N/A	N/A

UDPB, Universal definition for perioperative bleeding; PRBC, packed red blood cells; FFP, fresh frozen plasma; PLT, platelet concentrates; PCCs, prothrombin complex concentrates; rFVIIa, recombinant activated factor VII; N/A, not applicable. *Correction of preoperative anemia or hemodilution only; the number of PRBCs used should only beconsidered in the UDPB when accompanied by other signs of perioperative bleeding.

Desmopressin (DDAVP) is a vasopressin used in the management of von Willebrand factor (vWF) deficiency or hemophilia. It is suggested that in addition to up-regulation of plasma vWF and factor VIII, it has direct effects on platelet reactivity.

The aim of the present study is to analyze the effect of desmopressin and tranexamic acid on blood product use and postoperative bleeding in patients that were pretreated with P2Y12 inhibitors by cardiologists and undergone emergent coronary artery bypass grafting (CABG) surgery.

Material and Methods

Patients

After the institutional review board approval was obtained and Informed consent was obtained from all the patients participating in the study, and all the researchers signed the Declaration of Helsinki we retrospectively reviewed the data of 62 adult patients who underwent emergent isolated CABG surgery and pretreated with P2Y12- adenosine diphosphate (ADP) receptor blocker inhibitors, namely, ticagrelor by cardiologists from January 2017 to November 2018. The perioperative data of the patients included demographic data, laboratory findings, the amount of blood loss from chest tubes, the amount of blood product use, need of re-exploration, morbidity and mortality. The patient population was divided into two groups: Group I: Patients that received tranexamic acid and DDAVP perioperatively (n=26); and Group II: Patients that received only tranexamic acid perioperatively (n=36). The first primary outcome was postoperative blood loss from the chest tubes that is classified according to UDPB in adult cardiac surgery4. The second is the amount of blood product use defined as transfusion of packed red blood cells, fresh frozen plasma and platelets. The secondary outcomes were respiratory failure, prolonged inotropic support or renal failure during hospital stay and mortality. Patients with a history of hematologic disorders, hepatic and renal insufficiency, chronic renal failure requiring renal replacement therapy and also patients undergoing operations other than or in conjunction with CABG were excluded from the study.

CABG Procedure

All operations were performed in a standardized approach by a Terumo roller pump (Terumo Advanced Perfusion System 1, USA), membrane oxygenators (Inspire 8, LivaNova Sorin Group, Italy). Mild-to-moderate (28-32°C) hypothermia and pulsatile flow of 2.2-2.4 L/m2 were used. Myocardial protection was achieved with tepid antegrade blood cardioplegia, and a "hot shot" (250ml- 500ml) was delivered just before the removal of the aortic cross-clamp. The perfusion pressure was kept over 70mmHg at all times. Induction and maintenance of general anesthesia with endotracheal intubation were standardized in all the patients (fentanyl, midazolam, and isoflurane in oxygen with air). The same surgical team performed all of the operations.

Postoperative management

Postoperatively, patients were followed in the Intensive Care Unit (ICU), according to the protocols of our institution. Electrocardiography, systemic mean arterial pressure, central venous pressure, pulmonary artery and wedge pressures, cardiac output and index, arterial blood gases, and hourly urine output were monitored. Drainage from chest tubes were measured at 6, 12 and 24 hours after surgery. Hemoglobin and hematocrit levels before the surgery, and at hours 6, 12 and 24 after surgery were measured. Hematocrit values <25% were corrected with erythrocyte suspension administration. The amount of transfused packed red blood cells, Fresh Frozen Plasma (FFP), platelets and cryoprecipitate within the first 24 hr were recorded. Laboratory tests including PT, INR, PTT, ACT and platelets before the surgery, and at hours 12 and 24 after surgery were investigated. Serum electrolytes were measured in conjunction with arterial blood gas measurement. Fluid and electrolyte imbalances immediately were corrected with appropriate management. Reoperation due to bleeding during the first 48 hr of the surgery was also investigated.

Statistical analysis

All statistics were performed using SPSS version 17.0 for Windows (IBM Corporation, New York, USA). Continuous variables were expressed as mean ± SD and were compared by unpaired Student's T-test or Chi-Square test. Mann-WhitneyU-test was used for multiple comparisons and the Kruskal-Wallis test was used in non-normally distributed variables. Comparisons of rates were performed using the Fisher's Exact Method. Correlation between a predictor variable and a response variable was studied with regression analysis, and the results were expressed as Odds Ratio (OR) with a 95% Confidence Interval (CI). A P-value <0.05 was considered statistically significant.

Results

There were 30 women patients, 14 in Group I and 16 in Group II. Patient demographics and perioperative data are shown in Table 2. Preoperative patient characteristics and intraoperative data did not assure statistical significance between the groups. Mean age was 61.1±10.5 for Group I and 61.4±10.5 for Group

II. BMI, hypertension, diabetes, hyperlipidemia, and smoking habits were very similar in both groups. Also, Hgb, platelet and serum creatinine levels were similar. EF was 54.4±9.4 in Group I and 55.6±10.3 in Group II.

Table 2: Demographic Data

Clinical characteristics	Group I (Tranexamic acid+DDAVP) (n=26)	Group II (Tranexamic acid) (n=36)	p[a]
Age, years	61.1±10.5	61.4±10.5	0.835
Female, %	14	16	0.164
Body mass index, kg/m2	28.9±4.9	29.5±5.6	0.152
Hypertension, n	18	24	0.390
Diabetes mellitus, n	16	22	0.445
Hyperlipidemia, n	18	25	0.359
Smoking, n	20	29	0.433
Hemoglobin, g/dl	13.3 ± 1.85	13.4± 1.89	0.425
LV function, %	54.4±9.4	55.6±10.3	0.408
Serum creatinine, mg/dl	0.9±0.24	0.9±0.20	0.139
Platelet count preoperative, x103/mm3	204 ± 73.4	204± 60.5	0.647

Perioperative findings are shown in Table 3. CPB time, Cross-clamp time, Prolonged inotrope use, FFP transfusion at first 24 hours, and mortality showed no statistical significance. ICU stay time was lower in Group I, 56.6±27.3 hours and 65.9±40.6 hours, respectively. (p=0.042) Also, in-hospital stay was lower in Group I (6.4±2.0 days and 7.2±2.8 days, p=0.024) Ventilator support time was 6.7±3.5 hours in Group I and 12.5±16.2 hours in Group II (p<0.001).

Table 3: Perioperative Data

Perioperative characteristics	Group I (Tranexamic acid+DDAVP) (n=26)	Group II (Tranexamic acid) (n=36)	p[a]
CPB time, minutes	109.2±38.9	104.1±40.3	0.290
Cross-clamp time, minutes	63.5±24.4	60.2±23.8	0.256
ICU stay time, hours	56.6±27.3	65.9±40.6	0.042
In-hospital stay time, days	6.4±2.0	7.2±2.8	0.024
Ventilatory support times, hours	6.7±3.5	12.5±16.2	<0.001
Prolonged inotrope use, n	6	12	0.116
Chest tube drainage 24 hr. after surgery	425 ± 50	500 ± 75	0.029
Packed red blood cells transfusion at first 24 h, U	2±0.8	4.4±0.7	0.006
FFP transfusion at first 24 hr., U	1.2 ± 0.15	1.3 ± 0.21	0.386
Platelet transfusion at first 24 hr. U	0.8 ± 0.4	1.85 ± 0.2	0.022
Re-thoracotomy, n	0	6	0.032
Mortality, %	0	3.2	0.096

The main parameters we tried to identify in the study like chest tube drainage after surgery, transfusion amount, platelet transfusion and re-thoracotomy requirement showed statistically significant differences between the two groups. Chest tube drainage was significantly lower in Group I (425 ± 50 ml and 500 ± 75 ml, p=0.029). According to this, the red blood cells transfused to the patients were also lower in Group I, 2±0.8 U and 4.4±0.7 U, respectively. (p=0.006). Platelet transfusion in Group I was 0.8 ± 0.4 U and 1.85 ± 0.2 U in Group II, (p=0.022). Only 6 patients needed re-thoracotomy, all of whom were patients of Group II(p=0.032). Mortality was only seen in Group II (3.2%, p=0.096).

Discussion

Cardiac surgery involves bleeding and clotting complications separately or together. Due to the characteristics of cardiac surgery patients, antiplatelet agents are given in the preoperative period, especially in coronary artery patients. For this purpose, acetylsalicylic acid and P2Y12 receptor inhibitors (ticlopidine, clopidogrel, prasugrel, and ticagrelor) are used (RANUCCI). These drugs act over P2Y12 adenosine diphosphate (ADP)-dependent receptors, and present a risk of serious bleeding during and after the operation. These bleedings often require reoperation. For this reason, these drugs often are terminated before the operation.[10,11]

Fibrinolysisis triggered due to the use of CPB during cardiac surgery, which poses another risk for bleeding. These two causes increase the risk of bleeding by creating platelet dysfunction. In the Plato study it wasargued that ticagrelor reduces mortality caused by myocardial infarction, stroke and vascular.[12] The ticagrelor examined in the study reversibly attaches to the P2Y12 receptors, and has immediate effect. Ticagrelor blocks almost all of the platelet aggregation that is stimulated by ADP.[13,14]

The incidence of postoperative bleeding is between 2-6% in patients undergoing cardiac surgery.[5] Reoperation and bleeding also cause problems like increased ICU stays, kidney failure, sepsis, and increased mortality rates.[15]

Desmopressin, like TA used against bleeding, can also be used in bleeding disorders. Desmopressin (A.K.A. DDAVP or 1-deamino-8-D-arginine vasopressin) acts by increasing plasma levels in vWF and Factor 8.[16,17] Intracellular platelet calcium/sodium ion concentrations are increased by desmopressin by increasing the procoagulant platelet formation and platelet adhesion to collagen under flow.[17-19] It also increases the platelet functions[20], and used especially in von Willebrand insufficiency and hemophilia patients.[6]

Platelet dysfunction because of antiplatelet drugs increases the risk of bleeding. Data on bleeding control of patients with platelet dysfunction is not clear.[21] As the dysfunction is higher, the bleeding occurs at higher rates; however, when the drugs are terminated, cardiovascular morbidity increases as a rebound effect.[21] Platelet dysfunction is also increasing due to CPB, which increases the risk of intraoperative bleeding.[21,22]

Many studies were conducted on bleeding control and bleeding-reducing treatments. In a study, patients at high risk of bleeding were compared with placebo group, and it was found that 24-hour bleeding was 39% less in patients who received desmopressin.[2]

In a meta-analysis study conducted in 2008, Crescenzi et al.[23] examined 38 studies, analyzing the data of 2.488 cardiac or non-cardiac surgical patients, and showed that desmopressin reduced the use of blood products.

Similar results were shown in the study conducted by Desborough et al.[21] it was reported that the risk of red blood transfusion, blood loss, and reoperations decreased. When compared with the Control Group, the use of red blood products was 25% lower, blood loss was lower at a rate of 23%, and the risk of reoperation was also lower. In the subgroups, which received antiplatelet treatment, differences were detected, even if at statistically low levels. No differences were detected in terms of overall mortality and thrombotic events.

In the study conducted bySteinlechner[24] on aortic valve replacement, desmopressin increased vWF, normalized platelet function, and reduced postoperative blood loss.

Salzman et al.[25] reported that desmopressin decreased blood loss from 2210ml to 1317ml compared to the placebo group; however, he also noted that the patients with the most blood loss were those with low vWF in the preoperative period. Similarly, Despotis et al.[26] also reported that the blood loss decreased to 624ml from 1028ml.

In the present study, a statistically significant decrease was detected in chest tube drainage, red blood transfusion, and platelet transfusion in the first 24 hours (0.029, 0.006, and 0.022, respectively). The need for reoperation decreased significantly for patients included in the study (p=0.032). However, although there was a decrease in fresh frozen plasma transfusion, it was not at a significant level. Our results are broadly consistent with the previous data on desmopressin.

In the literature, there are studies that indicate positive effects of desmopressin on bleeding, as well as studies reporting that it has no effect on bleeding. In the study conducted by Teng et al.[20] it was found that there was a decrease in the amount of bleeding with desmopressin, but it was not clinically significant. It was suggested that desmopressin does not affect ticagrelor pharmacokinetics. It was also reported that desmopressin does not prevent platelet aggregation caused by ticagrelor, but increases hemostatic activity.

In the study conducted by Carles et al.[27], it was reported that desmopressin reduces postoperative and total blood loss, but has no effects on red blood transfusion. Also, no effects of it were detected on mortality.Again, in the study of Bignami2, its effect on postoperative blood loss and RBC transfusion could not be demonstrated. Wademan[28] conducted a study and did not recommend routine use of desmopressin, but also argued that desmopressin could reduce postoperative bleeding in patients used aspirin, in patients whose CBP time exceeded 140 minutes, and in patients with platelet dysfunction.

The present study also showed a significant decrease in the intensive care stay, hospitalization time, ventilator support time, chest tube drainage, RBC transfusion quantity, platelet transfusion and reoperations; however, no statistically significant differences were detected in the amount of TDP, CPB time, Cross clamp time and mortality.

These differences in the literature are also seen in the guidelines. Desmopressin is not recommended to reduce the bleeding in 2017 EACTS/EACTA Guideline.[6] However, it was stated that it could be used to reduce bleeding and blood transfusion in patients with acquired or congenital platelet dysfunction.[2,6,28]

In a systematic study of Cochrane[27], and in a meta-analysis[23,28], it was argued that desmopressin did not reduce bleeding and the need for blood transfusion in cardiac surgeries. In a recent meta-analysis, it was reported that desmopressin had low effects on blood loss and transfusion.

The bleeding management of patients with platelet dysfunction has not yet been clearly defined. Routine use of desmopressin was not recommended, and it was stated that it could be used in patients with congenital or acquired platelet dysfunction.[6,7,21,29-32]

Although there are improvements in surgical ability and strategies, bleeding still remains as a serious problem. The amount of bleeding can be reduced by using various drugs in the control of bleeding, and efforts are spent to reduce the need for blood transfusion. The results of our study show parallelism

to the literature. In this study, it was found that desmopressin especially reduced the RBC need and total blood loss. Hypotension hyponatremia, flushing, and thrombotic event risks, which were the reported side effects of desmopressin in the literature, were not detected in our study. We believe that desmopressin can be used as an anti-bleeding medication, especially in cardiac surgery patients with platelet dysfunction.

Study Limitations

The present study has some limitations as it had a retrospective design, and not using TEG or ROTEM. Another limitation is that we did not compare other anticoagulant drugs as our patients in the study were using only ticagrelor preoperatively.

Conclusion

Desmopressin is an easy-to-apply and cheap drug. In this respect, it was frequently evaluated as an attractive option in bleeding prevention studies. Although its effect on bleeding is not clear in the literature, it was shown in many studies that it reduces total blood loss. However, further studies are required to reach an absolute consensus.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Original Article

A new prognostic marker in failing heart: Peak mitral regurgitation velocity to left ventricular outflow tract time velocity integral ratio

Kalp yetersizliğinde yeni bir prognostik belirteç: Pik mitral regurjitasyon velositesinin sol ventrikül çıkış yolu velosite zaman integraline oranı

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Abstract

Aim: Systemic vascular resistance (SVR) is useful for risk estimation and therapy guidance in HF. It has been shown that the ratio of peak mitral regurgitation velocity (MRV) to left ventricular outflow tract velocity-time integral (LVOT VTI) correlated positively with SVR. We aimed to assess the association of MRV/LVOT VTI ratio with established prognostic markers and its prognostic role for predicting one year and long term composite end-points in patients with HF and reduced ejection fraction (HFrEF).

Material and Methods: We prospectively enrolled a total of 72 patients with HFrEF and 10 control subjects. Patients were followed up patients for median 40.5 months. Primary composite endpoint (CEP) was defined as any of these outcomes including requiring mechanical circulatory support, cardiac transplantation, and all-cause mortality.

Results: CEP(+) patients had higher MRV/LVOT VTI ratio than others (0.48±0.15 vs. 0.39±0.18 p=0.012). MRV/LVOT VTI ratio was positively correlated with functional status (β=0.539, p=0<001), serum BNP level (β=0.479, p<0.001),troponin I (β=0.415, p<0.001), and Uric acid level (β=0.235 p=0.018) and negatively correlated with SEATTLE score derived life expectancy (β=-0.248, p=0.032). Adjusted with other parameters, every 0.1 increase in MRV/LVOT VTI ratio increased the one-year CEP risk by 37% and long-term CEP risk by 35%. In Kaplan Meier analysis, patients with MRV/LVOTVTI ratio ≥ 0.39 had more long-term CEP compared to others.

Conclusion: MRV/LVOT VTI ratio seemed to be a useful predictor of poor prognosis associated with other established HF prognostic markers.

Keywords: systemic vascular resistance; heart failure and reduced ejection fraction; peak mitral regurgitation velocity to left ventricular outflow tract velocity-time integral

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Öz

Amaç: Sistemik vaskuler rezistans (SVR), kalp yetersizliğinde risk tahmini ve tedavi klavuzluğunda kullanışlıdır. Pik mitral regurgitasyon velositesinin (MRV) sol ventrikül çıkış yolu velosite zaman integraline (LVOT VTI) oranının SVR ile pozitif yönde korele olduğu gösterilmiştir. Bu çalışmada düşük ejeksiyon fraksiyonlu kalp yetersizliği (DEF-KY) hastalarında MRV/LVOT VTI oranının bilinen prognostik belirteçlerle ilişkisi ve 1 yıllık ve uzun dönem birleşik son noktayi öngördürmedeki prognostik rolünü değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Prospektif olarak 72 DEF-KY hastası ve 10 sağlıklı kontrolü çalışmaya dahil ettik. Hastalar medyan 40.5 ay takip edildi. Birincil birileşik son nokta (BSN) mekanik dolaşım desteği, kalp transplantasyonu ve tüm nedenlere bağlı ölüm olarak tanımlandı.

Bulgular: BSN(+) hastalarında daha yüksek MRV/LVOT VTI oranı saptandı (0.48±0.15 vs. 0.39±0.18 p=0.012). MRV/LVOT VTI oranı fonksiyonel sınıf (β=0.539, p=0<001), troponin I (β=0.415, p<0.001), serum BNP seviyesi (β=0.479, p<0.001), ve ürik asit düzeyi (β=0.235 p=0.018) ile pozitif yönde korele ve SEATTLE skor ile elde edilen yaşam beklentisi (β=-0.248, p=0.032) ile negatif korele izlendi. Diğer parametrelerle birlikte MRV / LVOT VTI oranındaki her 0,1 artış bir yıllık BSN riskini % 27 ve uzun dönem BSN riskini % 24,6 artırdı. Kaplan Meier analizinde MRV / LVOTVTI oranı ≥ 0.39 olan hastalarda diğerlerine göre uzun dönemde daha fazla BSN görüldü.

Sonuç: MRV / LVOT VTI oranı diğer bilinen DEF-KY prognostik göstergeleri ile ilişkili olarak, kötü prognozun faydalı bir belirteci olarak görünmektedir.

Anahtar kelimeler: sistemik vaskular rezistans; kalp yetersizliği; pik mitral regurgitasyon velositesinin sol ventrikül çıkış yolu velosite zaman integraline oranı

Introduction

In patients with both acute and chronic decompensated heart failure (HF), invasive hemodynamic indices like cardiac index and pulmonary capillary wedge pressure have been widely used [1]. In addition to these indices, systemic vascular resistance (SVR) is useful for risk estimation and therapy guidance in advanced HF [2]. Particularly for the patients with cardiogenic shock, SVR assessment may provide better recognition of ineffective tissue perfusion.

SVR is estimated by the ratio of the transsystemic pressure gradient to the transsystemic flow [3]. However, the only accepted method for SVR estimation is invasive hemodynamic monitoring and using invasive techniques such as routine right heart catheterization for this purpose may lead to potential procedural risks. Fortunately, two-dimensional (2D) echocardiography and Doppler provide the noninvasive assessment of left ventricular function and intracardiac hemodynamics [4–7].Therefore, as a noninvasive technique, Doppler echocardiography may be useful for the estimation of pressure and flow, as well as an indirect estimation of SVR. It has been shown that the ratio of peak mitral regurgitation velocity (MRV) to left ventricular outflow tract velocity-time integral (LVOT VTI) correlated positively with SVR obtained by invasive hemodynamic monitoring [2]. In the literature, there is limited data about the prognostic value of MRV/LVOT VTI ratio in HF.

Herein, we aimed to assess the association of MRV/LVOT VTI ratio with established prognostic markers and its prognostic role for predicting one year and long term composite end-points in patients with HF and reduced ejection fraction (HFrEF)

Material And Methods

Study Participants and Comorbidities

We prospectively enrolled a total of 72 patients with HFrEF and age- and gender-matched 10 apparently-healthy control subjects between November 2013 and April 2014. Patients were followed up for median 40.5 months (min. 0-max 75 months. Patients' comorbidities, medications, physical examination, and laboratory findings were recorded. Patients were categorized according to their New York Heart Association (NYHA) functional classes and cardiomyopathy etiology (ischemic vs nonischemic). Patients with poor echocardiographic windows, primary valvular disease, known malignancy, active inflammatory conditions, cerebrovascular diseases were excluded. We excluded severe mitral regurgitation (grade 4 MR) and also very mild mitral regurgitation which not permit to evaluate MRV. Patients with left Ventricular Ejection Fraction <40 was regarded as HFrEF by

contemporary guidelines. Patients' risk factors were also noted: smoking (smoking history within the last month defined current smoker, otherwise ex-smoker), diabetes mellitus (fasting blood glucose >125 mg/dL, HbA1c >6.5%, and current usage of antidiabetic medication) and hypertension (defined as systolic blood pressure 140 mmHg and/or diastolic blood pressure 90 mmHg or current antihypertensive medication). Patients' medications at admission and discharge as well as during one-year follow-up were also noted.

Admission kidney and liver function tests were measured from routine blood work and cardiac troponin I, Brain Natriuretic Peptide (BNP), and serum uric acid levels were obtained. Patients' baseline vital signs (systolic and diastolic blood pressure, heart rate) were also recorded. SEATTLE derived life expectancy was calculated using The Seattle Heart Failure Model [8] .

Informed consent was obtained from all the patients participating in the study, and all the researchers signed the Declaration of Helsinki. Approval for the study was granted by the local ethics committee.

Echocardiographic Examination and MRV/ LVOT VTI Ratio

Patients' echocardiographic examinations were done by using a 3.5-MHz transducer (Vivid 7, GE-Vingmed Ultrasound AS, Horten, Norway).Echocardiographic examinations were done to ambulatory patients without HF exacerbations who maintained at least 30 minutes supine position. All echocardiographic examinations performed according to the recommendations of the American Society of Echocardiography [9]. Left ventricular ejection fraction (LVEF) was assessed by modified Simpson Method. Left ventricular dimensions were evaluated by M mode recordings. Mitral and tricuspid regurgitation was graded by color flow area assessment. MRV was measured in apical four-chamber view by continuous Doppler. LVOT VTI was measured in apical three-chamber view, 3-5 mm length sample volume was positioned in left ventricular side just proximal before flow acceleration.

Assessment of Clinical Outcomes

Primary composite endpoint (CEP) was defined as patients confronting any of these outcomes including requiring mechanical circulatory support, cardiac transplantation and suffering all-cause mortality.

Follow-up data of all the patients were obtained from the hospital database and records of the Ministry of Health. Patients, whose follow- data could not be received through these systems, were reached by telephone interview with patients or their relatives

Statistical Analysis

The continuous variables were reported as the mean±standard deviation (SD) and the categorical variables were expressed as the number of patients and percentages. Kolmogorov-Smirnov tests were used to assess the normality of the data distribution. The correlation analysis was made with Pearson and Spearman's correlation coefficient. We analyzed the effects of different variables on the occurrence of CEP in univariate Cox regression analysis and determined the variables with an unadjusted p-value <0.1 as potential risk markers. In addition to MRV/LVOT VTI parameter, we included the contributors of this formula to the univariate analysis and evaluated the individual predictive value of each parameter. Multicollinearity analysis was performed before multivariate analysis. We composed the final model by using backward elimination at multivariate Cox regression analysis. Receiver operating curve (ROC) analysis was performed to investigate the efficacy of MRV/LVOT VTI ratio in predicting one-year and long-term mortality and the cut-off values were determined. Based on the cut-off values, patients were divided into two groups for MRV/LVOT VTI ratio parameter. Kaplan–Meier curve analysis was used for survival analysis in between these groups. Statistical significance was defined as $P < 0.05$. Data were analyzed by using SPSS 20.0 software.

Reproducibility Analysis

To evaluate the intraobserver variability of MRV/LVOT VTI ratio measurements, 20 patients were randomly selected and second set of echocardiographic examinations of these patients were performed on consecutive days. To evaluate interobserver variability, two echocardiographers (MSC and EHOC) examined the same patients on the same day separately. The intraobserver agreement on MRV/LVOT VTI ratio measurement was very good: the intraclass coefficient of correlation was 0.96. The interobserver agreement was also very good: the intraclass coefficient correlation was 0.94.

Results

MRV/LVOT VTI ratio was almost two times higher in HF group (0.47±0.16 vs. 0.26±0.04, p<0.001 respectively). While comparing patients with CEP (-), CEP(+) patients had higher MRV/LVOT VTI ratio than others (0.48±0.15 vs. 0.39±0.18 p=0.012). The comparison of baseline characteristics, laboratory and echocardiographic parameters between CEP (+) and CEP (-) groups were summarized in Table 1 and Table 2. There was an incremental trend for MRV/LVOT VTI ratio through advanced HF classes, and it reached the highest in NYHA class 3-4 group (p<0.001).

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Table 1. Baseline characteristics and physical examination findings of study cohort

Variable	CEP (+) (n=51)	CEP (-) (n=31)	P
Age, years	57.2±14.2	55.4±13.8	0.564
Sex, male, n (%)	39 (76.5)	26 (83.9)	0.423
BMI	27.8±5.3	27.7±4.8	0.877
Ischemic CMP, n (%)	36 (70.6)	11 (35.5)	0.002
Hypertension, n (%)	22 (43.1)	17 (54.8)	0.304
Hyperlipidemia, n (%)	18(35.3)	8(25.8)	0.371
DM, n (%)	28 (54.9)	10 (32.3)	0.046
NYHA III-IV, n (%)	38 (74.5)	8 (25.8)	<0.001
Systolic Blood Pressure, mmHg	103.7(15.9)	118.1±22.3	0.001
Diastolic Blood Pressure, mmHg	65.3(12.5)	71.7(13.7)	0.040
Raller, n (%)	32 (62.7)	9 (29.0)	0.003
PND,n (%)	43(84.3)	10(32.3)	<0.001
Pretibial edema, n (%)	30(58.8)	5(16.1)	<0.001
Diuretic, n (%)	46 (90.2)	15 (48.4)	<0.001
ACEinh/ARB, n (%)	46(92.0)	25(86.2)	0.411
Beta blocker, n (%)	46(92.0)	24(82.8)	0.213
MRA, n (%)	34(68.0)	17(58.6)	0.401
Atrial fibrillation, n (%)	10 (19.6)	3 (9.7)	0.233
MCS, n (%)	6 (11.8)	0 (0)	0.060
All-cause Mortality, n (%)	47 (92.2)	0 (0)	<0.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CEP, composite endpoint; CMP, cardiomyopathy; DM, Diabetes mellitus; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnea.

Table 2. Laboratory and echocardiographic parameters of study cohort

Variable	CEP (+) (n=51)	CEP (-) (n=31)	P
Hemoglobin, g/dL	12.5±1.9	13.7±1.8	0.008
HCT(%)	39.8±5.1	41.6±5.2	0.115
WBC	7.7±2.5	7.1±1.8	0.246
hsCRP, mg/L	31.8±25.6	9.8±8.5	0.165
Glucose, mg/dL	144.6±70.4	130.2±62.6	0.352
Creatinine, mg/dL	1.4±0.6	1.0±0.5	0.003
AST,	53.4±118.4	24.7±1.9	0.191
Uric acid, mg/dL	9.5±2.3	6.7±1.9	<0.001
Albumin, mg/dL	3.7±0.5	4.3±0.4	<0.001
BNP,pg/mL	1766.5±1377	1088.7±1027	0.023
Sodium, mmol/L	133.9±5.3	137.2±4.5	0.005
Potassium, mmol/L	4.4±0.7	4.3±0.5	0.532
LVEF, %	24.1±10.2	37.2±17.9	<0.001
LVEDD, mm	64.6±9.5	55.0±9.6	<0.001
LVESD, mm	55.1±10.3	41.8±12.8	<0.001
LAD,mm	49.0±7.5	41.8±7.6	<0.001
TAPSE,mm	14.9±4.7	20.1±5.1	<0.001
MR grade 2 and 3	25 (49.0)	9 (29.0)	0.075
MRV	4.3±0.5	5.0±0.7	<0.001
LVOT VTI	10.3±4.0	14.7±5.8	<0.001
MRV/LVOT VTI	0.48±0.15	0.39±0.18	0.012

Abbreviations: CEP, composite endpoint; HCT, hematocrit; hsCRP, high sensitive C-reactive protein; LA, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVOT VTI; left ventricular outflow tract velocity time integral; MRV, mitral regurgitation velocity; TAPSE, Tricuspid Annular Plane Systolic Excursion;

MRV/LVOT VTI ratio was positively correlated with functional status (β=0.539, p=0<001), serum BNP level (β=0.479, p<0.001), troponin I (β=0.415, p<0.001), and Uric acid level (β=0.235 p=0.018) and negatively correlated with SEATTLE score derived life expectancy (β=-0.248, p=0.032) (Figure 1)

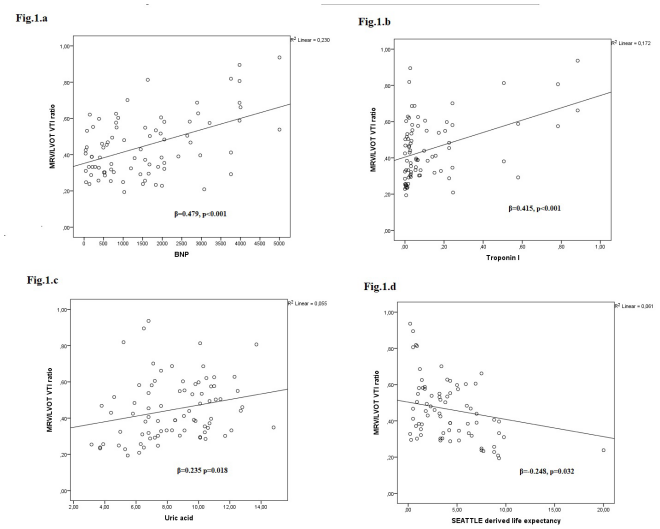

Figure 1. Correlations between MRV/LVOT VTI with Brain Natriuretic Peptid (Fig 1.a), troponin I (Fig 1.b), uric acid (Fig 1.c), SEATTLE score derived life expectancy (Fig 1.d). Each dot represents one patient; the straight line represents the best fit line obtained by linear regression analysis.

Abbreviations: MRV/LVOT VTI: peak mitral regurgitation velocity to left ventricular outflow tract velocity-time integral

In multivariate Cox regression analysis, adjusted with diastolic blood pressure, hemoglobin, every 0.1 increase in MRV/LVOT VTI ratio increased the one-year CEP risk by 37% (HR=1.371, 95% CI: 1.113-1.690 p=0.003) (Table 3). Additionally, adjusted with diastolic blood pressure, hemoglobin,creatinine level, every 0.1 increase in MRV/LVOT VTI ratio increased the long-term CEP risk by 35 % (HR=1.350, 95% CI: 1.139-1.601 p=0.001) (Table 4).

In ROC analysis, a cut of value 0.45 for MRV/LVOT VTI ratio 65.2% sensitivity and 65.5% specificity for prediction of one- year mortality (AUC=0.645 95%CI:0.515-0.776, p=0.042). In Kaplan Meier analysis, patients with MRV/LVOT VTI ratio ≥0.45 .had more one-year CEP compared to others (Chi-square:6.391, p=0.011) (Figure 2a and Figure 2b). Additionally, patients in ≥0.45 MRV/LVOT VTI ratio group had 3.3 times higher risk of CEP during one-year follow-up (HR: 3.268, CI 95%: 1.382-7.727, p=0.007)

For the prediction of long term mortality, a cut of value 0.39 for MRV/LVOT VTI ratio demonstrated 68% sensitivity and 67.7% specificity (AUC=0.706 95% CI:0.580-0.833, p=0.002). In Kaplan Meier analysis, patients with MRV/LVOT VTI ratio ≥0.39 had more long-term CEP compared to other patients (Chi-square:9.048, p=0.003) (Figure 2c and Figure 2d). Besides, adjusted with other parameters, being in the high MRV/LVOT VTI group increased the long-term CEP risk approximately 3 times (HR:2.750, 95%CI: 1.464-5.166, p=0.002).

Table 3: Univarite and multivariate Cox regression analysis demonstrating the predictors of one-year composite end point

Parameter	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age, years	0.980 (0.952-1.009)	0.980		
Male, yes	1.300 (0.516-3.275)	0.578		
Ischemic CMP	0.487 (0.262-0.905)	0.023		
NYHA	2.752 (1.663-4.554)	<0.001		
Systolic Blood Pressure	0.946 (0.918-0.975)	<0.001		
Diastolic Blood Pressure	0.931 (0.890-0.973)	0.002	0.928 (0.883-0.975)	0.003
Rales	2.701 (1.119-6.522)	0.027		
ACEi/ARB	0.787 (0.344-1.799)	0.570		
Beta blocker	2.115 (0.631-7.092)	0.323		
MRA	1.081 (0.587-1.993)	0.225		
Hemoglobin	0.691 (0.543-0.879)	0.003	0.777 (0.606-0.996)	0.047
WBC	0.925 (0.765-1.117)	0.417		
Platelets	1.001 (0.997-1.006)	0.589		
Creatinine	2.299 (1.250-4.228)	0.007		
Na	0.887 (0.819-0.961)	0.003		
K	0.842 (0.430-1.649)	0.616		
CRP	1,003 (0.999-1.008)	0.163		
LVEF	0,909 (0,849-0.972)	0.005		
sPAB	1.023 (0.996-1.051)	0.090		
MR Grade 2 and 3	1.211 (0.542-2.704)	0.640		
MRV	0.117 (0.047-0.291)	<0.001		
LVOT VTI	0.821 (0.723-0.933)	0.003		
MRV/LVOT VTI (per 0.1)	1.240 (1.002-1.536)	0.018	1.371 (1.113-1.690)	0.003

* Because of the multicollinearity issues between NYHA and LVEF parameters were excluded from multivariate Cox regression analysis.

Table 4: Univarite and multivariate Cox regression analysis demonstrating the predictors of long term composite end point

Parameter	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age, years	1.002 (0.981-1.023)	0.882		
Male, yes	1.390 (0.726-2.658)	0.320		
Ischemic CMP	0.626 (0.443-0.886)	0.008		
NYHA III-IV	4.424(2.339-8.369)	<0.001		
Systolic Blood Pressure	0.968 (0.952-0.985)	<0.001		
Diastolic Blood Pressure	0.959(0.934-0.985)	0.002	0.942 (0.913-0.973)	<0.001
Rales	2.468(1.391-4.377)	0.002		
ACEi/ARB	1.445(0.519-4.021)	0.481		
Beta blocker	1.676(0.601-4.671)	0.323		
MRA	1.081(0.587-1.993)	0.802		
Hemoglobin	0.777(0.666-0.906)	0.002	0.848 (0.729-986)	0.032
WBC	1.045(0.924-1.183)	0.184		
Platelets	1.000(0.997-1.004)	0.876		
Creatinine	2.173(1.390-3.399)	0.001	2.274(1.382-3.742)	0.001
Na	0.906(0.857-0.958)	0.001		
K	1.124(0.715-1.766)	0.613		
CRP	1,004 (1.000-1.008)	0.034		
LVEF	0,924 (0,889-0.961)	<0.001		
sPAB	1.032 (1.014-1.050)	<0.001		
MR Grade 2 and 3	1.613(0.929-2.800)	0.089		
MRV	0.193(0.106-0.350)	<0.001		
LVOT VTI	0.865(0.808-0.927)	<0.001		
MRV LVOT VTI (per 0.1)	1.193(1.034-1.378)	0.016	1.350 (1.139-1.601)	0.001

* Because of the multicollinearity issues, LVEF and NYHA parameters were excluded from multivariate cox regression model.

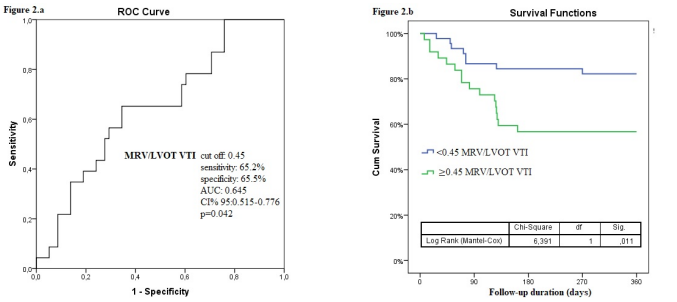

Figure 2.ROC curve analysis showing the predictive value of MRV/LVOT VTI to predict one-year composite endpoint (Fig 2.a), Kaplan-Meier survival curve demonstrating one-year composite endpoint among groups specified based on MRV/LVOT VTI ratio cut-off value 0.45 (Fig 2.b).ROC curve analysis showing the predictive value of MRV/LVOT VTI to predict long term composite end point (Fig 2.c), Kaplan-Meier survival curve demonstrating long-term composite endpoint among groups specified based on MRV/LVOT VTI ratio cut-off value 0.39 (Fig 2.d).

Abbreviations: AUC: area under the curve; MRV/LVOT VTI: peak mitral regurgitation velocity to left ventricular outflow tract velocity-time integral; ROC: receiver operating curve.

Discussion

The present study demonstrated that MRV/LVOTVTI ratio independently and significantly predicted the one year and long term CEP in HFrEF patients. Additionally, MRV/LVOT VTI ratio showed positive correlations with functional capacity, troponin I and serum BNP, uric acid and negative correlation with SEATTLE score derived life expectancy. Therefore, MRV/LVOT VTI ratio seemed to be useful predictor of poor prognosis associated with other established HF prognostic markers.

Patients with symptomatic heart failure have lower long-term survival rates of approximately less than five years [10]. Although prognostic evaluation is challenging, it is essential in the management of HF patients for deciding more advanced and individualized therapies. HF affects multiple organs and systems, and neurohormonal activation takes a mainstay role in the HF progression [11,12]. Previously, the activation of the sympathetic nervous and renin-angiotensin system was reported in HF [13,14]. Therefore, an increase in SVR may be expected due to the increased levels of vasoconstrictive neurohumoral factors in the course of the disease and also may suggest progression of the HF. In advanced HF and cardiogenic shock, alterations in vascular tone determine the SVR and cardiac output [1] In this context, assessment of SVR may be helpful in therapy guidance by adjusting the vascular volume, inotropes, and vasodilators. However, the determination method of SVR limits its use due to the potential complications related to the invasive monitoring process. In the prompting study about the non-invasive determination of SVR, Abbas et al. showed that SVR positively correlated with an echocardiographic index that was simply calculated by dividing the MRV to the LVOT VTI, and this formula allowed indirect and noninvasive assessment of SVR [2].

In the setting of HF hospitalizations, SVR is valuable in the diagnosis of pulmonary edema [1]. While SVR was found elevated in exacerbated systolic HF, it was found extremely high in the patient group with pulmonary edema [1]. Accordingly, indirect measurement of SVR may be useful in HF diagnosis, because, HF generates a gradual decline in cardiac contractility and to overcome this, neurohormonal vascular tone increases causing an elevated SVR. In our study, we found that MRV/LVOT VTI ratio significantly elevated in patients with HF compared with the healthy subjects that may point to the underlying pathophysiology of HF. In the patient group, we observed that MRV/LVOT VTI ratio positively correlated with NYHA functional classes. Moreover, it showed positive correlations with troponin and BNP which are already described as prognostic markers in HF [15,16]. Interestingly, this echocardiographic index negatively correlated with SEATTLE score derived life expectancy, which was previously developed by reviewing the clinical trials and published data to predict HF prognosis[8]. Especially in the advanced HF population, this scoring system revealed better discrimination of high-risk patients [17]. In the present study, Cox regression analysis showed that MRV/LVOT VTI ratio was an independent predictor of CEP for one-year and long term follow-up. The significant relation between SEATTLE score derived life expectancy and MRV/LVOT VTI ratio may indicate that non-invasive assessment of cardiac hemodynamics with Doppler echocardiography may provide a further determination of patients with poor prognosis.

Besides, we had additional points that deserve to be mentioned. The components of MRV/LVOT VTI may have certain individual affects on outcomes. In univariate analysis, decrease in individual contributors (MRV and LVOT VTI) were found to be associated with poor prognosis. However, we evaluated MRV/LVOT VTI along with its individual contributors and found that this compound parameter was an independent predictor of worse clinical outcomes better than its contributors. Intuitively, higher MRV/LVOT VTI may result from low LVOT VTI values in the setting of a combination of decreased systolic blood pressure

and elevated left atrial pressure, which are already proven mortality markers of HfrEF. MRV/LVOT VTI seems to predict outcomes more accurately than its contributors.

Our study is preliminary investigating the prognostic value of MRV/LVOT VTI in HFrEF. We determined the cut-off values of MRV/LVOT VTI in predicting the occurrence of CEP and organized study population based on these cut-offs. We found that being in higher MRV/LVOT VTI group was associated with increased CEP risk by nearly three times. These findings should be assessed in large scale studies.

Study Limitations

Although the present study provided valuable information about the non-invasive and indirect measurement of SVR in patients with HF, the number of recruited patients was relatively small. Also, invasive analysis of SVR was not applied because it is an invasive method and the implementation is effortful, and for our study patients as they were not admitted with acute decompensated HF, the indication of this assessment is debatable.

Conclusion

In patients with HFrEF, MRV/LVOT VTI ratio as an indirect measure of SVR emerged as an independent prognosticator of one-year and long term CEP, associated with established HF prognostic markers. This simple, easily measurable non-invasive parameter may be feasible in determining the high-risk subjects and tailoring more individualized therapies.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Orjinal Makale

Çölyak hastalığı tanısı alan çocuklarda kemik mineral yoğunluğu ve kemik metabolizması belirteçlerinin değerlendirilmesi

Evaluation of bone mineral density and bone metabolism markers in children diagnosed as celiac disease

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Öz

Amaç: Çölyak hastalığında kalsiyum ve D vitamini eksikliğine bağlı metabolik kemik hastalığı en sık ekstraintestinal semptomlardan biridir. Bu çalışmada, çölyak hastalığı olan çocuklarda tanı esnasında kemik mineral yoğunluğunun değerlendirilmesi ve kemik mineral metabolizmasıyla ilişkili faktörlerin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Çalışmaya hastanemiz çocuk gastroenteroloji bölümünde Aralık 2015-Aralık 2019 tarihleri arasında çölyak hastalığı tanısı alan 43 çocuk hasta alındı. Retrospektif olarak hastaların klinik, antropometrik, patolojik ve laboratuar özellikleri [kalsiyum, fosfor, alkalenfosfataz (ALP), parathormon (PTH), 25-OH vitamin D düzeyleri] incelendi. Tanıda Dual Energy X-Ray Absorptiometry (DEXA) yöntemi ile ölçülmüş olan lumbal (L1-L4) kemik mineral yoğunluğu düzeyleri değerlendirilerek kronolojik yaşa ve boy yaşına göre Z-skorları hesaplandı.

Bulgular: Ortalama yaşları 9,9±4,8 (2,5-17,7) yıl olan 43 hastanın (34 kız/9 erkek) verileri değerlendirildi. %30,2'si (n=13) 0-6 yaş, %30,2'si (n=13) 7-11 yaş aralığında ve % 39,5'i (n=17) 11 yaş üzerindeydi. Yaşa göre KMY Z-skoru -0,83±1,1 (-3,6-1,6), boy yaşına göre KMY Z-skoru -0,18±1,1 (-3,6-1,8) saptandı. Hastaların %51,2'sinde (n=22) yaşa göre KMY Z-skoru>-1, %34,9'unda (n=15) -1 ve -2 arasında ve %14'ünde (n=6) <-2 saptandı. Yaşa göre KMY Z-skorunun<-2 olma oranı 11 yaştan büyük çocuklarda anlamı olarak yüksekti (p<0,001). Hastaların KMY Z-skorları ile serum D vitamini, kalsiyum, fosfor, ALP ve PTH düzeyleri arasında ilişki saptanmadı (p>0,050).

Sonuç: Çölyak hastalarında tanı yaşının gecikmesi kemik mineral yoğunluğunu olumsuz etkilemektedir. Erken yaşta tanı konulması kemik mineral kaybını engeller ve osteopeni/osteoporoz gelişmiş olan hastalarda tedavi olanağı sağlayarak morbiditeyi azaltır.

Anahtar kelimeler: çocuk; çölyak hastalığı;kemik mineral yoğunluğu

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Abstract

Aim: Metabolic bone disordersduetocalsiumand vitamin D deficiencyareone of themostfrequentextraintestinalsymptoms in Celiacdisease. In this study it is aimed toevaluate bone mineral density in patients with Celiacdisease duringdiagnose and evaluatethe factors related to bone mineral metabolism.

Material and ethods: The study included 43 children diagnosed as Celiacdisease between December 2015 and December 2019. Clinical, anthropometric, pathological and laboratory (calsiyum, phosphor, alkalenphosphataz (ALP), parathormon (PTH), 25OHvitamin D levels) properties of patients were detected retrospectively. Lumbal (L1-L4) bone mineral densityleve lsmeasuredvia DEXA (Dual Energy X-Ray Absorptiometry) were evaluatedand Z scoresduetocronologicalageandheightagewerecalculated.

Results: Meanage of 43 patients (34 girl/9 boys) was 9.9±4.8 (2.5-17.7) years. 30.2% (n=13) was 0-6 years old, 30.2% (n=13) was 7-11 years and 39.5% (n=17) wasover 11 years. BMD Z scoreduetochronologicalage was -0.83±1.1 (-3.6-1.6) and -0.18±1.1 (-3.6-1.8) duetoheight age. BMD Z scoresduetochronologicalagewas>-1 in 51.2% of thepatients (n=22), between -1 and -2 in 34.9% (n=15) and<-2 in 14% (n=6). BMD Z scoresduetochronologicalage<-2 in over 11 age was statistically high (p<0.001). No relation between BMD Z scoresandplasma vitamin D, Ca, P, ALP and PTH levels (p>0.050).

Conclusion: Delayed diagnoseageseffects bone mineral densitynegatively in Celiacdisease. Diagnose in earlyagesdecreases bone mineral leakanddecreasesmorbidity in patients with osteopeniandosteoporosisviatreatmentposibilities.

Keywords: child; celiacdisease; bone mineral density

Giriş

Çölyak Hastalığı genetik duyarlılığı olan bireylerde farklı klinik görünümlerde ortaya çıkan, çocukluktan erişkin döneme uzanan geniş bir yaş aralığında tipik ve atipik bulgular ile seyreden, ince bağırsaklardaglutene karşı anormal immün yanıt sonucu gelişen bir hastalıktır [1,2].Çölyak hastalığında(ÇH) ekstra intestinal bulgular büyük oranda proksimal emilim bozukluğuna bağlı oluşmaktadır. Günümüzde ishal, karın şişliği, iştahsızlık gibi hastalık belirtileri gittikçe daha az görülmekte olupatipikçölyak hastalığı daha sık görülmektedir[3].

Çölyak hastalığında büyüme geriliği, puberte gecikmesi, tedaviye dirençli demir eksikliği anemisi, D vitamini eksikliği, kalsiyum eksikliğine bağlı metabolik kemik hastalığı, erken yaşta osteopeni ve osteoporozuile gelebilmektedir. ÇH'yebağlı düşük kemik mineral yoğunluğu, ince barsaktak iinflamasyonasekonder gelişen intestina lmalabsorpsiyonsonucu kalsiyum ve vitamin D eksikliğinden kaynaklanmaktadır[3,4]. Düzleşmiş mukozadan kalsiyum ve D vitamini emiliminin bozulmasına, endojen kalsiyum kullanımının artmasına veya dışkı ile kaybedilmesine bağlı, negatif kalsiyum dengesi ve parathormon (PTH)'nunkompansatuar yanıtı kemik kaybının esas nedenidir. Kemik ağrıları, yalancı kırıklar ya da kemik deformiteleri olabileceği gibi osteomalazi durumunda genellikle semptom görülmez. Bu nedenle yeni tanı konulan hastalarda kemik mineral yoğunluğu(KMY) ölçümü yapılmalıdır[5].

Çalışmamızın amacı, ÇH tanısı alan çocuklarda tanı esnasında KMY belirlenmesi ve kemik mineral metabolizmasıyla ilişkili faktörlerin araştırılması amaçlanmıştır.

Gereç ve Yöntemler

Çalışmaya Aralık 2015-Aralık 2019 tarihleri arasında hastanemiz çocuk gastroenteroloji polikliniğinde çölyak hastalığıtanısı alan hastalar dahil edildi. Çalışma Helsinki İlkeler Deklerasyonu'na uyularak gerçekleştirildi ve Hitit Üniversitesi Tıp Fakültesi Etik Kurulu'ndan onay alındı (11.12.2019/109).

Çölyak hastalığı tanısı Avrupa Çocuk Gastroenteroloji Hepatoloji ve Beslenme Derneği (ESPGHAN) 2012 kriterlerine göre kondu [6]. İnce bağırsak biyopsilerinin histopatolojik değerlendirmesi modifiye Marsh (Oberhuber) sınıflaması ile yapıldı [7]. Retrospektif olarak hastaların hastane bilgi yönetim sistemine kayıtlı klinik, antropometrik, patolojik ve laboratuarverileri [kalsiyum, fosfor, alkalenfosfataz (ALP), parathormon (PTH), 25 OH vitamin D düzeyleri] incelendi. HastalarınHolojic DXA Quality Control Phantom marka alet ile DEXA yöntemiyle ölçülmüş olan lumbal (L1-L4) kemik mineral yoğunluğu düzeyleri değerlendirildi ve kronolojik yaşa ve boy yaşına göre KMY Z-skorlarının hesaplanmasında sağlıklı Türk çocuklarının KMY verileri kullanıldı[8]. Hastaların boy, vücut ağırlığı ve vücut kitle indekslerinin (VKİ) değerlendirilmesinde ve bu ölçümlerin standart deviasyon skorlarının (SDS) hesaplanmasında Neyzi ve arkadaşları tarafından Türk

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çocukları için hazırlanmış olan persentil çizelgeleri referans alındı [9]. Cinsiyete göre çocuğun boyunun 50. persentildeki yaş karşılığıboy yaşı olarak kabul edildi.

İstatistiksel analizler IBM SPSS Statisticsfor Windows 22.0 yazılımı ile gerçekleştirildi Nitel değişkenleri karşılaştırmak için Pearson ki-kare testi ya da beklenen frekansı 5'ten küçük hücre olduğunda Fisher'in kesin testi kullanıldı. Sayısal değişkenlerin normal dağılım gösterip göstermediği Shapiro-Wilk testi ile incelendi, normal dağılan değişkenleri 2 grupta karşılaştırmak için bağımsız gruplarda t-testikullanıldı. Normal dağılmayan değişkenleri 2 grupta karşılaştırmak için Mann-Whitney U testi kullanıldı. Normal dağılan değişkenler arasındaki ilişki Pearson bağıntı katsayısı ve normal dağılmayan değişkenler arasındaki ilişki ise Spearman sıra bağıntı katsayısı kullanılarak incelendi. p<0,05 değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular

Ortalama yaşları 9,9±4,8 (2,5-17,7) yıl olan 43 hastanın (34 kız/9 erkek) verileri değerlendirildi. Tanıda hastaların %46,5'i (n=20) pubertaldi. Olguların klinik özellikleri Tablo 1'de, laboratuar özellikleri Tablo 2'de gösterilmiştir.

Tablo 1. Olguların klinik özellikleri

	Ortalama±SD	En küçük-En büyük
Yaş (yıl)	9,9±4,8	2,5-17,7
Vücut Ağırlığı (kg)	29,9±14,6	11,4-65,5
Vücut Ağırlığı SDS	-1,1±1,1	-3,5-0,8
Boy (cm)	130,0±27,0	86,5-178,3
Boy SDS	-0,9±1,3	-4,2-1,9
VKİ (kg/m2)	16,4±2,1	12,9-22,4
VKİ SDS	-0,8±1,1	-3,1-1,0
Puberte evresi (median)	1	1-5

SD: standart deviasyon, SDS: standart deviasyon skoru VKİ: vücut kitle indeksi

Tablo 2. Olguların laboratuar özellikleri

	Ortalama±Standartdeviasyon	En küçük-En büyük
Kalsiyum (mg/dl)	9,7±0,4	8,9-10,9
Fosfor (mg/dl)	4,7±0,6	2,7-6,0
Alkalenfosfataz (U/L)	203,0±100,1	100,0-466,0
Parathormon(pg/ml)	45,0±21,5	19,6-109,3
25 OH vit D (ng/ml)	13,5±7,7	4,6-35,1

Hastaların ortalama KMY düzeyi 0,6±0,2 (0,3-1,0) gr/cm2 olup, yaşa göre KMY Z-skoru -0,83±1,1 (-3,6-1,6), boy yaşına göre KMY Z-skoru -0,18±1,1 (-3,6-1,8) saptandı. Hastaların %51,2'sinde (n=22) yaşa göre KMY Z-skoru >-1, %34,9'unda (n=15) -1 ve -2 arasında ve %14'ünde (n=6) <-2 saptandı.

Olguların %30,2'si (n=13) 0-6 yaş, %30,2'si (n=13) 7-11 yaş aralığında ve % 39,5'i (n=17) 11 yaş üzerindeydi. Yaşa göre KMY Z-skorunun<-2 olma oranı 11 yaştan büyük çocuklarda anlamı olarak yüksekti (p<0,001) (Tablo 3).

Tablo 3. Hastaların yaşa göre KMY Z skorları dağılımı

Yaş grubu	Yaşa Göre KMY Z-skoru		
	<-2	-1 ve -2 arası	>-1
0-6 yaş (n=13)	%0 (n=0)	%53,8 (n=7)	%46,2 (n=6)
7-11 yaş (n=13)	%0 (n=0)	%46,2 (n=6)	%53,8 (n=7)
>11 yaş (n=17)	%35,3 (n=6)	%11,8 (n=2)	%52,9 (n=9)

Hastaların %16,7'si (n=7) tipik, %64,3'ü (n=28) atipik ve %19'u (n=8) sessiz ÇH idi. Marsh evresine göre ise, %46,5'i (n=20) Tip 3a, %25,6'sı (n=11) Tip 3b, %27,9'u (n=12) Tip 3c olarak saptandı.KMY Z-skorları ile çölyak tipi ve Marshhistopatolojik evresi arasında ilişki saptanmadı (p>0,050) .

Hastaların yaşı ve puberte durumu ile kronolojik yaşa göre ve boy yaşına göre KMY Z-skorlarında farklılık saptanmadı (sırasıyla p=0,150, p=0,225). Yaşa göre KMY Z-skoru ile vücut ağırlığı, boy ve VKİ SDS arasında pozitif korelasyon saptandı (sırasıyla r=0,574; p<0,001, r=0,420; p=0,005, r=0,368; p=0,015).

Hastaların yaşa ve boy yaşına göre KMY Z-skorları ile serum D vitamini, kalsiyum, fosfor, ALP ve PTH düzeyleri arasında ilişki saptanmadı (p >0,050).

Tartışma

Çölyak hastalığı hem çocuklarda hem de erişkin yaş grubunda görülen ve yaşam boyu devam eden bir hastalıktır ve çok geniş bir yelpazede klinik bulgularla karakterizedir. Erken yaş grubunda ishal, karın şişliği, büyüme geriliği gibi tipik belirtiler ön planda iken, yaş ilerledikçe osteoporoz, malignite, epilepsi vs. gibi gastrointestinal sistem dışı belirtiler ön plana geçer [10]. Düşük kemik mineral yoğunluğu tedavi edilmemiş çölyak hastalarında önemli bir komplikasyondur. Çölyak hastalığınabağlı düşük kemik mineral yoğunluğu, intestinalmalabsorpsiyona bağlı gelişen kalsiyum ve D vitamini eksikliğinden kaynaklanmaktadır.Osteoporoz, rikets ve osteomalazi, ÇH'nınatipik bulgularındır[5,11]. Tedavisiz hastalarda KMY'nun normalden düşük olduğu, sıkı glutensiz diyet tedavisi ile hızla normale döndüğü gösterilmiştir [5]. Medave arkadaşlarının yaptığı çalışmada KMY ölçümü yapılan 41 hastadan %22'sinde osteopeni, %12.2'sinde osteoporoz ve ayrıca iki hastada rikets (%14,3) saptanmıştır [5]. Tau ve arkadaşlarınınçalışmasında yaşları 1-11 arasında değişen 24çölyak tanılı hastaya yapılan lombervertebra DEXA ölçümünde Z skoru değerlerinin oldukça düşük olduğu (-1.36±1.20) ve olguların % 17'sinin Z skorunun -2'den daha düşük olduğu ortaya çıkmıştır bulunmuştur[3]. Zanchi ve ark. tedavisiz 54 çölyaklı çocukta yaptıkları DEXA taramasında %18 oranında osteopeni (Z skoru -2 SD ile -1 SD arası) tespit ettiler [12]. Altıaylık glutensiz diyet sonrasında ise hastaların kemik

mineral yoğunluğunda iyileşme olduğunu, bu nedenle çölyak hastalığı olan ve glutene kısa süre maruz kalmış çocuklarda kemik metabolizması için ileri tetkiklerin gereksiz olduğunu belirtmişlerdir[12,13]. Çalışmamızda ise %34,9 oranında osteopeni ve %14 oranında osteoporoz saptandı.

Tanıda, Marshhistopatolojik evresinin osteoporoz gelişme riski taşıyan düşük KMY oluşumunu tahmin edebileceği öne sürülmektedir. Öte yandan tanı anında hastaların KMY'nunMarsh derecesiyle ilişkili olmadığını ve ÇH olan çocuklarda düşük KMY için klinik ve laboratuar belirteçlerin olmadığını ileri süren çalışmalar da mevcuttur[14]. Çalışmamızda KMY Z-skorları ile Marshhistopatolojik evresi arasında ilişki saptanmadı.

Balcı ve ark.tarafından yapılan çalışmada, çalışmamıza benzer şekilde ÇH tanısı almış hastalarda KMY Z-skorları ile serum kalsiyum, D vitamini, parathormon vediyetle kalsiyum alımı arasında anlamlı bir farklılık bulamamışlardır [14]. Çölyak hastalığı ilişkili osteoporozla ilgili önemli nokta, glutensiz diyet tedavisi ile KMY'da tam iyileşme çocuklarda mümkünken, bu durumun yetişkinler için geçerli olmamasıdır [14,15]. Literatürde çölyak hastalığı olan çocuklarda yaş arttıkça KMY Z-skorlarında azalma olduğu ve yaş ile orantısal olarak kemik mineral kaybının arttığını bildirilmiştir. Çalışmamızda da benzer şekilde yaşa göre KMY Z-skorunun<-2 olma oranının 11 yaştan büyük çocuklarda anlamı olarak yüksek olduğu saptandı. Sıkı glütensiz diyetin kemik mineralizasyonunu önemli ölçüde artırdığı vurgulanmaktadır[16]. Ergenlikten önce uygun tedaviyi alan hastaların yetişkin yaşlarda osteoporotik hale gelmeyecekleri bildirilmektedir [14].

Sonuç

Çölyak hastalarında tanı yaşının ileri kayması kemik mineral yoğunluğunu olumsuzetkilemektedir. Erken yaşta tanı konulması kemik mineral kaybını engeller ve osteopeni ve / osteoporoz gelişmiş olan hastalarda tedavi olanağı sağlayarak morbiditeyi azaltır.Bu durum, hastaların erken teşhis ve tedavisini gerekli kılmaktadır.

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Original Article

Do we really need patch and shunt for carotid endarterectomy?

Karotis endarterektomide yama ve şanta gerçekten ihtiyacımız var mı?

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Abstract

Aim: The efficacy of carotid endarterectomy (CEA) for stroke prevention in asymptomatic and symptomatic patients is well known. We aimed to share long term follow up results for primary closure technique for CEA without shunting and investigated risk factors for complications in this patient group.

Material and Methods: Between September 2013-2019, 122 patients with isolated CEA with primary closure were enrolled in this retrospective study. Dopppler ultrasound (DUSG) scanning was used as the primary imaging tool for the determination of residual and recurrent stenosis. During the follow-up period duplex ultrasonography was performed in the second month, sixth month and annually thereafter. Ipsilateral cerebrovascular events and mortalities were recorded during follow up period.

Results: The mean age was 69,1 ± 7,1 (48-90) years. The median follow-up time was 47 (5 to 78) months. Hospital mortality was reported in 1 patient (0,8%). Early postoperative cerebrovascular accident were seen as ipsilateral disabling stroke in 1 patient (0,8%), ipsilateral non-disabling stroke in 1 patient (0,8%), reversible ischemic neurological deficit (RIND) in 1 patient (0,8%) and massive intracranial bleeding in 1 patient (0,8%). Late mortality was reported in 4 (3,3%) patients. 2 (1,6%) were cardiac reasons and 2 (1,6%) were non cardiac reasons. During the follow-up period ipsilateral cerebrovascular accident (CVA) were seen in 3 patients (2,5%) and these were; ipsilateral disabling stroke in 1 patient (0,8%), ipsilateral non-disabling stroke in 1 patient (0,8%), RIND in 1 patient (0,8%).According to the latest duplex scanning during follow up period 4 (3,3%) patients had below 50% restenosis, 2 (1,7%) patients had above 70% restenosis and 1 (0,8%) patient had total occlusion.

Conclusion: Primary closure technique for CEA can be used in selected patients with acceptable early and late complication rates, low mortality and low restenosis rate.

Keywords: carotid endarterectomy; carotid artery disease; carotid artery stenosis

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Öz

Amaç: Karotis endarterektomi (KEA) ameliyatının semptomatik ve asemptomatik hastalarda inmeyi önlemedeki etkinliği bilinmektedir. Biz bu çalışmada şant kullanmadan, primer kapama tekniği ile gerçekleştirdiğimiz KEA operasyonlarının uzun dönem sonuçlarını paylaşmayı amaçladık.

Gereç ve Yöntemler: Ekim 2013 ile 2019 tarihleri arasında şant kullanmadan primer kapama tekniği ile opere olan 122 hasta bu retrospektif çalışmaya dahil edildi. Doppler ultrasonografi (DUSG) rezidüel ve tekrarlayan darlıkların tespiti için primer görüntüleme yöntemi olarak kullanıldı. Takip süresince hastalar ikinci, altıncı aylarda ve sonrasında yıllık olarak yapıldı. Takiplerde ipsilateral serebrovasküler olaylar ve mortalite kayıtları alındı.

Bulgular: Hastaların ortalama yaşı 69,1 ± 7,1 (48-90)'ydi. Median takip süresi 47 (5 - 78) aydı. 1 (0,8%) hastada hastane içi ölüm gerçekleşti. Erken dönemde; 1(0,8%) hastada ipsilateral sekel bırakan ve 1(0,8%) hastada da sekelsiz serebrovasküler olay izlendi. Yine 1(0,8%) hastada geridönüşümlü iskemik nörolojik defisit ve 1(0,8%) hastada kafaiçi kanama görüldü. Geç mortalite gelişen hasta sayısı 4 (3,3%) olarak kayıt edildi. Bunların 2 (1,6%)'si kardiyak nedenli ölümdü. Geç dönemde 3 (2,5%) hastada ipsilateral serebrovasküler hadise gelişti. Bunların 1 (0,8%)'i sekel bırakan, 1 (0,8%)'i sekel bırakmayan inmeydi. 1 (0,8%) hastada da geridönüşümlü iskemik nörolojik deficit görüldü. Geç dönemde DUSG sonuçlarına göre 4 (3,3%) hastada 50%'nin altında, 2 (1,7%) hastada 70%'in üzerinde darlık görüldü. 1 (0,8%) hastada da total oklüzyon meydana saptandı.

Sonuç: Primer kapama tekniği ile KEA seçilmiş hastalarda kabul edilebilir erken ve geç dönem komplikasyon, düşük mortalite ve tekrarlayan darlık oranlarıyla uygulanabilir.

Anahtar kelimeler: karotis endarterektomi; karotis arter hastalığı; karotis arter darlığı

Introduction

The efficacy of carotid endarterectomy (CEA) for stroke prevention in asymptomatic and symptomatic patients with severe carotid stenosis was shown in many studies. [1-4]

American Heart Association (AHA) defines stroke and mortality rates threshold values for CEA in the light of many clinical studies. Threshold values for stroke are below 6% in symptomatic patients (above 50% stenosis proved by angiography) and below 3% in asymptomatic patients (above 60% stenosis proved by angiography) for CEA. [5]

Today, there is no consensus about two basic subjects for severe asymptomatic or symptomatic carotid stenosis patients. First is which treatment strategy is the right choice CEA or carotid artery stenting (CAS) in this group of patients. Second is which option among primary closure, eversion, synthetic or autologous venous patch is the best choice while performing CEA.

In this study, we aimed to share long term follow up results for primary closure technique for isolated CEA without shunting and investigated risk factors for complications in this patient group.

Material and Methods

All patients were operated by the same senior surgeon in two different centres. Patients who underwent staged, reverse staged and concomittant procedures were excluded from the study.

Clinical and demographic data were obtained from hospital records and office charts. Preoperative data were age, gender, hypertension, smoking, atherosclerotic cardiac disease, diabetes mellitus, peripheral vascular disease, family history, hyperlipidaemia, previous cardiac surgery, chronic obstructive pulmonary disease, chronic renal failure, atrial fibrillation and history of carotid artery disease symptoms (including disabling and non-disabling stroke, reversible ischemic neurologic deficit (RIND), transient ischemic attack (TIA), amaurosis fugax). Results of preoperative imaging (duplex ultrasonography (DUSG), computerized tomographic angiography (CTA), digital subtraction angiography (DSA) or conventional angiography) were also noted. Perioperative data including carotid artery clamping time, using of shunt, type of surgery (elective, emergent or urgent) were recorded.

Preoperative and postoperative DUSG examinations were performed by using a General Electric Logiq S7 Expert scanner equipped with 9L linear multi frequency transducer. The B-mode settings were adjusted to optimize the quality of the grey-scale images and the pulse repetition frequency used with colour Doppler flow imaging was adjusted according to the flow velocity.

The characteristics of the plaques were described in accordance with the Gray-Weale Classification.[6,7] The degree of stenosis involving the internal carotid artery (ICA) was described in accordance with the Society of Radiologists in Ultrasound Consensus Criteria reported by Grant et al.[8] All stenosis were confirmed by CTA or DSA or conventional angiography.

DUSG scanning was used as the primary imaging tool for the determination of residual and recurrent stenosis. During the follow-up period DUSG was performed in the second month, sixth month and annually thereafter. Restenosis which was found during follow-up period was classified as the same classifying criteria like preoperative period. Ipsilateral cerebrovascular events and mortalities were recorded during follow up period.

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Emergent CEA was performed for revascularization of symptomatic patients within 2 weeks from stroke onset. Urgent CEA was performed within 6 hours from stroke onset. All patients signed standard informed consent forms for carotid endarterectomy and were informed about the potential risk of surgery.

All patients had dual anti-platelet (acetylsalicylic acid 100 mg and clopidogrel 75 mg) and anti hyperlipidemic therapy (atorvastatin 20 mg) during follow-up period.

Informed consent was obtained from all the patients participating in the study, and all the researchers signed the Declaration of Helsinki. Approval for the study was granted by the local ethics committee.

Surgical Technique

All procedures were performed under general anaesthesia. After positioning the patient, an incision was made anterior to the sternocleidomastoid muscle and exploration of common (CCA), external (ECA) and internal (ICA) carotid arteries was performed. After heparinisation (weight-based heparin dosing) (85 IU/kg), the vascular clamps were placed and arteriotomy was performed from CCA to ICA. Endarterectomy was applied and then atheromatous plaque was removed. A search for intimal flap was done and tacking sutures (with 7/0 non-absorbable polypropylene) was applied to the ICA if needed. If a large atheromatous plaque was protruding into the ECA, eversion endarterectomy technique was performed to the ECA. Finally the arteriotomy site was primarily repaired by 6/0 monofilament non-absorbable suture with continue technique under proper magnification. Protamine sulphate was not administered at the end of the procedure. After meticulous homeostasis and placement of minivac drain, wound closure and dressing was performed. For all patients conventionally accepted methods of determining the need of shunt insertion, including formal measurement of the ICA back flow and if needed back flow pressure were used. In this series all patients were operated without shunting. The vascular clamping time was recorded during the procedure.

Statistical Analysis

Data analyses were performed by using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). Whether the distributions of continuous variables were normally or not was determined by Kolmogorov Smirnov test. Continuous variables were shown as mean ± SD or median (min-max), where applicable. Number of cases and percentages were used for categorical data. While, the mean differences between groups were compared by Student's t test, otherwise, Mann Whitney U test was applied for not normally distributed data. Categorical variables were analysed by Fisher's exact test. A p value less than 0.05 was considered statistically significant.

Results

Between September 2013-2019, 122 patients with isolated CEA with primary closure were enrolled in this study. All patients were operated by same senior surgeon in two different centres. 75 patients (61,5%) were male and 47 patients (38,5%) were female. The mean age was 69,1 ± 7,1 (48-90) years. Degree of stenosis in contralateral ICA was under 50% in all patients who had bilateral stenosis.

In addition to degree of stenosis, type of plaque and symptomatology of patient were also taken into consideration while deciding surgery. 6 patients with 50-70% stenosis were operated because of their symptoms and type 1 or type II plaques. Preoperative demographic variables, clinical features and preoperative ultrasonographic parameters of the patients listed in Table I.

Table I. Preoperative Demographic Variables, Clinical Features and Preoperative Ultrasonographic Parameters of Patients.

Variables	Patients n (%)
Age (year)	69,1 ± 7,1 (48-90)
Gender (Male/Female)	75/47 (61,5%/ 38,5%)
Family History	71(58,2%)
Smoking	50 (41%)
HT	91 (74,6%)
HL	71 (58,2%)
COPD	42 (34,4%)
DM	47(38,5%)
CAD	23 (18,9%)
Previous Cardiac Surgery	6 (4,9%)
CRF	9 (7,4%)
PVD	20 (16,4%)
AF	0 (0%)
Preoperative Clopidogrel Usage	44 (36,1%)
Bilateral Carotid Artery Disease	35 (28,7%)
Symptomatic Carotid Artery Disease	45(36,9%)
Symptomatology	
TIA	17 (13,9%)
RIND	10 (8,2%)
Stroke (non-disabling)	8 (6,6%)
Stroke (disabling)	4 (3,3%)
Amourosis Fugax	6 (4,9%)
Degree Of Stenosis *	
50 – 70 %	6 (4,9%)
> 70%	85 (69,7%)
Near Occlusion	31 (25,4%)
Type Of Carotid Artery Plaque **	
Type I	44 (36,1%)
Type II	52 (42,6%)
Type III	19 (15,6%)
Type IV	7 (5,7%)

* According to the Society of Radiologists in Ultrasound Consensus Criteria
** According to Gray-Weale Classification
(HT: Hypertension, HL: Hyperlipidemia, COPD: Chronic Obstructive Pulmonary Disease, DM: Diabetes Mellitus, CAD: Coronary Artery Disease, CRF: Chronic Renal Failure, PVD: Peripheral Vascular Disease, TIA: Transient Ischemic Attack, RIND: Reversible Ischemic Neurologic Deficit, AF: Atrial Fibrillation)

117 patients (95,9%) were electively operated. 2 symptomatic patients (1,6%) were operated within two weeks of stroke onset and 3 patients (2,5%) were operated within 6 hours of stroke onset. We did not use shunt in any of the patients. We decided not to use shunt by intraoperative electroencephalography, and measuring stump pressure or backflow velocity. The median carotid artery clamping time was 19 (12 to 36) minutes. The median intensive care unit (ICU) stay was 1 (1 to 12) day, the length of median hospital stay was 3 (3 to 12) days and the median follow-up time was 47 (5 to 78) months.

Postoperative complications were reported in 11 patients (9%) and in hospital mortality was reported in 1 patient (0,8%). Early postoperative complications were seen in 11 patients (9%). These complications were; neck hematoma and bleeding (not required re-exploration) in 4 patients (3,4%), recurrent laryngeal nerve dysfunction in 2 patients (1,6%), hypoglossal nerve damage in 1 patient (0,8%), ipsilateral disabling stroke in 1 patient (0,8%), ipsilateral non-disabling stroke in 1 patient (0,8%), RIND in 1 patient (0,8%) and massive intracranial bleeding in 1 patient (0,8%).

Ipsilateral cerebrovascular event was reported in 4 patients and DUSG or CTA were performed. 3 patients had no stenosis or occlusion whereas 1 patient had total occlusion. This patient had RIND. The patient was re-operated. Thrombus was aspirated and arteriotomy was primarily sutured again. Neck hematoma and bleeding were reported in patients who use clopidogrel during preoperative period but this was not statistically significant. Patient with postoperative ipsilateral disabling stroke was the one who was operated urgently within 6 hours of stroke onset.

Late mortality was reported in 4 (3,3%) patients. 2 (1,6%) were cardiac reasons and 2 (1,6%) were non cardiac reasons. During the follow-up period ipsilateral cerebrovascular accident (CVA) were seen in 3 patients (2,5%) and these were; ipsilateral disabling stroke in 1 patient (0,8%), ipsilateral non-disabling stroke in 1 patient (0,8%), RIND in 1 patient (0,8%).

According to the latest duplex scanning during follow up period 114 (94,2%) patients were normal, 4 (3,3%) patients had below 50% stenosis, 2 (1,7%) patients had above 70% stenosis and 1 (0,8%) patient had total occlusion. This patient was the one who had late disabling stroke complication. Operative and the follow-up data are listed in Table II.

Table II. Operative and Follow-up Data of Patients.

Carotid Artery Vascular Clamping Time (min)	19 (12 to 36)
ICU Stay (day)	1 (1 to 12)
Length Of Hospital Stay (day)	3 (3 to 32)
Follow-up Time (month)	47 (5 to 78)
	n (patient) (%)
Type of Surgery	
Elective	117 (95,9%)
Emergent	3 (2,5%)
Urgent	2 (1,6%)
Early Postoperative Complications	
Neck Hematoma and Bleeding	4 (3,6%)
Recurrent Laryngeal Nerve Dysfunction	2 (1,6%)
Hypoglossal Nerve Dysfunction	1 (0,8%)
Ipsilateral Disabling Stroke	1 (0,8%)
Ipsilateral Non-disabling Stroke	1 (0,8%)
RIND	1 (0,8%)
Intracranial Bleeding	1 (0,8%)
Early Mortality	1 (0,8%)
Late Complications	
Ipsilateral Disabling Stroke	1 (0,8%)
Ipsilateral Non-disabling Stroke	1 (0,8%)
RIND	1 (0,8%)
Late Mortality	
Cardiac	2 (1,6%)
Non-cardiac	2 (1,6%)
Degree Of Restenosis *	
< 50%	4 (3,3%)
> 70%	2 (1,6%)
Occlusion	1 (0,8%)

* According to the Society of Radiologists in Ultrasound Consensus Criteria
(ICU: Intensive Care Unit, RIND: Reversible Ischemic Neurologic Deficit)

There is no statistically significant difference between preoperative variables and operative data when we compare patients who had late cerebrovascular accidents with had no complications.

When we compare patients who had restenosis after operation with patients with normal control DUSG, we found out that bilateral carotid artery stenosis was statistically significant in restenosis group (p=0,018). Also these patients, who had restenosis, had statistically significantly less type 2 plaque preoperatively (p=0,020). In addition to this, type 4 preoperative plaque was higher in restenosis group but this is not statistically important (p= 0,052). Comparison of the demographic and the clinical features of the patients who were accepted to have restenosis during the follow-up period are listed in Table III.

Patients who had cerebrovascular events during follow up period had higher PVD ratio than the others but this is not statistically significant (p=0,070).

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Table III. Comparison of Demographic and Clinical Features Of Patients Who Determined Restenosis During Follow-up Period.

Variables	Normal (n=114)	Restenosis (n=7)	p-value
Age (year)	68.8±7.0	72.7±8.1	0.167†
Gender Male Female	 69 (60,5%) 45 (39,1%)	 5 (71,4%) 2 (28,6%)	 0.705‡
Family History	67(58,8%)	3 (42,9%)	0.453‡
Smoking	46 (40.4%)	4 (57,1%)	0.446‡
HT	84 (73,7%)	6 (85,7%)	0.676‡
HL	85 (74,6%)	6 (85,7%)	0.680‡
COPD	39 (34,2%)	3 (42,9%)	0.693‡
DM	46 (40,4%)	1 (14,3%)	0.246‡
CAD	21 (18,4%)	1 (14,3%)	1.000‡
Previous Cardiac Surgery	6 (5,3%)	0 (0,0%)	1.000‡
CRF	9 (7,9%)	0 (0,0%)	1.000‡
PVD	17 (14,9%)	2 (28.6%)	0.302‡
Preoperative Clopidogrel Usage	41 (36%)	2 (28,6%)	1.000‡
Bilateral Carotid Artery Disease	29 (25,4%)	5 (71.4%)	0.018‡
Symptomatic Carotid Artery Disease	40 (35,1%)	4 (57.1%)	0,255‡
Preoperative Carotid Duplex US 50-70 % > 70 % Near Occlusion	 6 (5,3%) 80 (70,2%) 28 (24,6%)	 0 (0.0%) 5 (71,4%) 2 (28,6%)	 1.000‡ 1.000‡ 1.000‡
Type Of Plaque Type I Type II Type III Type IV	 40 (35,1%) 51 (44,7%) 18 (15,8%) 5 (4,4%)	 4 (57,1%) 0 (0,0%) 1 (14,3%) 2 (28,6%)	 0.251‡ 0,020‡ 1,000‡ 0,052‡
Type Of Surgery Elective Emergent Urgent	 109 (95,6%) 3 (2,6%) 2 (1,8%)	 7 (100%) 0 (0%) 0(0%)	 1,000‡ 1,000‡ 1,000‡
Carotid Artery Vascular Clamping Time (min)	19 (12-36)	20 (17-28)	0,627¶

† Student's T-test, ‡ Fisher's Exact Test, ¶ Mann Whitney U Test (HT: Hypertension, HL: Hyperlipidaemia, COPD: Chronic Obstructive Pulmonary Disease, DM: Diabetes Mellitus, CAD: Coronary Artery Disease, CRF: Chronic Renal Failure, PVD: Peripheral Vascular Disease)

Discussion

The primary goal in carotid artery revascularization is to prevent stroke in patients with carotid artery stenosis but there are two important questions which have not been answered yet. First one is CAS or CEA and the second one is which technique is most preferable while performing CEA.

On the basis of the extensive experience and several meta-analysis of randomized clinical trials comparing CAS with CEA disclosed no difference stroke or death rates in 30 days; in myocardial infarction (MI), stroke or death rates in 1 year. [9,10] In some studies, CAS was associated with a lower rate of MI and procedural morbidity such as cranial nerve injury [9], but others found CAS to be inferior to CEA or associated with higher rates of periprocedural stroke.[11,12] In some reports, there is near equivalence between CAS and CEA.[13,14] However, CEA has maintained superiority in most clinical trials and remains the best treatment option for most patients who require revascularization for carotid artery disease.

There are many randomised controlled investigations about which technique is superior about CEA. Mannheim et al. compared polyurethane patch to primary closure and stated that the rate of residual stenosis (≥ 50%) at 0 or 3-month follow-up was significantly lower in the patch group (2 operations, 1,1%) compared with the primary closure group (17 operations, 8,9%) (p=0.001, OR, 0,114; 95% CI, 0.026 to 0.5). And they have stated that; ≥ 70% recurrent stenosis was seen in 18 postoperative arteries (5.2%) (14 (8,6%) after primary closure and 4 (2,2%) after patch angioplasty), ≥ 50% recurrent stenosis was found in 31 arteries (8,9%) (22 (13,6%) after primary closure versus 9 (4,9%) arteries with patch closure). They reported that only patch angioplasty was found to influence the restenosis rate.[15]

Karen J. Ho et al. reported intermediate term outcome of CEA with bovine pericardial patch closure compared with Dacron patch and primary closure. They found that 30-day stroke and death were significantly lower in primary closure group. When they compared groups about five year restenosis rates, they found out that patch closure (especially bovine patch closure) had better outcomes but they also stated that none of the variables proved significant predictors of restenosis.[16] Similarly, Efthymios et al. stated that there was no statistically significant difference among primary closure, patch closure and eversion closure about stroke and death rates.[17]

In EVEREST (Eversion Carotid Endarterectomy Versus Standard Trials) study, 1353 patients were included and divided into two groups (678 patients in the conventional group, 675 patients in the eversion group). They found no statistical difference in late outcome (stroke, death and restenosis) between standard (patch and primary closure) and eversion CEA. Subgroup analysis showed that restenosis were statistically comparable) 2,8% vs 1,5%) for eversion and patch, respectively, while both significantly lower restenosis rates than primary closure.[18]

In several studies, with respect to the technical component of the operation, there is consensus that patch closure is superior to primary closure.[18,19] On the other hand, there are many studies reported that primary closure technique is comparable and even superior to patch closure technique thanks to new medical treatment regimens and careful selection of patients. [20] Similarly, in our series, recurrent stenosis was seen in seven patients and only 3 of them serious (4 patients (3,3%) < 50% stenosis, 2 patients (1,7%) > 70% stenosis and 1 patient (0,8%) occlusion).

Study Limitations

This study is a retrospective, descriptive study and there is no control group of patients who underwent alternative techniques for comparison. Despite these, we believe that our study add useful information to the literature about safety and efficacy of primary closure technique for the CEA.

Conclusion

As a conclusion, primary closure technique for CEA can be used by experienced centres safely in selected patients with acceptable early and late complication rates, low mortality and low restenosis rate.

Declaration of conflict of interest

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Original Article

The association of platelet-to-lymphocyte ratio with in-hospital acute stent thrombosis in non-st elevated acute coronary syndromes

Non-ST eleve akut koroner sendromda platelet/lenfosit oranının akut stent trombozunu öngörmedeki rolü

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Abstract

Aim: Cardiovascular diseases are the leading causes of mortality in the world. Interventional methods used in the treatment of coronary artery disease have revolutionized the treatment of the disease. Balloon angioplasty and coronary stenting are two miraculous treatment methods of the disease. Acute stent thrombosis(ST) is a serious and mortal complication of stent thrombosis. Platelet-to-lymphocyte ratio (PLR), a novel inflammatory marker, has previously been shown to be associated with cardiac problems. In this study, we aimed to investigate the association of PLR with in hospital acute stent thrombosis.

Material and Methods: 1300 patients without ST elevated myocardial infarction (NSTEMI)who underwent stent implantation between January 2013 and December 2013 in our hospital were included in the study. Demographic, clinical, angiographic and laboratory parameters of all participants were recorded.

Results: In the ST+ group hypertension, diabetes mellitus rates were higher, clopidogrel loading time was shorter. The mean PLR value was significantly higher in the ST+ group as compared to ST- group (133.3 ± 75.0 vs 110.1 ± 47.0, p= 0.005). In the multivariate analyses hypertension, diabetes mellitus, shorter clopidogrel loading time and PLR was found to be independent predictors of acute stent thrombosis.

Conclusion: Our results demonstrated that PLR is an independent predictor of acute stent thrombosis in Non-ST elevated acute coronary syndrome patients.

Keywords: acute stent thrombosis; platelet-to-lymphocyte ratio; coronary artery disease; inflammation

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Öz

Amaç: Kardiyovaskuler hastalıklar dünyada önde gelen mortalite nedenidir. Akut stent trombozu (ST) stent implantasyonunun çok ciddi ve mortal bir komplikasyonudur. Yeni bir enflamatuar belirteç olan platelet/lenfosit oranının (PLR) daha önce kalp problemleriyle ilişkili olduğu gösterilmiştir. Bu çalışmada, ST- segment yükselmesiz akut koroner sendromlarda (ST- segment yükselmesiz myokard enfarktüsü ve kararsız angina) PLR ile akut stent trombozunun (ST) ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmamıza Ocak 2013- Aralık 2013 tarihleri arasında stent implantasyonu yapılan, ST- segment yükselmesiz akut koroner sendrom hastası 1300 hasta dahil edildi. Tüm hastaların demografik, klinik, anjiyografik ve laboratuvar parametreleri kaydedildi.

Bulgular: ST (+) grupta hipertansiyon, diabetes mellitus oranları daha yüksekti, klopidogrel yükleme süresi daha kısaydı. Ortalama PLR değeri ST (+) grupta ST (-) gruba göre anlamlı olarak daha yüksekti (133.3 ± 75.0'a karşı 110.1 ± 47.0, p = 0.005). Çok değişkenli analizlerde hipertansiyon, diabetes mellitus, kısa klopidogrel yükleme süresi ve PLR'nin akut stent trombozunun bağımsız öngördürücüleri olduğu bulundu.

Sonuç: Bulgularımız PLR' nin, ST- segment yükselmesiz akut koroner sendrom hastalarında akut stent trombozunun bağımsız bir öngördürücüsü olduğunu göstermiştir.

Anahtar kelimeler: akut stent trombozu; platelet/lenfosit oranı; koroner arter hastalığı; inflamasyon

Introduction

Cardiovascular diseases including coronary artery disease, cerebrovascular disease, peripheral artery disease and aortic arteriosclerosis are the leading causes of mortality in the world. Especially coronary artery disease is the most lethal disease of this group. In the United States, coronary artery disease is still responsible for about one third of deaths in people over 35 years of age. In Europe, 47% (52% in females and 42% in males) of deaths that occur each year are due to cardiovascular diseases, mainly CAD and stroke.

In the study of Heart Disease and Risk Factors in Turkish adults (TEKHARF), coronary artery disease was found to be responsible for 42.5% of the deaths which has a known cause. The prevalence of heart disease in adults in Turkey were found to be 6.7%.[1]

Interventional methods used in the treatment of coronary artery disease have revolutionized the treatment of the disease. Balloon angioplasty was used for the first time in 1977 by Gruentzig and colleagues in the treatment of coronary artery disease in 1986(4), Puel and colleagues performed intracoronary stent implantation, which is the second important invention of interventional treatment of coronary artery disease .[2, 3]

Stent implantation has been the main treatment for acute coronary syndrome due to improvements in stent technology and operator techniques, the use of dual antiplatelet therapy and positive results with acute intracoronary stenting in patients with acute occlusions due to dissection during PTCA, AMI and other acute coronary syndromes.

In this miraculous treatment method, stent restenosis and stent thrombosis are the major obstacles to treatment.

Acute stent thrombosis, which occurs in the first 24 hours after stent implantation, is a serious and mortal complication. Stent thrombosis and stent restenosis are the major problems of stent implantation. Despite advances in pharmacological treatment, stent technology and implantation techniques, stent thrombosis is still seen about 1-2% after stent implantation.PLR, a novel inflammatory marker, has previously been shown to be associated with cardiac problems such as stent restenosis, plaque fragility, and no-reflow phenomena. To the best of our knowledge, there is no study that previously examined the association of acute stent thrombosis with PLR. Our aim in this study is to investigate the relationship between acute stent thrombosis and PLR.

Material and Methods

Patients who underwent percutaneous coronary intervention between January 2013 and December 2013 at Turkey Yuksek Ihtisas Training and Research Hospital were screened retrospectively. Patients who had only balloon angioplasty and stent thrombosis after 24 hours of stent implantation were not included in the study. STEMI patients were also excluded. 1300 patients who underwent stent implantation were included in the study. 35 of these patients had in

hospital acute stent thrombosis. These patients were divided into 2 groups according to whether acute stent thrombosis developed. Risk factors (age, gender, hypertension, diabetes mellitus, dyslipidemia, family history for CAD, cigarette use) for coronary artery disease were recorded at the time of admission. In addition, risk factors for stent thrombosis (stent length, stent diameter, stent type, when ADP receptor antagonist was administered to the patient, and indication for stent implantation) were recorded. Patients with hypertension and hyperlipidemia were defined as either receiving treatment for these diseases at the time of the procedure or having the disease according to the ESC / ESH criteria at that time. Diabetes was defined as meeting the American Diabetes Association criteria or receiving antidiabetic treatment at the time of the procedure. Fifteen patients included in our study were randomly selected to determine the universality of the diagnosis of acute stent thrombosis. These patients were evaluated by different operators under the same conditions. Complete blood count, renal function tests and lipid profile were studied in venous blood samples taken immediately before percutaneous coronary intervention. The white blood cell components were determined by the Coulter counter method (Coulter LH780 Hematology Analyzer, Beckman Coulter Corp., Hileh, Fla.). The PLR value was obtained by dividing the number of platelets by the number of lymphocytes. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Statistical Analysis

All calculations were done using the SPSS 22.0 "Statistical Package for Social Sciences" program. The Shapiro Wilk test was used to determine the distributions of the data. Continuous variables were expressed mean ± standard deviation or median (interval between quarters); categorical variables were expressed in percentage and number. Continuous variables were compared using Student's t test or Mann Whitney U test and categorical variables were compared using Chi-Square or Fisher's test. Univariate logistic regression analysis was used to determine the association between variables and stent thrombosis.By the variables which were found associated with stent thrombosis and had a p value smaller than 0,05, multivariate logistic regression analyses were performed. The results of the regression analysis were expressed by the risk ratio (HR) and 95% confidence interval. Ap value less than 0,05 was considered as statistically significant.

Results

796 of 1300 patients included in the study were males. The average age was 59,7. Acute stent thrombosis was seen in 35 of these patients.

Table 1 shows demographic characteristics, presence of diseases that are risk factors for atherosclerosis, ejection fractions, which vessels were diseased, which vessels were intervened, clopidogrel loading time, implanted stent length and diameter, or stent type (DES or BMS) of ST + and ST- patients. There was no difference between ST + and ST- groups in terms of age, gender, smoking status, stent diameter and length. In the ST + group, it was seen that diabetes (60% vs 33,6%, p: 0,001), hypertension (77,1% vs. 40%, p: 0,001), lower ejection fraction (44,6± 8.5 vs. 54.1 ± 7.8, p: 0,001) were more frequent and clopidogrel loading time was shorter.

Table 2 shows the results of regression analysis. Univariable regression analysis showed that DM (2.954 (1.487-5.868), p: 0,002), HT (5.062 (2.282-11.232), p<0,001), pre-procedural EF (0.903 (0.875-0.932), p<0,001), clopidogrel loading time (0.122 (0.037-0.401), p: 0,001), acute coronary syndrome as indication for stent implantation (0.292 (0.186-0.458), p<0,001) and PLR(1.008 (1.002-1.014), p: 0,005) was associated with stent thrombosis. In multivariate regression analysis, DM (4.045 (1.684-9.719), p: 0,002), HT (7.223 (2.725-19.150), p<0,001), clopidogrel loading time (0.067 (0.019-0.237), p<0,001) and PLR (1.008 (1.001-1.015), p: 0,018) were found to be independent predictors for stent thrombosis.

Discussion

PLR, a novel inflammatory marker is an independent predictor of acute stent thrombosis.

Early stent thrombosis (generally defined as stent thrombosis within 30 days of stent placement, first 24 hours acute, 1-30 days subacute stent thrombosis) develops in approximately 0.5% to 1% of patients with well-placed stent and receiving dual antiplatelet therapy (aspirin and clopidogrel). More than 50% of patients with stent thrombosis develop myocardial infarction. The mortality rate in acute stent thrombosis is 10-15%.[4, 5]

Shorter clopidogrel loading time is an independent marker for stent thrombosis. If stent is implanted before clopidogrel is effective stent is prone to thrombosis. Systemic diseases such

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Table1. Comparisons of demographic and clinical characteristics

Parameters	ST+ (N=35)	ST– (N=1265)	P value
Age, years	60.8 ± 12.3	59.7 ± 8.6	0.457
Male, n (%)	25 (73.7)	771 (61.5)	0.209
Diabetes Mellitus, n (%)	21 (60.0)	426 (33.6)	0.001
Hypertension, n (%)	27 (77.1)	506 (40.0)	<0.001
Smoking, n (%)	24 (68.5)	933 (73.7)	0.492
Preprocedural LVEF, n (%)	44.6 ± 8.5	54.1 ± 7.8	<0.001
LAD disease, n (%)	16 (45.7)	493 (38.9)	0.388
LCX disease, n (%)	4 (11.4)	279 (22.0)	0.284
RCA disease, n (%)	14 (40.0)	434 (34.3)	0.863
Clopidogrel loading time < 2h, n (%)	32 (91.4)	716 (56.7)	<0.001
Clopidogrel loading time > 2h, n (%)	3 (8.5)	549 (43.3)	<0.001
BMS/DES, n	28/7	567/698	0.094
Elective PCI, n (%)	8 (22.8)	699 (55.2)	<0.001
Stent diameter (mm)	3.05 ± 0.33	2.99 ± 0.45	0.453
Stent length (mm)	19.0 ± 6.2	19.3 ± 5.7	0.784
Glucose, mg/dl	126.4 ± 55.1	136.1 ± 66.3	0.322
Creatinine, mg/dl	0.88 ± 0.19	1.01 ± 0.52	0.149
Hemoglobin, g/dL	13.7 ± 1.6	13.4 ± 2.2	0.381
Platelet count, $10^3/mm^3$	233.8 ± 92.9	227.24 ±67.9	0.584
WBC count, $10^3/mm^3$	10.2 ± 3.6	10.2 ± 4.5	0.974
Neutrophil,$10^3/mm^3$	6.9 ± 3.2	7.9 ± 3.0	0.461
Lymphocyte, $10^3/mm^3$	2.0 ± 0.9	2.2 ± 0.7	0.096
Total cholesterol, mg/dL	183.4 ± 50.2	182.9 ± 47.0	0.952
Triglyceride, mg/dL	181.7 ± 126.4	170.5 ± 121.1	0.588
LDL-cholesterol, mg/dL	120.8 ± 35.5	116.6 ± 33.9	0.478
HDL-cholesterol, mg/dL	37.6 ± 10.1	39.0 ± 9.1	0.373
PLR	133.3 ± 75.0	110.1 ± 47.0	0.005

Abbreviations: Data are presented as mean ±SD, or number (%). BMS, bare-metal stent; DES, drug-eluting stent; LAD, left anterior descending; LCX, left circumflex; LVEF, left ventricular ejection fraction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PLR, platelet to lymphocyte ratio.; RCA, right coronary artery; STEMI, ST segment elevation myocardial infarction; WBC, White blood cell; PLR, Platelet to lymphocyte ratio

Table 2. Multivariate logistic regression analysis to predicting the acute stent thrombosis.

	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Diabetes Mellitus	2.954 (1.487-5.868)	0.002	4.045 (1.684-9.719)	0.002
Hypertension	5.062 (2.282-11.232)	<0.001	7.223 (2.725-19.150)	<0.001
Preprocedure LVEF	0.903 (0.875-0.932)	<0.001	0.969 (0.921-1.020)	0.224
Clopidogrel loading time	0.122 (0.037-0.401)	0.001	0.067 (0.019-0.237)	<0.001
Stent diameter	1.296 (0.659-2.550)	0.453	-	-
ACS(high troponin) or elective	0.292 (0.186-0.458)	<0.001	0.556 (0.299-1.033)	0.063
Stent length	0.992 (0.934-1.053)	0.784	-	-
PLR	1.008 (1.002-1.014)	0.005	1.008 (1.001-1.015)	0.018

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio; PLR, platelet to lymphocyte ratio.

as diabetes mellitus and hypertension are also independent predictors for stent thrombosis. These diseases are increasing the complexity of the disease and tendency to thrombosis.

Active increased inflammation can increase thrombosis. Atherosclerosis is a systemic chronic inflammatory disease. It is known that inflammatory markers such as hsCRP, P selectin, IL-6 are also effective in stent restenosis as well as in atherosclerosis. The association of increased platelet count with major adverse cardiac event and low lymphocyte count with adverse outcome in CAD have been shown in previous studies .[6-9]

A new inflammatory marker, platelet to lymphocyte ratio (PLR), was found to be related to atherosclerosis, to plaque vulnerability, and to no-reflow after primary PCI. [10-12]PLR has also been shown to be associated with mitral annular calcification, coronary slow flow, poor collateral vessel amount, occlusive peripheral disease and non-dipper HT.[13-15]

The effect of inflammation on acute stent thrombosis has been shown in previous studies .[16]

Initiation and progression of the atherosclerosis is associated with inflammation.[10] The association between inflammation, thrombosis, and atherogenesis is multifactorial and platelets has a major effect on this interaction.[17] Interaction between platelets, leukocytes, and endothelial cells cause autocrine and paracrine activation and leukocyte migration into the vascular wall.[18, 19] Chronic inflammatory processes induced by platelets at the vascular wall cause development of atherosclerosis.[20] Arterial thrombi which is an important partof the atherosclerotic process is also related with platelets.

Lymphopenia is associated with adverse cardiac outcomes. [21, 22] As a result of acute stres, cortisol is secreted and it can decrease lymphocyte production.[23] PLR is an independent predictor of worse outcomes in patients with CHD.[15, 24, 25] In non-ST-segment elevated myocardial infarction patients, the impact of PLR on all-cause mortalitywas independent of the platelet or lymphocyte counts alone. Twohypothesis was thought to be responsible from the superiority of PLR compared with separate individual platelet or lymphocyte counts. First, platelet and lymphocyte count can be affected from many conditions alone so the ratio is more stable. Second, PLR is the combination of two inversely related predictor and immune pathway

But best of our knowledge our study is the first to investigate the value of PLR as a predictor of in-hospital acute stent thrombosis in non-ST segment elevated acute coronary syndrome.

PLR is an easy, inexpensive, and fast independent predictor of stent thrombosis. Patients with a high PLR score can be followed up more closely for ST, giving priority for providing more favorable conditions for the procedure to this group of patients, and thus reducing mortality and morbidity rates.

The major limitation of our study is that the number of patients is small, the study is carried out in one center and the study design is retrospective.

Conclusion

Our study is the first study to show that high PLR value is an independent predictor of in-hospital acute stent thrombosis in non-ST segment elevated acute coronary syndrome patients. PLR, an easy, inexpensive and fast-achievable marker, may lead to follow-up of a particularly risky patient group for foreseeing acute stent thrombosis. Prospective, multicenter studies are needed to better understand PLR's predictive value for acute stent thrombosis in non-ST segment elevated acute coronary syndrome patients.

Declaration of conflict of interest

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Original Article

Prognostic factors for radiocephalic arteriovenous fistula maturation in patients with prior placement of a central venous catheter and relationship with inflammation

Santral venöz katateri olan hastalarda radyosefalik arteriyovenöz fistül matürasyonunu için prognostik faktörler ve inflamasyonla ilişkisi

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Abstract

Aim: A mature and functional arteriovenous fistula (AVF) is considered the best modality for vascular access(VA) for hemodialysis (HD) treatment but the incidence of early failure is high, especially in patients start their HD with a central venous catheter. The aim of this study was to evaluate the prognostic value and association of certain patient characteristics and specific inflammatory markers with early failure of AVF in patients who started their HD therapy with a CVC and a first autogenous radiocephalic AVF (RCAVF) was created after vascular consultation.

Material and Methods: A retrospective review of 168 patients with end-stage renal disease who underwent RCAVF creation by the same surgeon by using the same surgical technique and whose primary vascular access for HD treatment was obtained via CVC at the time of access consultation was performed. The patients enrolled into this study were categorized into two groups as Group 1: patients with early failure (n=46) and Group 2: patients with no failure (n=122). Demographic characteristics, medical comorbidities, preoperative doppler ultrasound mapping results, laboratory parameters, postoperative follow-up details of these patients were collected. Primary patency of all patients, early failure rate, maturation failure rate, duration of CVC was calculated.

Results: Female gender was found to be a significant risk factor in early failure of RCAVF (69.5% vs 36.1%; p=0.001). The number of patients whose diameter of cephalic vein< 2 mm were significantly higher in EF group (78.3% vs 22.1 ; p=0.028). The duration of CVC access of group 1 was significantly longer than group 2 (6.8 ± 3.6 months vs 2.3 ± 1.7 months, respectively; p<0.05). Overall maturation failure rate was 12.5% and primary patency at 1 year was 72.6%. Levels of C-Reactive protein (7.2 ± 9.6 vs 3.1 ± 3.3 mg/L, respectively; p=0.001) and neutrophil lymphocyte ratio (2.91± 0.30 vs 2.17 ± 0.22, respectively; p<0.05) was significantly lower at group 2 at one year.

Conclusion: In patients whose VA for HD treatment was provided by CVC, small cephalic vein diameter, female gender and systemic inflammation may play a role in early failure of RCAVF.

Keywords: autogenous radiocephalic arteriovenous fistula; early failure; cephalic vein; inflammation

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Öz

Amaç: Matüre ve fonksiyonel bir arteriovenöz fistül (AVF), hemodiyaliz (HD) tedavisi tedavisinde vasküler erişim için en iyi modalite olarak kabul edilir; ancak erken başarısızlık oranı HD tedavisine santral venöz kateter (SVK) ile başlayan hastalarda yüksektir. Bu çalışmanın amacı, HD tedavilerine SVK ile başlayan ve daha sonra ilk kez radiosefalik AVF (RSAVF) oluşturulan hastalarda belirli hasta özelliklerinin ve spesifik inflamatuar belirteçlerin AVF'nin erken başarısızlığı açısından prognostik değeri ve ilişkisini incelemekti.

Gereç ve Yöntemler: Aynı cerrah tarafından, aynı teknik kullanılarak RSAVF oluşturulan ve konsülte edildiği sırada HD tedavisi için damar erişimi SVK ile önceden sağlanmış son-dönem böbrek hastalığı bulunan 168 hasta retrospektif olarak tarandı. Bu çalışmaya alınan hastalar Grup 1: erken başarısızlık olan (n=46) ve Grup 2: erken başarısızlık olmayan (n=122) olarak iki gruba ayrıldı. Bu hastaların, demografik özellikleri, yandaş hastalıkları, preoperatif doppler ultrasomografi haritalama sonuçları, laboratuar parametreleri, postoperatif takip detayları toplandı. Tüm hastaların primer patens oranları, erken başarısızlık oranı, maturasyon başarısızlık oranı ve SVK süreleri hesaplandı.

Bulgular: Kadın cinsiyet RSAVF erken başarısızlığında anlamlı bir risk faktörü olarak bulunmuştur (%69.5 vs %36.1; p=0.001). Sefalik ven çapı< 2 mm olan hastaların sayısı Grup 1'de fazlaydı (%78.3 vs %22.1 ; p=0.028). Grup 1'de SVK erişim süresi Grup 2'den anlamlı olarak daha uzundu (6.8 ± 3.6 ay vs 2.3 ± 1.7 ay; p<0.05). Maturasyon yetersizlik oranı %12.5 ve 1-yıllık primer patensoranı%72.6 idi.Grup 2'de, Grup 1'e oranla 1.yılda C-Reaktif Proteindüzeyleri (7.2 ± 9.6 vs 3.1 ± 3.3 mg/L, respectively; p=0.001) ve nötrofil lenfosit oranı(2.91± 0.30 vs 2.17 ± 0.22, respectively; p<0.05) anlamlı derecede düşüktü.

Sonuç: Önceden HD tedavisi için damar erişimi SVK ile sağlanan hastalarda, küçük sefalik ven çapı, kadın cinsiyet ve sistemik inflamasyon, ilk defa açılan RSAVF'ün erken başarısızlığında rol oynayabilir.

Anahtar kelimeler: otojen radyosefalik arteriovenöz fistül; erken başarısızlık; sefalik ven; inflamasyon

Introduction

An increase in the global incidence of end-stage renal disease (ESRD) has led to the increasing demand for hemodialysis[1,2], which is the most common method for treating ESRD. A mature and functional arteriovenous fistula (AVF) is considered the best modality for vascular access (VA) when compared to arteriovenous grafts (AVG), and central venous catheters (CVC) [3-5], and a radiocephalic AVF (RCAVF) at the level of the wrist is the first choice for VA creation; however recent studies have shown high failure rates of up to 46%, with one-year patencies range from 52% to 83% .[6] Surgeons often confront with smaller-caliber vessels, and construction of an AVF is more likely to result in early failure, leading to increased morbidities, related to reoperations, longer hospitalization, and increased costs.[7,8] Early failure of AVF also delay the establishment of permanent dialysis access. It is, therefore, important to identify patients who will have a high likelihood of early AVF failure. Early failure is defined as any fistula not used for dialysis due to loss patency (thrombosis, etc.) or lack of maturation.

A fistula is considered mature when it is thought to be appropriate for cannulation with minimal complications, and to deliver the prescribed blood flow throughout the HD procedure. In other words, when a VA is cannulated successfully with two needles over a period of at least 6 HD sessions during 30 days, and delivering the prescribed blood flow throughout the HD procedure (at least 350 ml/ min), the VA is finally considered adequate for HD (functional and successfully used).[6,9]

In clinical practice, as many as 60%–80% of the incident, patients start their hemodialysis therapy with a CVC due to being unable to wait for the maturation of AVFs or having a condition in which AVF development is not feasible.[10,11] Among ESRD patients initiating hemodialysis with a CVC, the time at which they switch to a mature AVF is influenced by successful AVF maturation which depends on several factors including patient comorbidities and demographics; diameters of cephalic vein and radial artery; peri-operative and postoperative factors.[12-15] However, these studies are a mixed picture (i.e., not limited to RCAVFs) and included conflicting results and the evidence derived from these articles is not consistent Studies do not provide a solid platform for the planning of RCAVF formation, and does not assist in the process of informed consent (percentage likelihood of success

and/or failure). For example, many authors have agreed that duplex vein mapping increases utilization of AVF [16,17], but as vein diameter is dynamic (subject to constriction from changes in venous sympathetic tone), intraoperative measurements may differ from mapped vein diameters. Furthermore, Central Venous Pressure, positioning of the arm, hydration status, ambient room temperature, caffeine intake, and medications may contribute to misleading scans. As a result, though widely recommended, even duplex mapping may not improve functional AVF patency.[18]

Besides, several authors have noted the pivotal role of inflammation in neointimal hyperplasia, which is a foundation of AVF nonmaturation.[19-21] The relation between C-reactive protein (CRP) levels and the development of intimal hyperplasia[22]; thrombosis due to disproportionate intimal hyperplasia resulting in access thrombosis[23] has previously claimed. Likewise, neutrophile lymphocyte ratio (NLR) is a robust inflammatory indicator and associated with both coronary atherosclerosis and restenosis.[24] Given the undeniable role of inflammation in AVF stenosis as well as the histopathological similarity of AVF stenosis with atherosclerosis, a relationship between NLR and AVF stenosis/maturation was questioned.[25,26] Furthermore, previous studies have reported that CVC placement contributes to chronic inflammation independent of infection.[27,28]

The correlation of NLR with the AVF stenosis, as well as the role of NLR and CRP as a predictor of access failure and their pathogenic role in NIH is not clearly understood. Moreover, there are limited data about long-term serial changes in inflammatory marker levels and their relationship to access type in hemodialysis patients, and the contribution of access type to the inflammatory status of hemodialysis patients is not well described.[29,30]

The objective of this paper was to report our findings from the last 10 years in a university hospital located in Antalya. Since recent evidence has highlighted a failure of the literature to identify factors associated with maturation [31], we aimed to test the hypothesis that certain patients' characteristics (age, gender, vessel diameters, and medical comorbidities) affect the maturation of AVF. We also aimed to test the prognostic value and association of specific inflammatory markers (white cell count, neutrophil-lymphocyte ratio, C-reactive protein) with early failure of AVF in patients who started their HD therapy with a CVC and a first autogenous RCAVF was created after consultation to our department.

Material and Methods

Study Design, Setting and Patient Selection

We performed a retrospective chart review of all patients with ESRD who were referred to the department of vascular surgery service in Başkent University Faculty of Medicine, Alanya Practice and Research Center, Antalya-Turkey for creation of AVF for HD between 2010 and 2019. The study protocol was approved by Başkent University Institutional Review Board. Informed consent was obtained from all the patients participating in the study.

Between 2010-2019, we performed AVF construction in 468 patients with ESRD at our institution. Of them, 304 patients with first time autogenous AVF were included. Of the 304 patients, we selected 168 patients who had RCAVF created by the same surgeon by using the same surgical technique and whose VA for HD treatment was obtained via CVC at the time of access consultation and whose preoperative and intraoperative vessel diameters were recorded. Patients who had a life expectancy less than 12 months and to avoid factors influencing CRP levels, patients who had any sign of infection (fever, leukocytosis, cellulitis) or received PTA within 1 month before or after blood sampling, as well as those with rheumatic disease or cancer, were excluded in this study. We also excluded the AVFs that required 2-stage operations. The patients enrolled in this study were categorized into two groups as group 1: patients with early failure (n=46) and group 2: patients with no failure (n=122).

Each patient must be followed up at the vascular surgery and/or nephrology clinics for at least one year or until AVF failure. Data on the survival and prognostic predictors of AVF were extracted from the hospital's electronic database.

In our tertiary care university hospital, patients were regularly seen by the nephrologists, and the decision to start dialysis treatment was made based on the severity of the worsening of renal function. A detailed history and physical examination was undertaken from every patient, including age, gender, history, cause of chronic kidney disease, and the presence of comorbidities/risk factors and noted. The latter included diabetes mellitus (defined as the use of insulin or oral hypoglycemic agents), hypertension (systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or use of anti-hypertensives), dyslipidemia (defined as the use of anti-lipidaemic agents, e.g., statins, ezetimibe, etc.), coronary artery disease (defined as the history of angina, myocardial

infarction, or coronary intervention, including angioplasty and/or bypass grafting), and peripheral arterial disease (PAD) (defined as the history of intermittent claudication, critical limb ischemia, or revascularization of the lower limbs).

The common causes of ESRD among the patients included in this study were diabetes mellitus, hypertension, and glomerulonephritis.

Preoperative Vascular Evaluation

Physical assessment always began by non-dominant arm blood vessels. The study environment was calm and had a pleasant temperature of 20ºC to prevent the underestimation of vessel size due to vasoconstriction. Patients were also in a supine position without angling the elbow joint to avoid vessel compression. The decision to create RCAVF was made through physical examination of arterial inflow by careful palpation of axillary, brachial, radial and ulnar arteries and negative Allen Test; where venous outflow was evaluated by clinical examination through visual enhancement of the cephalic vein which was provoked by placing a tourniquet on the upper arm while the patient clenches and releases the ipsilateral hand several times.

Radial artery inner diameters were routinely assessed at the level of intended anastomosis construction to exclude arterial stenosis, atherosclerotic plaques, and arterial calcification. AVF was not created in the presence of calcifications of the feeding artery wall [32], and anastomosis was not created distal to stenosis above 50% in the radial artery. We did not attempt to construct RCAVF with RA diameters below 1.5 mm. When the decision concerning RA suitability is doubtful, we look at venous mapping results and often decide for the RCAVF formation attempt when there is a large, distensible CV present with normal Doppler venous waveform, and well-established phenomena of respiratory filling

Criteria for venous size as a predictor of RCAVF outcome fluctuated even more than RA diameter cut-offs across published studies. Minimal CV internal diameters associated with RCAVF outcomes in the range of 1.6-2.6 mm were reported.[33-36] Similar to arterial preference, we did not use CV below 1.5 mm.[34] Venous outflow was assessed accurately to exclude venous outflow stenosis and accessory veins. Evaluation of vein compressibility and thrombus exclusion was performed before tourniquet placement.

Since the threshold diameters for both RA and CV diameters for a suitable RCAVF were 2.0 mm, and diameters between 1.6-1.9 were defined as "grey zone", so we decided to compare the groups taking 2.0 mm as a threshold.[34-37]

Evaluation of the dominant arm was performed solely when the non-dominant arm evaluation was unsatisfactory.[38]

Laboratory Tests

All laboratory studies were performed by Başkent University Laboratories (Alanya, Antalya-TR) using automated methods. The laboratory parameters of the patients in the study are the median of the variables in one-year, starting from the preoperative evaluation to postoperative 12th month. In the author's institution, an automated hematology analyzer model (Cell Dyn, Ruby LH 780, Abbott, Abbott Park, IL, USA) was used to measure all CBC specimens, including WBC, hemoglobin, platelet counts and WBC differential percentages. The machine was calibrated three times daily for quality control. CRP and biochemical parameters were measured by an automated clinical chemistry analyzer using the spectrophotometric method (Architect c8000, Abbott, Abbott Park, IL, USA). iPTH value was measured by an automated analyzer using chemiflex technology (Architect i2000SR immunoassay analyzer, Abbott, Abbott Park, IL, USA).

Surgical Technique

All patients were scheduled for a primary AVF creation between the radial artery and cephalic vein (Figure 1).

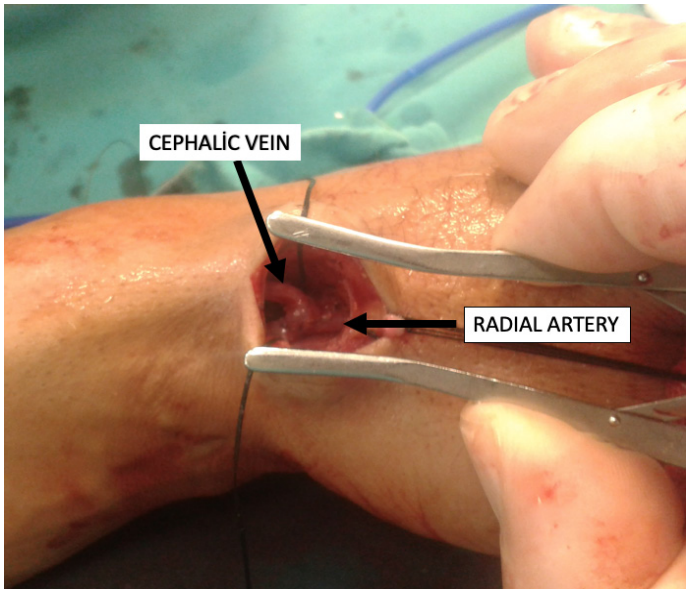


Figure 1: Autogenous radio-cephalic arteriovenous fistula

All the patients gave their informed consent before surgery.

The creation of AVF was performed under local anesthesia (2% Lidocaine-Xylocaine). A longitudinal 3-4 cm skin incision was used, as this was found to give good access to both vein and artery. While evaluated during preoperative planning, a vein diameter of less than 2.5 mm on the preoperative ultrasound duplex did not preclude the surgeon from exploring the vessel in the operating room. Intraoperatively, hydrodilatation maneuver was routinely done with a 4-fr infant feeding catheter for a vein with a diameter <2 mm. During the hydrodilatation, the continuity of the cephalic vein and any recognizable resistance changes were followed closely. If the surgeon felt that it responded adequately, the vein was then used for an AV fistula. If it did not, the patient received a prosthetic graft or another type of autogenous fistula, which is out of the scope for this study. Following clamping, for the standard arteriotomy, the radial artery was incised 6 mm. An end-to-side anastomosis was created between the cephalic vein and the radial artery using continuous polypropylene sutures (7/0 Prolene) with the aid of 2.5x magnifying loupes. A palpable date thrill was taken as an indicator of successful AVF creation.

Anticoagulation

Following exploration of the arteries and veins and before placing the clamp, 5,000 IE heparin was routinely administered intravenously to all patients during AVF creation.

Follow-up

Antibiotherapy and antiaggregant treatment were not used routinely during the postoperative term.

Postoperative surveillance was scheduled at two weeks and then every month for an additional three to six months to monitor the AVF outcomes and possible complications. All AVFs were assessed clinically 6-8 weeks postoperatively for the presence of a strong thrill over a sufficiently dilated (e.g., 8-10 cm length and >5- 6 mm diameter) vein with a superficial course. Clinical criteria were used for the detection of nonfunctioning AVFs. The inability to cannulate the AVF or to obtain sufficient dialysis blood flow within 6 weeks with three sessions per week after fistula creation was classified as maturation failure, regardless of whether it is patent. If the AVF was considered mature, CVC was removed from the patient; otherwise, CVC was continued to be the route of VA for HD and an additional surgical, or endovascular intervention would be performed to promote fistula maturation or patency. US was performed for all patients with nonmaturating AVFs.

Outcome Measure Definition, Primary And Secondary End-Points

The primary endpoint was fistula maturation and functioning AVF, which was defined by the determination of both vascular surgeon and nephrologist. We aimed to evaluate our patients' characteristics that have been reported to be associated with AVF non-maturation and loss of patency in the literature. Primary patency, success rate, assisted primary patency, and primary failure rates were also primary endpoints. We examined the relationship between demographic characteristics including age, gender, diabetes, hypertension, peripheral vascular disease, coronary artery disease, body-mass index, smoking, the type and duration of CVC used; preoperative and intraoperative physical examination and measurements of vessels diameters were also used.

Secondary endpoints were included preoperative (after CVC access)- perioperative and postoperative (max 12-months) blood work studies including CRP, neutrophil, leukocyte, hemoglobin, platelet, albumin, low-density lipoprotein, triglyceride, parathyroid hormone, calcium, phosphorus values and examination of the relationship between maturation process and inflammation.

Reporting Standards for Arterio-Venous Accesses of the Society for Vascular Surgery and the American Association for Vascular Surgery were used to define access functionality and patency.[39] Primary patency was defined as the interval from the time of access creation to any intervention designed to maintain or reestablish patency or to access thrombosis or the time of measurement of patency. Early failure status was assigned to patients with loss of primary patency of the AVF within three months as recorded in the three-month follow-up. Early failure is defined as any fistula that was not used for dialysis either due to loss patency or lack of maturation. This included AVFs that may have required balloon angioplasty to assist with maturation. Early thrombosis of AVF was defined as an immediate failure due to thrombosis of the fistula within 24 hours of creation. Maturation failure is defined as insufficient access flow to maintain dialysis or the inability to cannulate an AVF, within 6 weeks with three sessions per week after fistula creation.[40] Generally, the physical examination conducted

by an experienced dialysis nurse is sufficiently reliable for determining whether the fistula is mature and, therefore, ready for the puncture.[32,41] However, in cases of slow-maturing fistulae, obesity or non-maturation, an ultrasound examination and assessment of hemodynamic parameters (AVF blood flow,) could help to determine whether an AVF is suitable for cannulation or instead failed to mature and is therefore likely to undergo thrombosis as well as having a low flow volume. AVF maturation was defined as the clinical use of the AVF with two needles for 75% of dialysis sessions over a continuous 4 week period, including either a mean dialysis machine blood pump speed of >300 ml/min over four consecutive sessions or a measured Kt/V.1.4 or a urea reduction ratio (URR) >70%(BB).

Statistical Analysis

Data are given as percentages and means ± SD. Rates were calculated for each patient by dividing the number of events/procedures by the duration of follow-up in years. Survival on dialysis was calculated by the Kaplan-Meier method. Group differences were analyzed by the Student's t test and Mann Whitney-U test. The Chi square analysis was used to compare occurrence rates of adverse events and categorical variables. All tests were two sided, and differences were considered significant at P<0.05. Data were collected, tabulated, and statistically analyzed using an IBM personal computer with statistical package of the social sciences, version 25.0 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 168 patients were recruited in the study. The demographics and preoperative vessel diameter measurements of all patients included in the study are listed in Table 1.

Of the total 168 patients, 76 (45.2%) were female, and female gender was found to be a significant risk factor in EF of RCAVF (69.5% vs 36.1%; p=0.001). The most common comorbidity was HT (n=123, 73.2%), followed by DM (n=91, 54.2%). There were no significant differences between the groups in terms of age, BMI, DM, HT, KAH, PVD and smoking habits, as shown in Table 1. Even there was a tendency, the radial artery diameters were not significantly higher in NF group than in EF group (p=0.074). The number of patients whose CV diameter < 2 mm were significantly higher in EF group (78.3% vs 22.1 ; p=0.028) (Table 1).

Table 1: Baseline demographic characteristics and preoperative vessel measurements

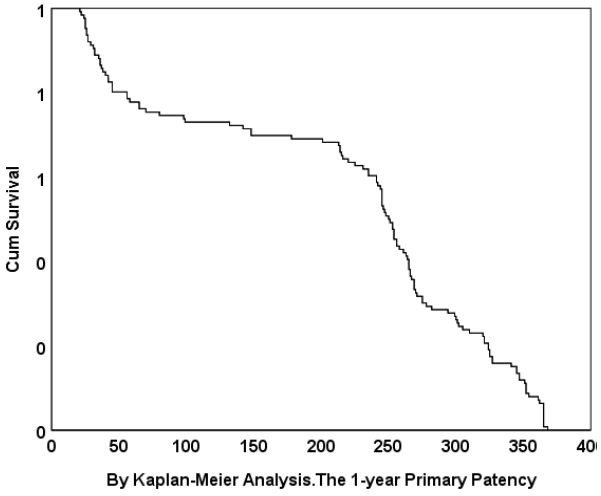
	Group:1 Early Failure (n=46)		Group:2 No Failure (n=122)		
Demographics	N or median		N or median		P
Age	63.1±7.8		61.6 ± 8.7		0.654
BMI	25.2 ± 4.8		25.7±5.1		0.694
Gender					
Female	32	69.5%	44	36.1%	0.001
Male	14	30.5%	78	63.9%	
Diabetes Mellitus					
No Diabetes Mellitus	20	43.5%	57	46.7%	0.626
Diabetes Mellitus	26	56.5%	65	53.3%	
Hypertension					
No Hypertension	12	26.1%	33	27.1%	0.485
Hypertension	34	73.9%	89	72.9%	
CAD					
No CAD	37	80.4%	96	78.7%	0.485
CAD	9	19.6%	26	21,3%	
PVD					
No PVD	42	91.3%	112	91.8%	0.694
PVD	4	8.7%	10	8.2%	
Smoking					
No Smoking	32	69.6%	93	76.2%	0.745
Smoking	14	30.4%	29	23.8%	
Cephalic vein diameter (mm)					
1,5-1.9	36	78.3%	27	22.1%	0.028
>2.0	10	21.7%	95	77.9%	
Radial artery diameter (mm)					
1.5-1.9	16	34.8%	32	26.3%	0.074
>2.0	30	65.2%	90	73.7%	

Abbreviations: BMI: Body-mass index; CAD: Coronary artery disease; PVD: peripheral vascular disease.

Abbreviations: BMI: Body-mass index; CAD: Coronary artery disease; PVD: peripheral vascular disease.

In group 1, of the 46 patients which was classified as early failure, an early thrombosis of AVF was diagnosed in 25 patients (54.3%) and a maturation failure was diagnosed in 6-8 weeks follow-up control in 21 patients (45.7%). In group 2, 39 patients (84.7%) were succesfully treated with thrombectomy ± balloon angioplasty; whereas a new creation of brachiocephalic AVF was required in 7 patients (15.3%). Considering group 1, their duration of CVC access was significantly longer than group 2 (6.8 ± 3.6 months vs 2.3 ± 1.7 months, respectively; p<0.05).

Considering the all study group, the overall maturation failure rate was calculated as 12.5%. Primary patency at 1 year was 72.6%. Kaplan-Meier survival analysis of RCAVF primary patency is shown in figure 2.



	Median ± SE (Estimate)	%95 Confidence Interval Std. Error
Primary Failure	29 ± 2.43	24.237 - 33.763
Primary Patency	250 ±3.96	242.235 - 257.765

Figure 2: Kaplan–Meier survival analysis of arteriovenous fistula(AVF) primary patency. AVF primary patency rate was 72.6 %.

Regarding outcomes for the secondary endpoints, no statistically significant difference among the groups was found in levels of albumin, calcium, intact PTH, serum TG, LDL, blood hemoglobin, WBC and PLT count depicted in table 2. CRP level was higher than the normal range (normal range <3.0 mg/l) at the first 30-days and did not differ between the groups. CRP levels of group 2 were significantly lower than group 1(7.2 ± 9.6 vs. 3.1 ± 3.3 mg/L, respectively; p=0.001) at 1-year. Likewise, the same pattern was followed by the NLR. Median NLR was high in postoperative 30 days in both groups (3.44 ± 0.49 vs. 3.21 ± 0.64, respectively; p=0.342). NLR at 1-year was significantly lower in group 2 when vompared to the NLR of group 1 (2.91± 0.30 vs. 2.17 ± 0.22, respectively; p<0.05).

Table 2: Laboratory parameters of the patients

Parameter	Group 1 (N=46)	Group 2 (N=122)	
	mean ± sd	mean ± sd	p
Serum CRP (mg/L) First 30 days	9.3±11.8	8.7±10.7	0,059
Serum CRP (mg/L) One year	7.2 ± 9.6	3.1 ± 3.3	<0.05
Serum Albumin (gr/dl)	3,3(±0,6)	3,5(±0,5)	0,123
Serum Calcium (mg/dl)	8,4(±1,7)	8,5(±1,0)	0,810
Intact PTH (pg/ml)	264(±183)	258(±194)	0,878
Serum TGL (mg/dl)	150(±72)	163(±94)	0,497
Serum LDL (mg/dl)	90,8(±45)	95,7(±33)	0,371
Blood Hemoglobin (g/dl)	9,9(±1,6)	10,0(±1,2)	0,620
White blood cells (109 cell/l)	7.1 ± 2.2	7.3 ± 2.1	0.290
PLT (K/mm3)	230,9(±80)	220,6(±63)	0,535
NLR (first 30 days)	3.44 ± 0.49	3.21 ± 0.64	0.342
NLR (one year)	2.91± 0.30	2.17 ± 0.22	<0.05

Discussion

The process of AVF maturation is complex and remains poorly understood, despite numerous studies describing the pathophysiology of the process and biomechanical factors associated. High failure rates for arteriovenous fistula (AVF) are a persistent problem, and Cook et al claimed that failure of maturation may occur in up to 53% of AVF in their invited commentary.[42] Our single-center study of incident hemodialysis patients with enrolled 168 patient-12 month follow-up has demonstrated the cumulative AVF patency rate of 72,6% at 1 year. Previous studies reported AVF cumulative survival rates ranging from 44 to 87%, but the comparison could be misleading as the rates were reported in different definitions.[43] Bashar et al., reported 52 functionally matured fistula from a total of 97 fistulae (53.60%).[44] Al-Jaishi et al analyzing pool of 12,383 patients from 62 unique cohorts reported primary and cumulative AVF patency rates of 60% and 71% respectively.[45] The low to moderate primary patency rate warrants the search for critical factors that affect vascular access outcomes.

Certain clinical factors including female gender, age ≥65 years and forearm AVF placement remain as significant risk factors for AVF failure despite the use of routine vein mapping (46). Bashar et al. found female gender to be associated with a poor maturation rate (26). Miller et al found that fistula adequacy is worse in women, with higher risk of technical failures and early thrombosis.[47] Wasse et al.reported that females were 36% less likely than males to use an AVF at dialysis initiation. [48] The exact mechanism of different AVF outcomes between genders is unclear, but it has been suggested that difference in vascular diameter, reactivity and impaired ability of venous dilatation to arterial pressure being the possible explanations. [47] We did not find age as a prognostic factor for early failure. There has been conflicting results in literature about age. Some studies identified old age as a poor prognostic indicator[49,50], whereas others did not.[51,52] DM is one of the most common causes of ESRD (53), the second most common cause in our study, but it was not associated with adverse outcome of fistula maturation during the first three months of its creation, namely resulting in early failure[54], but it may have a negative impact on late AVF survival [55] since DM promotes platelet aggregation [56] and vascular calcification.[57]

We perform a detailed preoperative vascular evaluation as well as a detailed careful physical examination. We believe that physical examination plays a pivotal role in making a proper decision to create RCAVF. When the decision concerning RA suitability is doubtful, we look at venous mapping results and

often decide for the RCAVF formation attempt when there is a large, distensible CV present with normal Doppler venous waveform and well established phenomena of respiratory filling. In a study by Wells et al, US was considered unnecessary in majority of patients who fulfilled the clinical criteria for AVF creation.[58] Two subsequent randomized controlled trials also did not find additional advantage of vein mapping over clinical assessment in patients with favourable anatomy, in terms of early AVF failure and cumulative AVF survival rate.[59,60] Wong et al admitted that preoperative vein mapping may improve AVF maturation rates but the difference did not reach statistical significance and suggested that larger clinical trial is needed to confirm the clinical benefit .[18] On the other hand, Hossain et al. reported that the primary failure rate in the ultrasound group was 18% compared with 47% ($P < 0.001$) in the group of patients who did not undergo ultrasound examination. In patients without preoperative ultrasound, there were higher rates of new access creation (31% vs 9%; $P< .001$) and fistula abandonment (66% vs 39%; $P < .001$).[61]

There is also an ongoing debate about the threshold of vessel diameters. Wong et al reported that cephalic vein diameter less than 1.6 mm was associated with early radiocephalic AVF failure.[62] Mendes et al found low AVF success rate of 16% in vein diameter of 2 mm or less, as compared to 76% of those >2 mm in a cohort of 44 patients.[36] On the other hand, Lee etal., did not find vein size to be statistically significant in predicting fistula maturation, and AVF can be successfully created in mean vein diameter of <2 mm in more than 70% of patients.[63] Eslami MH et al, a larger target vein diameter was the most predictive variables predicting early failure.[64] The conflict about the use of US is because of veins dynamic status: subject to constriction from changes in venous sympathetic tone, intraoperative measurements may differ from mapped vein diameter and postoperative ultrasound protocols do not take dynamic enlargement with access augmentation (occlusion of the outflow) into account. The use of vein diameter and to a lesser degree, arterial diameter has been tested as a predictor for fistula maturation with reasonable success. There is an increasing agreement that a minimal arterial diameter >2 mm and venous >2 mm should be considered as a cut-off point, as anything less than that is likely to be associated with nonmaturation.[65,66] In our study, not the radial artery diameter but the CV vein diameter found to play a significant role in early failure. A diameter of CV< 2mm was found to be important in early failure.

It is well known that the low resistance circuit, resulting from the creation of the anastomosis between the artery and the vein, triggers an immediate increase in blood flow and elevation of blood pressure in the veins. Elevation of blood flow rate is responsible for a rapid increase in wall shear stress (WSS) and venous tensile stress induced by the velocity gradient on the luminal vessel surface.[67] On the other hand, WSS changes are the major determinants of vessel dilatation and remodeling. In rodent models of venous thrombosis created by ligation of inferior vena cava to induce venous hypertension and altered WSS, thrombus initiation is associated with a rapid vein wall inflammatory reaction involving early endothelial activation and neutrophil infiltration, similarly to observations conducted in the arterial side.[68] In studies studying local hemodynamic conditions in AVF using computational fluid Dynamics, Ene-Lordache and Ramuzzi suggested that despite the significant increase in flow rate, in selected locations, the WSS is oscillating and in average it is low in magnitude.[69] The same team also showed that, while the flow is almost laminar in the proximal arterial limb, in the venous segment leading the velocity field is highly unstable and multidirectional [70] leading a transitional laminar to turbulent-like flow developing in areas of the juxta-anastomotic vein. The presence of disturbed WSS patterns (unstable in direction and magnitude) may induce different physical stimuli in endothelial cells that actually lead to the proliferation of neointimal cells and to induction of a proinflammatory state preventing vessel wall dilatation and outward remodeling of arterial and venous vessels that take place when endothelial cells are exposed to unidirectional WSS directed along vessel axis.

The relationship between high levels of CRP and HD was previously described.[21] CRP serum concentration increases in cases of inflammation, infection and tissue damage. Kaygin et al. found a threefold increase in serum CRP levels in unsuccessful AVF cases and a positive correlation.[21] Wali et al.[71] have stated that AVF insufficiency appears as a result of platelet activation and intimal hyperplasia which is caused by the secretion of mediators because of primary and/or secondary defects in vascular endothelium due to mucoid or myxoid degeneration, mural calcification, inflammatory reaction or erythrocyte/macrophage infiltration on the vascular wall. Chou et al[22] identified CRP level as an independent risk factor for fistula thrombosis. These investigators suggested that CRP level strongly predicts access thrombosis events in maintenance hemodialysis patients, possibly because CRP is a marker of intimal hyperplasia in AVFs.

Morena et al.[72] have stated that due to mineral metabolism deterioration in HD patients and due to inflammation, thrombosis risk increases in the group where CRP, Calcium, PTH increases. In addition, some studies have identified CRP

level as a risk factor for the development of access thrombosis. [73,74] In our study, we did not find a difference in terms of calcium and pth.

The patients enrolled in our study started their HD therapy with a CVC due to being unable to wait for the maturation of AVF. A history of CVC placement or prolonged use of CVC was a poor prognostic predictor of AVF survival[75,76], but the mechanisms by which preexisting CVCs affect AVF maturation remain elusive. Systemic inflammation, a common condition occurring in the setting of CVC placement [27,77], has been proposed as a pathogenetic mechanism underlying neointimal hyperplasia [78], which is a foundation of AVF failure.

Available evidence suggests that CRP is an objective measure of a patient's inflammatory state and that it accurately reflects the generation of proinflammatory cytokines, such as IL-6 and tumor necrosis factor-alpha.[29, 30] There are limited data about long-term serial changes in inflammatory marker levels and their relationship to access type in hemodialysis patients, and the contribution of access type to the inflammatory status of hemodialysis patients is not well described.[29,30] Our study corroborated the findings of previous studies [77] that CVCs in comparison to fistulas have a greater state of inflammation defined by CRP levels in incident hemodialysis patients.Banerjee et al [79], reported that CRP levels decreased over time in cases of an AVF, with the highest inflammatory state 30 days after access placement, and found a significant decrease in CRP levels when there was a change from a CVC to an AVF was associated with decreased CRP levels compared with patients who used CVCs at both times. As also consistent with our study, Goldstein et al. [77], who investigated the levels of inflammatory markers at the time of dialysis initiation and again 6 months later, found that patients with persistent CVC use from dialysis initiation through 6 months had consistently high inflammatory levels over the period, whereas the levels of inflammatory markers were attenuated in patients who changed from a catheter to an AVF. Their findings are consistent with our study as we also obtained a significant decrease in CRP levels after changing the VA from CVC to AVF- not in 30 days but in 1 year-. This finding was strengthened further by our findings on the association of the inflammatory state reflected by NLR.

NLR level increased with CVC and stay high when a mature functioning AVF was obtained. In patients whose CVC was removed, a dramatic decrement in NLR was observed in one year. The clinical trials showed that IL-6, pentraxin and complement system had roles in AVF dysfunction [80,81]. Yilmaz et al. [25] reported that in chronic HD patients with established AVF access, patients who developed late stenosis were found to have higher level of NLR. An increased level of NLR reflects inflammation .[24,80-83] Spark et al. Evaluated NLR to predict mortality in patients with chronic critical limb ischemia. They found that an elevated NLR along with a high troponin level (>0.1) was the only independent predictor of mortality in those patient.[84] In a study of 83 patients who underwent infrapopliteal percutaneous interventions for critical limb ischemia, Chan et al.[85] reported that those with NLR > 5.25 had an increased risk of death.

This finding that change in CRP levels and NLR are associated with change in access type adds additional support to the body of the observational evidence, suggesting that the catheter itself contributes to an increase in inflammatory marker levels in hemodialysis patients.

Study Limitation

Nevertheless, this study was limited by being a retrospective study. Hence, some data might have been unavailable, such as blood flow measurements and the results of other inflammatory marker blood tests. This study was conducted with a homogeneous cohort of ESRD patients from a single institution. Hence, the results might not be the same in other settings where people have different reference ranges for WBC counts or dissimilar material types of CVC are used.

Conclusion

As a conclusion, early failure of RCAVF is an obstacle we have to overcome. Certain clinical factors including female gender, anatomical factors including a diameter of CV < 2mm was found significant in early failure. A history of CVC placement or prolonged use of CVC is a poor prognostic predictor of AVF survival in which systemic inflammation plays an important role. A significant decrease in CRP levels was observed after changing the VA from CVC to AVF- not in 30 days but in 1 year-. This finding was strengthened further by our findings on the association of the inflammatory state reflected by NLR.

Declaration of conflict of interest

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Original Article

Low prognostic nutritional index is associated with adverse outcomes in patients with hypertrophic cardiomyopathy

Düşük prognostik nütrisyonel indeks hipertrofik kardiyomiyopatili hastalarda kötü sonuçlar ile ilişkilidir

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Abstract

Aim: The aim of the study was to investigate poor nutritional status assessed by prognostic nutritional index (PNI) on the prognosis of patients with hypertrophic cardiomyopathy(HCM).

Material and Methods: A total of 420 patients with HCM were assessed. The primary end point was defined as the occurrence of CV death that included sudden cardiac death (SCD), death due to HF and cardioembolic stroke-related death.

Results: During the follow-up, primary end point was developed in 25 (6.0%) patients. Receiver operating characteristic (ROC) analysis showed that using a cut-off level of 40, PNI predicted the occurrence of primary end point with a sensitivity of 76% and specificity of 76.7%. In the multivariate model, low PNI was significant predictor of the primary end point.

Conclusion: This study showed that lowerPNI level is an independent predictor of CV death in patients with HCM.

Keywords: cardiovascular death; hypertrophic cardiomyopathy; prognostic nutritional index

Öz

Amaç: Çalışmanın amacı prognostik beslenme indeksi (PNI) ile değerlendirilen zayıf beslenme durumunun, hipertrofik kardiyomiyopatili (HKMP) hastaların prognozu üzerine etkisini araştırmaktır.

Gereç ve Yöntemler: Toplam 420 HKMP hastası değerlendirildi. Çalışmanın birincil sonlanım noktası, ani kardiyak ölüm (AKÖ), kalp yetmezliği (KY) nedenli ölüm ve kardiyo embolik inme ilişkili ölümü içeren kardiyovasküler ölüm saptanması olarak tanımlandı.

Bulgular: Takip süresi boyunca 25 (% 6.0) hastada birincil sonlanım noktası saptandı. ROC (Receiver operating characteristic curve) analizi, PNİ kesme seviyesi 40 kullanarak PNİ'nin % 76 hassasiyet ve% 76.7 özgüllük ile birincil son nokta oluşumunu öngördüğünü gösterdi. Tek değişkenli ve çok değişkenli modelde düşük PNİ değeri, primer sonlanım noktası için önemli bir belirleyici olarak saptandı.

Sonuç: Bu çalışma, düşük PNİ düzeyinin HKMP hastalarında KV ölümün bağımsız bir öngördürücüsü olduğunu göstermiştir.

Anahtar kelimeler: kardiyovasküler ölüm; hipertrofik kardiyomiyopati; prognostik nütrisyonel indeks

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Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common genetic cardiomyopathies characterized by ventricular hypertrophy, myocardial fibrosis, and impaired ventricular relaxation[1]. Myocyte hypertrophy and disarray, interstitial fibrosis as well as small vessel disease are main pathological trademarks of the myocardium in HCM[2]. The clinical course of HCM is highly variable, ranging from asymptomatic status with a normal life expectancy to adverse clinical outcomes such as severely limiting dyspnea, advanced heart failure (HF), systemic embolic events, stroke, malignant arrhythmic events and sudden cardiac death. The annual mortality rate of HCM patients is thought to be about 1%. Sudden cardiac death (SCD) and embolic stroke are major causes of death in patients with HCM[3, 4]. In addition, some patients develop systolic dysfunction causing increased morbidity and mortality[5]. Identifying high-risk HCM patients plays a key role in risk stratification, treatment strategy selection, preventing complications and improving outcomes. Although a set of clinical risk factors and imaging results are investigated for risk stratification in HCM patients presently, the clinical outcomes of HCM are still broadly unpredictable given that HCM is generated by various etiologies, has a genetic diversity with heterogeneous and complex clinical expression and the pathophysiological mechanisms are very complicated.

In recent decades, much attention has been given to assess the role of inflammation and oxidative stress in both for pathogenesis and to determine the prognosis of HCM. Several studies established increased circulating inflammatory markers in HCM such as TNF-α, IL-6, MCP-1 and monocyte count to high-density lipoprotein cholesterol ratio(MHR), neutrophil-to-lymphocyte ratio (NLR)[6-9]. Recent studies have shown that poor nutritional status is associated with increased inflammation and neurohormonal activation, indicating poor prognosis in various cardiovascular diseases. Malnutrition, which is associated with decreased immune system function, impaired respiratory function and poor wound healing, has been shown to be a predictor of outcome in patients with chronic illness, including end-stage renal disease, malignancy and advanced HF[10, 11]. Although nutritional status examination is more complex, objective and well-recognised indices such as prognostic nutritional index (PNI) have been developed. PNI, calculated from the serum albumin concentration and total lymphocyte count, is a simple and objective indicator that assesses immuno-nutritional status of patients[12]. Some studies demonstrated that nutritional status measured by PNI is an independent prognostic factor in patients with various cardiovascular diseases such as acute or chronic HF, ST segment elevation myocardial infarction (STEMI), stable coronary artery disease (CAD). However this association has not been previously assessed in patients with HCM. The aim of the present study was to evaluate PNI on the clinical end points in patients with HCM.

Material And Methods

Study population

The study population included 442 consecutive patients clinically diagnosed with HCM at our hospital between October 2003 and December 2016. A diagnosis of HCM was made based on the current guidelines of the American College of Cardiology / European Society of Cardiology (ACC/ ESC), was the presence of a hypertrophied left ventricle with a maximal wall thickness of ≥15 mm on echocardiography in patients without alternative explanations capable of producing a similar degree of hypertrophy or systemic diseases. Individuals with metabolic diseases (e.g, Anderson Fabry disease) and related syndromes (e.g, Noonan syndrome) were eliminated. Patients with clinical conditions other than cardiomyopathy that could increase plasma levels of inflammatory markers such as active cancer, active infection, renal or hepatic insufficiency, chronic inflammatory disease, congenital heart disease, cardiac valve disease were excluded from study. Also patients without a recorded measurement of admission laboratory parameters and sufficient clinical information were excluded. According to these exclusion criteria, 22 patients were excluded from the study and a total of 420 patients were included in the study. Data regarding clinical features, risk profiles, laboratory and echocardiographic parameters of all patients were collected from clinical follow-up visits, patients' files and the electronic database The present study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

Echocardiography

On admission to the hospital, all patients underwent transthoracic echocardiography using commercially available ultrasound equipment. They had undergone two-dimensional and M-mode echocardiography with continuous, pulsed and colour Doppler imaging at the time of diagnosis and the last follow-up visit with the Vivid 7 system (GE Healthcare, Wauwatosa, Wisconsin). EF was calculated by using modified Simpson method. Maximum wall thickness was accepted as the greatest thickness in any single segment and was evaluated at end-diastole on the basal, mid or apical short-axis views. LV outflow tract obstruction was measured either in a

rest state or during a Valsalva maneuver. Obstructive HCM was defined as LV outflow tract obstruction >30 mmHg.

Laboratory parameters

Peripheral venous blood was drawn from the antecubital vein and was obtained in the morning after a 12-hour fast. All biochemical analyses were determined using standard methods. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in metres. Patients were considered to have hypertension if their blood pressure was ≥140/90 mmHg or if they were taking any anti-hypertensive medication. Diabetes mellitus was defined as fasting blood glucose level of 126 mg/dL or greater and treatment with anti-diabetic medications. PNI was calculated using the following formula: 10 x serum albumin value (g/dL) + 0.005 x total lymphocyte count in the peripheral blood (per mm^3). Patients were divided into two groups according to their admission PNI.

Definitions & study end points

The primary end point was defined as the occurrence of CV death that included sudden cardiac death (SCD), death due to HF and cardioembolic stroke-related death. SCD was accepted unexpected and instantaneous collapse leading to death due to any cardiac cause occurring in the absence of symptoms or within 1 h of the onset of symptoms in a patient who had previously experienced a relatively stable or uneventful clinical course or witnessed unexpected death. HF related death was accepted as death preceded by symptoms of heart failure >1h. [13]. The follow-up duration was commenced with the first visit and ended with the occurrence of death or the last visit. Follow up for clinical end points was performed by review of medical records in our hospital. We decided a cardiac event that occurred outside our hospital by phone calls with patients, their relatives and/or their general practitioners. The cause of death was assessed by evaluating the hospital records, official hospital release forms or death certificates obtained from National Survival Registry. All-cause death and presence of NYHA III-IV symptoms were defined as secondary end points.

Statistical analysis

Statistical analysis was performed using the SPSS 20.0 Statistical Package Program for Windows (SPSS, Inc., IL, and USA). Continuous variables were presented as mean ± SD and median with interquartile ranges of appropriate and categorical variables as frequency and percentage. Kolmogorov-Smirnov test was used to test normality of distribution. Differences between groups were evaluated by using Student's t test for normally distributed variables and Mann–Whitney U test for variables without normal distribution. The Chi-square or Fisher's exact test was used to compare categorical variables as appropriate. The association between PNI and development of adverse outcomes of HCM were estimated with univariate and multivariate Cox proportional hazards regression analyses. Survival estimates were calculated by the Kaplan-Meier method and the long-rank test was used for comparison. Receiver operating characteristic curve (ROC) analysis was used to determine the optimum cut-off levels of PNI to predict primary end point. A p-value < 0.05 (using a two-sided test) was considered significant.

Results

We assessed consecutive 420 patients with HCM in this study. Baseline clinical, demographic echocardiographic and laboratory characteristics of the study population were summarized in Table 1. A total of 244 patients (58.1%) were male, and the mean age of the study population was 48.4 ±15.2 years old. After a median (interquartile range) follow-up period of 6.0 (5.0–8.0) years, primary end point was developed in 25 (6%) subjects (sudden death in 10 (2.4 %), death for progressive HF in 14 (3.3 %) and cardioembolic stroke-related death in 1 (0.2 %)). Patients with CV death had a higher prevalence of atrial fibrillation (44.0% vs.18.2%, p =0.002), higher NYHA class (68.0% vs. 12.7%, p <0.001), higher left atrial diameter (LA) (43.8 ± 4.4 mm vs. 40.9 ± 5.4 mm, p = 0.013), lower ejection fraction (EF) (53.6 ±10.5 mm vs. 60.8 ±7.4 mm, p < 0.001) and higher level of C-reactive protein (CRP) (11.3 (4.8-22.7) vs. 4.8 (3.9-5.8), p< 0.001) compared the patients without CV death. Also serum albumin concentration, serum lymphocyte count and PNI values (37.5±5.0 vs. 43.7 ±4.8, p < 0.001) were significantly lower in patients with CVD than in patients without CV death. Follow-up data and clinical outcomes regarding primary and secondary end points were presented in Table 2. During follow-up period, all-cause death was observed in 34 subjects (8.1%) and presence of NYHA III-IV symptoms was observed in 66 subjects (15.7 %) which were the secondary end points among the study population. Low PNI values were significantly associated with both primary and secondary end points of the study.

We also compared baseline clinical characteristics of the study patients according to PNI levels (Table 3). The patients in low PNI group (<; n = 140) had a higher prevalence of atrial fibrillation, higher NYHA class, larger LA dimension, larger left ventricular enddiastolic diameter (LVEDD), lower EF, higher values of CRP and lower values of lymphocyte and albümin counts than the patients in high PNI group.

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Table 1. Baseline clinical, echocardiographic and laboratory characteristics of the study patients according to the presence of cardiovascular death

Variables	Total n = 420	CV Death(+) n = 25	CV Death (–) n = 395	p value
Age	48.4 ±15.2	49.6± 14.8	48.4± 15.2	.692
Gender (Male), n (%)	244 (58.1%)	13 (52.0%)	231(58.5%)	.524
Hypertension n (%)	74 (17.6%)	5 (20.0%)	69 (17.5)	.747
Diabetes n (%)	66 (15.7%)	5 (20.0 %)	61 (15.4%)	.544
Smoking n (%)	63 (15.0%)	4 (16.0%)	59 (14.9%)	.885
Body-mass index (kg/m2)	26(24-29)	25(23-27)	26 (24-29)	.108
Coronary artery disease	131 (31.2%)	7(28.0%)	124 (31.4 %)	.723
Atrial fibrillation	83 (19.8%)	11 (44.0 %)	72 (18.2%)	.002
NYHA III or IV, n (%)	67 (16.0%)	17 (68.0%)	50 (12.7%)	<.001
β-blocker, n (%)	397 (94.5 %)	23 (92.0%)	374(94.7%)	.567
Amiodarone,n (%)	10 (2.4%)	1 (4.0%)	9 (2.3%)	.584
Echocardiographic parameters				
LVEDD (mm)	42 (40-46)	43 (40-47)	42 (40-46)	.800
Maximal LV wall thickness (mm)	20.7 ± 4.7	20.7± 4.6	20.7± 4.7	.990
LVEF (%)	60.4±7.8	53.6 ±10.5	60.8 ±7.4	<.001
LVOT Gradient (mmHg)	24.1 ±33.1	12.6 ±23.5	24.8 ±33.5	.072
LA diameter (mm)	41.1 ± 5.4	43.8± 4.4	40.9± 5.4	.013
SPAB	30 (28-35)	35 (30-40)	30 (28-35)	.003
Apical aneurysm, n (%)	16 (3.8 %)	1 (4 %)	15 (3.8 %)	.959
Syncope	57 (13.6%)	1(4.0%)	56 (14.2 %)	.150
Family history	76 (18.1%)	5(20.0%)	71 (18.0%)	.799
NSVTat 24 Hour Holter monitoring	70 (16.7%)	7 (28.0%)	63 (15.9%)	.117
Laboratory parameters				
Hemoglobin (g/dl)	13.4 ±3.1	13.0 ±1.6	13.5 ±3.1	.454
WBC (×103 µL)	8.2±5.2	8.0±2.9	8.3 ±5.3	.843
Neutrophil (×103 µL)	5.0±2.0	5.3±2.7	4.9 ±1.9	.381
Lymphocyte (×103 µL)	2.3±0.6	1.8±0.4	2.3±0.6	<.001
Monocyte (×103 µL)	591 ±254	680±284	585 ±252	.072
Platelet (×103 µL)	235 (198-293)	218(182-300)	236(198-291)	.485
Glucose, mg/dL	112±45	115 ±53	112±45	.782
Creatinine (mg/dl)	0.9 (0.8-1.0)	0.9 (0.7-1.0)	0.9 (0.7-1.0)	.855
Uric acid (mg/dl)	6.0 (5.3-6.5)	6.3 (5.1-7.5)	5.9 (5.4-6.5)	.174
TSH, UI/mL	1.6 (1.0-2.3)	1.6 (0.9-2.6)	1.6 (1.1-2.3)	.802
Albumin (g/dl)	4.3± 0.5	3.7± 0.5	4.3± 0.4	<.001
PNI	43.3± 5.0	37.5 ±5.0	43.7±4.8	<.001
hsCRP	4.8 (4.0-5.8)	11.3 (4.8-22.7)	4.8 (3.9-5.8)	<.001

Data are presented mean ± SD or n (%).
CRP: C-reactive protein; LA: Left atrium; LVEDD: left ventricular enddiastolic diameter; LVEF: left ventricular ejection fraction; ; LVOT: left ventricular outflow tract; NSVT: non sustained ventricular tachycardia; NYHA: New York Heart Association; PNI: prognostic nutritional index; TSH: thyroid-stimulating hormone; WBC: white blood cell

Table 2. Comparison of primary and secondary endpoints according to the PNI values

Parameter	All n=420	Low PNI n = 140	High PNI n = 280	P
Cardiovascular death	25(6.0 %)	19 (13.6 %)	6(2.1%)	<.001
Sudden cardiac death	10 (2.4 %)	7 (5 %)	1 (0.4 %)	0.013
Heart failure related death	14 (3.3 %)	12 (8.6 %)	2 (0.7 %)	<.001
Stroke related death	1 (0.2 %)	0 (0.0 %)	1 (0.4 %)	.480
All-cause death	34 (8.1 %)	27 (19.3 %)	7 (2.5 %)	<.001
NYHA III or IV	66 (15.7 %)	52 (37.1 %)	14 (5.0 %)	<.001

Table3. Comparison of the baseline characteristics among the quantiles of PNI

Variables	Low PNI(+) n = 140	High PNI (–) n = 280	p value
Age	50.4± 15.5	47.5± 14.9	.407
Gender, Male n (%)	83 (59.3%)	161 (57.5%)	.727
Hypertension n (%)	29 (20.7%)	45 (16.1)	.239
Diabetes n (%)	25 (17.9%)	41 (14.6%)	.394
Smoking n (%)	26 (18.6%)	37 (13.2%)	.147
Body-mass index (kg/m2)	26(24-28)	27(24-29)	.103
Coronary artery disease	48 (34.3%)	83 (29.6 %)	.333
Atrial fibrillation	36 (25.7 %)	47 (16.8%)	.030
NYHA III or IV n (%)	57 (40.7%)	10 (3.6%)	<.001
Echocardiographic parameters			
LVEDD (mm)	45 (41-48)	42 (39 -45)	<.001
Maximal LV wall thickness (mm)	20.3± 3.7	20.9 ± 5.1	.199
LVEF (%)	56.8 ±9.4	62.1 ±6.2	<.001
LVOT Gradient (mmHg)	20.0 ±33.6	26.1 ±32.7	.075
LA diameter (mm)	42.8± 5.3	40.3± 5.3	<.001
SPAB	33 (30-40)	30 (28-35)	<.001
Syncope	17(12.1%)	40 (14.3 %)	.546
Family history	18 (12.9%)	58 (20.7%)	.059
NSVTat 24 Hour Holter monitoring	29 (20.7%)	41 (14.6%)	.116
Laboratory parameters			
Hemoglobin (g/dl)	13.0 ±2.3	13.6 ±3.3	.077
WBC (×103 µL)	8.2±2.6	8.3 ±6.0	.933
Neutrophil (×103 µL)	5.2 ±2.3	4.8 ±1.8	.082
Lymphocyte (×103 µL)	2.1±0.7	2.4±0.5	.<.001
Monocyte (×103 µL)	600 ± 249	586 ±257	.604
Platelet (×103 µL)	227 (189 -275)	240 (201 -304)	.041
Glucose, mg/dL	121 ± 56	108 ± 38	.011
Creatinine (mg/dl)	0.9 (0.8-1.1)	0.8 (0.7-1.0)	.041
Uric acid (mg/dl)	5.9 (5.1-6.7)	6.0 (5.4-6.5)	.723
TSH, UI/mL	1.4 (1.0-2.3)	1.6 (1.1-2.3)	.619
Albumin (g/dl)	3.7± 0.2	4.6± 0.3	<.001
hsCRP	4.9 (4.3-8.8)	4.7 (3.4-5.7)	.009

Data are presented mean ± SD or n (%).
CRP: C-reactive protein; LA: Left atrium; LVEDD: left ventricular enddiastolic diameter; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NSVT: nonsustained ventricular tachycardia; NYHA: New York Heart Association; PNI: prognostic nutritional index; TSH: thyroid-stimulating hormone; WBC: white blood cell

Area under the curve was 0.817 (95% CI: 0.777–0.853; p <0.001). Using a cut-off level of 40.0, PNI predicted the occurrence of primary end point with a sensitivity of 76% and specificity of 76.7% (Figure1). A Kaplan–Meier analysis showed a significantly lower primary endpoint-free survival rate in patients with low PNI (log rank, P <0.0001, Figure 2). Also, patients with low PNI had a higher all cause death and NYHA III-IV symptoms compared with patients with high PNI (Figure 3). Univariate Cox regression analyses showed that atrial fibrillation, NYHA III-IV, LVEF, LA diameter, CRP and low PNI were significantly associated with the primary end point (for all; p < 0.05) (Table 4). However, in the multivariate model, low PNI (HR: 4.8; 95% CI: 1.6-14.4; p=0.005) and CRP (HR: 1.04; 95% CI: 1.006-1.074; p=0.019) were significant predictors of the primary end point (Table 4).

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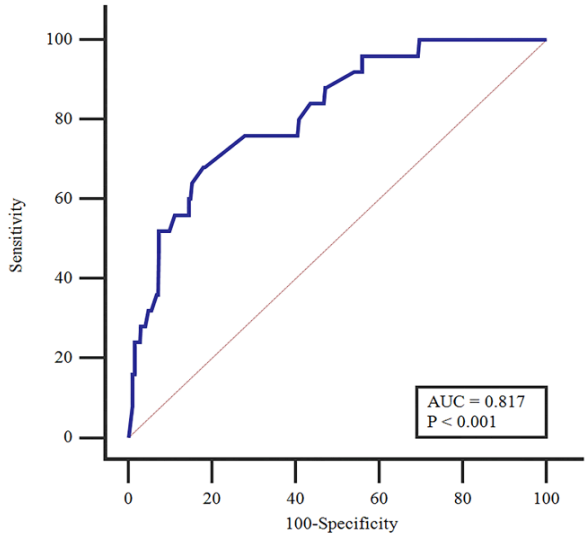

Figure 1: Receiver operating characteristic curve analysis of PNI to predict cardiovasculer death (primary end point) in patients with hypertrophic cardiomyopathy.

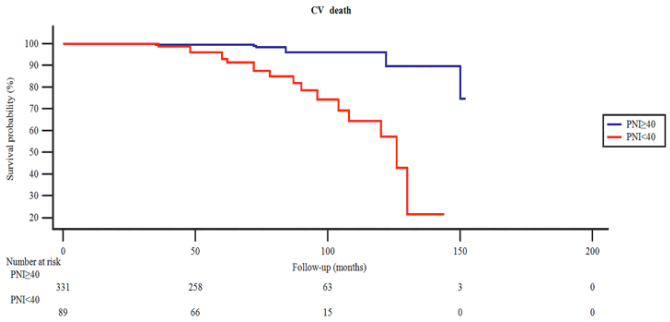

Figure 2: Kaplan–Meier analysis for primary end point according to PNI cut-off 40.0 in patients with hypertrophic cardiomyopathy.

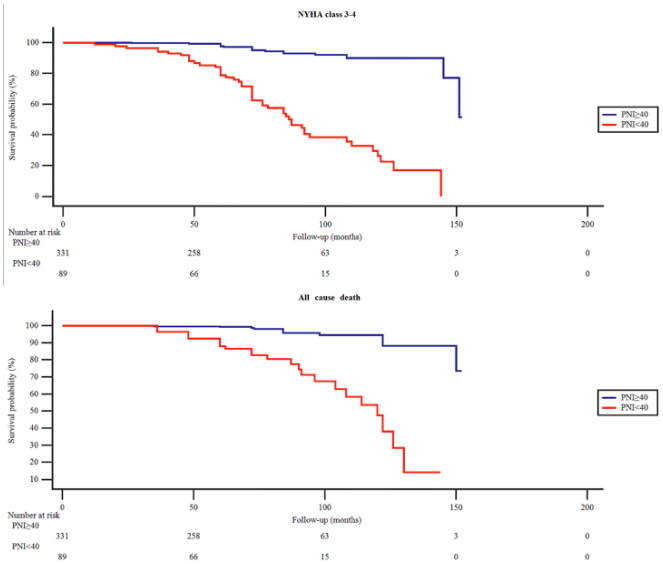

Figure 3: Kaplan–Meier analysis for secondary end points according to PNI cut-off 40 in patients with hypertrophic cardiomyopathy.

Discussion

This study showed that low PNI was associated with adverse outcomes in patients with HCM. The study's most important findings are the following: (1) Cardiovascular death significantly higher in the low PNI group; (2) all cause death significantly higher in the low PNI group; low PNI was significantly associated patients with presence of NYHA III or IV symptoms.

HCM is a common genetic cardiac disease characterized by LV hypertrophy, myofibrillar disarray and myocardial fibrosis. The clinical course of the disease is highly heterogeneous: many patients have no or moderate symptoms throughout their lifetime, but in some patients, HCM may lead to severe symptoms such as heart failure or even may result sudden cardiac death. Although the risks of sudden cardiac death have mostly dominated the HCM literature, progressive inability and heart failure is also a crucial complication of the disease. Heart failure is usually associated with left atrial enlargement, which reflects increased left ventricular filling pressures secondary to predominantly caused by diastolic dysfunction. In addition to diastolic dysfunction, some patients with severe LVH experience LV wall thinning and develop progressive left ventricular systolic dysfunction during their clinical course. Although previous studies have reported the progression of wall thinning detected in up to 15% of patients with HCM, Thaman et al demonstrated that wall thinning ≥5 mm occurred in 58% of patients with severe LVH. Impairment of the systolic function in hypertrophic cardiomyopathy below cut-off point set at 50% was previously shown to have crucial impact on the poor prognosis of patients with regard to major adverse event rates.

Reported HCM-associated mortality risk has undergone considerable modification over time. Recently, mortality in adult patients has reduced to approximately 0.5% per year owing to treatment interventions, especially implantable cardioverter defibrillators (ICD) and heart transplantation. Moreover, because the sudden death rate in HCM patients has reduced as a result of growing usage of ICDs, death due to heart failure is coming up as the prevalent mode of demise. In our study, presence of NYHA III-IV symptoms were seen in 66 (15.7%) patients and death due to HF in 14 (3.3%) patients. Pasqualucci et al showed that in a significant percentage of HCM patients, mortality can occur within 3 years after HF symptoms onset, in spite of a preserved LVEF [14]. Maron et al evaluated the nonobstructive HCM patients and

Table 4. Univariable and multivariable cox regression analysis for prediction of CVD

	Univariable analysis			Multivariable analysis		
	HR	95 % CI	P Value	Adjusted HR	95 % CI	p value
Age	1.012	0.984-1.040	0.419			
Gender, male	0.899	0.408-1.978	0.791			
Atrial fibrillation	2.862	1.281-6.391	0.010	0.993	0.353-2.793	0.990
Hypertension	0.849	0.316-2.279	0.745			
Diabetes	0.861	0.322-2.301	0.765			
Coronary artery disease	1.529	0.633-3.691	0.346			
Amiodarone	0.701	0.094-5.240	0.729			
β-blocker	1.529	0.357-6.546	0.567			
NYHA III or IV	4.900	2.222-10.804	<.001	1.551	0.546- 4.407	0.410
Body-mass index	0.874	0.750-1.019	0.085			
LVEDD (mm)	1.038	0.965-1.118	0.317			
Maximal wall thickness (mm)	0.988	0.901-1.183	0.802			
LVEF (%)	0.930	0.901-0.960	<.001	0.977	0.931-1.026	0.350
LVOT Gradient (mmHg)	0.987	0.971-1.003	0.113			
LA diameter (mm)	1.066	1.007-1.128	0.029	1.012	0.934-1.097	0.767
NSVT at 24-hHolter monitoring	0.702	0.286-1.725	0.440			
Syncope	4.630	0.625-3.291	0.134			
Hemoglobin (g/dl)	0.931	0.766-1.131	0.472			
Platelet (×103 µL)	0.997	0.991-1.003	0.331			
WBC (×103 µL)	1.003	0.906-1.111	0.954			
Neutrophil (×103 µL)	1.109	0.920-1.201	0.465			
Lymphocyte (×103 µL)	1.021	0.732-1.426	0.901			
Monocyte (×103 µL)	1.001	0.999-1.002	0.455			
Glucose (mg/dl)	0.996	0.914-1.345	0.295			
Creatinine (mg/dl)	1.037	0.484-2.222	0.925			
Uric acid (mg/dl)	1.047	0.866-1.266	0.635			
Albumin(g/dl)	0.101	0.047-0.214	0.470			
TSH, UI/mL	0.992	0.875-1.124	0.898			
hsCRP (mg/dl)	1.061	1.030-1.092	<.001	1.040	1.006-1.074	0.019
PNI	0.795	0.737-0.857	<.001			
PNI < 40.0	8.453	3.142-22.745	<.001	4.818	1.602-14.490	0.005

Bolded values indicate statistically significant odds ratio.
CI: confidence interval; CRP: C-reactive protein; LA: Left atrium; LVEDD: left ventricular enddiastolic diameter; LVEF: left ventricular ejection fraction;; LVOT:left ventricular outflow tract; NSVT: nonsustained ventricular tachycardia; NYHA: New York Heart Association; TSH:thyroid-stimulating hormone; WBC:white blood cell

demonstrated that, despite the relatively benign course of this disease, still 10% of patients progressed to NYHA class III-IV during follow-up [15]. These investigations highlight the need for parameters that could be used to determine HCM patients at risk for HF development before the endstage phase ocur. Several biomarkers, particularly B-type natriuretic peptide (BNP)[16], increased circulating inflammatory markers such as TNF-α [7, 8], IL-6 [17], MCP-1[18], NLR [9] and MHR [6] have recently been shown to be useful in stratifying risk in patients with HCM. Previous studies have shown that several nutritional indicators, including body mass index (BMI), serum albumin, total cholesterol, and total lymphocyte count, predict survival in patients with various cardiovascular diseases. Nakagomi et al. have shown that malnutrition was significantly associated with higher concentrations of inflammatory markers in patients with chronic HF [19]. In patients with HF, however, serum albumin level is influenced by several non-nutritional factors including fluid status, hepatic congestion, renal dysfunction and inflammation. Similarly, BMI is influenced by fluid status, indicating that the measurement of albumin or BMI alone is insufficient as a nutritional risk assessment. In contrast, PNI measured using both serum albumin and lymphocyte count may overcome the shortcomings of each indicator. PNI was first reported by Buzby et al. as an objective nutritional risk index

in 1980 and then Onodera et al. have reported the association between PNI and surgical risk for patients with malignancy [20, 21]. PNI has been used as a predictive nutritional marker in patients with various diseases, such as malignancy [22], acute or chronic HF [23, 24], heart failure with preserved ejection fraction (HFpEF) [25], pulmonary embolism (PE) [26], stable coronary artery disease (CAD) [27] and ST segment elevation myocardial infarction (STEMI) [28]. The clinical significance of nutritional risk assessment in patients with HCM has not been well established. To our knowledge, there is no clinical study presenting the association between PNI and adverse cardiac events in HCM in the literature.

There are several potential explanations for the relationship between low PNI and adverse cardiovascular events in patients with HCM. Low PNI is accompanied by hypoalbuminaemia, reflecting malnutrition and inflammation, which are associated with worse HF outcome [29, 30]. In many cases (approximately 50%), HF occurred in the clinical setting of HCM with preserved systolic function presenting a particularly malignant prognosis [31]. Several recent reports have provided data about prognostic value of nutritional status in HF patients with preserved systolic function [18]. In a recent study, importance of PNI was investigated in 1673 patients (52% HFpEF) hospitalised for acute HF[24]. A higher PNI tertile was related to better survival free from allcause death and patients with lower PNI had worst prognosis. Japanese Heart Failure Syndrome with Preserved Ejection Fraction study registered 535 consecutive hospitalised HFpEF patients. This study showed that serum albumin level on admission, was independently related with the composite outcome of all-cause death and heart failure hospitalisation during a median follow-up period[32]. PNI permits quantification of the interaction between HF, inflammation and malnutrition using both albumin level and total lymphocyte count, which is a second indicator for inflammation. An activated inflammatory state has been reported to be an important factor in the incidence and maintenance of HF. The physiological stress induced by advanced HF results in an increased production of cortisol and a shift in the leukocyte differential toward a decreased percentage of lymphocytes (%L)[33]. Lymphocyte concentration is a readily available, inexpensive, and simple prognostic marker in patients with symptomatic heart failure who do not have corticosteroid use, recent trauma, myocardial infarction, infection, surgery or history of malignancy. Lymphopenia has been described in numerous advanced disease states, including HF. In the lights of these findings PNI appears to generate a potent indicator for diverse mechanisms of malnutrition, including neuro-hormonal disorders, decreased caloric intake and impaired perfusion, in patients with HF by combining albumin and lymphocyte levels[33]. In our study, PNI also has a significant positive correlation with serum CRP level, which supports its role in systemic inflammation. This result confirmed that nutritional and immunological situations are important when considering the long-term outcome in patients with HCM. Moreover, we found that lower PNI was independently correlated with a lower left ventricular ejection fraction (LVEF), Its role can be defined as an identifier for high-risk patients who may benefit closely follow-up. In previous studies, some various cutoff values have been detected for PNI. These reports found the optimal cutoff values were 44.5, 45 or 40 [21-23]. According to the ROC curve analysis of the currrent study an optimal cut-off value of 40.0 was obtained.

Nutritional status evaluation is recommended in the guidelines in patients with HF and some studies have reported that nutritional intervention may be beneficial for these patients. However, no study has investigated patients with HCM. It remains uncertain how patients with low PNI should be managed. Further investigations are required to evaluate whether nutritional interventions improve clinical outcomes in HCM patients.

Limitations

Our study has several limitations. First; this was a single center, retrospective, observational study. Second; PNI levels were evaluated only once and did not asses their changes over time during the follow-up period. Third; because of methodological limitations of retrospective analysis, it is not possible to define the exact causal relationship between PNI level and adverse cardiovascular outcomes. Hence, the small sample size may limit the power of statistical test in revealing significant predictors and demonstrating the effects of PNI on different subgroups. Further prospective investigations on larger cohorts are necessary to confirm our findings, to clarify the underlying mechanism and to elucidate the prognostic utility of PNI more accurately.

Conclusion and Future Perspectives

This study identified nutritional status assessed by the PNI, a simple index calculated from routine biochemistry and hemogram tests, as an independent predictor of long-term adverse cardiovascular outcomes in HCM patients. Lower PNI

scores were associated with CV deaths in HCM patient. This result confirmed that nutritional and immunological situations are important when considering the long-term outcome in patients with HCM. Our study suggested that the PNI might be useful for risk stratification of HCM patients in clinical practice. Further investigations on independent multicenter cohorts should be performed in order to validate our findings.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

This study was performed in keeping with the principles outlined in the Declaration of Helsinki and approved by institutional ethics committee of our hospital.

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Original Article

Pulmonary hypertension screening in patients with systemic sclerosis, in a tertiary center, in Turkey; a cross-sectional original study

Türkiye'de tersiyer bir merkezde sistemik skleroz hastalarında pulmoner hipertansiyon taraması; kesitsel orjinal çalışma

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Abstract

Aim: Development of Pulmonary Hypertension (PH) in Systemic Sclerosis (SS) significantly reduces the survival of the disease and early diagnosis and treatment is very important.

The aim of this study was to investigate the presence of PH in patients who were followed and treated by rheumatology clinic with the diagnosis of SS and who did not have a known diagnosis of PH.

Materials and Methods: This cross-sectional study was completed with 51 patients with SS and a control group of 51 volunteers with similar characteristics in terms of gender and comorbidity. Demographic, laboratory and echocardiographic data were recorded.

Results: The median age of the patients with systemic sclerosis was 53 (46-60) years and the control group was 50 (45-55) years. 42 (82.4%) of the SS patients were female and 39 (76.5%) of the control group were female. Right heart catheterization was performed to 3 patients with high pulmonary artery pressure (>40 mmHg) on transthorasic echocardiography. Group 1 PH was diagnosed in two of three patients (3.9%); group 2 PH was diagnosed in one of three patients (1.9%).

Conclusion: In our study, we detected pulmonary hypertension in 5.8% of 51 patients with systemic sclerosis in a tertiary center. Although these patients have undergone PH screening at certain frequencies, it is noteworthy that we achieved this finding. We believe that we have detected patients with pulmonary systolic pressure at the border and showing rapid progression. Our study supports the more frequent screening of SS patients with borderline pulmonary artery pressure elevation.

Keywords: systemic sclerosis; pulmonary hypertension; echocardiography; right heart catheterization

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Öz

Amaç: Sistemik Sklerozda (SS) Pulmoner Hipertansiyon (PH) gelişimi hastalığın sürvisini önemli ölçüde azaltmaktadır ve erken tanı ve tedavi çok önemlidir. Çalışmamızda SS tanısıyla romatoloji kliniği tarafından takip ve tedavi altında olan ve ve bilinen PH tanısı olmayan hastaların PH varlığı açısından taranması amaçlanmıştır.

Gereç ve Yöntemler: Bu kesitsel çalışmaSS tanısı olan 51 hasta ve cinsiyet ve komorbidite açısından benzer özellikte 51 gönüllüden oluşan kontrol grubuyla tamamlandı. Demografik, laboratuvar ve ekokardiyografik verileri kayıt edildi.

Bulgular: Sistemik skleroz hasta grubunun ortanca yaşı 53 (46-60), kontrol grubunun 50 (45-55) idi. SS hastalarının 42 (%82,4)'si kadın, kontrol grubunun 39 (%76,5)'sı kadın cinsiyetten oluşmaktaydı. Transtorasik ekokardiyografide pulmoner arter basıncı yüksek saptanan (>40 mmHg) 3 hastaya sağ kalp kateterizasyonu yapıldı. İkisinde grup 1 PH (%3,9); birinde grup 2 PH (%1,9) saptandı

Sonuç: Çalışmamızda, tersiyer bir merkezde sistemik skleroz tanısıyla takipli ve tedavi altında olan 51 hastada %5,8 oranında pulmoner hipertansiyon saptamış bulunmaktayız. Bu hastaların belirli sıklıklarla PH taramasından geçirilmiş olmasına rağmen bu bulguya ulaşmamız dikkat çekicidir. Muhtemelen sınırda pulmoner arter basınç yüksekliği olan hızlı progresyon gösteren hastaları saptadığımızı düşünmekteyiz. Çalışmamız, sınırda pulmoner arter basınç yüksekliği olan SS hastalarının daha sık taranması gerektiğini desteklemektedir.

Anahtar kelimeler: sistemik skleroz; pulmoner hipertansiyon; ekokardiyografi; sağ kalp kateterizasyonu

Introduction

Systemic sclerosis (SS) is a systemic disease of unknown with multiple organ and tissue system involvement, skin being the most common target, and results inflammation, vasculopathy and fibrosis. The most differentiating characteristic of the disease is skin fibrosis called scleroderma, however it may also involve internal organs such as the gastrointestinal tract, kidney, lung and heart, therefore it is termed as systemic sclerosis.

Lung involvement is one of the most severe and lethal organ involvement. Pulmonary hypertension (PS) is another lethal complication that is frequent in SS(1). In SS, the incidence of pulmonary arterial hypertension (PAH) is reported to be 10-15% (2-4) and 3 years of survival has been reported in patients with PAH developed(5). Although SS patients with PAH have been known to have poorer treatment response than idiopathic PAH patients, recent studies showed that similar responses can be achieved with aggressive treatment(6,7). Early diagnosis and treatment is critical in SS related PAH and it is recommended to screen the patients for PH in their follow-ups(8).

In our study, we aimed to investigate the presence of PH in patients who were followed and treated in our hospital with the diagnosis of SS and who did not have a known diagnosis of PH.

Material and Methods

This is a cross-sectional study that aims to investigate the presence of pulmonary hypertension in patients who are being treated with systemic sclerosis diagnosis. Fifty-one patients aged 18 years and over who had admitted to Dışkapı Training and Research Hospital and been treated and followed up for at least 3 years by the Rheumatology outpatient clinic with the diagnosis of Systemic Sclerosis were included in the study. SS diagnosis was based on the diagnostic criteria of American College of Rheumatology(9). The control group of the study consisted 51 subjects with similar age and gender. Autoimmune disease, cardiac valve disease, structural, coronary and congenital heart diseases, arrhythmias, active infection, lung disease, thyroid disease, malignancy, kidney failure, liver disease, electrolyte disorders and pregnancy have been determined as exclusion criteria for the formation of SS patient and control groups. SS and control groups were similar in terms of the presence of hypertension, diabetes mellitus, hyperlipidemia. Moreover, patients who had known severe pulmonary involvement and those with prior diagnosis of pulmonary hypertension were excluded from the SS patient group.

Venous blood samples were obtained from peripheral antecubital vein after 10 hours of fasting.

Whole blood count, fasting blood glucose, renal function tests and erythrocyte sedimentation rate and CRP values were tested. In addition, antinuclear antibody (ANA), anticentromere antibody (ACA) and anti SCL70 antibody tests results were also included as retrospective autoimmune antibody tests.

Height and weight measurements of all participants were

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made and body mass indexes were calculated. Diagnosis year, medications used and comorbidities were recorded, and patients were classified in terms of diffuse and limited scleroderma involvement(9).

Informed consent forms were obtained from all patients. Helsinki Declaration was adhered in the study. Approval of the hospital ethical committee was obtained.

Echocardiographic examination

Transthoracic echocardiographic examinations were performed by using a 2.5-5 MHz transducer with Philips iE33 system (Andover, MA, USA) echocardiographic imaging device.

The examination was performed in the left decubitus position by an experienced cardiologist who was blinded to clinical and laboratory characteristics of the participants. Measurements were repeated three times and their average was used. Essential echocardiography parameters like left atrium, left ventricle end-systolic and end-diastolic dimensions, diastolic ventricular septum and diastolic left ventricle posterior wall thickness were measured by using M-mod echocardiography in parasternal long axis view. Left ventricular ejection fraction (EF) was measured from apical 4- and 2-chamber with Modified Simpson's method and their averages were calculated. Procedure was performed in accordance with international recommendations (10).

With the widest area at the end of systole, the right atrium area in apical 4-chamber view was measured by tracing the right atrium endocardium from the lateral of tricuspid annulus to septal annulus, excluding the area between the leaflets and the annulus, inferior and superior caval veins and apendix(11).

Color Doppler was used to evaluate valvular insufficiency. Left ventricular diastolic filling patterns were evaluated, E and A peak flow rates were recorded and deceleration time was calculated by using pulse-flow Doppler examination.

For the evaluation of left ventricular myocardium functions, Em and Am, which are the left ventricular diastolic velocities for diastolic functions, and the S velocity, which is the systolic function indicator, was obtained by placing the sample volume of Doppler on mitral lateral annulus in apical 4-chamber view.

Peak tricuspid flow rate was calculated from apical four-chamber view based on tricuspid insufficiency flow, and using the Bernoulli equiation, the pulmonary artery systolic pressure (PASP) was calculated by adding the estimated right atrium pressure. Tricuspid annular plane systolic change (TAPSE) was obtained by placing the M-mode cursor on the lateral of tricuspid valve annulus.

Pulmonary artery acceleration time was calculated by measuring the time from the beginning of the pulse flow Doppler envelope to the peak flow occurred.

Pulmonary hypertension was defined as PASB >40 mmHg(12) or tricuspid peak flow velocity over 3.4 m/s in echocardiography, or PH verification with right heart catheterization in patients with tricuspid peak flow velocity between 2.8-3.4 m/s and other accompanying echocardiographic findings of pulmonary hypertension(13). In right heart catheterization of these patients, tt was planned to measure the mean pulmonary artery pressure and pulmonary capillary end pressure. In systemic sclerosis, PH can develop due to pulmonary arterial vasculopathy (Group 1 PH), interstitial lung disease (pulmonary fibrosis (Group 3) or due to increased left cardiac filling pressure (i.e. cardiac involvement) (Group 2) and due to pulmonary venoocclusive disease (Group 1)(14).

According to the latest ESC guidelines(13), precapillary pulmonary hypertension was defined as mean pulmonary artery pressure (MPAP) >25 mmHg and pulmonary pulmonary capiller end pressure (PCEP) ≤15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units (WU). Post capillary pulmonary hypertension was defined as MPAP >25 mmHg and PCEP >15 mmHg and PVR ≤3 WU. For differential diagnosis in the presence of precapillary PH, interstitial lung disease-related PH presence (group 3PH) was also evaluated. For this purpose, in light of previous studies, it was defined with forced vital capacity <70% in respiratory function test and ILD-related findings in the computed thoracic tomography(15,16). Isolated pulmonary arterial hypertension was defined as the detection of precapillary pulmonary hypertension without the findings of overt interstitial lung disease (i.e. those that do not fit the above description). Pulmonary vaso-occlusive disease was defined as the normal arterial end pressure in the presence of radiographic pulmonary edema(17).

Statistical Analysis

Statistical analyses were performed by using SPSS 23.0 (Statistical Package for Windows, Chicago, Illinois, USA). Continuous variables with normal distribution are presented mean±standard deviation, those without normal distribution are presented as median and interquartile range. Categorical data were represented with numbers and percentages. Kolmogorov-Smirnov test was used to determine the normal distribution of the data.

Student t-test or Mann-Whitney U test was used for numerical variables and chi-square test was used for categorical data.

Results

Total of 102 patients, 51 systemic sclerosis patients and 51 healthy subjects, were included in the study. Demographic characteristics and laboratory results of both groups and the overall population are shown in Table 1. The median age of the systemic sclerosis group was 53 (46-60) years and control group was (45-55) years and there was no significant difference between the groups (p=0.182). There were 42 (82.4%) female patients. In the SS group, number and ratio of hypertensive patients was 16 (31.4%) and 18 (35.3%) in the control group (p=0.834). Median erythrocyte sedimentation rate of the SS group was 20 (15-29.7) mm/h and median ESR of the control group was 8 (7-10) and this difference was statistically significant (p<0.001). Median CRP of the SS group was 4.5 (2.6-10.5) mg/dl and median CRP of the control group was 4.5 (2.6-10.5) and the difference was statistically significant (p=0.001).

Clinical and serological features of the systemic sclerosis patients are shown in Table 2. There was diffuse cutaneous involvement in 22 (43.1%) patients and limited cutaneous involvement in 29 (56.9%) patients. The median diagnosis year of the patients was 5 (3-9) years. In SS group ANA positivity ratio was 78.4%, anticentromere antibody positivity was 25.5%, anti=SCL 70 antibody positivity was 17.6%. All patients had cutaneous involvement and 23 patients (62.7%) had Reynaud syndrome. The evaluation of the patients based on their medication revealed that 40 patients (78.4%) had the most frequent hydroxychloroquine use.

Table 1. Basal characteristics of the participants

Parameters	Study population S=102	Systemic sclerosis S=51	Control group S=51	P value
Age, year	52(45-57)	53(46-60)	50(45-55)	0.182a
Female sex, s(%)	81(79.4%)	42(82.4%)	39(76.5%)	0.624b
Hypertension, s(%)	34(33.3%)	16(31.4%)	18(35.3%)	0.834b
Diabetes mellitus, s(%)	10(9.8%)	4(7.8%)	6(11.8%)	0.739b
Hyperlipidemia, s(%)	28(27.5%)	13(25.5%)	15(29.4%)	0.824b
Smoking, s(%)	19(18.6%)	8(15.7%)	11(21.6%)	0.611b
Body mass index, kg/m2	23(22-25)	23(22-24)	23(22-25)	0.914a
Fasting blood glucose, mg/dl	90(87-98)	91(87-98)	89(86-98)	0.506a
Creatinine, mg/dl	0.8(0.72-0.89)	0.82(0.76-0.96)	0.80(0.67-0.88)	0.096a
Hemoglobin, g/dl	13.4(13-14)	13.2(12.2-14.1)	13.5(13.3-13.8)	0.143a
ESR (mm/hour)	12(8-20)	20(15-29.7)	8(7-10)	<0.001b
CRP (mg/dl)	3(2-5.2)	4.5(2.6-10.5)	3(2-4)	0.001b

S=Number, ESR=Erythrocyte sedimentation rate, CRP=C reactive protein
a: Mann Whitney- U test, b: Pearson chi-square

Table 2. Clinical and serological characteristics of patients with systemic sclerosis

Disease class, s (%)	Diffuse cutaneous SS	22(43.1%)
	Limited cutaneous SS	29(56.9%)
Sex	Female sex	42(82.4%)
Diagnosis year (year)	5 (3-9) years	
Autoantibody profile, s (%)	ANA	40(78.4%)
	ACA	13(25.5%)
	Anti SCL 70	9(17.6%)
Organ/system involvement, s (%)	Reynaud phenomenon	32(62.7%)
	Skin	51(100%)
	Lung	5(10.2%)
	Joint	2(3.9%)
	Gout	6(11.8%)
Treatment, s (%)	Hydroxychloroquine	40(78.4%)
	Steroid	17(33.3%)
	Methotrexate	9(17.6%)
	CCB	21(41.2%)
	Acetylsalicylic acid	15(38.4%)
	Azathioprine	5(9.8%)
	Cyclophosphamide	2(3.9%)
	Mycophenolate mofetil	1(2%)

SS= Systemic sclerosis; ANA = Antinuclear antibody; ACA = Anticentromere antibody, CCB=Calcium channel blocker

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Echocardiographic data of SS patients and the control subjects is presented in Table 3. There was no difference between the groups in terms of left ventricular end diastolic diameter and left ventricular end systolic diameter. The comparison of left atrium diameter revealed median left atrium diameter of 3.4 (3.1-3.7) in the SS group and 2.9 (2.9-3.1) in the control group, and the difference was statistically significant (p<0.001).

Table 3. Echocardiographic features of participants

Parameters	Systemic sclerosis N=51	Control group N=51	P value
LVEDD, cm	4.3 ±0.43	4.23 ±0.17	0.117a
LVESD, cm	2.9±0.32	2.9±0.29	0.576a
Left atrium diameter, cm	3.4 (3.1-3.7)	2.9(2.9-3.1)	<0.001b
Septum thickness, cm	0.96±0.13	0.97±0.06	0.924a
Posterior wall thickness, cm	0.94±0.12	0.96±0.07	0.242a
Left ventricular EF, %	60(60-65)	60(60-62)	0.597b
Mitral filling samples			
E (m/s)	0.633±0.193	0.782±0.133	<0.001a
A (m/s)	0.715±0.171	0.586±0.153	<0.001a
E/A	0.931 ±0.357	1.377 ±0.245	<0.001a
Deceleration time (ms)	180(165-218)	180(170-185)	0.778b
Mitral lateral annulus			
E'm peak velocity (cm/s)	9.7±2.9	12.7±2.3	<0.001a
A'm peak velocity (cm/s)	11.1±3.1	9.5±3.0	0.011a
S m peak velocity (cm/s)	9.2±2.3	10.2±1.7	0.016a
E/Em	7±2.8	6.3±1.6	0.179a
Tricuspid regurgitation velocity, m/sn	2.5(2.3-2.7)	2.1(2.0-2.2)	<0.001b
Pulmonary velocity, m/sn	0.84±0.17	0.80±0.08	0.082a
PASB (mmHg)	28(25-30)	25(20-29)	<0.001b
TAPSE, mm	25(23-27)	23(21-26)	0.215b
Pulmonary acceleration time, ms	103.3±22.5	138.3±5.7	<0.001a
Right atrium area, cm2	12.8±2.4	11.9±1.1	0.018a

a: Student's T test ; b: Mann Whitney U test
LVEDD= Left ventricle end-diastolic diameter; LVESD= Left ventricle end-sistolic diameter; EF= Ejection fraction; E=Early diastolic peak velocity; A=Late diastolic peak velocity; E'm=Mitral lateral anulus early diastolic myocardial peak velocity; A'm= Mitral lateral anulus late diastolic myocardial peak velocity; S m=Mitral lateral anulus peak systolic velocity; PASP= Pulmonary artery systolic pressure; TAPSE= Tricuspid annular plan systolic excursion

The evaluation of mitral diastolic filling patterns showed that E/A ratio was 0.931±0.357 in the SS group and 1.377±0.245 in the control group and the difference was statistically significantly lower (p<0.001). In tissue Doppler examination, mitral lateral annulus Em velocity was 9.7±2.9 cm/s and statistically significantly lower than the control group, which was 12.7±2.3 cm/s (p<0.001). E/Em ratio was 7±2.8 in the SS group and 6.3±1.6 in the control group, and the difference was not statistically significant (p=0.179).

Median tricuspid insufficiency peak flow velocity was 2.5 (2.3-2.7) m/s in the SS group and it was statistically significantly higher than 2.1 (2.0-2.2) m/s in the control group (p<0.001). Median pulmonary artery systolic pressure of the SS group was 28 (25-30) mmHg and median pulmonary artery systolic pressure of the control group was 25 (20-29) mmHg and the difference was statistically significant (p<0.001). In the SS group, the median pulmonary acceleration time was 103.3±22.5 ms and it was statistically significantly shorter than the median pulmonary acceleration time of the control group which was 138.3±5.7 ms (p<0.001). Mean right atrium area of the SS group was 12.8±2.4 cm2 and 11.9±1.1 cm2 in the control group, and it was statistically significantly larger in the SS group (p=0.018).

Right heart catheterization was performed for 3 patients who had been detected to have high pulmonary artery pressure. One patient had mean pulmonary artery pressure=32 mmHg; PCEP=8 mmHg, PVR=4 WU, minimal interstitial lung disease finding in the thorax tomography and FVC was >70% in SFT. Therefore, the patient was considered as group 1 PH and endothelium antagonist treatment was started.

Second patient had MPAP=26 mmHg; PCEP=7 mmHg, PVR=4 WU in the right heart catheterization, there was no lung involvement and endothelium antagonist treatment was started.

Third patient had MPAP=26 mmHg, PCEP=15 mmHg, PVR=3 WU in the right heart catheterization, the patient also had accompanyin hypertension, left ventricle hypertrophy and wide left atrium; left ventricular ejection fraction was normal. The patient was considered as diastolic dysfunction-related group 2 pulmonary hypertension.

As a result of our study, pulmonary hypertension ratio verified by right heart catheterization in patients with systemic sclerosis was found to be 5.8%; group 1 PH in two patients (3.9%), group 2 PH in one patient (1.9%).

Discussion

Based on the results of this cross-sectional study, pulmonary hypertension was detected in 5.8% of the study population by randomized cross-sectional screening of patients with systemic sclerosis who were receiving treatment and being follow-up and had no known diagnosis of pulmonary hypertension. These patients had been closely monitored in a tertiary center and pulmonary hypertension was thought to be excluded in them, therefore detecting pulmonary hypertension in three patients is worthy of attention.

The reported prevalence of pulmonary hypertension in systemic sclerosis has ranged from 5%(18) to 30%(19) based on the definition and exclusion criteria used in prior studies. DETECT study was conducted in 62 centers and included total of 466 SS patients from North America, Europe and Asia who had been diagnosed more than 3 years ago and had DLCO<60% in carbonmonoxide diffusion test, and 19% of the patients had group 1 PH, 6% had group 2 PH and 6% had group PH as proved by right heart catheterization(20). However, different than this reference study, in our study, not all patients who had shortness of breath complaint, reduced diffusion capacity in the carbonmonoxide diffusion test or severe pulmonary involvement in the thoracic tomography and been previously evaluated and examined with pulmonary hypertension pre-diagnosis in their rheumatology follow-up visits were included in our study. In our study, patients who were asymptomatic in terms of pulmonary hypertension, complied with their rheumatology follow-up visits and their drug treatment, were included.

Pulmonary involvement is the most serious and mortality-increasing condition in systemic sclerosis. Median survival is 3 years in systemic sclerosis patients with pulmonary arterial hypertension development(5). Although the treatment response is more difficult than that of those with idiopathic PH, early diagnosis and treatment is crucial. 2015 European Cardiology Society/European Respiratory Society PH guidelines recommend annual PH screening for SS patients(13). In our hospital, patients undergo annual echocardiography examination for cardiac involvement and respiratory function tests for pulmonary involvement in the rheumatology clinic. However, detecting 5.8% pulmonary hypertension in a randomized screening of pulmonary hypertension at a random time is worth noting. This may be due to the rapid progression observed in patients with borderline pulmonary artery systolic pressure in echocardiography. In the literature, it has been reported that 42% of the systemic sclerosis patients with MPAP 21-25 mmHg in right heart catheterization experienced PH development after MPAP increased over 25 mmHg after a second catheterization during median 48-month follow-up(21), and that the possibility of overt PAH development is higher in patients with borderline MPAP at the time diagnosis in comparison to the those with MPAP 20 mmHg. Borderline SPAP may have been detected in previous echocardiography of the patients who were found to have PH in our study. This result supports the notion that systemic sclerosis patients with borderline arterial pressure should be monitored more frequently.

Types of pulmonary hypertension that can be seen in systemic sclerosis are group 1 pulmonary HT that occurs due to vasculopathy in small pulmonary arteries, group 3 PH that is related to interstitial lung disease and hypoxia, and group 2 pulmonary hypertension which occurs due to systolic and diastolic dysfunction as a result of myocardial fibrosis. In addition, pulmonary veno-occlusive disease is not rare and can be a cause of PH in SS patients (14). Several of these mechanisms may be the cause of PH together in the same patient and its differentiation can be difficult in clinical practice. Isolated Group 1 PH is generally the most common type (14). In the DETECT study, 60% of the patients with PH were Group 1 PH, 20% were Group 2 PH, 20% were Group 3 PH (lung disease/hypoxia). In our study, pulmonary hypertension was detected in 3 patients, two of them were Group 1 and one was Group 2, and one of the patients in Group 1 PH was considered as such since interstitial pulmonary involvement was minimal.

In our study, diastolic functions of the SS group was found to be significantly more deteriorated than the control group. In SS, systolic and/or diastolic dysfunction may be related to fibrosis, left

ventricular hypertrophy, hypertension and renal disease(22,23).

As hypertension, age and diabetes mellitus presence, factors that can affect the diastolic functions, were similar between the groups, we believe that this finding is associated with systemic sclerosis-related fibrosis; diastolic dysfunction in systemic sclerosis is not rare according to literature(24), cardiac involvement starts with diastolic dysfunction.

Subtypes of systemic sclerosis are generally classified as diffuse cutaneous and limited cutaneous(25). This classification is associated with skin involvement and independent from organ involvement. However, organ involvement can be more frequent and onset earlier in SS patients with diffuse involvement(26). The only exception is that pulmonary arterial hypertension can be equally frequent in both diffuse and limited cutaneous involvement(27). Two group 1 PH patients were determined have diffuse cutaneous type and one Group 2 PH patients had limited cutaneous type. In our study, we were unable to make an association between skin involvement and PH presence as we had few number of patients with PH.

In our study, we used echocardiographic evaluation for PH screening and the parameters like carbonmonoxide diffusion test, NTproBNP, which were included in the DETECT algorithm(20), were not evaluated, however, our study plan was different than the previous PH screening studies. In our study, SS patients who had been evaluated and thought to be excluded in terms of PH in their rheumatology follow-up visits were evaluated in terms of pulmonary hypertension. The studies involving PH screening in systemic sclerosis studies conducted a broader evaluation within a wider timeframe and unlike our study, all patients who had been evaluated in rheumatology visits were included in the studies(18,19). Therefore, the prevalence of PH may be higher in these previous studies. In another study, it was reported that patients with DLCO≥80% may still have PH(28). In our patients detected with PH, we believe that PH may be excluded in rheumatologic follow-up in a similar way.

Limitation of the study

We believe that the cross-sectional design of our study was a limitation. A prospective study where SS patients are followed up and incidence of PH is determined in addition to its prevalence could have been more valuable. Due to our study design, we were unable to access the previous echocardiography and other examinations in rheumatology follow-up and therefore could not evaluate the rate and duration of PH development. The PASP 40 mmHg threshold value for the right heart catheterization indication may be a high threshold and therefore the prevalence of PH could be lower than its actual value.

Conclusion

In our study, we detected pulmonary hypertension in 5.8% of 51 patients who have been treated and monitored with systemic sclerosis diagnosis in a tertiary center. Two of these three patients were in 1 PH class and one was in 2 PH class. It is noteworthy that we have detected PH in patients who had been closely monitored, screened for pulmonary HT in their follow-up visits and thought to be excluded in terms of PH. We believe that our study supports the notion that the presence of pulmonary hypertension, a serious condition that significantly increases morbidity and mortality in systemic sclerosis, should be evaluated with more detailed algorithms and that especially the patients with borderline pulmonary artery systolic pressure should be more closely monitored.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Original Article

Relationship between monocyte to high-density lipoprotein ratio and contrast-induced nephropathy in patients with non-st elevation myocardial infarction

Monosit/yüksek-dansiteli lipoprotein oranının st elevasyonu olmayan miyokard enfarktüslü hastalarda kontrasta bağlı nefropatiyle ilişkisi

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Abstract

Aim: Contrast-induced nephropathy (CIN) is associated with worse prognosis in patients with non-ST-elevation myocardial infarction (NSTEMI). Early identification patients with a high risk of CIN are very crucial to improve outcomes. The monocyte to high-density lipoprotein ratio (MHR) is a novel inflammatory marker. We aimed to investigate the MHR had a predictive role for CIN development in patients with NSTEMI.

Material and Methods: NSTEMI who underwent percutaneous coronary intervention (PCI) were included in the study. MHR was calculated and CIN was defined as an increase in serum creatinine 25% or 0.5 mg/dl from baseline in the first 48- 72 hours.

Results: A total of 370(200, 54.1% men) patients were included in this study and 104 (28.1%) of them had DM. 25 (6.7%) of patients had CIN.MHR was significantly higher in patients with CIN (0.014± 0.004 vs 0.011± 0.006-respectively, p: 0.017). MHR was also significantly correlated with creatinine levels after PCI (r:0,104, p: 0.047). CIN group also experienced a more complicated in-hospital clinical course. Additionally; weight and MHR were detected as independent risk factors of CIN in logistic regression analysis.

Conclusion: Preprocedural MHR may be used as cheap, easy and simple marker of CIN. It may help with the early identification of patients with NSTEMIwho are at high risk of CIN.

Keywords: myocardial infarction; contrast-induced nephropathy; monocyte to high-density lipoprotein ratio.

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Öz

Amaç: Kontrast madde kullanımına bağlı nefropati (KBN) gelişimi perkutan koroner girişim (PKG) yapılan ST elevasyonu olmayan miyokard enfarktüsü (NON-STEMI) geçiren hastalarda sık görülmekte olup artmış mortalite ve morbidite ile ilişklidir. KBN açısından yüksek riskli hastaların önceden tespiti ve tedavisi, klinik sonuçların iyileşmesinde etkili olacaktır. Monosit yüksek dansiteli lipoprotein (HDL) oranı (MHO) klinikte yeni tanımlanan inflamasyon belirteçlerinden biridir. Çalışamızda işlem öncesi MHO' nın PKG yapılmış NON-STMI hastalarında KBN gelişimi arasıdaki ilişki araştırılmıştır.

Gereç ve Yöntemler: Çalışmamızda retrospektif olarak NON-STEMI tanısıyla PKG yapılanhastalar incelenmiştir. Hastaneye başvuruşunda alınan örneklerden MHO oranın hesaplanmış ve KBN; işlemden 48-72 saat sonra bakılan serum kreatininde bazal değere göre % 25 ya da 0,5 mg/dl artış olarak tanımlanmıştır.

Bulgular: Toplam 370(200, %54.1 erkek) hasta geriye dönük incelenmiş, 25 (%6.7) hastada KBN geliştiği saptanmıştır. Ayrıca hastaların 104'ünde (%28.1) Diabetes Mellitus (DM) olduğu görülmiştür. MHO; KBN gelilşen grupta gelişmeyen gruba göre anlamlı olarak yüksek saptandı (sırasıyla 0.014± 0.004 ve 0.011± 0.006, p: 0.017). Ek olarak MHO ile PKG sonrası kreatinin değerleri arasında pozitif korelasyon saptandı (r:0,104, p: 0.047). Beklendiği gibi KBN gelişen hastların yatışları sırasında daha çok komplikasyon olduğu görüldü. Ayrıca; kiloveMHO değerleri KBN gelişimi için bağımsız risk faktörleri olarak bulundu.

Sonuç: MHO ucuz, basit ve kolay şekilde saptanabilen inflamasyon belirteci olup, PKG yapılan NON-STEMI hastlarında KBN'nin saptanmasında ve tedavinin yönlendirilmesinde faydalı olabilir.

Anahtar Kelimeler: miyokard enfarktüsü; kontrast madde kullanımına bağlı nefropati; monosit yüksek dansiteli lipoprotein oranı

Introduction

Contrast-induced nephropathy(CIN), is afrequent complication of contrast use, after coronary procedures such as percutaneous coronary interventions (PCI) in patients with acute coronary syndromes (ACS) including non- ST elevation myocardial infarction (NSTEMI) and strongly associated with high mortality and morbidity (1-6).The aetiology of CIN is not clearly clarified.Although many risk factors for the development of CIN have been demonstrated such as chronic kidney disease (CKD), diabetes mellitus (DM), reduced left ventricular systolic function, nephrotoxic drugs and age over 70 years (6-8), the main pathophysiology of CIN is still underinvestigation. Thepossible causes of CIN developmentincludesincreased oxidative stress,endothelial dysfunction,direct tubular toxicity,inflammation andrenal parenchymal hypoxia (9,10). Recently studies have shown that The platelet to-lymphocyte ratio (PLR), elevated preprocedural high sensitive- C-reactive protein (Hs-Crp), and the neutrophil-to-lymphocyte ratio (NLR) have been shown to be associated with increased risk of CIN levels were associated with CIN in patients with ACS(11-13).

Monocyte to high density lipoprotein cholesterol (HDL-C) ratio (MHR)has been entered a new inflammatory marker and several studies have shown that there is strongcorrelation between MHR various adverse cardiovascular events (14-16). Although the relationship between the risk of developing CIN and MHR was demonstratedin small sized patients with ST-segment elevation myocardial infarction(STEMI) (17), whether there is a relationship between MHR and CIN in the patient with NSTEMIis still unclear. Thus, the aim of this study was to assess whether there is a relationship MHR and CIN after urgent PCI in patients with NSTEMI.

Materials and methods

Study population

370 consecutive patients who admitted withNSTEMIundergoing urgent PCI were retrospectively enrolled in the study, between February 2015 and December 2017at the Avicenna Hospital Cardiology Depratment. All patients were administered with (PCI).Patients with cardiac arrest, active infection or previously proven systemic inflammatory disease, contrast medium administration within the previous 10 days, end-stage renal failure (serum creatinine >3 mg/dl), advanced stage liver (alanine aminotransferase >50 IU/L) or malignancy and patients using lipid-lowering drugs were excluded from the study.Patients were identified as NSTEMI: Anginal symptoms occurringat rest, with positive cardiac enzymes and markers, deficiency of ST-segment elevation on theelectrocardiogram. Unstable angina pectoris

was defined as (a) the absence of ST-segment elevation as defined 1mm or more, (b) negative cardiac enzymes and markers, and (c) angina pectoris with at least one of three characteristic: 1) chest pain happen at rest and often for a prolonged period (usually> 20 min); 2) chest pain being severe and usually described as frank pain, or 3) chest pain happen with a crescendo pattern. Diabetes mellitus was defined by fasting serum glucose levels of at least 126 mg/ dl, a random plasma glucose level of >200 mg/dl and/or if the patient was taking oral anti-diabetic drugs, or insulin. Hypertension was described as a systolic blood pressure (BP) > 140 mmHg and/or a diastolic BP > 90 mmHg on two different occasions or treatment with any antihypertensive drugs for a known diagnosis of hypertension. Hypercholesterolaemia was described as baseline total cholesterol greater than 200 mg/ dl and/or a low-density lipoprotein cholesterol (LDL-C) level greater than 130 mg/dl or previously diagnosed and treated hypercholesterolemia.Current smokers are respondents who have smoked regularly in the previous 6 months. A family history of coronary artery disease was described as a coronary event occurring in men before 55 years old or a coronary event occurring in women before 65 years of age.The hospital local ethics committee approved our study. Our study was performed in accordance with the Helsinki Declaration.

Coronary angiography and intervention

Coronary angiography(CA) and PCI (Siemens Axiom Artis zee 2006; Siemens Healthcare, Erlangen, Germany) were performed by a percutaneous femoral approach according to standard clinical practice. Patients underwent CA within the 1-72 hours after admission.All patients, nonionic, low-osmolar contrast media (iohexol, Omnipaque 350 mg/ml; GE Healthcare, Cork, Ireland) was used. All patients were administered acetylsalicylic acid (loading dose of 300 mg) and clopidogrel (loading dose of 600 mg) before PCI.All patients were recommended aspirin 100 mg daily plus clopidogrel 75 mg daily for at least 12 months. Unfractionated heparin (a first bolus dose of 60 U/kg) was administered in the emergency department and followed by additional intraprocedural boluses in order to achieve an activated clotting time >250 seconds.Culprit lesion was treated with according to standard PCI technique by using a6-French guiding catheter (Launcher; Medtronic, Minneapolis, Minnesota, USA).The type of stents used (bare metal or drug eluting) and the decision to use glycoprotein IIb/IIIa antagonists were of the interventional cardiologist choice. All nephrotoxic drugs were stopped upon admission.After the PCI, all patients were treated with intravenous hydration (isotonic 0.9% saline intravenously at a rate of 1 ml/kg per hour for 6-12 hours). The infusion rate was reduced to 0.5 mL/kg per hour if severeleft ventricular dysfunction or overt heart failure was present.We performed echocardiography (Vivid 3; GE Medical System, Horten, Norway) to all patients within 48 hours of admission to the hospital. The left ventricular systolic performance was calculated usingthe modified Simpson's method. Other medical treatments (adrenergic blocking agents, renin-angiotensin-aldosterone system inhibitors, statins, diuretics) were determined by the physicians according to suggestions of the international guidelines.Contrast-induced nephropathy was described as an increase in serum creatinine of 0.5 mg/dl, or a 25%relative increase from baseline at 48-72 hours after the PCI .

Laboratory analysis

Blood samples were drawn by antecubital venipuncture into EDTAtreatedor plain tubes according to hospital protocol. The results offasting blood samples collected within the 24-h of hospitalizationwere used in the analyses. Patients whose lipoprotein levels werenot measured within the 24-h of hospitalization were excluded fromthe study. For definition of CIN, creatinine levels were measureddaily. Complete blood count (CBC) measurements were conductedusing Cell-Dyn 3700 (MAPSS Laser Differential; Abbott Laboratories,Abbott Park, IL, USA) for hemoglobin, total white blood cell count(WBC), monocyte, neutrophil and lymphocyte counts. Total cholesterol,HDL-C and triglyceride levels were measured enzymatically(Hitachi 7350 autoanalyzer, Hitachi Ltd., Tokyo, Japan) and LDL-Clevels were measured from these lipid parameters with Friedewaldformula. Monocyte to HDL-C ratio was calculated by dividing monocytecount (109/L) to HDL-C level (mmol/L) and reported as 109/mmol.The serum creatinine level was measured in allpatients upon hospital admission (prior to CA),daily for the three days after PCI, upon dischargefrom the coronary care unit and upon hospital discharge.WBC and differential counts were measuredat the time of admission before the patients weretransferred to the catheter laboratory. The total numbers ofneutrophils and lymphocytes were determined using anautomated blood cell counter (XE-2100, Sysmex Inc., Kobe,Japan), and NLR were automatically calculated by loading allthe data to the statistical program used. The estimated glomerularfiltration rate (eGFR) was calculated using the Modificationof Diet in Renal Disease formula [20] and utilizingthe baseline creatinine level.

Statistical analysis

All analyses were performed using SPSS version 22 for Windows (SPSS Inc, Chicago, Illinois). Numerical variables are Presented as mean ± standart deviation or median (minimum-maximum levels) according to distributions of parameters and nominals as percentages. All variables were subjected to Kolmogorov Smirnov testing to determine whether they were normally distributed. The independent samples t test was used to compare the values of continuous variables between the 2 groups. Nonparametric values were compared using the Mann-Whitney U test. The chi-square test was used to compare categorical data. To evaluate the effects of various factors on CIN development, we performed multivariate regression analyses using the backward Logistic Regression (LR) method. Variables for which the unadjusted P <0 .05 was considered significant.

Results

A total of 370(200, 54.1% men) patients were included in this studyand 104 (28.1%) of them had DM. 25 (6.7%) of patients had CIN. There was not significant difference between the patients with and without CIN in terms of weight, age and gender.General risk factors that DM, smoking and hypertension were same in both groups. Additionally; previous medications, Grace scores, HbA1c, peak troponin levels, left ventricular ejection fraction(LVEF), contrast volume, numbers of PCI and CABG rates were not differed between two groups. The baseline clinical and procedural characteristics of patients were shown in Table I and II. MHR, PLR, NLR and high sensitive C reactive protein (Hs-Crp) were significantly higher in patients with CIN (Table II) (Figure 1 and 2). MHR was also significantly correlated with creatinine levels after PCI (r:0,104, p: 0.047). Additionally,patients developed CIN experienced a more complicated in-hospital clinical course(Table II) (Figure 3) and weight and MHRwere detected as independent risk factors of CIN in logistic regression analysis (Table III).

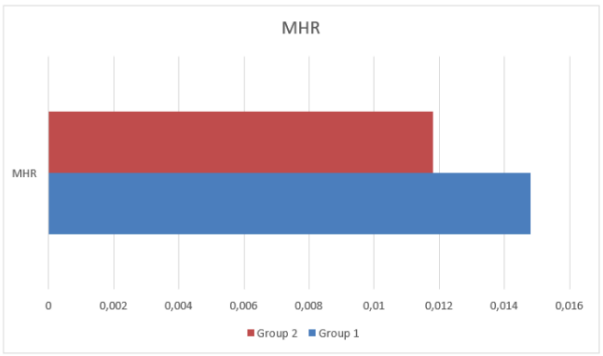

Figure 1: MHR: Monocyte to high-density lipoprotein ratio, NLR: , Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, Group 1 : Patients with CIN, Group 2: Patients without CIN. P < 0,05.

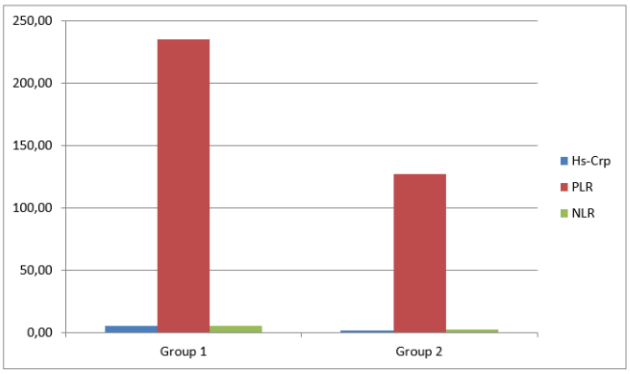

Figure 2: Group 1 experienced a more complicated in-hospital clinical course (Group 1: In patients with CIN, Group 2 : In patients without CIN ,p<0.05)

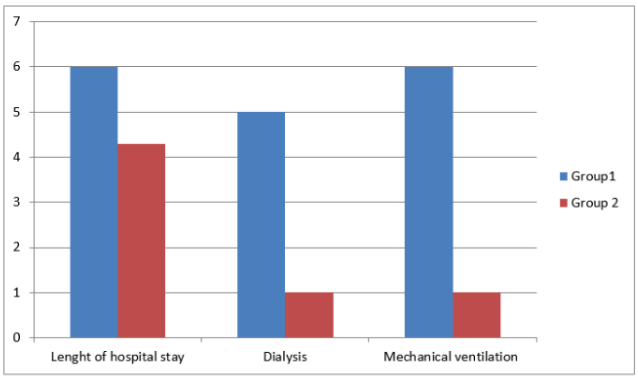

Figure 3: Group 1 experienced a more complicated in-hospital clinical course (Group 1: in patients with CIN, Group 2: In patients without CIN, p <0.005)

Table 1. Main Characteristics of Patients

	Patients with CIN N: 25	Patients with-out CIN N:345	P
Age (year)	57.4± 11.8	56.8± 10.8	NS
Men (n%)	14 (56%)	186(53.9%)	NS
Weigth (kg)	75.4±3.9	75.7±5.6	NS
HT (n%)	17(60%)	207 (68%)	NS
HL (n%)	14 (56 %)	110 (31.9%)	0.014
DM (n%)	11 (44 %)	93 (27 %)	NS
Smoker (n%)	5 (20%)	104(30.1%)	NS
Previous Miyocardial Infarction(n%)	9(36%)	91 (26.4%)	NS
Previous CABG(n%)	2 (8%)	103(29%)	0.019
Creatinine before PCI (mg/dl)	1.09±0.09	1.02±0.07	NS
EF(n%)	51.8±8.6	53.5±8.0	NS
eGFR (ml /min 1,73^2)	94.4± 16.5	89.2± 14.9	0.048

NS: Non significant, HT: Hypertension, DM: Diabetes Mellitus, HL: Hyperlipidemia, EF: Ejection fraction, CABG: Coronary artery bypass grefting,

Table 2. In-hospital clinical course of Patients

	Patients with CIN N: 25	Patients without CIN N:345	P
MHR	0.0148± 0.004	0.0118± 0.006	0.017
PLR	235,18±150,66	127,54±53,44	<0,001
NLR	5,47±3,64	2,59±1,82	<0,001
WBC	8.1±1.8	7.7±2.2	NS
HGB	13.7±1.8	13.5±1.5	NS
PLT	254.5±85.1	249.4±62.4	NS
NEU	5.2±1.5	4.7±1.8	NS
LYM	1.9±0.9	2.1±0.7	NS
MON	0.63±0.15	0.57±0.32	NS
HDL	44. 0±7.3	50.9±11.3	0.003
LDL	127.5±37.9	122.7±38.2	NS
TG	196.7±120.3	167.9±100	NS
NON HDL	157.9±39.0	156.7±42.8	NS
Glucose (mg/dl)	125.8±50.4	121.9±56.8	NS
HBA1C (%)	5.7±0.6	5.5±0.6	NS
HsCRP	5,76±4,9	2.1±3.3	<0,001
Uric Acid	5.7±1.7	5.5±1.6	NS
GRACE score	120.9±11.7	121.3±16.5	NS
Contrast volume ml	224.8± 16.3	228.2± 16.7	NS
Time to reperfusion h	4.2± 2.0	5.0± 2.2	0.029
Troponin peak (ng/dl)	2.1± 0.9	2.2± 0.8	NS
Length of hospital stay (days)	6.0± 2.6	4.3± 0.6	<0,001
Dialysis (n%)	5 (20%)	1 (0.3 %)	<0.001
Mechanical ventilation (n%)	6 (6&)	1 (0.3%)	<0.001
In-hospital mortality(n%)	2 (8%)	15 (4.3%)	NS
Medical treatment (n%)	4(16%)	36 (10.4 %)	NS
PCI (n %)	18 (72 %)	227 (80.3%)	NS
CABG (n%)	3 (12%)	31 (9 %)	NS

NS: Non significant, CABG: Coronary artery bypass grefting, PCI: Percutaneous coronary intervention, MHR: Monocyte to high-density lipoprotein ratio, NLR: , Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio

Table 3. Independent risk factors of CIN in logistic regression analysis

Variables	OR (95% C.I)	P
Weigth	0,8(0,7-0,9)	0,002
Age	1,1(1,0-1,2)	0,001
MHR	0,6(0,3-0,9)	0,048
eGFR	1,1(1,0-1,2)	<0,001
HT	1,5 (0,5-4,3)	0,38
DM	1,9 (0,7-4,9)	0,14

HT: Hypertension, DM: Diabetes Mellitus, EF: Ejection fraction, MHR: Monocyte to high-density lipoprotein ratio

Discussion

Our study showed that preprocedural MHR was an independent predictor of the development of CIN in the patients with NSTEMI undergoing PCI. Weight was also independent predictor for CIN in such patients.

Contrast-induced nephropathy during the course of NSTEMI is associated with increased morbidity and mortality(18). Inflammation may also play an important role in the initiation and extension phases of CIN (19). Early identification of patients with a high CIN risk plays critical role to allow the necessary interventions. Many of these biomarkers cannot be done in several centers at the time of admission. Therefore markers that can be used before the procedure and are widely available in many centers are needed. Monocytes account for the major source of pro-inflammatory and prooxidant factors, and they interact with endothelial cells and platelets leading to inflammation, thrombosis, and endothelial dysfunction (20,21). On the other hand, HDL-C has anti-inflammatory, antioxidant, and antithrombotic effects (22). So increased the MHR reflects the inflammatory process. MHR is also an important marker that reflect the inflammatory status in patients with atherosclerosis and has been demonstrated to predict the cardiovascular events in patients with ACS (14). As an inflammatory marker, the MHR has many advantages of being obtainable before the procedure. We observed that admission MHR was an independent predictor for CIN development. A recent study also revealed admission MHR as a risk factor for CIN in patients with STEMI and ACS (19). Preprocedural MHR measurement may help to identify patients with high risk of CIN and to take protective preventions such as reducing contrast volume and increasing fluid administration.

Contrast volume is an important risk factor for CINand dose minimization, on the background of a known baseline reduced renal function, may serve as an important strategy to limit the incidence of CIN (8).However, we used a relatively small amount of contrast, and we did not find significant difference in terms of dose of contrast used in all patients with and without CIN. We suggested that other factors, such as impaired renal function and DM, age and weight might contribute more to the development of CIN than contrast volume.

Also in our study; PLR, NLR and Hs-CRP were significantly higher in patients with CIN which were concordant with the previous studies(18,23-25). We also found that CIN was associated with increased incidence of adverse events during hospitalization.

This study has some limitations. First, it is a single-center

study. Second, the number of patients studied with CIN was relatively small, which could limit the number of independent predictors identified. However, we found some important results, consistent with the literature. Also, we only calculated MHR before the procedure. Serum HDL-C level and monocyte count may change with time; thus, single measurements of these parameters may not reflect any trend.

Conclusion

MHR is a risk factor for the development of CIN in patients with NSTEMI. The MHR is a simple marker of inflammation that can easily be obtained on admission and can be used to predict CIN risk.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Original Article

Relationship between patellar tendon–lateral femoral condyle friction syndrome and patellofemoral instability

Patellar tendon – lateral femoral kondil sürtünme sendromu ile patellofemoral instabilite arasındaki ilişki

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Abstract

Aim: The etiology of the patellar tendon–lateral femoral condyle friction syndrome (PTLFCFS) is not fully known and the number of studies on the diagnosis, treatment, and prognosis of PTLFCFS is limited. The aim of this study was to evaluate the relationship between PTLFCFS and patellofemoral instability in magnetic resonance imaging (MRI).

Material and Methods: Six morphological parameters were measured in MRI to evaluate patellofemoral stability in patients with PTLFCFS (study group n = 82) and patients without detection PTLFCFS (control group n = 204) in the knee MRI examination. These parameters include the Insall–Salvati ratio, ventral trochlear prominence, sulcus angle, lateral trochlear inclination angle, patellar inclination angle, and patellar lateralization measurement. In addition, the chondromalacia patella relationship was also evaluated.

Results: The Insall–Salvati ratio, patellar inclination angle, patellar lateralization, sulcus angle, and ventral trochlear prominence were significantly higher and lateral trochlear inclination angle was significantly lower in the study group than in the control group. The incidence of chondromalacia patella was significantly higher in the study group. In the study group, there was a positive correlation between the chondromalacia patella and the ventral trochlear prominence.

Conclusion: Among the factors causing PTLFCFS, patellofemoral instability was found to be effective. The measured parameters having high sensitivity and specificity suggest that these parameters can be used as risk factors and for the diagnosis.

Key-words: Patellar tendon–lateral femoral condyle friction syndrome; patellofemoral instability; magnetic resonance imaging

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Öz

Amaç: Patellar tendon-lateral femoral kondil sürtünme sendromunun (PTLFKSS) etiyolojisi tam olarak bilinmemektedir ve PTLFKSS'unun tanısı, tedavisi ve prognozu ile ilgili çalışmaların sayısı sınırlıdır. Bu çalışmada amacımız PTLFKSS ile patellofemoral instabilite ilişkisini manyetik rezonans görüntüleme (MRG) ile değerlendirmektir.

Gereç ve Yöntemler: Diz MRG'sinde PTLFKSS saptanan hastalarda (çalışma grup n=82) ve PTLFKSS saptanmayan hastalarda (kontrol grup n=204) patellofemoral stabiliteyi değerlendirmek için altı morfolojik parametre MRG'de ölçüldü. Bu parametreler Insall-Salvati oranı, ön troklear çıkıntı, sulkus açısı, lateral troklear eğim açısı, patellar eğim açısı ve pateller laterilizasyon ölçümü idi. Ayrıca kondromalazik patella ilişkisi de değerlendirildi.

Bulgular: Çalışma grubunda kontrol grubuna göre Insall-Salvati oranı, patellar eğim açısı, patellar lateralizasyon, sulkus açısı ve ön troklear çıkıntı anlamlı olarak daha yüksek ve lateral troklear eğim açısı ise anlamlı olarak daha düşük bulundu. Kondromalazik patella insidansı çalışma grubunda anlamlı derecede yüksekti. Çalışma grubunda kondromalazik patella ile ön troklear çıkıntı arasında pozitif bir korelasyon vardı.

Sonuç: PTLFKSS' ye sebep olan faktörler arasında patellofemoral instabilitenin etkili olduğu bulundu. Ölçülen parametrelerin yüksek sensitivite ve spesifiteye sahip olması; bu parametrelerin hem risk faktörü, hem de tanıda kullanılabileceği önerilmektedir.

Anahtar kelimeler: Patellar tendon-lateral femoral kondil sürtünme sendromu; patellar insitabilite; manyetik rezonans görüntüleme

Introduction

The knee is a hinge type joint in which the patellar tendon, ligaments, and sections of fascia lata provide passive stabilization, whereas the quadriceps muscle and aponeurosis provide active stabilization [1]. Excessive movement of the joint is restricted externally by Hoffa (infrapatellar fat pad) and the femoral and tibial condyles [1,2].

Patellar tendon–lateral femoral condyle friction syndrome (PTLFCFS) is considered as one of the leading causes of anterior knee pain, especially seen in young people [3]. Although the etiology of PTLFCFS is not fully known, its pathology is considered to result from the deterioration of knee biomechanics due to previous trauma. Generally accepted view is that the development of inflammation in the Hoffa and the direct contact of the lateral femoral condyle and patellar tendon due to trauma lead to clinical symptoms [1,4].

Magnetic resonance imaging (MRI) is an excellent diagnostic tool for knee imaging. With MRI, all the structures of the knee can be evaluated simultaneously, and this method allows a comprehensive understanding of the causes of anterior knee pain.

In PTLFCFS, an MRI examination shows an increased focal signal to the superolateral of the infrapatellar fat pad due to edema [1,4,5].

The aim of this study was to evaluate the quantitative parameters demonstrating patellofemoral instability of the knee using MRI in patients with PTLFCFS

Materials and Methods

The ethical compliance of this retrospective study was approved in accordance with the Helsinki Declaration by the Hospital Local Ethics Committee, Ankara, Turkey. Between May 1, 2016, and February 1, 2019, 1542 patients who were admitted to the orthopedics and traumatology department were evaluated. The inclusion criteria were as follows: (1) patients between 18-40 years old; (2) patients who had knee MRI in our radiology database. The exclusion criteria were as follows: (1) a history of major trauma, surgery or arthroscopy, tumor, patellar dislocation, inflammatory knee disease; (2) patients with findings of internal derangement, meniscal pathology, joint effusion; (3) artifacts precluding a proper MRI examination.

Eighty-two patients (18–40 years old) who had for more than 3 weeks due to anterior knee pain and increased focal signal to the superolateral of the infrapatellar fat pad in fat-suppressed proton density-weighted images were evaluated as a study group, whereas 204 patients (23–40 years old) with absence of anterior knee pain and no pathological findings in the superolateral of the infrapatellar fat pad were evaluated as a control group. Quantitative parameters used to evaluate patellofemoral stability were performed in MRI and two groups were compared with each other.

MRI protocol

MRI examinations were performed using a 1.5 T scanner (Gyroscan Intera, Philips Medical Systems, Nederland B. V.) with a

standard dedicated knee coil. During scanning, the patients were given a supine position with their knees at full extension. The imaging protocol constituted the following five routine sequences: coronal fast spin-echo T1-weighted, sagittal fat-suppressed proton density-weighted, coronal fat-suppressed proton density-weighted, axial fat-suppressed proton density-weighted and sagittal fast spin-echo T2-weighted.

All measurements were conducted by two radiologists, who have a blinded manner for the findings of each other.

Patients with an increased focal signal to the superolateral of the infrapatellar fat pad in at least two consecutive planes in the sagittal, axial, coronal images were included in the study group. The focal signal increase was considered as positive when it was at least 20% higher than the signal of the neighboring fat pad (1,4,5) (Figure 1 a,b,c).

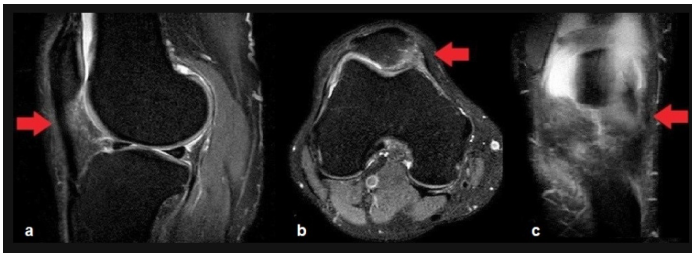

Figure 1. 34-year-old man with anterior knee pain for 4 months. Sagittal **(a)**, axial **(b)**, coronal **(c)** fat-suppressed proton density-weighted images of the left knee magnetic resonance imaging showing increased focal signal to the superolateral of the infrapatellar fat pad (red arrows).

The quantitative parameters were measured manually using the Extreme Picture Archiving and Communications System (PACS) system (Ankara, Turkey) for the study and control groups. All the measurements were performed at the osseous surfaces. Length measurements in millimeters (mm) and angle measurements were made in degrees (^{0}).

Insall–Salvati ratio: In the sagittal plane were made from the section where the largest width of the patella was measured. Insall–Salvati ratio is the ratio of the patellar tendon to the patellar length (Figure 2a).

Ventral trochlear prominence: In the midsagittal plane were made from the section where the deepest point of the trochlea was measured. Ventral trochlear prominence is the distance between the line paralleling the ventral cortical surface of the distal femur and the most anterior cortical point of the femoral trochlear floor (Figure 2b).

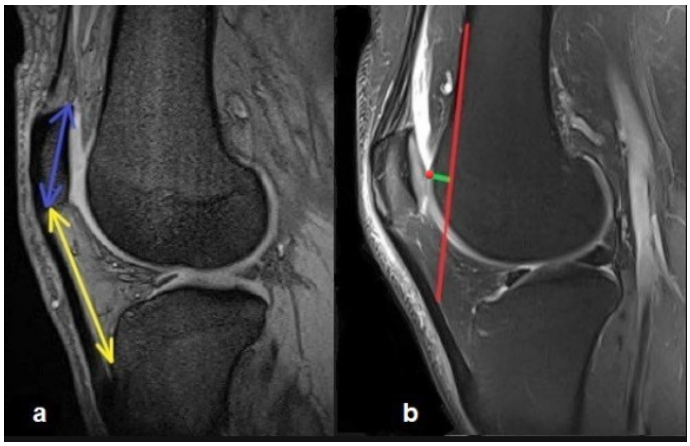

Figure 2. Sagittal magnetic resonance images shows; **(a)** Insall–Salvati ratio: Patellar tendon length (yellow line)/Patellar length (blue line), **(b)** Ventral trochlear prominence: is the distance (green line) between the line paralleling the ventral cortical surface of the distal femur (red line) and the most anterior cortical point of the femoral trochlear floor (red point).

Sulcus angle: In the axial plane, it was assessed 3 cm above the tibiofemoral joint line. The sulcus angle is formed by the lowest point of the intercondylar sulcus and the highest points of the medial and lateral femoral condyles. (Figure 3a).

Lateral trochlear inclination angle: is the angle between the line passing through the lateral trochlear facet and the tangent line crossing the posterior condyles (Figure 3b).

Patellar inclination angle: It is an angle between the patellar axis (between medial and lateral articular margins of patella) and the tangent line crossing the posterior condyles (Figure 3c).

Patellar lateralization (patellar lateral lateralization): The patellar lateralization is the distance between the most lateral point of the patella and the lateral margin of the trochlea (Figure 3d).

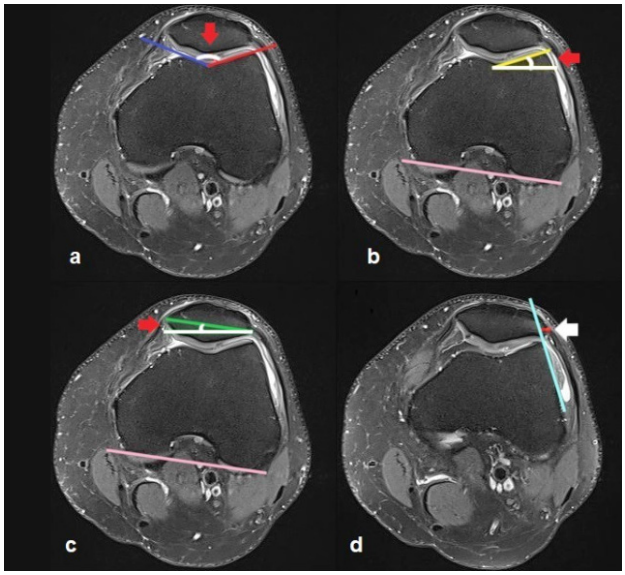

Figure 3. Axial magnetic resonance images shows; **(a)** Sulcus angle: The angle (red arrow) between the medial femoral condyle (blue line) and the lateral femoral condyle lines (red line), **(b)**: Lateral trochlear

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inclination angle: The angle (red arrow) between the line passing through the lateral trochlear facet (yellow angle) and the tangent line crossing the posterior condyles (pink line), **(c)** Patellar inclination angle (tilt): The angle (red arrow) between the patellar axis (green line) and the tangent line crossing the posterior condyles (pink line), **(d)** Patellar lateralization (patellar lateral lateralization): is the distance (red line) between the most lateral point of the patella (white arrow) and the lateral margin of the trochlea (turquoise line).

The relationship between patellofemoral instability and the chondromalacia patella was also evaluated using the same parameters. Chondromalacia patella type was evaluated using MRI-adapted Outerbridge classification for chondral defects. The patients with multiple cartilage injuries were classified according to the most serious injury.

Grade 1: Focal hyperintense areas with normal contour

Grade 2: Blister-like swelling/fraying of articular cartilage extending to the surface

Grade 3: Partial cartilage thickness loss with focal ulceration

Grade 4: Full cartilage thickness loss and reactive change in the bone.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software (IBM SPSS 25.0, IBM Corporation, Armonk, NY, USA). The data were analyzed using Kolmogorov-Smirnov for normal distribution. The Mann-Whitney U test (non-parametric) was used for analysis because the data did not conform to a normal distribution. Spearman (nonparametric) correlation test was used for correlation among the groups. Pearson's Chi-Square test was used for the analysis of categorical variables. Receiver operating characteristic (ROC) curve analysis was used to calculate the cut-off value (cut-off), specificity and sensitivity of the data. Mean and standard deviation values were used for analysis. $P < 0.05$ was considered statistically significant.

Results

The mean age of the patients was 23.61 ± 2.94 years, and 51.2% of the patients were males. No difference was found between the study and control groups in terms of age and gender ($p > 0.05$) (Table 1). In our study, the Insall–Salvati ratio, patellar inclination angle, patellar lateralization, sulcus angle, and ventral trochlear prominence were significantly higher and lateral trochlear inclination angle was significantly lower ($p < 0.05$) in the study group than in the control group (Table 1). The incidence of chondromalacia patella was also significantly higher in the study group ($p < 0.05$) (Table 1).

Table 1. Comparison of the demographic and quantitative parameters of the study and control groups

		Study group (n=82) Mean±SD/n (%)	Control group (n=204) Mean±SD/n (%)	p*
Age		23,61±2,94	23,73±3	0,534
Gender	Male	42 (51,2)	105 (51,5)	0,969*
	Female	40 (48,8)	99 (48,5)	
Insall–Salvati ratio		1,33±0,05	1,25±0,14	<0,001
Patellar inclination angle (⁰)		24,76±6,94	8,51±2,13	<0,001
Patellar lateralization (mm)		7,81±3,13	0,71±1,12	<0,001
Sulcus angle (⁰)		140,4±5,9	119,22±3,91	<0,001
Lateral trochlear inclination angle (⁰)		14,61±4,19	27,28±3,51	<0,001
Ventral trochlear prominence (mm)		8,4±1,01	6,65±0,75	<0,001
Chondromalacia patella	Normal cartilage	33 (40,2)	159 (77,9)	<0,001*
	1	15 (18,3)	15 (7,4)	
	2	10 (12,2)	14 (6,9)	
	3	12 (14,6)	9 (4,4)	
	4	12 (14,6)	7 (3,4)	

SD = standard deviation, * Mann-Whitney U test, ** Pearson's Chi-Square test were used for statistical analysis

In both study and control groups, chondromalacia patella was found to be positively correlated with Insall–Salvati ratio, patellar inclination angle, patellar lateralization, sulcus angle, and ventral trochlear prominence, whereas chondromalacia patella was found to be negatively correlated with lateral trochlear inclination angle ($p < 0.05$). In the study group, there was a positive correlation between the chondromalacia patella and the ventral trochlear prominence ($p < 0.05$), whereas no correlation was found between the chondromalacia patella and the Insall–Salvati ratio, patellar inclination angle, patellar lateralization, sulcus angle, and lateral trochlear inclination angle ($p > 0.05$) (Table 2).

Table 2. The relationship between chondromalacia patella and quantitative parameters				
	Study and control groups (n:286)		Study group (n:82)	
	r	p*	r	p*
Insall–Salvati ratio	0,212	<0,001	0,074	0,507
Patellar inclination angle (⁰)	0,296	<0,001	-0,038	0,738
Patellar lateralization (mm)	0,365	<0,001	0,013	0,910
Sulcus angle (⁰)	0,271	<0,001	-0,127	0,256
Lateral trochlear inclination angle (⁰)	-0,346	<0,001	0,005	0,964
Ventral trochlear prominence (mm)	0,313	<0,001	0,242	0,028
*Spearman correlation test was used for statistical analysis				

The sensitivity, specificity, area under the curve and cut-off values for the Insall–Salvati ratio, patellar inclination angle, patellar lateralization, sulcus angle, lateral trochlear inclination angle, and ventral trochlear prominence are shown in Figure 4 and Table 3.

Table 3. Sensitivity, specificity, area under the curve, and cut-off values of the quantitative parameters						
Test Result Variable(s)	AUC	Cut-off	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
					0,859	0,940
Patellar inclination angle (⁰)	1,000	11,6	%100	%100	1,000	1,000
Patellar lateralization (mm)	0,986	2,45	% 95,1	% 90,7	0,976	0,997
Lateral trochlear inclination angle (⁰)	0,988	21.3	%96,3	%94,1	0,980	0,996
Sulcus angle (⁰)	0,995	127,5	%96,3	%97,1	0,989	1,000
Ventral trochlear prominence (mm)	0,929	7,65	%87,8	%92,2	0,889	0,969
AUC= area under the curve						

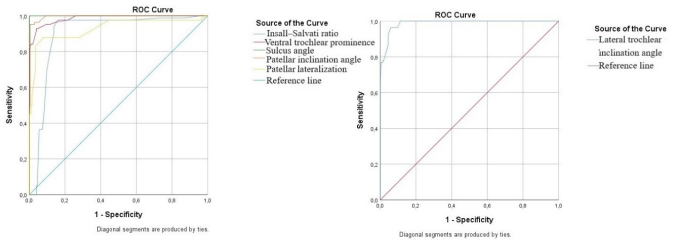

Figure 4. ROC analysis of the quantitative parameters.

Discussion

PTLFCFS is a disease typically characterized by anterior knee pain that emerges with activity [1]. In the literature, the number of studies on the diagnosis, treatment, and prognosis of PTLFCFS is limited.

In the present study, the Insall–Salvati ratio, patellar inclination angle, patellar lateralization, sulcus angle, and ventral trochlear prominence increased significantly in the study group, whereas the lateral trochlear inclination angle was found to be significantly lower than in the control group. In addition to the quantitative parameters in the literature, to our knowledge, ventral trochlear prominence was measured for the first time in the present study for the diagnosis of PTLFCFS and we found a positive correlation between ventral trochlear prominence. And the incidence of chondromalacia patella was significantly higher in the study group and there was a positive correlation between the chondromalacia patella and the ventral trochlear prominence.

Studies in the literature have reported that biomechanical changes cause this syndrome in young patients under the age of 40 [4,6]. Subhawong et al. evaluated the quantitative parameters measured in patients with PTLFCFS with respect to gender and age and found no statistically significant difference [7]. Consistent with the literature, the patients in the present study were young; 51.2% of the patients were males, and both age and gender were similar to that of the control group [7]. We consider that the incidence of pathology is higher in young people than in elderly due to the fact that young people perform activities that constantly operate the knee joint [sports, training, etc.]; chondromalacia patella is common in young people, and the knee is more frequently exposed to trauma. We consider that the pathology is similarly common in both genders due to the fact that both genders are at similar risk.

Munch et al. found that an increased level of patellar height leads to greater knee instability [8]. Matcuk et al. found that the Insall–Salvati ratio was higher in patients with PTLFCFS

than those without PTLFCFS and stated that high index rates could be considered as a risk factor [3]. Widjajahakim et al. reported a significant correlation between superolateral Hoffa fat pad edema and the Insall–Salvati ratio [9]. Bonadio et al. stated that a high patella leads to more tension of the patellar tendon during knee movements and that this can easily cause compression of the bursa between the lateral femoral condyle [10]. Consequently, inflammation can develop in the Hoffa and lead to edema and pain [10]. Li et al. found that the Insall–Salvati ratio rate was high in patients with PTLFCFS and that the sensitivity and specificity were 82% and 96.6%, respectively, at a cut-off value of 1.20 [1]. In the present study, the Insall–Salvati ratio was found to be significantly higher in the study group than in the control group. We believe that the patellar tendon is stretched and the structures underneath are compressed during knee flexion in patients with a high Insall–Salvati ratio. We also believe that inflammation and pain develop in the region in response to this.

It has been reported that the patellar inclination angle is the source of anterior knee pain in patients without clinical instability or clinical history. A patellar inclination angle of more than 13° has been reported to be a risk factor [4,11]. Matcuk et al. and Barbier–Brion et al. found that patellar inclination angle was significantly higher in patients with PTLFCFS [3,4]. In the present study, the patellar inclination angle was found to be significantly higher in the study group than in the control group. Patellar inclination angle exceeding the cut-off value may have led to the volume on the posterior side of the patella to be reduced and the posterior side of the patella to not sit properly on the joint.

Barbier–Brion et al. stated that patellar lateralization was significantly higher in the PTLFCFS group than in the control group and calculated sensitivity and specificity for a cut-off value of 6 mm as 75% and 83%, respectively [4]. Patellar lateralization was found to be significantly higher in the study group in the present study. Lateral displacement of the area where the posterior surface of the patella sits may have facilitated PTLFCFS by disturbing joint stabilization.

Matcuk et al. and Subhawong et al. described that the sulcus angles of patients with PTLFCFS were similar to those of the control group [3,7]. However, Gürsoy et al. reported that the sulcus angle was significantly higher in the PTLFCFS group compared with the control group [12]. Widjajahakim et al. reported that superolateral Hoffa fat pad edema was not associated with the sulcus angle [9]. In the present study, the sulcus angle of the study group was significantly higher than that in the control group. We believe that flattening the sulcus angle of the tibia may have caused damage by increasing the compression on the bursas of the triangular cartilage structure on the posterior side of the patella.

Matcuk et al. reported that the lateral trochlear inclination angle was lower in patients with PTLFCFS and that angles <11° were associated with high risk [3]. Li et al. found that the lateral trochlear inclination angle was low in patients with PTLFCFS and that sensitivity and specificity were 98.9% and 32%, respectively, for a cut-off value of 16.3 [1]. Gürsoy et al. found a decrease in the lateral patellofemoral angle [12]. Barbier–Brion et al. found that the lateral trochlear inclination angle was similar between the patient and control groups [4]. Widjajahakim et al. reported that superolateral Hoffa fat pad edema was not associated with the lateral trochlear inclination angle [9]. In the present study, the lateral trochlear inclination angle was found to be low. We believe that the decrease in the lateral trochlear inclination angle leads to an increase in the sulcus angle, thereby increasing the contact with the lower surface of the patella. Consequently, the structures under the patella remain under compression, leading to increased friction on the lower face of the patella.

Widjajahakim et al. described that anterolateral shifts increase the risk of Hoffa edema [9]. Barbier–Brion et al. reported that trochlear dysplasia increased the prevalence of PTLFCFS [4]. In the present study, ventral trochlear prominence significantly increased in the study group, and a positive correlation was found between the ventral trochlear prominence and the level of chondromalacia patella. Large ventral trochlear prominence may have increased the risk of PTLFCFS, as it may lead to the deterioration of knee joint instability and the stretching of the patella ligament. We believe that as the amount of cartilage damage behind the patella increases and the amount of edema in the Hoffa fat pad also increases in a correlated manner, leading to an increase in the ventral trochlear prominence. This may have led to an increase in the prevalence of PTLFCFS by increasing knee instability.

Various sensitivity and specificity values have been reported in the literature for different angles and lengths [1,4]. In the present study, sensitivity and specificity rates for appropriate cut-off values for current angles and lengths were found to be 87.8%–100% and 84.8%–100%, respectively. The high sensitivity and specificity values suggest that changes in existing angle and length values may be used both as risk factors and diagnostic purposes.

Chondromalacia patella is characterized by damage to the knee joint cartilage and leads to instability. In their study, Gürsoy et al. reported that the patellar shift in patients with chondromalacia patella and lateral patellofemoral angles was similar to that in patients without chondromalacia patella, whereas trochlear depth was shorter, sulcus angle was wider, and the Insall–Salvati ratio was higher [12]. In the present study, it was found that the prevalence of PTLFCFS increased in patients with chondromalacia patella. In the entire sample, a positive correlation was found between the Insall–Salvati ratio, patellar inclination angle, patellar lateralization, sulcus angle, and ventral trochlear prominence, whereas a negative correlation was found among the lateral trochlear inclination angle. Joint instability caused by chondromalacia patella, increased pressure on the bursas, especially the Hoffa, and increased inflammation may have led to an increase in the prevalence of PTLFCFS. In relation to the increase in the chondromalacia patella, we think that the instability of the knee is further deteriorated and that the inflammation is further exacerbated.

The major limitation of this retrospective study was the fact that radiologists who evaluated the parameters simultaneously determined the presence of the increased focal signal to the superolateral of the infrapatellar fat pad. Second, the diagnosis of articular cartilage damage in these patients could not be confirmed by any gold standard method, such as arthroscopy and surgery.

Conclusion

Patellofemoral instability was found to be effective among the factors causing PTLFCFS. The Insall–Salvati ratio, ventral trochlear prominence, sulcus angle, lateral trochlear inclination angle, patellar inclination angle, and patellar lateralization of the study group were found to be different than those of the control group. In addition, high sensitivity and specificity values identified for these parameters indicate that these parameters may be used both as a risk factor and for diagnostic purposes.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Original Article

Procedural and mid-term outcomes of carotid artery stenting and carotid endarterectomy in asymptomatıc patients: A single center experience

Asemptomatik hastalarda karotis arter stentleme ve karotis endarterektominin prosedürel ve orta dönem sonuçları: Tek merkez deneyimi

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Abstract

Aim: Atherosclerotic carotid artery stenosis (CS) is responsible for ~20% of strokes. The management of CS in an asymptomatic patient has been less clear. In situations were carotid endarterectomy (CEA) is thought to be more risky, surgeons must also have enough experience and capability to perform carotid artery stenting (CAS) to provide suitable, patient-tailored treatment. In this study, the same investigator performed all interventions (CAS and CEA), and one type of stenting device and EPD was used. In addition, periprocedural monitoring was carried out for at least 24 h. The objective of this study was to compare procedural results and 12-month follow-up outcomes of patients who were treated by the same operator- either CAS or CEA- in one year.

Material and Methods: A retrospective single-center review involving asymptomatic patients with severe stenosis of the ICA caused by atherosclerotic disease who was treated with either stenting with embolic protection (Group 1, n=17) or carotid endarterectomy (group 2, n=18) according to their clinical and anatomical risk profile between 1 January 2018 and 31 December 2018 at Numune Research and Training Hospital, Department of Cardiovascular Surgery, Ankara-Turkey was conducted. A duplex ultrasound (DUS) and neurological assessment was obtained prior to hospital discharge as a baseline, 30-days, 6 months, and 1 year thereafter. Patients' demographic and clinical characteristics, angiographic variables, primary endpoints including the composite of death, stroke and myocardial infarction during the 30 days after the procedure or ipsilateral stroke during the 365 days after the procedure was compared. Primary endpoints also including primary technical success, periprocedural clinical success, primary patency, clinical failure, periprocedural adjunctive maneuvers and secondary endpoints including complications, freedom from clinically driven target-lesion revascularization at 12 months, freedom from death, freedom from all stroke and freedom from restenosis rates were assessed and compared between the groups.

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Results: High-risk anatomical criteria were present in 8 (47.0%) patients, high-risk clinical criteria were present in 11 (64.7%) patients. Group 2 patients were older (67.7±7.4 vs 71.2± 6.9, p<0.05), but hyperlipidemia (58.8% vs 44.4%, p<0.05), chronic renal insufficiency requiring hemodialysis (11.7% vs 0.0%, p<0.05) and left ventricular dysfuntion (17.6% vs 0.0%, p<0.05) were significantly more frequent in Group 1. CCDS of group 1 was significantly lower than group 2 (4.7 ± 1.3 vs 7.3 ± 1.2; p<0.05, respectively). The lesions of the patients undergoing CEA were significantly longer (12.7 ± 2.6 vs 18.5 ± 4.2 mm.; p<0.05) and more calcified (11.7% vs 50.0%, p<0.05) than the patients in group 1. Likewise, the degree of stenosis in group 2 was significantly more than that of group 1 (81.4 ± 4.2 vs 88.3±6.4 %; p<0.05, respectively). Primary technical success was 100% for both groups. Periprocedural clinical success was 100% for Group 1, and 94.4% for group 2. Primary patency rates at 1/6/12 months were 100%/ 94.1%/94.1% for group 1, and 100%/100%/94.4% for group 2. Freedom from restenosis and freedom from CD-TLR at 12 months was 94.1% and 94.4% for group 1 and group 2. No death, major strokes, miyocardial infarction and systemic complications occured.

Conclusion: This study showed similar short and mid-term results for CEA and CAS in asymptomatic patients with significant carotid disease. Although we have shown good results for both CEA and CAS, CAS should be limited to those cases that are not suitable for open surgery and treatment of asymptomatic carotid artery disease with CEA should be considered for patients with few risk factors and long life expectancy. Both CEA and CAS reduce the long-term stroke risk in asymptomatic patients. The appropiate treatment strategy should be selected according to the patient's individual risk factors and imaging data.

Keywords: asymptomatic; carotid artery stenting; carotid endarterectomy

Öz

Amaç: Aterosklerotik Karotid Arter Stenozu (CS) tüm inmelerin %20'sinden sorumludur. Asemptomatik CS yönetimi daha belirsizdir. Hastaya özel tedavi için, Karotis Endarterektomi (KEA) işleminin daha riskli olduğu durumlarda, cerrahlar ayrıca karotis arter stentlemesi (KAS) yapabilecek tecrübe ve kapasitede olmalıdır. Bu çalışmada, tüm işlemleri (KAS ve KEA) aynı cerrah yapmış ve tek tip stent ve emboli koruma aracı kullanılmıştır. Ayrıca, prosedür sırasındaki monitorizasyon 24 saate yayılmıştır. Bu çalışmanın amacı, aynı operatör tarafından 1 yılda KAS veya KEA uygulanan asemptomatik CS hastalarının işlem ve takip sonuçlarını karşılaştırmaktır.

Gereç ve Yöntemler: İnternal karotid arter ciddi oklüzyonu nedeniyle klinik ve anatomik risk profillerine göre, 1.Ocak.2018-31.Aralık 2018 tarihleri arasında Ankara Numune Eğitim ve Araştırma Hastanesi Kalp-Damar Cerrahi Kliniğinde KAS (Grup 1, n=17) veya KEA (Grup 2, n=18) uygulanan asemptomatik hastaların retrospektif incelemesi yapıldı. Doppler Ultrason ve nörolojik değerlendirme hastalar işleme alınmadan, taburcu olmadan, prosedür sonrası 30.gün, 6.ay ve 1.yılda yapıldı. Hastaların demografik ve klinik özellikleri, anjiyografik değişkenleri, işlem sonrası 30 gün boyunca ölüm, inme ve miyokard enfarktüsü ve 1 yıllık ipsilateral inme oranları karşılaştırıldı. Teknik başarı, prosedür başarısı, birincil açıklık , klinik başarısızlık, işlem sırasında yardımcı manevraları içeren diğer birincil sonlanım noktaları ve komplikasyonlar, 12 ayda klinik olarak yönlendirilen hedef lezyon revaskülarizasyonundan kurtulma, ölümden kurtulma, tüm felçlerden kurtulma ve restenoz oranlarından kurtulma oranlarını içeren ikincil sonlanım noktaları değerlendirildi ve gruplar arasında karşılaştırıldı.

Bulgular: Sekiz hastada (47.0%) yüksek riskli anatomik kriter ve 11 hastada (%64.7) yüksek riskli klinik kriterler mevcuttu. Grup 2'deki hastalar daha yaşlı (67.7±7.4 vs 71.2± 6.9, p<0.05) idi, ancak hiperlipidemi (58.8% vs 44.4%, p<0.05), hemodiyaliz gerektiren kronik böbrek yetmezliği (11.7% vs 0.0%, p<0.05) ve sol ventrikül disfonksiyonu (17.6% vs 0.0%, p<0.05) sıklığı Grup 1'de fazlaydı. Grup 1'deki hastaların CCDS skoru Grup 2'ye göre düşüktü (4.7 ± 1.3 vs 7.3 ± 1.2; p<0.05). CEA yapılan hastaların lezyonları daha uzun (12.7 ± 2.6 vs 18.5 ± 4.2 mm.; p<0.05) ve daha kalsifikti (11.7% vs 50.0%, p<0.05). Benzer şekilde, grup 2'de damardaki darlık derecesi grup 1'e göre yüksek bulundu (81.4 ± 4.2 vs 88.3±6.4 %; p<0.05). Primer teknik başarı her iki grup için de %100 idi. Prosedürel klinik başarı Grup 1 için %100, Grup 2 için %94.4 idi. Primer patens oranları grup 1 için 1/6/12. aylarda 100%/ 94.1%/94.1%, grup 2 için 100%/100%/94.4%. restenozdan ve klinik olarak yönlendirilen hedef lezyon revaskülarizasyondan kurtulma oranları grup 1 için %94.1, grup 2 için %94.4 idi. Hiçbir hastada ölüm, major inme, miyokard infarktüsü ve sistemik komplikasyon gerçekleşmedi.

Sonuç: Bu çalışma, önemli karotis hastalığı olan asemptomatik hastalarda KEA ve KAS için benzer kısa ve orta dönem sonuçları göstermiştir. Hem KEA hem de KAS için iyi sonuçlar göstersek de, KAS açık cerrahi için uygun olmayan vakalarla sınırlı olmalı ve az risk faktörü ve uzun yaşam beklentisi olan hastalar için asemptomatik karotid arter hastalığının KEA ile tedavisi düşünülmelidir. Hem KEA hem de KAS asemptomatik hastalarda uzun süreli inme riskini azaltır. Uygun tedavi stratejisi, hastanın bireysel risk faktörlerine ve görüntüleme verilerine göre seçilmelidir.

Anahtar Kelimeler: asemptomatik; karotis arter stentleme; karotis endarterektomi

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Introduction

Approximately 6.5 million strokes occur per year.[1] Stroke is the second leading cause of death and is the leading cause of premature mortality and morbidity for both men and women.[2,3] Atherosclerotic carotid artery stenosis (CS) is responsible for ~20% of strokes.[4,5] Patients with vascular disease and risk factors such as diabetes mellitus (DM), hypertension, hyperlipidemia, and smoking are at significantly higher risk of developing carotid artery atherosclerosis. Not all patients with carotid atherosclerosis are at increased risk of stroke; however, a strong association between the severity of stenosis and stroke risk still exists. The prevalence of severe asymptomatic CS is as high as 3.1% .[6]

CS refers to a >50% stenosis of the extracranial internal carotid artery (ICA), with stenosis severity estimated using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method.[7] Of all strokes, 10–15% occurs due to thromboembolism that stems from a 50–99% ICA stenosis.[8] CS is defined as 'symptomatic' if associated with symptoms in the preceding 6 months and 'asymptomatic' if no prior symptoms can be identified, or when symptoms occurred beyond 6 months. Unfortunately, carotid atherosclerosis is often asymptomatic until a disabling or fatal stroke occurs. Even when asymptomatic, stenosis of the carotid artery has been reported to place an individual at more than a 3% increased risk of having a stroke in the following year (greater than 50% increased relative risk).[9]

CS often is treated with aggressive medical therapy (statins, antiplatelet and antihypertensive agents), smoking cessation, treatment of comorbidities, and surgical intervention—either carotid artery stenting (CAS) or carotid endarterectomy (CEA)- and CS revascularization has conventionally been performed by CEA. CAS was developed as an alternative to CEA, and in the current era, it is a widely used procedure for carotid artery occlusive disease, especially in patients at high risk for CEA.[10]

There are subtle differences in recommendations regarding CAS in symptomatic patients. Guidelines stipulate that CEA should be preferred over CAS in symptomatic patients with 70-99% CS as class Ia recommendation and with 50-69% CS as class IIa recommendation [11, 12] -especially if >70 years old [13]- ; and CAS as an alternative for patients who present with adverse anatomical features or medical comorbidities that are considered to make them high risk for CEA.[14] Though the risk of operative stroke/death is higher with CAS, major randomized clinical trials (RCTs) report event rates under the recommended 6% cut-off value for both treatment modalities. But as a general recognition, guidelines recommend that CEA be performed as early as possible after the neurologic symptom seen in patients with symptomatic carotid stenosis (≥50%).

On the other hand, the management of CS in an asymptomatic patient has been less clear, and there is also an ongoing debate. Since the reduction in the incidence of stroke among asymptomatic patients with established severe CS has not been shown in prospective studies with BMT, uncertainty remains regarding the optimal technique for long-term prevention of vascular events. It is clear that both CEA and CAS reduce long-term stroke risk in asymptomatic patients. With regard to periprocedural outcomes of RCTs, most recent ESVS guidelines recommend patients with an "average surgical risk", and asymptomatic CS of 60–99% should be considered for CEA and suggest CAS in asymptomatic patients who have been deemed "high risk for CEA and who have an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, documented perioperative stroke/death rates are <3%, and if the patient's life expectancy is >5 years as class IIa recommendation.[8] Factors that are classified as a high risk for CEA include age >80 years, clinically significant cardiac disease, severe pulmonary disease, contralateral ICA occlusion, contralateral recurrent laryngeal nerve injury, previous radical neck surgery or radiotherapy, in situ tracheotomy, severe cervical spine arthritis, surgically inaccessible carotid stenosis.[15] A relative contraindication to CAS is octogenarians, where high complication rates have been reported from several trials.[16]

Potential advantages include avoidance of general anesthesia, avoidance of an incision in the neck with the risk of cranial and cutaneous nerve damage, and a reduction in the rate of general complications of the surgery, for example, myocardial infarction. However, CAS does not remove the atherosclerotic lesion and may dislodge emboli during catheterization, causing the periprocedural stroke. We know that the risk of the permanent

neurological deficit because of diagnostic cerebral angiography alone is considerable and estimated to be about 1%.[17] Percutaneous transluminal angioplasty (PTA) is a critical component of CAS procedures and carries significant embolic risk.[18] Its use before or after stent deployment is being scrutinized. Concern regarding the risk of distal embolization of debris being dislodged from the atheromatous plaque during stent deployment and resulting in neurological deficit has led to the introduction and increasing use of cerebral embolic protection devices (EPD), but evidence on protection devices used during CAS is scarce since a small amount of randomized evidence comparing the different cerebral protection systems exists.[1] However, ESVS guidelines' class of recommendation for the use of EPDs in patients undergoing CAS is defined as class IIa.[8]

The local anatomic and lesion factors increase the fluoroscopy time and risks associated with CAS [19] whereas systemic factors and comorbidities increase the risks associated with CEA.

The main aim of treating CS is the prevention of stroke in the long term. CEA is effective at preventing ipsilateral stroke over long-term follow-up periods of 10 years or longer.[20] To provide an alternative, CAS needs to have similar long-term effectiveness, but in situations were CEA is thought to be more risky, surgeons must also have enough experience and capability to perform CAS to provide suitable, patient-tailored treatment, should not choose the one which the operator is experienced. Better selection of high-risk surgical patients or high-risk CAS patients is critical in providing the best therapy for each individual patient. In this study, the same operator performed all interventions (CAS and CEA), and one type of stenting device and EPD was used. In addition, periprocedural monitoring was carried out for at least 24 h. The objective of this study was to compare procedural results and 12-month follow-up outcomes of asymptomatic patients who were treated by the same operator- either CAS or CEA- in one year.

Material and Methods

Study Design and Patient Population

A retrospective single-center review involving asymptomatic patients with severe stenosis of the ICA caused by atherosclerotic disease who was treated with either stenting with embolic protection (Group 1, n=17) or carotid endarterectomy (group 2, n=18) between 1 January 2018 and 31 December 2018 at Numune Research and Training Hospital, Department of Cardiovascular Surgery, Ankara-Turkey was conducted. The study was approved by the regional ethics committee at Başkent University. Procedural data were prospectively recorded; data on complications were retrospectively recorded from the computerized chart. Informed consent was obtained from all the patients participating in the study.

Patients were recruited in clinical practices and referred for possible revascularization of known or suspected CS; they were then screened for eligibility on the basis of findings from duplex ultrasonography. Before enrollment, a neurologist confirmed each patient's asymptomatic status (defined as having been free, in the ipsilateral hemisphere, from stroke, transient ischemic attack, and amaurosis fugax for 180 days before enrollment).

Planning

In order to compliment treatment strategy towards individual patients, primary interest has been developed in identifying whether any carotid lesion characteristics place a patient at high risk for operative stroke with CAS or CEA. Various lesion-related and procedure-related risk factors have been described, which may increase the CAS-related risk of operative stroke and high surgical risk for CEA, many of which have been identified on secondary analyses of major RCTs. The formal decision for the type of treatment was taken by the surgeon. Only patients with an asymptomatic 60-99% stenosis according to NASCET criteria, which may be associated with an increased risk of late ipsilateral stroke, were recruited in the study. Those patients who were eligible and carried high surgical risk for CEA [8] was operated via CAS (Group 1), whereas patients who had "average surgical risk" and criteria associated with increased difficulty for CAS was operated by CEA. The criteria were previously described and were similar to the criteria for other registries and ESVS guidelines.[8, 21-24] Enrollment criteria were shown in table 1.

Furthermore, operator characteristics which had reported to in-

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Table 1: Inclusion criteria of groupsa

CAS (Group 1; n=17)	CEA (Group 2; n=18)
1. Eligibility Criteria • Target vessel diameter 4.5–9.5 mm for Protege Stent • Internal carotid artery diameter 3–7 mm for SpideFX device • Age <70 y • Tolerate aspirin, clopidogrel and heparin • Must meet high-risk criteria for high-risk patients • Must comply with follow-up and provide informed consent 2. Patients High-Risk for CEA Anatomical High Risk • Contralateral carotid artery occlusion • Tandem stenoses >70% • Surgically inaccesible lesions: High cervical (above C2) or infraclavicular • Bilateral carotid artery stenosis requiring treatment • Hostile neck* Clinical High Risk • Two or more diseased coronary arteries with >70% stenosis • Unstable angina (CCS class III or IV) • Congestive Heart Failure (NYHA class III/IV) congestive heart failure class 3– 4 • Left ventricular ejection fraction <30% • Recent myocardial infarction (>24 hours and <4 weeks) • MI within 30 days and need carotid revascularization • Need open heart surgery within 30 days • Severe pulmonary disease** • Chronic Renal Insufficiency *** • Permanent contralateral cranial nerve injury	1. Average surgical risk 2. Inability to obtain femoral artery access 3. Increased risk of Stroke for CAS (particularly Age>70) Access related • Aortic arch/supra-aortic vessel calcification • Aortic arch elongation (type II/III arch) • Tandem lesion in CCA or innominate • ICA-CCA angulation ≥60º Lesion related • Severe stenosis >85% • Circumferential calcification • Ulcerated lesion • Ostial lesion • Lesion length >10–15 mm • Lesions which will require multiple stent use • Sequential lesions • Echolucent plaque (on ultrasound) Distal ICA • Tortuosity • Diffuse atherosclerosis • Tandem lesion • Thrombus • Small caliber
CEA: Carotis endarterectomy, CAS: Carotid Artery Stenting, CCS: Canadian Cardiovascular Society, NYHA: New York Heart Association *Defined as prior neck irradiation, radical neck dissection, cervical spine immobility, tracheostomy ** Defined as the need for home oxygen, pO2 <60 mmHg on room air, or FEV1.0 <50% predicted *** Serum creatinine > 3.0 mg/dl or currently on dialysis	CEA: Carotis endarterectomy, CAS: Carotid Artery Stenting, ICA: internal carotid artery

[a] Based on conditions that were used to determine patients at high risk for carotid endarterectomy in carotid stenting trials and registries, such as *ARCHER, CABERNET, CREATE, SAPPHIRE, and BEACH.*

crease the risk of stroke with CAS such as, inexperience, aortic arch injection, failure to use EPD, predilatation prior to EPD was prohibited.

For CAS, operator experience is critically important. A pooled analysis of early carotid stent trials for symptomatic carotid stenosis showed that operators with low (mean ≤3.2 procedures per year) or intermediate (mean 3.2–5.6 procedures per year) in-trial case volume had 10.1% and 8.4% risk of operative stroke/death, respectively. High-volume operators (>5.6 procedures per year) like in our study, had the lowest operative stroke/death rate at 5.1%.[25]

Exclusion criteria are listed in table 2 and previously described [21-23, 26]

Table 2: Exclusion criteria

Clinical criteria	Angiographic criteria
• Atrial fibrillation (chronic or paroxysmal) not treated by coumadin • Bleeding requiring blood transfusion within 1 month CABG or vascular surgery within 30 days (before or after intervention) • Life expectancy <12 months • Intolerance to heparin, or aspirin, or clopidogrel. • No femoral arterial access • MI within 72 hours • Prior stent of target carotid artery • Symptoms within 6 months • CVA or retinal embolus within 1 month, with any majör neurological deficit • Allergy to nickel or titanium • Allergy to radiographic contract that cannot be pretreated. • WBC <3000/mm3, PLT <50,000/mm3 or >700,000/mm3 • Any intracranial tumor	• Target vessel is occluded • Critical (99+%) stenoses ("string sign") • Ostium of common carotid artery requires treatment • Tandem lesions that cannot be covered by 1 stent • Ipsilateral intracranial stenosis requires treatment • Any AVM or aneurysm requiring treatment

Procedures

CAS

Before the procedure, all patients received aspirin (100 mg/d) and clopidogrel (75 mg/d) for at least 2 days plus a loading dose of clopidogrel (300 mg) if they had not previously been on clopidogrel. The patients still received their regular antihypertensive medications, with the exception of beta-blockers, on the morning of the procedure.

Patients are placed in a supine position; both groins are prepared routinely. The head is placed in a cradle and gently secured to decrease patient motion during critical portions of the procedure. The procedure is performed with the patient awake under local anesthesia, although minimal sedation is acceptable in particularly anxious subjects. After retrograde femoral access with a 5F sheath under US control, 1 mg/kg unfractionated heparin was administered to maintain activated clotting time >250 sec throughout the procedure. Continuous arterial pressure and electrocardiographic monitoring were performed during the procedure.

Diagnostic angiography was performed using a diagnostic catheter (5-Fr Omni Flush; Cordis, Fremont, CA, USA) including arch angiography to opacify the aortic arch and supra-aortic vessels in order to evaluate the anatomic characteristics such as lesion location, the severity of the stenosis, tortuosity of the target vessels, distance from the origin of the treated artery to the beginning of the descending aorta, the vertical distance from the top of the arch to the origin of the target vessel, angulated takeoff of the vessel (≤ 30 degrees between the aortic arch and the innominate artery [for right-sided lesions] or left CCA [for left-sided lesions]), index lesion calcification, ulceration, and eccentricity.

Following selective catheterization of the ipsilateral mid-distal common carotid artery (CCA) (typically with a Simmons II catheter), a selective arteriogram of the carotid bifurcation is performed, paying careful attention to choose a view that provides minimal overlap of the ICA and external carotid arteries (ECA) and provides maximum visualization of the target lesion. A complete cerebral arteriogram, if not performed previously, is performed as a baseline and to identify intracranial pathologies, such as aneurysms and arteriovenous communications, and to determine the patency and completeness of the circle of Willis. After selective catheterization, the diagnostic catheter and 5F sheath were removed (while maintaining constant visualization of the guidewire in the ECA during this process) and a long (70 to 90 cm, depending on patient body habitus) 6F sheath was advanced with its dilator, into the CCA. If a difficulty occurs in advancing the long-sheath into CCA, as an alternative, the long sheath can be advanced into the transverse arch over a guidewire, the dilator is removed, and an appropriate selective diagnostic catheter is advanced into the CCA. A stiff guidewire was then advanced into the ECA, then using the wire and catheter for support the sheath was advanced into the CCA. In the alternative method, care must be taken to minimize the probability of dissection or distal embolization from the junction of the aortic arch and the innominate or left CCA, because you could not use the protection of the sheath dilator. Following maintenance of the sheath access to distal CCA, the dilator and the 0.035-inch guidewire were removed and ultimately exchanged for a 0.014-inch wire. We prefer to attach the sheath sidearm to a slow, continuous infusion of the heparin-saline solution to avoid stagnation of blood in the sheath. We performed a selective angiogram of the carotid bifurcation again, for demonstrating the area of maximal stenosis, the extent of the lesion, and normal ICA and CCA above and below the lesion, and road-mapping.

The SpiderFX Embolic Protection Device (Medtronic, MN-USA) (Figure 1) was advanced across the lesion, with the aid of road-mapping and deployed into the distal extracranial ICA, just prior to the horizontal petrous segment. The capture wire in the Spider system was not used to cross the target lesion in any procedure.

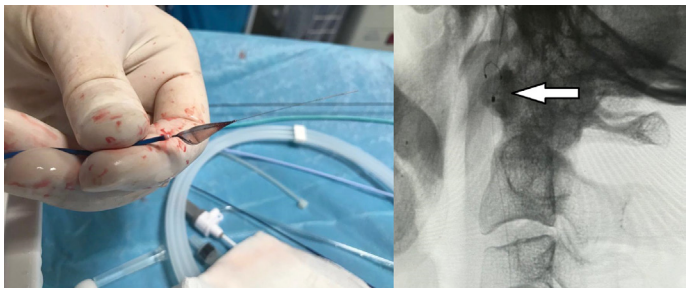

Figure 1. The SpiderFX Embolic Protection Device (Medtronic, MN-USA)

We never perform predilatation before EPD deployment. Atropine (0.5 to 1.0 mg intravenously) was administered as prophylaxis against bradycardia during balloon inflation in the carotid bulb. If hypotension occurred, the patients received 2 to 3 mg dopamine and rapid administration of additional fluids. The lesion was predilated with a 3- to 5-mm angioplasty balloon (Armada, Abbott, Cal-USA). After the predilation, the balloon was removed, another bifurcation angiogram was performed through the sheath. After proper road-mapping, The Protege RX Carotid Stent System (Medtronic, MN-USA) via a 6F-delivery system compatible with 0.014" guidewire was deployed. Although the stent was reported to have a specific release technology (EX.P.R.T.TM) essentially eliminating premature deployment or jumping, two or three stent rings were exposed and waited for 5 to 7 seconds, allowing the distal stent to become fully expanded, well-opposed, and fixed to the ICA

above the lesion for safety. Subsequently, the remainder of the stent can be deployed more rapidly with little worry that it will migrate. If necessary, the lesion was post dilated with a 5-mm balloon; larger balloons are rarely necessary. No specific balloons were used for calcific lesions. Residual stenosis of 10% or so was completely acceptable; the goal was protection from embolic stroke, not necessarily a perfect angiographic result. After CAS was completed, the delivery catheter was reversed, so the opposite end was used to capture and retrieve the filter, followed by completion angiography of the carotid bulb/bifurcation and distal extracranial ICA to assure that a dissection or occlusion did not occur.(Figure 2)

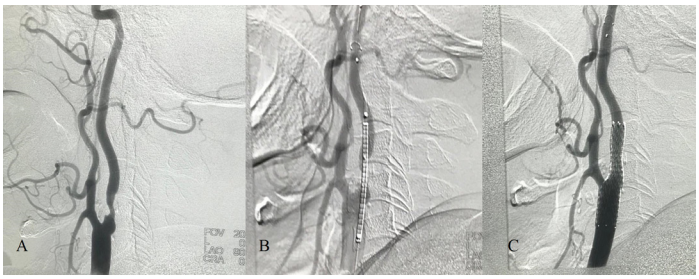

Figure 2. Procedural Images. (A) Lesion (B)Measurements (C)Postprocedural angiography.

CEA

Traditional endarterectomy was performed under general anesthesia with patch closure (prosthetic). As a clinic routine, we prefer standard arteriotomy and plaque elevation. We never mobilize the carotid bifurcation until the carotid arteries have been clamped to avoid the potential of embolization of atherosclerotic plaque or thrombus in the area of the critical stenosis. As carotid clamping reduces cerebral perfusion, which may cause hemodynamic brain injury, we prevented this by routinely using a temporary shunt.

Postoperative Care

A duplex ultrasound (DUS) was obtained prior to hospital discharge as a baseline index. Subsequent DUS examinations are performed at 30-days, 6 months, and 1 year thereafter. DUS, [27] was undertaken with a standardized protocol that stipulated 16 doppler waveform samples at every examination (eight samples were taken from each side of the neck: six at 1–2 cm intervals along with the CCA and ICA, one from the ECA, and one from the vertebral artery). Waveform samples were to be obtained at a 60-degree angle between the ultrasound beam and the long axis of the vessel. The highest systolic velocity measurement from each treated carotid pathway was used to identify restenosis.

The immediate neurologic assessment of the patient upon completion of the procedures was performed by the operator, secondary and follow-up neurologic assessments were performed within 24 hours and in doppler follow-up days by a neurologist. Patients in group 1 continued with dual antiplatelet therapy (a daily combination of aspirin (75-100 mg) and clopidogrel (75 mg) for 1 month, then only aspirin indefinitely. Patients in group 2, received single antiplatelet therapy with either aspirin or clopidogrel (class 1A).[8]

Definitions and Study Endpoints

Asymptomatic: Patients with no neurologic symptoms referable to the cerebral hemisphere ipsilateral to the carotid stenosis or a history of previous neurologic events without subsequent event within 180 days. Patients with prior symptoms referable only to the hemisphere contralateral to the target vessel or symptoms in either hemisphere occurring 180 days or longer prior to the initial evaluation were also considered asymptomatic.

Measurements of angiographic carotid stenosis (percentage by diameter) in CTA or DSA images were standardized by NASCET methodology as recommended.[28]

Cumulative Carotid Disease Severity Score (CCDS) [29]: a global disease severity score for the carotid lesions which categorize the grades of severity of carotid artery disease prior to CEA or CAS, including a 0 to 3 scale corresponding to absent, mild, moderate, and severe that can be obtained for each of the risk factors.

Specific anatomical factors that may affect perioperative CAS outcomes were reported, including lesion length, lesion location, severity, calcification were recorded. Lesion length was defined using the American Heart Association/American College of Cardiology classification for coronary lesions as modified by Ellis et al,(30) in which the distance from the distinct proximal to the distal shoulder of the lesion is assessed in the projection that best elongates the portion of stenosis that is >50%. Lesion location was defined at the distal common carotid artery or proximal ICA, including the bulb, or a combination of the common distal carotid and ICA (bifurcation lesion). Target site calcification was defined as no or mild calcification vs heavily calcified lesions (>50% circumferential calcification), which was based primarily on computed tomography angiography or ultrasound imaging, or both.

Primary Endpoints

The primary endpoint was the composite of death, stroke (ipsilateral or contralateral, major or minor) and myocardial infarction during the 30 days after the procedure or ipsilateral stroke during the 365 days after the procedure. Stroke or cerebrovascular accident is defined as a cerebral infarction that manifests as a sudden onset of focal neurological deficits that persist for more than 24 hours.[31] The National Institutes of

Health Stroke Scale (NIHSS), which is a serial measure of the neurologic deficit on a 42-point scale across 11 categories, including paralysis, speech difficulty, and sensory and visual loss, was used to report stroke severity.[31] A minor stroke is a new neurologic event that persists for more than 24 hours but completely resolves or returns to baseline within 30 days and changes the NIHSS by 2 to 3 points. A major stroke is a new neurologic event that persists after 3 days and changes the NIHSS by at least 4 points. An ipsilateral stroke is a stroke affecting the cerebral hemisphere supplied by the treated carotid artery. TIA is defined as a temporary focal neurologic deficit that changes the NIHSS by one or more points or retinal deficits that persists for <24 hours with a return to baseline or complete resolution of the event.[32] The periprocedural occurrence of MI in 30 days of the procedure was also reported. Accepted confirmatory evidence of an MI includes the combination of either chest pain or equivalent symptoms consistent with myocardial ischemia or electrocardiographic evidence of ischemia, including new ST-segment depression or elevation >1 mm in two or more contiguous leads, plus a significant elevation of cardiac enzymes (creatine kinase-MB or troponin) to a value 2 or more times the individual clinical center's laboratory upper limit of normal.[33,34]

The other primary endpoints were primary technical success, periprocedural clinical success, primary patency at 1st-6th, and 12th months, clinical failure rates. For CEA, primary technical success is defined as the successful exclusion of the carotid plaque and closure of the artery with patch and less than a 30% residual stenosis. For CAS, primary technical success defines successful access to the carotid arterial system using a remote site; successful deployment and placement of the EPD and the carotid stent excluding the entire length of the carotid lesion; patent carotid stent with normal flow and without a significant twist, kinks, or obstruction (>30% luminal stenosis or a pressure gradient >10 mm Hg) by intraoperative measurements; and successful removal of the EPD without evidence of EPD-related vascular injuries.

Periprocedural clinical success: Vascular closure or deployment of the carotid stent. The definition of clinical success for both carotid interventions includes the absence of periprocedural stroke, death and MI and ipsilateral stroke as the result of carotid stenosis-related treatment, patch or stent infection or thrombosis, failure of device integrity, including stent fracture or pseudoaneurysm formation.

Primary patency refers to patency that is obtained without the need for an additional or secondary surgical or endovascular procedure.

Clinical failure includes a failure to complete a CEA or deploy the stent at the intended location, carotid or stent thrombosis or infection, restenosis, conversion to open or endovascular repair, or death as a result of carotid stenosis or carotid artery-related treatment.

Periprocedural adjunctive maneuvers were classified as planned procedures or unplanned procedures. *Planned procedures* comprise techniques that are part of a preformulated procedural strategy, and *unplanned procedures* are necessary for the management of unintended complications or an otherwise unsatisfactory outcome.

Secondary Endpoints

The secondary endpoints included complications, freedom from clinically driven target-lesion revascularization at 12 months, freedom from death, freedom from all stroke and freedom from restenosis rates.

Target lesion revascularization (TLR): any surgical or percutaneous revascularization procedure involving the original target lesion site, including repeat balloon angioplasty, stenting, endarterectomy, or any other open vascular reconstruction of the treated lesion.

Restenosis: restenosis, defined as 70% or more diameter-reducing stenosis, or target-artery occlusion occurring at the ultrasound scans at 1,6 or 12 months. The <70% threshold to define high-grade restenosis is the most accepted threshold and has been used in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, and the Endarterectomy versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis (EVA-3S) trial.[35-37] Assessment of restenosis was done when the peak systolic velocity at any location within the treated internal or common carotid artery reached or exceeded 3·0 m/s. The decision to use 3·0 m/s as the definition for restenosis was also made before unblinding of the restenosis data. Several single-institution reports [38-41] support the use of 3·0 m/s or more as an appropriate threshold to identify high-grade restenosis

Complications were categorized as procedure related and systemic. All complications graded as moderate (2) or severe (3) are considered *major complications*, and those graded as mild (1) can be considered *minor complications*.

Statistical Analysis

Baseline variables are summarized with the use of descriptive statistics. Continuous variables were expressed as mean, median and ± standard deviation. Categorical variables are summarized as counts, percentages (%). Categorical values between technical success, complication and revascularization rates will be evaluated by Chi-Square analysis. For time-

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to-event variables, Kaplan–Meier estimates were used. The power of the study calculated in this way was calculated as 0.82 in the G-Power 3.1.9 package program and the sufficient sample width was determined as 17. All statistical evaluations will be made using SPSS 25.0 software (SPSS, Chicago, Illinois) and p <0.05 will be considered statistically significant.

Results

Patient Characteristics and High-Risk Inclusion Criteria

Baseline demographics and the lesion characteristics of the study group are shown in Table 3 and high-risk inclusion criteria characteristics is shown in Table 4. High-risk anatomical criteria were present in 8 (47.0%) patients, high-risk clinical criteria were present in 11 (64.7%) patients. Group 2 patients were older (67.7±7.4 vs 71.2± 6.9, p<0.05). Among the demographic risk factors, hyperlipidemia (58.8% vs 44.4%, p<0.05), chronic renal insufficiency requiring hemodialysis (11.7% vs 0.0%, p<0.05) and left ventricular dysfuntion (17.6% vs 0.0%, p<0.05) were significantly more frequent in Group 1.

Table 3: Baseline demographics and lesion characteristics of the patients

Parameter	Group 1 (CAS, n=17)	Group 2 (CEA, n=18)
Patient demographic and clinical characteristics		
Age (SD)*	67.7±7.4	71.2± 6.9
Men (%)	12 (70.6%)	13 (72.2%)
Smoking (%)	7 (41.1%)	8 (44.4%)
Hypertension (%)	14 (82.3%)	15 (83.3%)
Diabetes Mellitus (%)	7 (41.1%)	7 (38.8%)
Hyperlipidemia (%)*	10 (58.8%)	8 (44.4%)
COPD (%)	2 (11.7%)	2 (11.1%)
Chronic Renal Insufficiency req HD(%)*	2 (11.7%)	0 (0.0%)
Left ventricular dysfunction(%)*	3 (17.6%)	0 (0.0%)
Prior MI (%)	5 (29.4%)	6 (33.3%)
Prior PCI/CABG	8 (47.0%)	8 (44.4%)
Lesion/procedure characteristics		
Left Lesion Side	9 (52.9%)	10 (55.5%)
Stenosis (%vessel of diameter)*	81.4±4.2	88.3±6.4
Cumulative Carotid Disease Score*	4.7 ± 1.3	7.3 ± 1.2
Lesion Length (mm)*	12.7 ± 2.6	18.5 ± 4.2
Lesion Location Proximal Internal Carotid Artery Bifurcational* High Cervical*	 14 (82.4%) 0 3 (17.6%)	 14 (77.8%) 4 (22.2%) 0 (0.0%)
Target site calcification (heavy calcified)*	2 (11.7%)	9 (50.0%)
Ulcerated lesion	2 (11.7%)	3 (16.6%)

Taking lesion characteristics into consideration, CCDS of group 1 was significantly lower than group 2 (4.7 ± 1.3 vs 7.3 ± 1.2; p<0.05, respectively). The lesions of the patients undergoing CEA were significantly longer (12.7 ± 2.6 vs 18.5 ± 4.2 mm.; p<0.05) and more calcified (11.7% vs 50.0%, p<0.05) than the patients in group 1. Likewise, the degree of stenosis in group 2 was significantly more than that of group 1 (81.4 ± 4.2 vs 88.3±6.4 %; p<0.05, respectively).

Table 4: High Risk Inclusion Criteria for group 1

Anatomic criteria	N (%)
• Contralateral carotid occlusion	2
• High cervical or intrathoracic stenosis	3
• Cervical spine immobility, tracheostomy	1
• Hostile neck (previous neck surgery)	1
• Post-radiation therapy	1
Clinical criteria	
• Ejection fraction <30%	3
• 2-vessel disease and history of angına	3
• Severe pulmonary disease	1
• MI within 30 days	1
• Chronic Renal Insufficiency	2
• Unstable angina (CCS class III or IV)	1
Other	2
• Patients' preference	

Procedural

Primary technical success was 100% for both groups. All procedures were completed without a clinical failure.

Among group 1, 15/17 (88.2%) procedures were performed as preformulated. Planned periprocedural adjunctive maneuvers were required in two patients: in one patient (69 y, CHF req dialysis, prior CABG, CCDS=4 and contralateral carotid occlusion) management of concomittant common iliac artery critical stenosis was treated with stent placement and in the other patient (64 y, prior MI and PCI, CCDS=5, LVEF<30%, with history of previous neck surgery), during the balloon dilatation, we had to administer dopamine infusion (because of bradicardia and hypotension despite administration of atropine) for 4 hours. No unplanned procedure was performed as an periprocedural adjuntive maneuver. Grossly visible debris was observed in the SpiderFX filter in 7 (41.1%) patients, as in one of them we had difficulty recovering the filter. The mean fluoroscopy time for group 1 was 13.2±5.1 minutes and mean contrast dose used was 84.6 ± 12.5 mL.

Taking group 2 into consideration, no blood transfusion required and all operations were performed without hemodynamic instability. In one patient (with a high calcified bifurcation lesion) surgical dissection was difficult and we had to mobilize the bifurcation before clamping. Mean duration of the operation for CEA was 62.3 ± 12.1 minutes.

All patients stayed in intensive care unit for 24 hours under

continous monitorization. No patients experienced, major stroke, myocardial infarction, or death. In one patient in group 2 (the same patient whose dissection was difficult), facial numbness due to frontal lobe minor stroke was seen. It did not cause any neurological disability and resolved after 2 months. As a result, periprocedural clinical success was 100% for Group 1, and 94.4% for group 2 (p>0.05).

Other non-neurological events included vasovagal reactions in 5 patients (Group 1: two patients (11.7%) vs Group 2: three patients (16.6%); p>0.05), all treated succesfully by administration of intravenous fluids and atropine, and in one patient dopamine.

Follow-up

In-stent restenosis was diagnosed in two patients as one of them from group 1 at 6th month control follow-up, and the other patient from group 2 at 12th month control follow-up, both treated succesfully by baloon angioplasty. Primary patency rates at 1/6/12 months were 100%/ 94.1%/94.1% for group 1, and 100%/100%/94.4% for group 2. Both patients were female with DM and hyperlipidemia. Freedom from restenosis and freedom from CD-TLR at 12 months was 94.1% and 94.4% for group 1 and group 2. No death and major strokes and systemic complications occured. Complications are listed in table.6.

Table 6: Complications

Complication	Group 1	Group 2
Bradycardia/hypotension	1= temporary, hospital stay not prolonged. (minor)	0
Distal microembolization detected as new small infarctions in brain imaging studies	0	1= frontal lobe minor stroke- facial numbness. No neurological disability-resolved in 2 months (minor)
Cranial Nerve palsy	0	0

Discussion

Our study shows that it is possible to achieve acceptable results with CAS at a single centre among the asymptomatic group. For an asymptomatic patient with severe CS, the most important question is how to prevent an ischemic stroke. We showed in our study that, for those patients not suitable for standard open repair, a CAS procedure could be an alternative in selected cases.

We selected the asymptomatic group to study and compare, because there is still an ongoing debate about how best to treat the asymptomatic patient. Furthermore, trials and ESVS guidelines target symptomatic patients generally favor CEA over CAS.[8, 42-44]

In symptomatic carotid stenosis >70%, the ipsilateral stroke risk is about 13%/year with the best medical treatment and it is reduced to 4.5% by CEA.[28] Looking at randomised trials comparing CAS with CEA for symptomatic patients, the international carotid stenting study (ICSS) is the largest RCT comparing CAS with CEA in patients with symptomatic CS and reported an 8.0% frequency of any stroke/death at 120 days after CAS.[45] Furthermore, SPACE trial reported a frequency of 7.7% of any stroke or death at 30 days after CAS [36] and the EVA 3S trial reported exceptionally high rates of periprocedural stroke/ death with CAS (9.6%) led to the trial being stopped prematurely.[37] The CREST Trial was a large multicentre RCT, including 1321 symptomatic and 1181 asymptomatic patients. The most important result they found the overall periprocedural incidence of stroke or death was statistically significantly higher after CAS than CEA in symptomatic patients (p = 0.02), this was not statistically significant for asymptomatic patients. They reported a 4.4% periprocedural stroke or death frequency in total, among symptomatic patients 6.0% and for the asymptomatic 2.5% .[34]

Since carotid artery revascularization is most often recommended to prevent stroke in asymptomatic patients, the risk of neurological complications after CAS is particularly important. The RCTs carried out comparing CEA with CAS in asymptomatic population have produced unreliable results due to heterogeneous patient populations with different endpoints being used, use of a variety of endovascular devices, varying EPDs between studies. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial compared CAS with CEA in 334 patients at high operative risk [46], and reported that CAS was associated with a 56% reduction in perioperative death, stroke, and MI compared to CEA, a 39% reduction in death and ipsilateral stroke at 1 year, and similar cardiac and stroke reduction. This difference was explained by the SAPPHIRE population having greater co-morbidities (75.5% of patients undergoing CEA had coronary artery disease), leading to a significantly higher rate of MI in the CEA compared to the CAS group. The Asymptomatic Carotid Trial-1 (ACT-1) reported that CAS was non-inferior to CEA with regard to the composite endpoint of death, stroke or MI within 30 days of the procedure in 1453 asymptomatic patients with severe CS.[47] In CREST, which included symptomatic and as-

ymptomatic patients who were deemed to be at average risk, the estimated 10-year rate of ipsilateral stroke (excluding the perioperative period) was 6.9% after stenting (i.e., 0.7% per year) and 5.6% (0.6% per year) after endarterectomy.[34] The ACST2 trial report a 1% rate of periprocedural disabling stroke, fatal MI and death in all included participants.[48]

The most widely used estimator of long-term stroke risk in asymptomatic patients is severity of stenosis.[49,50] The ACSRS study (Asymptomatic Carotid Stenosis and Risk of Stroke) determined predictors of ipsilateral TIA/stroke in asymptomatic patients on medical therapy, incorporating plaque morphology characteristics from ultrasound.[51] It was previously claimed that the addition of clinical and ultrasound-detected plaque features to stenosis severity improved the ability to predict stroke. Furthermore, Mathur et al [52] showed that CAS performed for lesions with >90% stenosis was associated with a higher 30-day stroke rate of 14.9%, compared with 3.5% in patients with lesion severity of <90%. But as another conflict, neither the ACAS nor ACST trials found any evidence that stenosis severity or contralateral occlusion increased late stroke risk.[20,53,54] Ulcerated plaque morphology was detected in 11.7% of patients in group 1, and 16.6% of the patients in group 2. The lesions in group 2 was more stenotic and the CCDS was increased. But the number of patients included in our trial was too small to permit conclusions with regard to the relative benefit of each technique or prediction of stroke, however in 12-months, a minor stroke was diagnosed in one patient in the CEA group after the procedure. Accordingly, there have been increasing calls to lower the acceptable stroke/death thresholds set by many guidelines as <3% for asymptomatic group. In CREST and ACT1, which mandated EPD use, 30-day stroke/death rates of 2.5% and 2.9% were reported, respectively [47,55], and are acceptable based on current guidelines. Our major stroke rate was 0%, minor stroke rate was 2.85%. in this study no strokes occured in 12-month follow up . This might be due to the combination of our small sample size, the wide use of statins (100%), and a strict protocol for patient selection.

As an other conflict, Mukherjee D. and Roffi M claimed that randomized trials did not demonstrate a significant difference between CAS and CEA in terms of procedure-related major strokes, and the statistical difference was actually related to the high association of CAS with minor strokes.[56] Likewise, a 2017 review of 6526 patients from five RCTs and a mean follow-up of 5.3 years demonstrated a higher risk of periprocedural stroke plus nonperiprocedural ipsilateral stroke with CAS (OR 1.50; 95% CI 1.22-1.84), primarily due to increased minor stroke rates in the periprocedural period.[4] On the other hand, Hussain et al., reported that over long-term follow-up (up to 13 years), CEA was associated with approximately 55% increased hazard for major adverse events (30- day death, stroke, MI, stroke during 13-year follow-up).[57] Alhaidar et al [58], evaluated a sample of 54640 patients – a database of 705 hospitals-, and finally concluded that 30-day periprocedural mortality, stroke, MI, and combined outcome (mortality, stroke, or MI) were not significantly different between CEA and CAS, like Jalbert et al [59] who found similar rates of death,stroke/TIA, periprocedural MI, and a composite of these endpoints.

But as a result, perioperative stroke is an important complication and should be prevented. The major postulated mechanism is the post-dilatation of the stent after implantation. A retrospective study of 3,772 CAS procedures demonstrated a 2.4-fold increase in the risk of perioperative stroke and death rates associated with post-dilatation compared with no post-dilatation strategies.[60] This increased risk is likely mediated by two distinct mechanisms, the principal one likely being an increased embolic showering, causing ischemia during the procedure, whereas on occasion persistent hemodynamic depression related to procedure-related carotid baroreceptor stimulation may lead to neurologic events related to reduced cerebral blood flow. Double-layer nitinol [60] or mesh-covered stents [61], hybrid stents has been under evaluation to minimize/eliminate plaque prolapse.

Use of EPDs may reduce the peri-procedural stroke rate following CAS. A systematic review reported a reduced 30- day death or stroke rate from 5.5% to 1.8% in patients undergoing CAS without and with EPDs respectively.[62] Data from a large registry have also confirmed the finding that EPDs reduce the death or stroke rate in patients undergoing CAS, with the use of EPDs being an independent protective factor.[63] The benefit of EPDs was also evident in a prospective registry of 1455 patients: in those treated with EPD, in-hospital death/ stroke rates were at 2.1% vs. 4.9% in patients treated without EPD. [64] The best results within RCTs were seen in the CREST and ACT-1trials, where cerebral protection was mandatory and CAS practitioners were trained in its use.[47,55] In contrast, the SPACE trial observed lower ipsilateral stroke rates in CAS patients without EPD (6.2%) vs. with EPD (8.3%).[36] Although EPDs have been widely accepted as necessary adjuncts during CAS and the risk of stroke in this study is similar to the risks reported in other high-risk registries, it is important to em-

phasize that strokes may occur despite the use of EPDs and failures may be due to the inability to deliver the device, device- induced complications such as vessel dissection, and incomplete capture or retrieval of debris leading to acute stroke. We observed grossly visible debris in 41.1% of the patients and in one of them we had difficulty recovering the filter. We claim that the clustering of strokes after prolonged and complex interventional procedures, and the relationship between filter deployment duration and stroke, suggests that some adverse events may be potentially avoidable by careful patient selection. That important result brings us to the beginning: patient-tailored therapy including clinical, anatomical risks

Also new techniques like proximal balloon occlusion protection was advocated as superior to distal filters in reducing embolization or in 2019 Langhoff et al [65] addressed a new device combining a balloon with an integrated embolic protection filter designed to increase embolic protection during post-dilation and reported promising results. Schermerhorn MD et al, compared transcarotid artery revascularization with flow reversal technique with transfemoral CAS, and concluded that among patients undergoing treatment for carotid stenosis, transcarotid artery revascularization, compared with transfemoral CAS, was significantly associated with a lower risk of stroke or death.[66]

Factors that influence the choice of stent include device availability, clinical trial or postmarketing registry participation, stent cell structure, stent shape and specific EPD characteristics. Considering this factors, we preferred to use the Protégé RX Carotid Stent System, which is a nitinol open cell-tapered stent that comes pre-mounted on a 6 F, 0.014" rapid exchange delivery system and the safety and efficacy of the Protege RX carotid stent system in the carotid indication has not been demonstrated with EPDs other than with the SpiderFXTM EPD.

Open-cell stents have a free cell area of >5 mm2 and adapt well to the contour of the vessel making delivery easier but physically cover less of the target lesion, potentially posing a higher risk of embolization as atherosclerotic material may prolapse through the stent struts. Closed-cell stents may kink the vessel if placed inappropriately. No published high-quality RCTs compare open-cell to closed-cell stents and available evidence is conflicting. Published studies have shown a variety of results.[67] Wissgott et al., evaluated eight stent systems including Protégé RX Carotid Stent System and drew attention to its high radial force (collapse observed at 0.20 bar) and good wall adjustment.[68] Also with regard to the re-stenosis rate, a significant difference between the open-cell and closed-cell stents could not be demonstrated from the literature.[68]

We have to pay attention to the fact that periprocedural stroke is more likely with CAS; however, this difference has reduced with time with increasing skills of the operators and emerging endovascular techiques and technology. From 1991 to 2010, published data have shown a 6% annual reduction in operative stroke/death.[69] This reduction also exists for CEA and BMI. In a meta-analysis of 41 studies, the rate of ipsilateral stroke was 2.3/100 person-years in studies completing recruitment before 2000, compared with 1.0/100 person-years during the 2000–2010 period (P < 0.001) .[70)] A 60–70% decline in annual stroke rates was also observed in medically treated patients in both trials over the recruitment period from 1995 to 2010.[20,53] Moreover, we have to remember that periprocedural stroke after carotid revascularization is not always secondary to thromboembolism and often occurs due to haemodynamic disturbance.

Because of the learning curve associated with CAS, as well as it being performed in low numbers by multiple specialties, there are concerns as to whether the death/stroke rates reported for CAS in these trials can be replicated in 'real-world' practice.[71] Since CAS is a technically demanding procedure, establishing minimum volume requirements is important. Nallamothu BK et al. evaluated CAS in the United States among elderly patients between 2005 and 2007 and found higher 30-day mortality in patients treated by operators with lower annual volumes of CAS, reported the median annual operator volume as only 3.0 per year. They classified an annual operator volume with a 12-23 CAS procedures/year as medium experience, and did not find any significant difference with high experience (>24 procedures / year) centers.[72] We performed 17 CAS procedures in one year, which can be classified as a medium experience. Patients treated by operators with <6 procedures per year were found to have an elevated risk of 30-day mortality.[72]

Previous meta-analyses have shown that the superiority of CEA over CAS disappears in patients aged <70 years.[1,5]. Lindström et al also found the results for CAS to be better in younger patients, although not significant in this relatively small series in the Swedish study.[73] Increased age is an independent predictor of poor outcome after CAS.[74,75] We performed CEA in older patients and this preferance reflected into the results as a significant difference among the groups in terms of age.

Naggara et al [76] reported the results of a pooled analysis of 34,398 CAS patients and showed that CAS for left ICA stenosis was associated with higher 30-day perioperative stroke/death rates compared with CAS for right CS (7.5% vs 6%). They sug-

gested that this higher rate was secondary to the difficult access from the aortic arch to the left common carotid artery. However, other studies, including our study, have not found a significant difference in 30-day stroke or death rates, or both, between right- and left-sided CAS.[74,77]

Target site calcification has also been correlated with a higher 30-day stroke rate.[18] A single-center study by Setacci et al [39] noted that the presence of target site calcification was associated with a higher 30-day perioperative stroke rate of 6.5% in contrast to 2.3% in patients without calcification. Because of this fact, CEA was performed more often in patients with target site calcification in our study as 50% of patients in CEA vs 11.7% of patients in CAS. This algorithm may have prevented the possible difference in rates of stroke and technical success between two procedures.

Female sex, hypertension, DM and dyslipidaemia were reported as independent predictors of restenosis or reocclusion at 2 years after CAS whilst smoking was statistically significantly associated with restenosis after CEA.[75] Following CEA only, 5.2-9.5% developed restenosis at 1-5 years.[78] On the other hand, in a systematic review, the cumulative restenosis rate (>70%) was about 4% in the first 2 years after CAS, and this compares well with CEA.[79] In our study, patients in the CEA group were older, but risk factors including hyperlipiemia, chronic renal insufficiency requiring hemodialysis and left ventricular dysfunction were more frequent among patients in CAS group. Our rate of restenosis within 12-months and the concomitant risk factors are consistent with the literature -5.71% all study group- as during follow-up, we diagnosed restenosis in 2 patients (1 from each group) who were female with DM and hyperlipidemia.

Taking perioperative stroke and death rates, following a comprehensive Medline search of over a 15-year period, Khan and Qureshi [80] reported that clinical factors, including age of >80 years, DM, chronic renal failure, and symptomatic indications, are associated with high risk. Considering the angiographic variables, they also reported ulcerated and calcified plaques, left carotid artery intervention, >10-mm target lesion length, >90% stenosis, ostial involvement, type III aortic arch, >60°-angulated internal carotid and common carotid arteries, and PTA without EPDs as predictors of increased perioperative stroke.

A few other studies [18,77] have analyzed the correlation of CAS outcome and the target lesion length and concluded that longer lesions were associated with a higher 30-day perioperative stroke rate. Mathur et al [52] reported a 30-day stroke rate of 11.4% for lesions longer than 10 to 15 mm vs 3.8% for lesions shorter than 10 mm; whereas Sayed et al [81] reported a stroke rate of 17% vs 2.1%, and Setacci et al [39] reported a stroke rate of 5.6% vs 2.6% for these lesions, respectively. Lal BK et al [38] specified a threshold for lesion length and reported that plaque length > 13 mm was associated with a 6.1% death/stroke after CAS vs. 1.9% after CEA. We preferred to perform CEA in long lesions to prevent this risk; as this choice was reflected in the results of our study.

Since the lesion severity for each type of intervention need to be reported to assess periprocedural risk and precise classification methodology for reporting lesion characteristics affecting outcomes have not been defined and universally accepted; we decided to use CDSS system which allows the calculation of a global disease severity score for the carotid lesion before CEA or CAS. In our study, CDSS of group 1 was significantly lower than group 2, as lesions which were more calcified, longer and stenotic were preferred to be treayed with CEA.

On the other hand, extended neck surgery has been shown to significantly increase the complexity of surgical intervention resulting in a higher risk of cranial nerve injury as well as more challenging dissection when compared to de novo open carotid intervention. Radiation into the cervical region has been shown to have various effects on the extent of fibrosis scarring as well as injury to the carotid artery itself.[29] Contralateral carotid stenosis or occlusion has traditionally been considered a predictor for adverse outcome after CEA according to NASCET data.[28] The location of the lesion relative to the carotid bifurcation and the base of the skull are anatomic variables that may increase the complexity of CEA. Those previously described anatomical factors,as well as the clinical criteria that had been reported to increase the risk after CEA formed the high-risk inclusion criteria for CAS. After detailed investigation of the literature, we developed an algorithm for enrolling the patients -evaluating risks- to the groups and providing a patient-tailored treatment.

Moreover, there are studies in the literature that pointed out the risk about CAS was procedure dependent; not clinial.[82] The same group also did not find any significant difference in the risk of MI between the two procedures.

Prior studies of carotid revascularization procedures estimate 30-day re-admission rates at a range of 4.2% to 11.1% .[82,83] In our study, 30-day re-admission rate was 2.85%. ACT trial had suggested that CAS was not inferior to CEA in asymptomatic patients in terms of readmission.[47] Dakour A et al, collected data from 700 hospitals and after evaluating 95,687 patients

they concluded that 30-day all-cause readmission rates were lower with CAS than CEA.[84]

In initial studies comparing CEA to CAS, rates of MI were <1% for both procedures, likely because cardiac biomarkers were not measured routinely (BE-36,37,38). The high-risk SAPPHIRE trial, which systematically collected cardiac biomarkers, was the exception, reporting MI rates of 5.9% for CEA and 2.4% for CAS (46). In the average-risk group studied in CREST, the incidence of MI after CAS was 1.7%; 3.4% with CEA under general anaesthesia; and 1.8% with CEA under locoregional anaesthesia.[85] It was also reported that any type of perioperative stroke was associated with a threefold poorer long-term survival, similar to the poorer 4-year survival observed in patients suffering a perioperative MI.[8] MI was found more associated with CEA, likely due to the periprocedural anaesthetic risk, as are cranial nerve injuries (CNI) and haematomas (although many CNIs are non-permanent).[5] In CREST, the rate of cranial nerve injury for CEA was 4.6%.[55] However, 34% of deficits had resolved at 1-month follow-up and 81% resolved by 1 year. No difference in quality of life associated with cranial nerve injury was detected at 1-year follow-up . In our study, no patients experienced major stroke, myocardial infarction, or death.

The most common complications are vasovagal or vasodepressor responses, possibly due to stretching the carotid baroreceptor during balloon inflation and stent deployment, or mobilizing the bifurcation before clamping which was reported up to 20% in the literature. Our results are consistent with the literature and all patients treated medically.

Concomitant administration of warfarin and dual antiplatelet therapy may predispose elderly patients to serious bleeding complications, including intracranial hemorrhage which Safian et al. reported a prevalance of 1.3%.[22]

Stent thrombosis is a feared complication of CAS that we did not observe in our study group. Stent insertion may cause intimal injury leading to platelet adhesion and thrombus formation. Guidelines suggest administration of dual antiplatelet therapy pre and post procedurelly along with antihypertensives, bet-blockers and lipilowering agents. We administered those medications as a standard for all patients. Novel medical therapies may also show benefit in reducing the long-term stroke risk in asymptomatic patients. A subgroup analysis of the Cardiovascular Outcomes for People using Anticoagulation Strategies (COMPASS) RCT showed that addition of low-dose rivaroxaban to aspirin (in 1919 patients with previous carotid artery revascularisation or asymptomatic CS of at least 50% reduced the overall major adverse cardiovascular event rate without increasing the bleeding risk.[86]

Study Limitations

First, this is a retrospective observational study. Therefore, only associations but not causal relationships can be derived from the data. Another limitation of the study was that the data were self-reported by the operator performing the procedure. The number of patients included in our trial was too small to permit precise conclusions with regard to the relative benefit of each technique.

Conclusion

This study showed similar short and mid-term results for CEA and CAS in asymptomatic patients with significant carotid disease. CAS is a maturing procedure and has improved significantly over the past several years with the addition of protection devices and greater experience of the operators. Future developments of stents and protection devices will achieve better perioperative results. Till that time, although we have shown good results for both carotid surgery and stenting, CAS procedure should be limited to those cases that are not suitable for open surgery and treatment of asymptomatic carotid artery disease with CEA should be considered for patients with few risk factors and long life expectancy. Altough, it is clear that both CEA and CAS reduce the long-term stroke risk in asymptomatic patients, the appropiate treatment strategy should be selected according to the patient's individual risk factors and imaging data.

Declaration of conflict of interest

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Original Article

A lower systemic immune-inflammation index level is associated with response to cardiac resynchronization theraphy

Düşük sistemik immun-inflamasyon indeksi kardiyak resenkronizasyon tedavisine yanıt ile ilişkilidir

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Abstract

Aim: The systemic immune-inflammation index (SII), a novel inflammation-based biomarker combining platelet, neutrophil and lymphocyte counts, has been shown to be associated with worse clinical outcomes in several malignancies. However, the relationship between SII and response to cardiac resynchronization theraphy (CRT) has not been evaluated yet. The aim of this study was to investigate the association between SII and response to CRT in patients with heart failure (HF).

Material and Methods: A total of 88 patients (54.5% male; mean age 58.9±12.9 years) who underwent CRT device implantation were included in the study. Baseline clinical, demographic, laboratory and echocardiographic data of patients' were recorded. An echocardiographic CRT response was defined as a decrease in left ventricular end-systolic volume of ≥15% and/or absolute increase of 5% in left ventricular ejection fraction (LVEF) at 6-month follow-up after CRT implantation.

Results: Among included patients, a total of 51 (57.9%) patients were defined as "responders" after 6 months of CRT implantation. Lymphocyte count, LVEF and QRS width were significantly higher in responders compared to those responders. In addition, baseline creatinine and SII levels were significantly lower in responders than nonresponders. Multivariate logistic regression analysis showed that a SII of ≤973.3, LVEF and QRS width were independent predictors for response to CRT in the study population.

Conclusion: SII may be used as a novel, simple and reliable inflammatory biomarker in the prediction of response to CRT in patients with HF.

Keywords: inflammation; neutrophil; cardiac resynchronization therapy.

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Öz

Amaç: Trombosit, nötrofil ve lenfosit sayılarının kominasyonundan oluşan yeni bir inflamasyon belirteci olan sistemik immun-inflamsyon indeksinin (Sİİ) çeşitli malignitelerde kötü klinik sonlanımlarla ilişkili olduğu gösterilmiştir. Bununla birlikte, Sİİ ve kardiyak resenkronizasyon tedavisine (KRT) cevap arasındaki ilişki henüz çalışılmamıştır. Bu çalışmanın amacı, kalp yetersizliği (KY) hastalarında KRT tedavisine cevap ve Sİİ arasındaki ilişkiyi araştırmaktı.

Gereç ve Yöntemler: KRT cihaz implantasyonu yapılan toplam 88 hasta (%54,5 erkek; ortalama yaş 58,9±12,9 yıl) çalışmaya dahil edilmiştir. Hastaların temel klinik, demografik, laboratuar ve ekokardiyografik özellikleri kaydedildi. Ekokardiyografik KRT cevabı; implantasyondan 6 ay sonrasında sol ventrikül sistol sonu volümünde %15 ve üzerinde azalma ve/veya sol ventrikül ejeksiyon fraksiyonunda (SVEF) %5 ve üzerinde artış olması olarak tanımlanmıştır.

Bulgular: Çalışmaya alınan hastalardan 51 tanesi (%57,9) KRT'ye "cevap vermiş" olarak tanımlandı. Lenfosit sayısı, SVEF ve QRS genişliği KRT ye cevap veren hastalarda vermeyenlere göre anlamlı olarak daha fazlaydı. Ayrıca, bazal kreatinin ve Sİİ düzeyleri cevap veren hastalarda vermeyenlere göre anlamlı olarak daha düşüktü. Çok değişkenli lojistik regresyon analizinde; çalışma populasyonunda Sİİ'nin 973,3 ve altında olması, SVEF ve QRS genişliği KRT'ye cevabın bağımsız öngördürücüleri olarak saptandı.

Sonuç: KY hastalarında KRT tedavisine cevabın tahmininde Sİİ yeni, basit ve güvenilir bir inflamasyon belirteci olarak kullanılabilir.

Anahtar kelimeler: inflamasyon; nötrofil; kardiyak resenkronizasyon tedavisi.

Introduction

Cardiac resynchronization therapy (CRT) has emerged as an important alternative in treating chronic systolic heart failure (HF) patients with prolonged QRS complex duration [1]. Previous studies have shown that CRT induces reverse left ventricular (LV) remodeling in appropriately selected patients, improves symptoms and reduces morbidity and mortality [2,3]. Unfortunately, almost a third of patients do not respond favourably to CRT [4]. Several characteristics are associated with improved response, and thus survival following CRT implantation [5]. Optimization of patient selection for CRT will enable identification of nonresponders, who might benefit from other treatment strategies.

It has been shown that there is a relationship between the response to CRT and many hematologic inflammation-based parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and red cell distribution width (RDW) [6-8]. On the other hand, a novel parameter, combining neutrophil, lymphocyte and platelet counts, systemic immune-inflammation index (SII), as a promising inflammatory biomarker, has been described in recent years [9]. It has been reported that SII is associated with worse clinical outcomes in several malignancies [9-12]. However, the relationship between SII and response to CRT has not yet been investigated. In this study the relationship between SII and response to CRT in patiens with HF was studied.

Material and Methods

Study population

Subjects consisted of 101 consecutive patients undergoing CRT, between March 2016 and December 2018, at our cardiology department who were retrospectively enrolled into the study. Patients were included according to following criteria: (1) chronic HF with reduced LVEF (≤35%) and (2) prolonged QRS interval (≥120 msn). The exclusion criteria were: chronic hepatobiliary disease (n=1); known history of a hematologic disease (n=2); chronic inflammatory or autoimmune disease (n=4); malignancy (n=2); chronic medical therapy with steroid or nonsteroidal anti-inflammatory drugs (n=4). Thus, 13 patients were excluded and the study cohort included a total of 88 patients.

Data collected included demographic information and medical history such as age, gender, body mass index (BMI), hypertension, and diabetes mellitus. Patients' functional capacity status were evaluated according to the New York Heart Association (NYHA) classification [13]. The rhythm and QRS width of patients' were determined on admission 12-lead electrocardiography (ECG). Medical treatment including beta-blockers, angiotensin converting enzyme inhibitors (ACEi),

angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA) were computed as positive if the patients had these medications on admission.

Fasting venous blood samples were taken during hospitalization within 24-48 hours prior to CRT device implantation. Counts of platelets, lymphocytes, neutrophils and other hematological parameters were analyzed using an automated blood cell counter within 30 minutes after blood sampling. Biochemical analysis including blood urea nitrogen (BUN), creatinine, uric acid, and albumin levels were also measured using standard laboratory techniques. These laboratory results were collected from all patients and all of these data were obtained from the hospital database. SII was calculated using the formula: platelet count x neutrophil count/lymphocyte count. The NLR was calculated as the neutrophil count divided by the lymphocyte count.

The study protocol was approved by local institutional investigation committees.

Cardiac resynchronization theraphy device implantation

All pacemaker implantations were performed by left infraclavicular approach. Right atrial and right ventricular leads were implanted using a transvenous approach. LV leads were inserted by a transvenous approach through the coronary sinus into a cardiac vein of the free wall. A biventricular pacemaker (InSync III, Medtronic Inc, Minneapolis, Minnesota) or biventricular cardioverter-defibrillator (InSync III, Medtronic Inc, Minneapolis, Minnesota) was used for CRT implantation. The atrioventricular interval was optimized using Doppler echocardiography within 24-48 hours after implantation.

Echocardiography

Patients were imaged in the left lateral decubitis position with a commercially avaliable system (VIVID 7, General Electric-Vingmed, Horten, Norway). Images were obtained with a 2.5-MHz broadband transducer at a depth of 16 cm in the parasternal and apical views (standart long-axis, two- and four- chamber images). Standart two-dimensional and color Doppler data triggered to the QRS complex were recorded in cine-loop format. LV volumes were calculated using the Teicholz method, and LVEF was calculated from the conventional apical two- and four-chamber images using biplane Simpson's technique [14]. An echocardiographic CRT response was defined as a decrease in left ventricular end-systolic volume (LVESV) of ≥15% and/or absolute increase of 5% in LVEF at 6-month visit after implantation [15].

Transthoracic echocardiography was performed 1 week before pacemaker implantation and repeated 6 months later. All echocardiographic measurements after CRT implantation were performed with the device in active pacing mode.

Statistical Analysis

Continuous variables are presented as mean±standard deviation and caterogical variables as numbers, percentages or proportions. The normality of distribution of the continuous variables were determined using the Kolmogorov-Smirnov test. Between-group comparisons were performed using the chi-square test for caterogical variables, independent-samples t test for continuous variables with normal distributions and the Mann-Whitney U test for continuous variables with abnormal distributions. Multivariate logistic regression analyses were used to determine the independently associated predictors of response to CRT. Receiver operating characteristics (ROC) curve analysis was performed to identfy the optimal cut-off point value of SII for predicting response to CRT and the sensivitiy and specifity at that point was obtained. All analyses were two-sided and considered significant at a P-value <0.05. All statistical anlayses were performed using SPSS 20.0 software (IBM Inc., Chicago, Illinois, USA).

Results

The study population consisted of 88 patients. Response to CRT was observed at 51 patients (57.9%) at 6-months follow-up. All patients were taken conventional HF therapy during follow-up after CRT device implantation. Baseline clinical and demographic characteristics of responders and nonresponders are summarized in Table 1. The mean age of responders was slightly higher than those nonresponders, but it was not statistically significant (60.3±11.9 vs 56.8±14.1, p=0.322). There was no statistically difference between the responders and nonresponders in terms of gender, BMI, and etiology of HF. No significant differences in the frequency of hypertension and diabetes mellitus were observed between the groups. The NYHA functional capacity of the patients' were similar between the two groups. Although baseline LVEF (25.9±6.5 vs 21.4±5.7, p=0.002) were significant higher in responders than those nonresponders, other echocardiographic parameters including left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic volume (LVEDV) and right ventricular ejection fraction (RVEF) were similar between the two groups. Additionally, there was no statistically difference in terms of basal ECG rhythm and previous medical treatment between the responders and nonresponders. The QRS width was markedly higher in responders than those nonresponders (136.3±10.4 vs 127.8±10.5, p<0.001).

Table 1. Baseline clinical characteristics of the study patients in responders and nonresponders.

Variables	Responders (n = 51)	Non-responders (n = 37)	P-value
Age (years)	60.3±11.9	56.8±14.1	.322
Male, n (%)	25 (49.0%)	23 (62.2%)	.222
Body mass index, kg/m2	28.3±5.5	27.9±5.6	.451
Non-ischemic etiology, n (%)	34 (66.7%)	19 (51.4%)	.147
Hypertension, n (%)	35 (68.6%)	22 (59.5%)	.374
Diabetes mellitus, n (%)	14 (27.5%)	7 (18.9%)	.354
Echocardiographic features			
LVEDD, mm	68.4±7.9	69.8±10.4	.565
LVEDV, ml	234.9±75.6	249.4±88.6	.300
LVEF, %	25.9±6.5	21.4±5.7	.002
RVEF, %	51.9±18.2	56.8±7.2	.692
NYHA functional capacity, n (%)			.301
Class 1	1 (2.0%)	2 (5.4%)	
Class 2	4 (7.8%)	6 (16.2%)	
Class 3	41 (80.4%)	25 (67.6%)	
Class 4	5 (9.8%)	6 (16.2%)	
Rhythm, n (%)			.511
Sinus	44 (86.3%)	30 (81.1%)	
Atrial fibrillation	7 (13.7%)	7 (18.9%)	
QRS width, msn	136.3±10.4	127.8±10.5	<0.001
Prior medical theraphy, n (%)			
ACEi or ARB	47 (92.2%)	34 (91.9%)	.964
Beta-blocker	48 (94.1%)	35 (94.6%)	.924
MRA	44 (86.3%)	32 (86.5%)	.972

ACEi = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker; LVEDD = Left ventricular end-diastolic diameter; LVEDV = Left ventricular end-diastolic volume; LVEF = Left ventricular ejection fraction; MRA = Mineralocorticoid receptor antagonist; NYHA = New York Heart Association; RVEF = Right ventricular ejection fraction.

Pre-implantation laboratory results of responders and nonresponders are shown in Table 2. Baseline creatinine was significant higher in responders than those nonresponders (0.99±0.34 vs 1.11±0.29, p=.023). No significant differences in hemoglobin, BUN, albumin and uric acid levels were observed between the groups. There was no statistically difference in terms of RDW and platelet count between the responders and nonresponders. However, the lymphocyte count were significantly higher in responders compared to those nonresponders (2.01±0.62 vs 1.72±0.61, p=0.025). Consequently the SII was markedly higher in nonresponders than responders (631.3±386.7 vs 951.2±550.2, p=.004).

Table 2. Laboratory results of the study patients in responders and nonresponders before cardiac resynchronization therapy device implantation.

Variables	Responders (n = 51)	Nonresponders (n = 37)	P-value
Basal creatinine, mg/dL	0.99±0.34	1.11±0.29	.023
BUN, mg/dL	21.9±8.8	24.9±12.6	.342
Hemoglobin, g/dL	12.8±1.9	12.0±1.6	.107
Uricacid, mg/dL	7.06±2.4	6.56±3.05	.194
Albumin, g/dL	4.09±0.42	3.94±0.45	.248
RDW,(%)	15.7±1.59	15.8±1.37	.530
Lymphocyte count, (/mm3)	2.01±0.62	1.72±0.61	.025
Platelet count, (x109/L)	234±71	237±84	.946
SII, (x109/L)	631.3±386.7	951.2±550.2	.004

BUN = Blood ürea nitrogen; RDW = Red cell distribution width; SII = Systemic immune-inflammation index.

Multivariate logistic regression analysis model of predictors for response to CRT in the study patients are shown in Table 3. In the multivariate analysis; LVEF (p=0.040, odds ratio [OR] 1.122, 95% CI 1.005-1.251), QRS width (p=0.002, [OR] 1.105, 95% CI 1.038-1.185), and SII ≤973.3 (p=0.036, [OR] 5.542, 95% CI 1.112-24.699) were found to be independent predictors of response to CRT (Table 3). The optimal cut-off point of SII for prediction of response to CRT was found to be 973.3 (x109) in the ROC curve analysis (AUC:0.679, 95% CI 0.571-0.774, p=0.002). This cut-off value of SII ≤973.3 (x109) predicted response to CRT with a sensivity of 88.2% and specifity of 45.9% (Figure 1).

Table 3. Multivariate logistic regression analysis model of potential predictors for the response to cardiac resynchronization therapy.

Variable	Odds ratio (95% CI)	P-value
LVEF	1.122 (1.005-1.251)	.040
QRS width	1.105 (1.038-1.185)	.002
Basal creatinine	1.565 (0.189-12.926)	.678
SII ≤973.3	5.242 (1.112-24.699)	.036
Lymphocyte count	3.202 (0.918-11.167)	.068

LVEF = Left ventricular ejection fraction; SII = Systemic immun-inflammatory index.

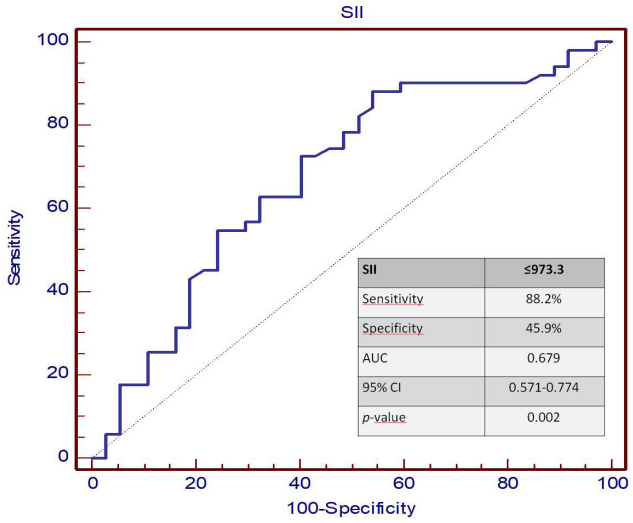

Figure 1. The reciever-operating characterisric (ROC) analysis for the systemic immune-inflammation index (SII) in prediction of response to cardiac resynchronization theraphy.

Discussion

To the best of our knowledge, this is the first study that has identified an association between the SII and response to CRT in patients with HF. In the present study we observed that SII measured within 24-48 hours prior to CRT implantation may have a role in predicting response to CRT. The SII was identified as a strong independent predictor of response to CRT, with an optimal cut-off value of ≤973.3. We also demonstrated an association between the response to CRT and other parameters which included LVEF and QRS width.

Cardiac resynchronization theraphy is considered an important treatment option of HF patients with prolonged QRS who are receiving optimal medical theraphy. However, prediction of response to CRT remains problematic and an important proportion of patients do not respond to CRT, although they are selected according to current patient selection criteria by international guidelines [16,17]. Additional echocardiographic, electrocardiographic, and blood markers have been investigated in several studies to identfy patients most likely to respond to CRT [18-21].

Full blood count is a readily avaliable, cheap and routine examination that provides accurate and reproducible information about erythrocyte, neutrophil, platelet and lymphocyte counts, RDW and parameters such NLR and PLR. On the other hand, SII has recently been described as a novel inflammatory biomarker [9]. It is calculated by the formula platelet count x neutrophil count /lymphocyte count and may be considered a combination NLR and PLR [9]. Many recent studies have demonstrated that SII is a strong independent predictor of major adverse events and prognosis in patients with several malignancies [9-12]. Patients with higher SII have increased recurrence rates, reduced survival and worse treatment response than patients with lower SII [9-12]. It is considered that a high SII level reflects an increased inflammatory condition. Thus, it has been shown that there was a correlation between the SII and other inflammatory markers, such as C-reactive protein (CRP), albumin, PLR and NLR [22,23]. It has been demonstrated that NLR and PLR are associated with response to CRT in patients with HF [6,7]. We first reported that a relationship between the NLR and response to CRT in our previous study [6]. In that study, we showed that a lower NLR was associated with good response to CRT [6]. Additionally, we also demonstrated that CRP levels were significantly reduced in responder patients in contrast to nonresponder patients [6]. Kerekanic et al. investigated the impact of CRT on serum levels of high sensitivity CRP (hs-CRP) in patients with chronic HF [24]. They demonstrated that hs-CRP levels reduced in responders after CRT implantation, but not in nonresponders [24]. Therefore, they suggested that hs-CRP could be widely used inflammatory biomarker for monitoring of CRT response [24]. In a study conducted by Balci et al., the role of baseline inflammatory markers in prediction of response to CRT was evaluated [7]. In their study, nonresponders to CRT had a higher NLR and PLR and lower lymphocyte count [7]. This result may reflect the deleterious effects of baseline inflammatory condition in patients with HF undergoing CRT [7]. In light of these data, it is well known that an increased inflammation is asscoiated with poor response to CRT. Patients who had a higher SII also had increased NLR, PLR and hs-CRP levels and these patients showed worse clinical outcomes in the follow-up [21,22]. In this context, it is not surprising that HF patients who have a higher SII levels also have poor response to CRT.

This is the first study to report the relationship between the SII and response to CRT in patients wit HF. Of note, a value of SII of ≤973.3 was an independent predictor of response to CRT in these patients. SII may be a useful, novel biomarker in prediction of response to CRT in addition to older inflammatory biomarkers such as hs-CRP, NLR and PLR.

Study Limitations

This study has some limitations. First, this retrospective study was conducted in a single-center with a small sample size. Second, the relationship SII and clinical outcomes were not evaluated. A prospective randomized multi-center study with a larger study population might increase the significance of the presented results.

Conclusion

SII, a novel inflammation-based biomarker combining platelet, neutrophil and lymphocyte counts, has been reported to be associated with clinical outcomes in several malignancies in many studies [9-12]. This is the first study to report a lower SII is associated with response to CRT in patients with HF. Pre-implantation SII, a readily avaliable and cheap biomarker, may help identfy patients who response to CRT.

Declaration of conflict of interest

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Derleme

Adeziv sistemlerde güncel yaklaşımlar

Current approaches in adhesive systems

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Öz

Diş çürüğü küresel ölçekte yaygın bir hastalıktır. Rezin kompozitler, diş dokularına adeziv sistemlerle bağlanarak çürükleri restore etmek için kullanılan en popüler malzemelerdir.Adeziv sistemler, içerdikleri bileşenler ile hem substrat yüzeyini hazırlar hem de restoratif materyale bağlanarak iki farklı yapı arasında hibrit bir tabaka oluşturur. Bu tabaka zamanla yıkıma maruz kalmaktadır.Bu nedenle, gelecekte yeni malzeme ve tekniklerin uygulanmasını desteklemek için hibrid tabakanın bozulma ve stabilizasyon mekanizmalarına ilişkin faktörlerin gözden geçirilmesi önemlidir.Bu derlemenin amacı dentin adezyonu kapsamında hibrit tabakaya yönelik çalışmaların etkilerini okuyucuya sunmaktır.

Anahtar kelimeler: adezyon; dentin proteinizasyonu; matriks metalloproteinazlar

Abstract

Dental caries is a common disease on a global scale. Resin composites are the most popular materials to restore caries by bonding to tooth tissues via adhesives. The constituents of the comtemporary adhesive systems not only prepare the dental subtsrate but also adhere to the restoration material by forming an hybrid layer.This hybrid layer thus the restorations are vulnerable to degradation in time.Hence, it is important to review the factors related to the mechanisms of degradation and stabilization of the hybrid layer to support the implementation of new materials and techniques in the future. The aim of this review is to present the effects of the studies on the hybrid layer for dentin adhesion.

Keywords: Adhesion; dentin proteininization; matrix metalloproteinases

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Giriş

Diş çürüğü dişin sert dokularında yıkıma neden olan, kronik, bulaşıcı ve multifaktöriyel bir hastalıktır. Çürük sonrası oluşan sert doku yıkımlarının tamiri için çürük dokunun uzaklaştırılması (kavite hazırlığı) ve kavitenin restoratif bir materyal ile yeniden şekillendirilmesi gerekmektedir. Kavite hazırlığında uzun yıllar boyunca benimsenmiş "korumak için genişlet" prensibi adeziv diş hekimliğinde görülen gelişmeler ile birlikte yerini yalnızca çürük dokusunun kaldırıldığı "minimal invaziv tedavi" prensibine bırakmaya başlamış, bu bağlamda adeziv sistemlerin başarısı ve adezyon kavramı ön plana çıkmıştır [1].

1.Adezyon

Adezyon (bağlanma) kelime olarak latincedeki "adhaerere" kelimesinden gelmektedir. Farklı moleküller arasındaki çekim kuvveti "adezyon"; aynı moleküllerin birbirleri arasındaki çekim kuvveti ise "kohezyon" olarak tanımlanır. Adezyonu oluşturan maddeye "adeziv" ; adezivin uygulandığı maddeye ise ''adherent" adı verilir. Adezyon için, adeziv ve adherent arasında tam bir temas olması gerekmektedir [2].

1.1 Adezyon Türleri

Mekanik Adezyon: Adezivin, adherent veya substrat yüzeyindeki girintili ve çıkıntılı düzensiz yüzeylere kilitlenmesi olarak tanımlanır. Bu kilitlenmede geometrik ve reolojik etkenler söz konusudur. Yüzey pürüzlülüğü veya mikroskobik olarak oluşan porözitenin neden olduğu mekanik adezyon geometrik etkenlere; materyalin akışkanlık özelliğinden dolayı bir çıkıntı etrafına akması ve büzülerek tutunması ise reolojik etkenlere örnektir [2].

Fiziksel Adezyon: Bu tür adezyon birincil ve ikincil kuvvetlerin etkisi ile oluşur. Birincil kuvvetler; iyonik, kovalent ve mekanik bağlar olmak üzere üç farklı şekildedir. İkincil kuvvetler ise hidrojen bağları, Van der Walls, Keesom dipol interaksiyon, London dispersiyon kuvvetleri ve Debye dipol indüksiyon kuvvetleridir [3]. Yüzey düz ve kimyasal olarak farklı ise oluşan tek bağlantı tipi fiziksel olmaktadır [4].

Kimyasal Adezyon: Atomların ara yüzeyde adezivden aderente doğru geçtiği bağlantı tipidir. Adeziv ve adherentin kimyasal ve fiziksel farklılıklarından dolayı, bu bağlanma tipinin genel bağlanma kuvvetine katkısı oldukça düşüktür [4].

2.Diş Hekimliğinde Adezyon

1955 yılında ilk kez Buonocore tarafından demonstrasyonu yapılmış ve %85'lik fosforik asitle mineye asit-etch uygulayarak rezin-mine bağlanma gücü artırılmıştır. Buonocore; asitlemenin basitçe rezin retansiyonu için ulaşılabilir mikroskopik yüzey alanını artırdığına inanmaktadır. Ancak; onun öğrencilerinden John Gwinnett (elektron mikroskopist) asitlenmiş mine yüzeyi ve rezin infiltrantın arayüzeyini daha yakından incelemiştir. Adeziv rezinlerin asit-etch uygulanmış mine prizmalarına penetre olabildiğini ve rezinin apatit kristallerini sarmalladığı alanda yapının asite daha dayanıklı hale geldiğini rapor ederek ilk gerçek hibrid tabaka tanımlanılmıştır [5]. Nakabayashi ve diğerleri ise; asitlenmiş dentinde açığa çıkan kollajen fibrillerin rezin infiltrasyonu ile desteklendiğini göstermiş ve bu yeni biyokompozit yapıyı "hibrid tabaka" olarak adlandırmışlardır. Böylece diş hekimliğinde kullanılan dental adeziv sistemlerin gelişimi başlamıştır[6].

2.1.Mineye Adezyon

Minenin inorganik içeriğinin fazla olması sebebiyle, asitlere karşı daha dirençli bir yapıya sahiptir ve yüzey enerjisi daha yüksektir. Laboratuvar sonuçlarına göre, fosforik asit uygulaması sonrasında, kompozitin mineye makaslama bağlanma kuvveti genellikle 20 MPa 'nın üzerindedir[7]. Bu bağlanma kuvveti birçok restorasyon için yeterli retansiyonu sağlamaktadır ve mikrosızıntının gerçekleşmesini önlemektedir. Mine yüzeyine asit uygulanması, farklı düzeylerde prizmatik ve interprizmatik mineral kristallerini ortadan kaldırarak mikroskobik pürüzlülük sağlar. Aynı zamanda asit uygulaması sonrasında minenin yüzey geriliminde düşüş gözlenir ve yüzeyin ıslanabilirliği artar. Bu şekilde oluşan mikroporözitelere rezininfiltrasyonu daha kolay bir hal almaktadır[1].Temel olarak minenin asitle pürüzlendirilmesi sonrasında oluşan porözitelere rezinin infiltre olması ve açığa çıkan hidroksiapatit kristallerinin monomerlerle sarılmasıyla minede mikromekanik adezyon gerçekleştiği bildirilmiştir [8].

2.2.Dentine Adezyon

Mineden farklı olarak dentinin nemli bir dokuya sahip olması, adezyon açısından en büyük güçlüğü oluşturmaktadır[9]. Dentin dokusunda tübüllerin içerisinde bulunan sıvı pulpanın hücreden fakir tabakasındaki kapiller damarlardan gelen plazma sıvısıdır. Dentine bağlanmada rol oynayan en kritik faktör dentin sıvısının miktarıdır. Dentin sıvısı miktarı dentinin derinliği, lokalizasyonu, dentin tübüllerinin yoğunluğu ve çapına göre değişir [1].

Nemli bir doku olmasının dışında dentine adezyonda rol oynayan diğer etkenler; dentinin içeriği (dentin tübüllerinin yoğunluğu, çapı, peritübüler ve intertübüler dentin oranı), kalınlığı ve yapısına bağlı olarak dentinin değişen geçirgenliği (demineralize ya da sklerotik dentin), yaşı, smear tabakası ve hibrid tabakanın varlığı ya da yokluğudur [2].

2.2.1.Smear Tabaka

Diş sert dokuları, bir frez ya da başka bir alet ile prepare edildikten sonra diş yüzeyinde kalan organik ve inorganik bileşenler yüzeyde "smear tabakası" adı verilen bir debris oluşturur. Yapısında inorganik dentin parçacıkları, denatüre kollajen parçacıkları, hidroksiapatit kristalleri, odontoblast uzantıları, kan hücreleri, bakteri ve tükürük bulunmaktadır[10]. Bu tabaka dentin kanallarının ağzında toplandığında "smear" tıkaçları denilen yapıları oluşturur. Smear tabakası ve tıkaçları dentin için doğal bir bariyer görevi görerek dentinal sıvının hareketini %80-90 oranında, diffüzyonunu ise %25-30 oranında azaltmaktadır [11].

Smear tabaka asit uygulaması ile kolaylıkla uzaklaştırılabilmektedir ancak mekanik olarak kaldırmak mümkün olmamaktadır. Smear tabakası ve smear tıkaçlarının asidik solüsyonlar ile uzaklaştırılması, açığa çıkan dentin yüzeyine sıvı akışını artırmakta ve dentine bağlanmayı negatif yönde etkilemektedir[9].

Dentin tübüllerinin içerisindeki sıvı hareketlerini ve dentin geçirgenliğini önemli derecede azaltan smear tabakası dentine çok zayıf bağlanmakla birlikte (5 Mpa) günümüz adezyon stratejilerinde bu bağlanmanın bir anlamı yoktur[2].

2.2.2.Hibrid Tabaka

Günümüz adeziv restoratif materyallerin temel bağlanma mekanizması hibrid tabakanın oluşumuna dayanmaktadır. Hibrid tabaka ilk olarak Nakabayashi(1992) tarafından demineralize dentin yüzeyine ve kanallarına monomerlerin infiltrasyonu ve sonrasında polimerizasyonu olarak tanımlanmıştır. Diş sert dokularında oluşan mikromekanik bağlanma tabakasına, hibrid tabakası ya da rezin ile güçlendirilmiş bölge adı verilmektedir [12].

Hibrid tabakası oluşumunda asit uygulaması sonrası demineralize edilmiş dentinin geçirgenliğini koruması en önemli etkendir. Hibrid tabaka ile ilgili yapılan birçok çalışma sonucunda birçok adeziv sistem ile elde edilen bu tabaka kalınlığının 1-5 mikrometre arasında değiştiği bildirilmiştir. Hibrid tabakanın kalınlığını etkileyen bir diğer faktör de dentinin asitlenmesi sonrasında oluşan demineralizasyonun derinliğidir. Oluşan demineralizasyon miktarı dentinin mineral yoğunluğu, kimyasal içeriği ve morfolojik özellikleri ile de değişebilmektedir[1]. Fakat yapılan bir çalışmada dentine bağlantı kuvveti ve hibrid tabakasının kalınlığı arasında bir ilişki bulunmadığı bildirilmiştir [13].

Dentine bağlanmanın temelinde, asit uygulamasıyla açığa çıkarılan kollajen fibrillere tamamen infiltre olan adeziv monomerlerin varlığıyla oluşan hibrid tabaka sayesinde yüksek kaliteli arayüz elde edildiği kabul edilmektedir. Modern adeziv sistemlerde genellikle yerleştirildiklerinden hemen sonra yüksek kalitedemarjinal sızdırmazlık ve bağlanma gücü başarısı rapor edilmekle birlikte, sonuçların in-vitro ve in-vivo olarak birkaç ay içinde bozunmaya başladığı bildirilmektedir[14].

Hibrid tabakanın temelini oluşturan expoz kollajenin enzimatik ve hidrolitik bozunması fiziksel ve kimyasal çeşitli faktörlere bağlıdır. Araştımacılar, hibrid tabakanın bileşenleri bozunmaya başlar başlamaz tabaka içerisinde su ile dolu kanallar oluştuğunu ileri sürmüşlerdir. Bu kanallar oral ve dentinal sıvıların erişmesine izin vererek tabakanın daha fazla bozunma olasılığını artırır. Bu bağlamda hibrid tabakanın güçlendirilmesi fikri ortaya çıkmıştır [15].

3.Adezyon Kapsamında Hibrid Tabakaya Yönelik Çalışmalar

3.1 Matrix Metalloproteinazların İnhibe Edilmesi

Matriks-metalloproteinazlar (MMPs) ilk olarak 1962 yılında bulunmuştur. Endopeptidaz ailesinin bir üyesi olan MMPs'ler ekstraselüler matrikste lokalizedirler[16,17]. Fizyolojik olarak MMPs hidroliz yoluyla, kollajen öncelikli olarak, degrade proteinler tarafından remodele edilen düzenli dokuya katılır. MMPs'lerin tükrük, dişeti oluğu sıvısı ve dentinde mevcut olduğu bulunmuştur. Dentinde tüm 23 insan MMPs'lerinden -2, -3 ,-8, -9 ve -20 MMPs'leri gösterilmiştir [18].

MMPs'ler, dentinogenezis sırasında odontoblast tarafından üretilir ve daha sonra inaktif şekilde dentin içine katılırlar. Asidik pH değeri 4,5'in altındayken MMPs'ler aktive olur ve tam fonksiyonel enzim haline gelirler [16,17]. Dentin-pulpa kompleksi ile ilgili olduğu kadar MMPs'lerin demineralizasyon öncesinde ve sırasında hücre dışı matriks organizasyonunda ve peritübüler dentin oluşumunda da rol aldığı varsayılmaktadır Bununla birlikte; bugüne kadar matür dentinde MMPs'lerin çok az fonksiyonu kesin olarak bilinmektedir [19].

Demineralize dentin; bağlı matriks metalloproteinazlar (-2,-3,-8 ,-9,-20) ve katepsinler içermektedir ve inaktif haldeki bu yapılar asit&etch işlemi ile aktive olarak hibrid tabakanın iç katmanlarına yavaşça degrade olur[5].

Etch&rinse tekniği ile oluşturulan bir rezin-dentin bağı 6 ay ile 5yıl içerisinde önemli ölçüde gücünü kaybeder. Bu; sekonder çürük, aşırı duyarlılık ve restorasyonların kaybına yol açabilir. Adezyon gücünün azalması ile ilgili, dentin kollajen ağının

yapısı ve MMPs'lerin ağırlıklı faktörler olduğu belirtilmiştir[20].

%37'lik fosforik asit kullanılarak aşındırma işlemi ile kolajen fibriller açığa çıkar ancak buraya uygulanan adeziv bonding ajanlarının infiltrayonu yetersiz olabilir. Sonuç olarak, hibrid tabakanın altında non-infiltre kollajen açık-desteksiz bir tabaka halinde kalır. Bu non-infiltre kolajen aktif MMPs içerir ve bu enzimlerin yapılan işlemler sonrası aktive olması sonucunda kolajen bozulabilir. Sonuç olarak hibrid tabaka parçalanır ve bağlanma kuvveti giderek azalır [20]. Bu bağlamda araştırmacılar MMPs'leri inhibe edecek materyal ve yöntemlere gereksinim duymuşlardır.

MMPs aktivasyon inhibitörleri şöyle sıralanabilmektedir; etilendiamin tetraasetik asit (EDTA), klorheksidin(CHX), carbodiimide, kitosan, çinko oksit(ZnO), tetrasiklin, galardin, proantosiyanidinler, epigallotechtin-3-Gallate (EGCG), quaternary amonyum tuzları.

Etilendiamin Tetraasetik Asit: Etilenediamin tetraasetik asit(EDTA) kök kanal sisteminin mekanik enstrumentasyonu sırasında ve irrigasyonunda en yaygın biçimde kullanılan ajanlardan biridir. EDTA, dentin yüzeyinden smear tabakayı arındırır fakat etkisi kendi kendine sınırlayıcı bir özellik taşımaktadır.

MMPs'lerin katalitik hidroliz faaliyetlerinde üçüncül yapı ile bağlanmaları için çinko iyonları ve kalsiyum gerekmektedir. Asitlenmiş dentinde açığa çıkan katyonlar ile EDTA şelasyon yaparak MMPs'lerin inaktivasyonunu sağlamaktadır. Bazı araştırmacılar açıktaki MMPs' leri inaktive edecek bir prosedür olarak mine ve dentin yüzeyine 0,5ml EDTA kullanımı koşulunu savunur[21]. EDTA'nın "etching" etkisi birkaç dakikada dentinin 1-2 µm'lik kısmını etkileyecek kadar zayıftır. Araştırmalarda %32-37 fosforik asitle 15sn. asitlemenin ardından asitlenmiş dentinin anti-MMPs şelatörleri ile tedavi edilmesi önerilmektedir. Asitlenmiş dentinde MMPs'leri inhibe edebilecek diğer olası şelatörler; 1,10-fenantrolin, etilen diamin tetrafosfonik asittir [22].

EDTA'nın 1 ile 5 dakika uygulanması insan dentininde MMP-2 ve MMP-9 aktivasyonuna karşı önleyici bir etki göstermektedir. Sonuçlar fosforik asit ve başka asit tipleriyle karşılaştırıldığında dentin-adeziv bağlanma gücünde bir artış sergilemiştir. Aynı zamanda EDTA'nın bu konudaki uzun dönem takip çalışmalarında dentin-adeziv arayüzündeki adezyonu koruduğu gösterilmiştir. EDTA'nın dezavantajı ise, suyla durulandıktan sonra dentin yüzeyinden tamamen kaybolabilmesidir. MMPs'lerin aktivitesini baskılayacak artık EDTA ortamda hiç kalmayabilir [23.24].

Klorheksidin: Klorheksidin(CHX) oral bakterilere karşı geniş bir aktivite yelpazesine sahip yaygın kullanılan bir antimikrobiyal ajandır. CHX yakın zamanda MMPs'lerin inhibe edilmesi yoluyla hibrid tabakayı koruyacak bir proteaz inhibitörü olarak incelenmiştir. Dentinal kollajen fibrillere rezin tam olarak infiltre olamazsa MMPs'ler sayesinde hibrid tabaka bozunmaya uğrayabilir. Dentine asit uygulandıktan sonra, CHX içeren su bazlı primer kullanılmasıyla dentine bağlanma gücünün ve hibrid tabakanın bütünlüğünün zaman içerisinde korunduğu rapor edilmektedir[25].

Yapılan bir çalışmada etch&rinse sistemlerde terapötik astar olarak klorheksidin kullanımı ile bu enzimlerin inhibe edilmesi amaçlanmıştır. Sonuç olarak bondun dentine adezyonunun uzun bir süre için muhafaza edildiği rapor edilmiştir. MMPs' lerin yanısıra adeziv bond kalitesini etkileyen diğer faktörlerin genellikle bir dereceye kadar etkili olduğu ve CHX ile MMPs inaktivasyonu nedeniyle daha uzun süreler için bağlanmanın kararlı kaldığı bildirilmektedir [25].

Carbodiimid: Carbodiimid (1-Etil-3-[dimetilamino propil]) ve carbodiiimid hidroklorür(EDC) stabil syanamid izomerlerdir. EDC ile dentine bağlanmanın stabilitesi ve onun çapraz bağlanma kapasitesini geliştirmek mümkündür. Kollajenin bu mekanizması rezidüel glutamik ve aspartik karboksilik asit grupları arasında çapraz bağlama aktivasyonunu içerir[26].

EDC, dentin matrixinin yüksek mekanik özellikleri ve kollajenin yavaş parçalanma oranları nedeniyle, arayüz stabilitesini artırmak için büyük bir potansiyele sahiptir. Bu yüzden EDC'nin MMPs'leri uzun vadede etkisiz hale getirdiğini söylemek mümkündür[27].

Kitosan: Kitin'in deasetilasyonu ile elde edilen lineer bir aminopolisakkarittir. B2 vitamini yani riboflavin ise, pentoz şeker olan ribitol ve lumikromdan oluşur. Kitosan ve riboflavin ile adeziv substratın modifikasyonu sağlanarak MMPs'lerin hidrolitik ve kollajenolitik degradasyonuna karşı kollajenin mekanik özellikleri ve demineralize dentinin stabilitesi arttırılmaktadır. Fakat kitosan içeriği, interfibriler alanlarda majör obliterasyon artışına kademeli olarak izin verir bu da olumsuz bir bağlanma ile sonuçlanabilir[28].

ZnO: Kenetleyici özelliklere sahip sentetik peptidomimetik olan bu inhibitör, MMPs'lerin ve katalitik alanın aktif bölgesinin inhibisyonunda kullanılabilir. Dental adezivlere ZnO parçacıklarının eklenmesi, minör dentin kollajen degradasyonu ve rezin-dentin bağında artan dayanıklılığa sebep olarak adeziv bağlanma etkinliğinin uzun süre korunacağı bildirilmektedir[29].

Tetrasiklin: Her ne kadar tetrasiklin'ler yaygın olarak protein sentezine müdahale ettikleri ribozomal seviyede hareket eden geniş yelpazeli antibiyotikler olarak bilinseler de aynı zamanda inflamasyon, hücre çoğalması ve anjiyogenezis gibi başka biyolojik hareketler de ortaya koyarlar[30].

Tetrasiklinler ve onların analogları bu antibiyotiklerin antimikrobiyal özelliklerinin mekanizmalarından bağımsız olarak MMPs'leri baskılarlar. Tetrasiklinlerin ve analoglarının Ca+2 ve Zn+2'ya bağlanma bölgelerinin kısmen MMPs'lerin hücre dışı aktivitesini baskılamaktan sorumlu olduğu iddia edilse de, ekstraselüler matrikste ve hücre içi bölgede de antimikrobiyal olmayan birçok mekanizma ile terapötik özellik göstermekte oldukları bilinmektedir [31].

Günümüzde üç tetrasiklin grubu mevcuttur; tetrasiklin ve doğal ürünler, yarı sentetik tetrasiklin komponentleri ve kimyasal açıdan modifiye olmuş tetrasiklin. Minosiklin ve doksisiklin, yani sentetik tetrasiklinlermedikal ve dental uygulamalara sahiptir[31].

Tetrasiklin ve yarı sentetik formları, doksisiklin, MMPs'lerin kollajen degradasyonu aktivitesini inhibe etme yeteneğine sahiptir[32]. Dentin yüzeyi asitleme prosedüründen sonra kollajenaz ve jelatinazı inhibe edebilme özelliğinden dolayı % 2'lik doksisilin sulu çözeltisi ön tedavi olarak kullanımı gündemdedir[33].

Galardin: Galardin MMPs substratlarının bir moleküler taklidi olarak tasarlanmış güçlü ve geniş spektrumlu hidroksamik tipinde sentetik MMPs inhibitörüdür. Çinko atomuna bağlanan MMPs'lerin aktif bölgesine girerek inhibisyon etkisi gösterir. Galardin birkaç MMPs'a karşı aktiftir.

Galardinin dentin MMPs'leri üzerindeki baskılayıcı etkisi analizlerle teyit edilmiş, bağlanma gücünü tehlikeye atmadan MMP-2'nin ve MMP-9'un aktivitesini tamamen önlendiği gözlemlenmiştir. Yapılan bir çalışmada, bağlanma yüzeyi 0,2 ml galardin-su solüsyonu ile muamele edilmiştir. Bağlanma gücünde yavaşlamış bir azalma ve nanosızıntı miktarında düşüş gösterilmekle birlikte bu durumlar tamamen bloke edilememiştir. Bu çalışmanın 1 yıllık takibi sonrasında ise adezyon gücünde %27'lik bir azalma olduğu rapor edilmiş ; ve bu sonucun kontrol gruplarında ölçülen %45'lik azalmadan anlamlı derecede daha az olduğu bildirilmiştir[25].

Proantosiyanidin: Flavonoid bileşimlerin kompleks bir alt grubu olan proantosiyanidinler (PA); çok çeşitli meyve, sebze, çiçek, fındık, kabuk ve tohumlarda bulunmuştur[34]. Daha çok üzüm çekirdeği ekstresi olarak bilinen ve çapraz bağlayıcı olan bu maddenin MMPs'leri de inhibe ettiği gösterilmiştir[35].PAkullanılan adeziv sistemler ile saf adeziv model karşılaştırıldığında, PA eklenmiş sistemlerin biyolojik bozunmaya karşı direnci artırdığı ve enzimatik bozunmadan sonra hibrid tabakanın daha iyi korunmasını sağladığı bulunmuştur. PA'nın kollajenin çapraz bağlanmasına etkili olduğu ve 10 sn. gibi kısa bir süre içinde biyolojik kararlılığı artırabildiği bildirilmektedir. Demineralize dentinde PA 'nın ön tedavi olarak kullanılması klinik olarak mümkün ve geçerli bonding sistemlerin dayanıklılığını artırmak için umut verici bir yaklaşımdır[36].

PA'nın; sıçanlarda mandibular kondilde kemik formasyonunu desteklediği, demineralize dentin sertliğini artırdığı ve yapay kök çürüklerinin ilerlemesini inhibe ettiği gösterilmiştir[37].

Çinko metakrilat: Çinko metakrilat(ZM) bir metalloproteinaz inhibitörüdür ve diğer metakrilat monomerler ile kopolimerize olabilir. Yapılan çalışmada ZM, MMP-2'yi inhibe etmiştir.Bu nedenle ZM ilavesinin adezyon gücüne etkisinin olabileceği kanısına varılmıştır[38].

Epigallotechtin-3-Gallate: EGCG, matriks-metalloproteinaz molekülünü bozarak MMP-2 ve MMP-9'un aktivitesini baskılamaktadır.

Diş hekimliğinde EGCG, bir adezive ilave edildiğinde Streptococcus mutans'ın büyümesi üzerindeki baskılayıcı etkisinden ayrı olarak periodontal hastalıkta osteoklast oluşumunda yer alan MMP-9'un aktivitesini ve salınımını engelleyebildiği rapor edilmiştir. Aynı zamanda MMP'leri baskılayarak dentinin erozyonunu-aşınmasını azalttığı bildirilmektedir. Anti-MMP özellikleri yüzünden EGCG içeren adezivler rezin-dentin bağının dayanıklılığını arttırma potansiyeline sahip olabilirler; fakat bu henüz tam olarak araştırılmamıştır[25].

Quarternary Amonyum Tuzları: Dört elementli amonyum bileşikleri antimikrobiyal özelliklere sahiptirler ve dental rezinlere eklenebilirler. Fakat suda çözülebilir moleküller oldukları için adeziv arayüzünden ayrılabilirler. Dört elementli amonyum molekülleri rezin matriksinde hareketsiz hale geldiklerinde bakteriyostatik aktiviteye sahip olabilmektedirler.

12-methacryloyloxydodecylpyridinium bromide (MDPB) gibi dört elementli amonyum metakrilat kullanılmasının avantajlarından biri onların adeziv monomerlerle birlikte polimerize olabilmeleridir. Clearfil Protect Bond (Kuraray Noritake Dental Inc. Osaka Japonya) MDPB'yi bileşimine dahil eden ilk ticari dentin adezivdir[39].

Yapılan bir çalışmada rezin-dentin bağlarının bozunması Clearfil Protect Bond veya Clearfil SE Bond (çok benzer kompozisyona sahip adeziv, ancak MDPB den yoksundur) kullanılarak değerlendirilmiş, sonuç olarakClearfil SE Bond'da bozunma paterni gözlemlenirken Clearfil Protect Bond'da bulgulanmamaktadır. Bu da MDP içeren adeziv kullanımının hibrid tabakayı desteklediğini göstermektedir[40].

Aynı zamanda benzalkonium klorid (BAC) molekülünde dört elementli amonyum grubu içeren bir antimikrobiyal maddedir. Bu madde birkaç yıl bir fosforik asit jele dahil edilmiş fakat bu jelin kullanılması mine ve dentine bağlanma gücünü etkilememiştir. Yakın zamanda BAC'nin anti-MMP özellikleri MMP-2, 8 ve 9'a karşı test edilmiştir. Sonuçlar bu maddenin MMP-2; 8 ve 9'u baskılama potansiyelini göstermiştir[40].

3.2. Kollajenin Mekanik Özelliklerini Artırma

Çapraz bağlantı, asitlenmiş dentin matriksinde kollajen degradasyonunun kararlılığını ve direncini arttırmada bir potansiyel metot olarak kabul edilir. Adeziv uygulanmadan önce, kollajen fibrillerinin çapraz bağlantı derecesinde artış, bağlantının dayanıklılığını arttırmasıyla sonuçlanabilmektedir. Kollajenin bozunma gücünü proteaz kullanımı sayesinde arttırmaktan başka, bazı çapraz bağlantı ajanlarının anti-MMPs özelliklere sahip oldukları gösterilmiştir. Bununla beraber, MMPs'ları ve sistein katepsinleri inaktive etmede çapraz bağlantı ajanları kullanılmasının önemli dezavantajlarından biri; arzu edilen terapötik etkiyi elde etmede ihtiyaç duyulan uygulama/aktivasyon zamanının klinik yapılabilirlik dahilinde olmamasıdır. Başka bir dezavantaj ise kötü mekanik özelliklere sahip suca zengin kollajen matriksinin hibrit tabaka içinde oluşmasıdır[42].

Yakın zamanda fiziksel metodlar, özellikle ultraviyole radyasyonu, diş hekimliğinde ve oftalmolojide denenmiştir. Ultraviyolenin (UVA) aktive ettiği riboflavin'in bağlanma gücünü arttırdığı, adeziv ara yüzeyini dengelediği ve dentin MMPs'lerinin aktivasyonunu önlediği gösterilmiştir. Riboflavin, adeziv diş hekimliğinde önemli bir potansiyele sahiptir çünkü UVA mavi ışık tarafından aktive olan,uygulanması kolay ve biyouyumlu bir materyaldir. UVA'nın aktive ettiği riboflavinin, dentin kollajeninin mekanik özelliklerini, kararlılığını, bozunma direncini arttırdığı ve kollejenolitik sindirime dirençli hale geldiği gösterilmiştir[43].

Dentindeki endojen MMPs'ların inaktivasyonu için diğer bir yaklaşım, asitlemeden hemen sonra onların peptid zincirlerinin çapraz bağlanmasıdır. Bu onların enzim aktivitesi için gerekli olan moleküler hareketliliği kaybetmesine neden olur [44].

"Gluteraldehit"in vitro olarak 10 yıldır bir çapraz bağlama maddesi olarak kullanılmaktadır. Bununla birlikte residüel gluteraldehitin tedavi edilen dokudan yıkanarak uzaklaştırılmasının sitotoksik olduğu gösterilmiştir.%5 gluteraldehit, %35 HEMA, %60 su karışımlarından oluşan adeziv sistemler (Gluma Desensitizer, Heraeus Kulzer); dentin desentizerleri olarak bu amaçla kullanılmaya devam etmektedir[45].

Bir çalışmada rezin-dentin bağlantısında çekme dayanımıüzerinde üç farklı çapraz bağlama ajanı; gluteraldehit(GD), üzüm çekirdeği ekstresi(PA), Genipin(GE) etkisini araştırmak amaçlanmıştır. Dentin matrixinde kimyasal modifikasyon GD ve PA tarafından en iyi şekilde düzenlenmiş ve bağlanma gücünü anlamlı olarak artırdıkları rapor edilmiştir[46].

3.3. Deproteinizasyon

Asit uygulaması ile dentin demineralizasyonu karışık ve yüzeysel bir prosedür olmakla birlikte dentin dokusunda smear tabakası kaldırılarak 3-7,5µm arasında bir kollajen örgü açığa çıkmaktadır[47]. Klinik olarak, uygun bir dentin bonding için ideal senaryo demineralize dentinin tüm uzatılarına homojen olarak rezinin penetrasyonu, solvent/su eliminasyonu ve rezin monomer polimerizasyonu sonucunda hibrid tabaka oluşmasıdır. Ancak bu prosedür teknik hassasiyet gerektirmekte ve klinik başarıyı oldukça etkilemektedir. Araştırmacılar hibrid tabaka varlığının dentine adezyon açısından dezavantajları olabileceğini bildirmişlerdir.

Nanosızıntı terimi 1995 yılında Sano tarafından marjinal boşlukların yokluğunda var olan spesifik bir sızıntı olarak tanımlanmıştır. Bu sızıntı hibrid tabakanın altında adeziv rezinin tamamen infiltre olmadığı ve polimerizasyonun zayıf olduğu submikron poroziteler yoluyla lateral olarak oluşur[48]. Ayrıca bağlanmayı etkileyen hibrid tabakanın altındaki nonkapsüle kollajen hidrolitik bozunmaya hassastır ve bond stabilitesini tehlikeye atabilir. Araştırmacılar asit-etch'den sonra açığa çıkan kollajenin çeşitli ajanlarla uzaklaştırılmasının (deproteinizasyon) dentin dokusunda hibrid tabaka oluşumundan bağımsız, mineye benzer mikromekanik adezyona olanak sağlayabileceğini bildirmişlerdir. Bu bağlamda deproteinizasyonun dentin adeziv prosedürlerinde teknik hassasiyeti azaltabileceği; mikrosızıntı, makaslama ve çekme kuvvetlerinde süregelen artış sağlayabileceği öne sürülmektedir[49].

Dentinde kollajen yapının uzaklaştırılması için kollajenaz gibi deproteinize edici enzimler ve ajanlar kullanılmaktadır. Bu amaçla kullanılan en genel ajan olan sodyum hipoklorit(NaOCl), organik materyalleri çözebilen non-spesifik bir proteolitik ajandır. Bu ajan ile tedavi edilen dentin,

minerallerden zengin olmakla birlike uzun vadede daha stabil arayüzler oluşturabilen bir yapıya sahiptir. Sodyum hipoklorid ile yapılan deproteinizasyonun adeziv tabakasının bozunum riskinin azaltacağı düşünülmektedir. Ancak bu varsayımı güçlendirmek için daha ileri çalışmalar gereklidir[49].

Yapılan bir çalışmada, farklı dentin bölgelerinde adeziv sistemlerin bağlanma gücüne NaOCl ön tedavisinin değerlendirilmesi amaçlanmıştır. 40 insan dişi farklı adeziv sistemler (Adper Single Bond 2,Clearfil SE Bond, Adper SE Plus, G-Bond) kullanılmak üzere rastgele, ön işlemler (kontrol ve NaOCl-deproteinizasyon) ve dentin bölgeleri (proksimal, yüzeysel oklüzal[SO] ve derin oklüzal[DO]), olmak üzere gruplara ayrılmıştır. Her bir örneğin oklüzal ve proksimal yüzeylerine silindirik kavite hazırlanmıştır. Deproteinizasyon için adeziv sistemlerin uygulanmasında önce dentine 60 saniye %10 NaOCl uygulanmıştır. Her numuneden 2 oklüzal ve 1 proksimal dilim elde edilmiş ve push-out testi ile fraktür biçimleri analiz edilmiştir. Adeziv sistemler ve dentin bölgesinde bağlanma gücü açısından istatiksel olarak anlamlı bir fark bulunmamıştır ve NaOCl ile yapılan ön tedavi, bağlanma kuvveti değerlerini önemli ölçüde etkilememiştir. Öte yandan iki aşamalı self-etch adeziv sistemlerin kullanıldığı dentin yüzeylerinde en yüksek bağlanma gücü sonuçları rapor edilmiştir[50].

NaOCl ve Nd:YAG lazer ile deproteinizasyonu yüzey tedavilerinin dentin permeabilitesinde longtudinal etkileri halen araştırılan bir konudur. Yapılan bir araştırmada dentin geçirgenliği, permeabilite cihazı ile dentin sıvı akışı ölçülerek değerlendirilmiştir. 80 tane sığır dentin numunelerinin smear tabakası varlığında ve EDTA ile smear tabakasının yok edilmesinden sonra geçirgenlikleri ölçülmüştür. Daha sonra tedavi şekline göre 8 alt gruba ayrılmışlardır (n=10) ; Grup C- kontrol; Grup L- Nd:YAG lazer; Grup F- fluorid; Grup FL- fluorid+Nd:YAG lazer; Grup A,-adeziv; Grup AL- adeziv+Nd:YAG lazer; Grup D-10% NaOCl+adeziv; ve grup DL-NaOCl+ adeziv+Nd:YAG lazer. Nd: YAG lazer 60 mJ / darbe / 10 Hz / 47.7 J / cm (2) / 1 W ışınlanmış ve 60 saniye boyunca temas olmaksızın eli açık uygulanmıştır. Permeabilite, tedaviden 24 saat sonra ölçülmüştür. Numuneler 5 gün boyunca eroziv (numunenin Coca-Cola içerisine günde 4 kez/90 sn. batırılması) ve abraziv (fırçalama) değişikliklere maruz bırakılmıştır. Günün ilk ve son eroziv ve abraziv değişiklikler sonrasında permeabilite tekrar ölçülmüştür. Sonuçlar istatistiksel olarak analiz edilmiş ve Tukey testleri yapılmıştır. Sonuç olarak; Grup FL ve grup A hariç tüm gruplar geçirgenliği azaltmıştır. Lazer ekspojürü ile kombine tedavilerde permeabilitede anlamlı bir azalma gözlenmiştir. Adeziv ve Nd:YAG lazer birleşimi ise 24 saat sonrası en düşük geçirgenliği sağlamıştır. NaOCl ile deproteinizasyon ve Nd: YAG lazer birleşimi ise eroziv/abraziv uygulamalardan sonra en düşük geçirgenlik oranını göstermiştir[51].

Kalsiyum hipoklorid'in dentin deproteinizasyonu için kullanımı da güncel yaklaşımlar arasındadır. Bu konuda yapılan bir çalışmada CaOCl ile deproteinizasyonun asitlenmiş dentinin yüzey morfolojisi ve kompozit restorasyonların mikrosızıntısına olan etkisi ve deproteinizasyondan sonra dentinin yapısı analiz edilmiştir. Çalışmada, 40 tane 3. molar kullanılmışve dentin tedavisine göre 4 gruba ayrılmıştır: Tedavi öncesi ajan kullanılmamış, 30 sn süreyle %10'luk NaOCl; 30 saniye süreyle %10'luk CaOCl ve 30 saniye süre ile %15'lik NaOCl. Hazırlanan kaviteler aseton bazlı adeziv sistemler ve rezin kompozitlerle kapatılmıştır. Daha sonra 5000 devir ile ısı değişikliklerine maruz bırakılan ve 4 saat boyunca metilen mavisine daldırılıp 1 mm kalınlığında plakalar halinde kesilen örnekler, stereomikroskop altında değerlendirilmiş ve her grupta infiltrasyon derecesi(skor 0-3) tayin edilmiştir. 4 dişe gruplarına göre yüzey tedavisi uygulanmış ve dentin yapısal olarak analiz edilmiştir. Sonuç olarak deney grupları arasında anlamlı bir fark bulunamamıştır. CaOCl kompozit-dentin arayüzey morfolojisini değiştirdiği gözlenmiş ve arayüzde kalsiyum artışına yol açtığı belirtilmiş fakat mikrosızıntı açısından diğer materyallerden farkı bulunmadığı rapor edilmiştir[52].

Asitlenmiş dentinin deproteinizasyonu için NaOCl kullanımının kırılgan zon oluşturma,sitotoksisite, kötü tad ve koku gibi çeşitli dezavantajları vardır. Bu dezavantajlar,deproteinizasyon için daha farklı ajanların araştırılması ile sonuçlanmıştır.

Aguilera ve arkadaşları, asitlenen ve asitleme sonrasında NaOCl ile deproteinize edilen dentinde tek aşamalı aseton bazlı adeziv sistem kullanılarak sağlanan dentin bağlantısını ultramorfolojik olarak ve bağlanma gücü açısından değerlendirmişlerdir. Adeziv sistem ve kompozit materyalin uygulanmasından sonra bağlanma kuvveti ölçümleri yapıldığında istatistiksel olarak gruplar arasında anlamlı bir fark bulgulanmamıştır. SEM ile yapılan ultramorfolojik incelemelerde ise asitleme sonrası NaOCl ile yapılan deproteinizasyon işleminin hibrid tabaka olmaksızın daha uzun ve yoğun rezin tagları oluşumunu sağladığı rapor edilmiştir. Bu sonucun tek aşamalı self-etch sistemlerinin kullanımında uygulanan %5'lik NaOCl konsantrasyonu ve uygulama süresinden kaynaklanabileceği, konuyla ilişkin ileri çalışmaların yapılması gerekliliği vurgulanmaktadır[53].

Silva ve arkadaşlarınındentinde asitleme sonrası %10 NaOCl

ile deproteinizasyon yapılmasının 6 aylık dönemde bağlanma kuvvetine etkisini araştırdıkları çalışmada; deproteinizasyon işleminin adeziv sistemlerin dentine bağlanma gücünü arttırdığını bildirmektedir[54].

Torres ve arkadaşları; total etch adeziv sistemlerin %10 NaOCl deproteinizasyonu ile kullanımının kompozit restorasyonları klinik başarısına etkisini araştırmışlardır. Amerika Birleşik Devletleri Kamu Sağlığı Hizmet Kriterleri doğrultusunda 5 yıllık klinik değerlendirme sonucunda 2 grup arasında istatistiksel olarak anlamlı bir farklılık oluşmadığı; ilave deproteinizasyon işleminin klinik olarak saptanabilir bir etki oluşturmadığı rapor edilmektedir[55].

Son çalışmalarda, hafif self etch adezivler için demineralizasyon ve rezin infiltrasyon derinliği, bağlanmanın bozulması faktörleri arasında bazı farklılıklar rapor edilmektedir. Dekalsifiye dentinde açığa çıkan kollajen fibriller ise etch&rinse sistemler ve hidrofilik self etch adeziv sistemlerin her ikisinde de en zayıf nokta olarak karşımıza çıkmaktadır. Mekanik bozulma ve serbest radikallerin bulunması demineralize kollajen matriksteki degradasyon prosesini arttırabilmektedir. Bu reaktif serbest radikaller normal doku hasarının çeşitli formları ve yaşlanma ile ilişkilidir.

Oksidanlar (örneğin, hidroksil radikali) eşleşmemiş elektron içerirler ve oldukça reaktiflerdir.Böylece moleküler düzeyde protein yapılarına zarar verebilmektedirler. Genellikle antioksidan olarak adlandırılan birçok serbest radikal oksijenin reaktif formudur ve etkin temizleyicidir. Askorbatın okside formları nispeten kararlı olupdentin kollajenleri üzerindeasitlemenin oluşturduğu denatürasyon etkisini basklayarak kompozit-dentin adezyonun bozulmasına karşı koruma sağlamaktadırlar. Ön tedavi olarak NaOCl kullanımında dentinde bulunan düşük adezyon gücü askorbik asit veya askorbat ile tersine çevrilebilmektedir[56].

Deproteinizasyon yapmayı amaçlayan yeni ajanlar kollajenaz ya da bromelain enzimi gibi enzimlerinin içerir. Bromelain, meyve veya ananas kökünden ticari olarak elde edilen protein sindirici enzim grubuna ait bir proteolitik enzim (proteaz) 'dir. Proteazların fonksiyonu, protein hidrolizini katalize ederek amino asitlere ayrışmasını sağlamaktır[57].

Bromelain enziminin, NaOCl ile karşılaştırıldığında kolajen ağının kaldırılmasında ve bu bağlamda nanosızıntının azaltılmasında daha etkili olduğunu bildiren çalışmalar vardır. Öte yandan bond bağlanma gücünü artırmada etkinliğini gösteren bir çalışma henüz yapılmamıştır[58].

Bu nedenle, yapılan bir çalışmada bromelain enziminin deproteinizasyon etkisi ve adeziv sistemin uygulanmasından önce makaslama bağlanma gücü değerlendirilmesi için % 5 NaOCl ile karşılaştırılmıştır. Sonuç olarak; bromelain enzimi kullanımı bond gücünü önemli ölçüde etkilemiş, istatiksel olarakanlamlı farklılık yaratacak düzeyde en yüksek bağlanım gücü bromelain enzimi ile tedavi edilen grupta bulgulanmıştır[59].

4.Sonuç

Estetik restoratif materyallerin vazgeçilmezlerinden olan adeziv sistemlerin yapısal özellikleri ve klinik uygulamalarının çok iyi bilinmesi restorasyonların başarısı için şarttır. Günümüzde etch and rinse ve self-etch sistem adezivlerinde çeşitli avantaj ve dezavantajları bulunmaktadır. Adeziv sistemlerin dezavantajlarını azaltabilmek adına sürekli iyileştirmelerin yapılması için araştırmalar devam etmektedir. Sürekli yeni teknolojilerin ve yaklaşımların geliştirilmesi ile birlikte özellikle yapısal içerikleri farklılık gösteren süt ve genç daimi dişlerle ilgili in-vivo ve in-vitro çalışmalara ihtiyaç duyulmaktadır.

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Olgu Sunumu

Konfüzyon ve halüsinasyon ile prezente olan olası primer santral sinir sistemi vasküliti: bir olgu

Possibleprimary central nervous system vasculitis presentıng with confusion and hallucination: a case

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Öz

Primer santral sinir sistemi vasküliti (PSSSV), sistemik vaskülit belirtisi olmadan beyin ve omurilikteki damarlarının nadir bir inflamatuar hastalığıdır. Tanı zorluğu nedeniyle tam insidansını belirlemek zordur. Klinik geniş nörodefisitler içerebildiği gibi subakut-kronik seyirlidir. Kesin tanı için önerilen biyopsi veya serebral anjiografinin beklendiği kadar yüksek özgüllüğü yoktur. Prodromal bir kliniğin bulunması, nörodefisit varlığı, sistemik bulguların ekartasyonu, MRG'de atipik lezyonların varlığı, anormal BOS analizi ile de olası PSSSV tanısına ulaşılabilir. Tedavide steroid ve siklofosfamid gibi immunsüpresif ajanlar kullanılmaktadır. Bu yazıda anormal BOS bulgularının olduğu ve MR spectroskopiden faydalanılarak olası PSSSV tanısı alan olgu sunulmuştur.

Anahtar kelimeler: vaskülit; konfüzyon; santral sinir sistemi

Abstract

Primary central nervous system vasculitis (PCNSV) is a rare inflammatory disease of the vessels of the brain and spinal cord without signs of systemic vasculitis. Due to the difficulty of diagnosis, it is difficult to determine the exact incidence. Clinical findings may include a wide variety of neurodeficides and are subacute-chronic. The biopsy or cerebral angiography recommended for definitive diagnosis does not have as high specificity as expected. The presence of a prodromal clinic, the presence of neurodeficitis, the elimination of systemic findings, the presence of atypical lesions on MRI, and abnormal CSF analysis can also lead to a diagnosis of PSSSV. Immunosuppressive agents such as steroids and cyclophosphamide are used in the treatment. In this article, we present a case with abnormal CSF findings and a diagnosis of possible PSSSV using MR spectroscopy.

Keywords: vasculitis; confusion; central nervous system

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Giriş

Primer santral sinir sistemi vasküliti (PSSSV), sistemik vaskülit belirtisi olmadan beyin ve omurilikteki damarlarının nadir bir inflamatuar hastalığıdır. PSSSV ilk olarak 1959'da ayrı bir klinik antite olarak tanımlanmış olup farklı klinik vakalar bildirilmiştir (1). Hastalığın literatürde bildirilen insidansı 2,4/milyon'dur (2). Bildirilen vaka sayısının az olmasının bir sebebi de tanı koymak için net bir tanı testinin bulunmamasıdır.

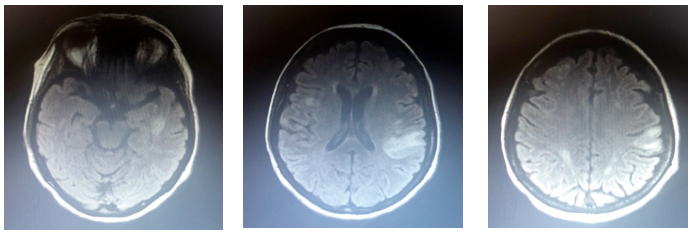
Histopatolojik tanı varlığında bile sistemik eşlik eden vaskülit olmadığı gösterilmelidir. Klinik, laboratuvar ve radyolojik bulgularla tanı desteklenmelidir (3). Birçok klinik prezentasyonla başvuru olsa da en sık görülen semptom baş ağrısıdır. Diğer semptomlar arasında hemiparezi, afazi, uyuşukluk, görsel semptomlar, ataksi gibi fokal nörolojik bozukluklar bulunur (1,4-7).

Kesin tanı için serebral anjiografive biyopsinin gerekliliği mutlak olarak belirtilse de sınırlamaları olduğunu belirten yayınlar da mevcuttur.Bu yayınlarda manyetik rezonans görüntüleme (MRG) ve anjiografi bulguları ile birlikte uyumlu bir BOS profili varsa biyopsiye gerek olmadan yüksek olasılıkla PSSSV tanısı konulabileceği belirtilmektedir(8).

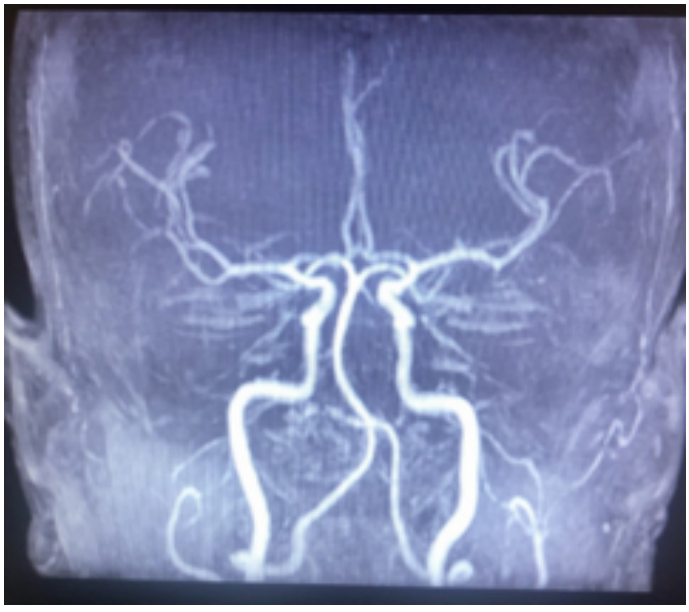
Bu yazıda, sağ alt ekstremitede ilerleyici güçsüzlük ve konfüzyon ile tarafımıza başvuran ve epileptik nöbeti olan, manyetik rezonans görüntüleme (MRG), MR anjiografi ve beyin omurilik sıvısı (BOS) analiz sonuçlarına göre olası PSSSV tanısı alan 64 yaşındaki kadın olgu irdelenmiştir.

Olgu

64 yaş kadın hasta sağ bacakta güçsüzlük, şuurda bozulma, anlamsız hareketler şikayeti ile nöroloji polikliniğine başvurdu. Şikayetleri 2 ay önce başlamış ve bu süreçte ilerlemiş. Kliniğine yatışında her iki alt ekstremitede güçsüzlük, denge kaybı ve konuşmada zorlanma, endişe ve korku hali mevcuttu. Ara ara halüsinasyon ve ajitasyon eşlik ediyordu. Öyküsünde bilinen diabetes mellitus dışında hastalığı yoktu. Nörolojik muayenesinde bilinç konfüze, yer ve zaman oryantasyonu bozuk, pupiller izokorik ışık refleksi +/+, ekstraoküler göz hareketleri serbest, sağ nazolabial oluk silik, sağ üst ekstemite 4/5, sağ alt ekstremite 3/5 kas gücünde, sol üst ekstremite kas gücü tam, sol alt ekstremite 4/5 kas gücünde idi. Hastanın çekilen kranial MRG'sinde sol parietal, sol frontal ve sağ parietooksipitalde 5-6 adet T2 ağırlıklı kesitlerde hiperintens görülen lezyon izlenmesi üzerine hasta ileri inceleme amaçlı nöroloji kliniğine yatırıldı (Şekil 1). Yatış sonrasında hastanın jeneralize tonik klonik nöbeti izlendi ve hastaya levetirasetam başlandı.Rutin biyokimya, hemogram tahlilleri ve vital bulgularında patolojik bulgu saptanmadı. Hastanın yapılan BOS analizindehücre saptanmadı, mikroprotein 84,5 mg/dl, glukoz 74 mg/dl idi. Bos sitolojisinde hücresel eleman saptanmadı. Hastanın hepatit, HIV, VDRL, TORCH, brusella antikor sonuçları negatif saptandı. Vaskülit paneli tetkiklerindeantinükleer antikor (ANA) 1/100 pozitif saptandı, anti ds DNA, ANCA, Scl 70, SS-A, SS-B negatif saptandı, protein C, protein S normal değerlerdeydi. ANA pozitifliği için romatoloji kliniği görüşü alındı ancak düşük titrede olduğu ve sistemik vaskülit için anlamlı olmadığı belirtildi. Hasta PSSSV ön tanısı ile yapılan MR spektroskopide sol parietal ve bilateral frontoparietal bölgede T2AG imajlarda hiperintens olan, asimetrik, multifokal yerleşimli beyaz cevher lezyonları ve SWAN sekanslarda subkortikal, multifokal serebral mikrohemoraji odakları izlendi (şekil 1). Kranial MR anjiografide (Kr MRA) patoloji saptanmadı (şekil 2).



Şekil 1. Kr MRG T2 ağırlıklı kesitlerde sağ frontotemporal, her iki paryetal, sağ frontal bölgede kortikal-subkortikal hiperintens lezyonlar



Şekil 2: Kr MRA normal sınırlarda

Klinik, laboratuar, BOS analiz ve MRG bulguları eşliğinde hastada ön planda PSSSV düşünülerek pulse steroid (1000mg/gün) tedavisi başlandı. Tedavi sonrası 2. günde hastanın konfüzyonunda ve parezisinde belirgin düzelme gözlendi. Beş gün pulse steroid sonrasında idame oral steroid tedavisine geçildive nörolojik muayenesi tamamen düzelerek taburcu edildi.

Tartışma

PSSSV oldukça nadir görülen bir hastalıktır. Beyin ve medulla spinalisteki küçük damarları etkiler (2). Etyolojisi tam olarak aydınlatılamamıştır.Klinik bulgular çok çeşitli olabileceği gibi radyolojik bulgular da çok çeşitli ve nonspesifik olabilir (1). Tanıda klinik, laboratuar ve radyolojik bulguların bir arada değerlendirilmesi önemlidir. Tanıda enfeksiyöz patolojiler, sistemik vaskülitler araştırılmalıdır (1,3). Kesin tanı histopatolojik olarak konulur. Ancak tanıda yardımcı olacak görüntüleme yöntemleri ve lomber ponksiyon incelemesi de mevcuttur. Beyin omurilik sıvısında ılımlı lenfosit artışı ve protein seviyelerinde yükselme izlenir (2). Bizim hastamızda da benzer şekilde artmış BOS protein seviyesi mevcuttu.

Vakaların %93'ünde MRG'de patolojik bulgu saptanmıştır (4). MRG'de multifokal, pek çok damar bölgesinde, tümör benzeri görünümler karşımıza çıkabilir. Kranial MRG'de herhangi bir özellik saptanamayan vakalar da mevcuttur. Bu durumda MR spektroskopi tanıda yardımcı olabilir (1). Bizim vakamızda öncelikle Kranial MRG'de her iki hemisferde multifokal olarak karşımıza çıkan tümör ile karışabilen lezyonlar izlenmiş ve ayırıcı tanıda MR spektroskopiden faydalanılmıştır.

Calabrese ve Mallek, PSSSV tanısı için klinik deneyim ve yayınlanmış çalışmalardan elde edilen kanıtlar temelinde tanı için bazı kriterler önermiştir. Buna göre; aşağıdaki kriterlerin üçünün de karşılanması durumunda kesin tanı konulur (9):

- kapsamlı bir temel değerlendirmenin ardından bilinmeyen kaynaklı bir nörolojik defisitin öyküsü veya klinik bulguları;

- klasik vaskülit özelliklerine sahip serebral anjiyogram veya vaskülit özelliği gösteren bir SSS biyopsi örneği;

- sistemik vaskülit veya anjiyografik veya patolojik özelliklerin sekonder olabileceği başka bir hastalık belirtisinin olmaması.

Genel olarak, anjiyografinin duyarlılığı % 40 ile% 90 arasında değişmektedir ve serebral anjiyogramlar %30 kadar düşük bir özgünlüğe sahiptir (10-13). Anjiyografi ile elde edilen bulgular PSSSV tanısını destekleyebilir. Ancak PSSSV'de hem teknik hem de tanı bağlamında anjiyografinin, altın standart olarak kullanılmasının sınırlamaları vardır. Öncelikli olarak, anjiyografiler, anormal bulgulara neden olan patolojik süreçler ve mekanizmalar hakkında daha fazla bilgi vermeden damar konturlarındaki bölgesel değişiklikler hakkında bilgi sağlar. Ateroskleroz, vazospazm, radyasyon vaskülopatisi, enfeksiyonlar, neoplazi, atriyal miksomalar, nörofibromatoz ve fibromüsküler displazi dahil olmak üzere bir dizi enflamatuar olmayan vaskülopati, PSSSV'dekine benzer anjiyografik bulgulara neden olabilir. Bu nedenle, anjiyografinin özgüllüğü sınırlıdır (8).

Klinik bulgulara eşlik eden histopatolojik tanı mevcut ise "kesin" PSSSV'den bahsetmek mümkündür. Ancak invaziv bir yöntem olması sebebiyle beyin biyopsisi çok tercih edilmemektedir. Klinik bulgulara eşlik eden laboratuvar ve radyolojik bulgular varlığında histopatolojik tanı yapılmamış ise "olası" PSSSV tanısı konulabilir (8). Bizim vakamızda da benzer şekilde klinik, laboratuar, BOS incelemesi ve radyolojik bulgular ile PSSSV tanısı konulup steroid tedavisine başlandı. İnvaziv bir yöntem olan beyin biyopsisi tercih edilmedi.

Ayırıcı tanıda Reversible Serebral Vazokonsriksiyon Sendromu (RSVS) mutlaka araştırılmalıdır. RSVS, kliniğin daha ani başlaması, baş ağrısı bulgularının ön planda olması ve kranial lezyonların gerilemesi ile PSSSV'den ayrılır.Ayırıcı tanıda bir diğer önemli durumsistemik vaskülit ve enfeksiyon ekartasyonudur (14).Bizim vakamızda da klinik bulguların subakut-kronik bir seyirde olması, sistemik vaskülit bulgularının olmaması ve tüm vaskülit sonuçlarının negatif saptanması ve enfeksiyöz panelde hiçbir etkene rastlanmaması PSSSV tanısı için güçlü kanıtlar oluşturmuştur.

Sonuç olarak ilerleyici nörodefisit, konfüzyon-psikoz ve nöbet prezentasyonu ve multifokal tümör benzeri asimetrik, atipik lezyonları olan hastalarda PSSSV mutlaka akılda bulundurulmalıdır. Tanı konulup hızlıca immunsupresan tedavi başlanması hastalığın progresyonu önlemede ve iyi prognoz açısından oldukça önemlidir.

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Olgu Sunumu

Nüks gösteren odontojenik keratokist vakasında enükleasyon sonrası kriyoterapi uygulanması: olgu bildirimi

Performing cryotherapy after enucleation in recurrent odontogenic keratocyst case: case report

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Öz

Odontojenik keratokist; lokal agresif davranış, yüksek rekürrens oranı ve ayırıcı histolojik görünüm gibi özelliklere sahiptir. İlk olarak Philipsen tarafından 1956'da tanımlanmıştır. Odontojenik keratokist, dişlerin laminasından veya primordiyal odontojenik epitelden kaynaklanan iyi huylu, çenelerde uniloküler veya multiloküler kistik yapı şeklinde görülen, intraosseöz bir kist olarak tanımlanır. Hayatın ikinci ve dördüncü dekadlarında pik yapmakla birlikte her yaş grubunda görülebilir. Mandibulada görülme oranı maksillaya göre daha fazla olmakla beraber, mandibulada ortaya çıkan odontojenik keratokist vaka yüzdesi %65-83 civarındadır. Mandibulada lezyonların çoğu posterior bölgede, angulusta ve yükselen ramusta görülür. Odontojenik keratokist tedavisi çoğunlukla; küretajlı/küretajsız enükleasyon, marsupyalizasyon, periferal osteotomi, Carnoy solüsyonu ile kimyasal küretaj, kriyoterapi, elektrokoter ve segmental rezeksiyon ile yapılır.Bu çalışmada, 50 yaşındaki erkek hastanın sağ mandibula ramus bölgesinde lokalize, nüks göstermesi nedeni ile iki sene üç ay sonra enükleasyonun ardından kriyoterapi uygulanan odontojenik keratokist vakası sunulmuştur. Nüks sonrası enükleasyon ile birlikte kriyoterapi kullanılarak opere edilen hastadan 9 ay sonra alınan panoramik radyografide yeni kemik oluşumu gözlenmiş ve nükse dair herhangi bir semptom saptanmamıştır.

Anahtar Kelimeler: Kriyoterapi; nüks; odontojenik kist.

Abstract

Odontogenic keratocyst has unique features such as local aggressive behavior, high recurrence rate and differential histological appearance. It was first described by Philipsen in 1956. Odontogenic keratocyst is defined as an intraosseous cyst, which is seen as a benign, unilocular or multilocular cyst in the jaws, which is caused by the lamina of the teeth or primordial odontogenic epithelium. It can be seen in every age group, although it peaks in the second and fourth decades of life. Although the incidence of mandibula is higher than maxilla, the percentage of cases in the mandible is 65-83%. Most of the lesions in the mandible are seen in the posterior region, at the angulus and at the rising ramus. Odontogenic keratocyst treatment is usually performed by curettage / without curettage enucleation, marsupialization, peripheral osteotomy, Carnoy solution with chemical curettage, cryotherapy, electrocautery and segmental resection.In this study, a 50-year-old male patient was presented with odontogenic keratocyst who underwent cryotherapy after enucleation for two years and three months due to recurrence in the right mandibula ramus region.New bone formation was observed in the panoramic radiograph taken 9 months after the patient was treated using cryotherapy with enucleation after recurrence and no symptoms of relapse were detected.

Keywords: Cryotherapy; odontogenic cyst; recurrence.

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Giriş

Odontojenik keratokist(OK), dental lamina artıklarından ve diş formasyonu öncesinde gelişen mine organı benzeri primordial dokulardan kaynaklanan, odontojenik kökenli, benign, unikistik ve multikistik formları olan intraosseöz bir kisttir[1]. Bu lezyon, literatürde ilk kez 1876 yılında Mikulicz tarafından belirtilmiş olup, Philipsen tarafından 1956 yılında tanımlamıştır[1,2].

OK'leri diğer odontojenik kistlerden ayıran başlıca özellikleri; yüksek rekürrens oranına sahip olmaları, spesifik histopatolojik özellikleri ve agresif biyolojik davranışlarıdır[2]. Bu bahsedilen özellikleri nedeniyle OK'ler literatürde oldukça fazla yer edinmiştir. Bazı literatürlerde, kist epitelinin malign formasyonlara uğradığı ve ameloblastomaya dönüştüğü olgular takdim edilmiştir[3].

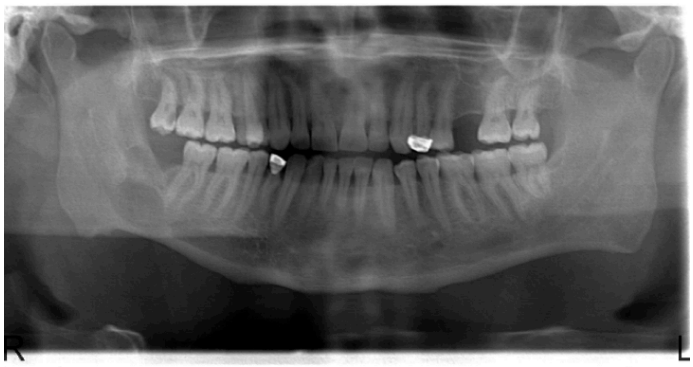
OK tedavisi hala tartışmalıdır. Tedaviler genellikle konvansiyonel ve agresif olarak sınıflandırılır. Konservatif tedavi çoğunlukla, küretajlı/küretajsız enükleasyonu ve marsupyalizasyonu içerir. Agresif tedavi ise genel olarak periferal osteotomi, Carnoy solüsyonu ile kimyasal küretaj, kriyoterapi, elektrokoter ve segmental rezeksiyonu içerir[4].

Kriyoterapi kelimesi, Yunanca "kriyos" (buz gibi, donmuş) ve terapi (tedavi) kelimelerinden türemiştir. Bu yöntemle lezyonlar dondurularak ortadan kaldırılmakta, fonksiyonel ve estetik olarak çok başarılı sonuçlara ulaşılmaktadır. Kriyoterapi günümüzde dermatoloji dışında tıbbın birçok alanında oldukça geniş bir uygulama alanı bulmaktadır. Kriyoterapide son yıllarda en çok sıvı nitrojen kullanılmaktadır. Kaynama noktası -195.6 santigrat derece olan likit nitrojen özellikle; benign ve malign kanserler, hemangiomlar, tonsillektomi, baş ve boyun cerrahisi, prostatektomi, Parkinson hastalığı ve hipofizektomide kullanılmaktadır[5].

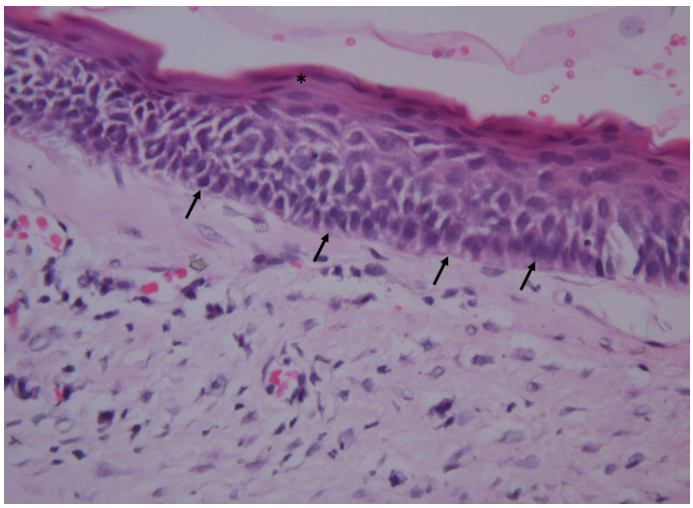
Enükleasyon ile birlikte uygulanan likit nitrojen kriyoterapisi tekniğinin amacı, görünür patolojik dokuyu çıkarmak, nüksetmeye yol açabilecek olası hücreleri dondurup öldürmek ve nekrotize etmektir. Likit nitrojen, hücreleri nekrotize etme özelliğine sahiptir ve osteojenik ve osteokondüktif özellikleri tahrip eden Carnoy çözeltisinin aksine inorganik kemik yapılarını korur. Kriyoterapi tekniği çevre anatomik yapıları ve kemiği korur ve daha iyi onarım sağlar. Ayrıca kemiğin inorganik yapısını korur ve patolojik kırıkları önleme amacıyla derhal rekonstrüksiyon yapılabilmesine imkan sağlar[6].

Olgu

Diş ağrısı şikayeti ile Gazi Üniversitesi Diş Hekimliği Fakültesi'ne Başvuran 46 yaşındaki erkek hastadan alınan panoramik radyografide sağ mandibula angulus bölgesinde iyi sınırlı, radyolüsent lezyon tespit edilmiş olup hasta Ağız, Diş ve Çene Cerrahisi Anabilim Dalı'na yönlendirilmiştir [Resim 1]. Hastadan alınan anamnezde sistemik ve genetik bir hastalığının olmadığı öğrenilmiştir. Yapılan intraoral ve ekstraoral muayenelerde iltihap, ekspansiyon ve ağrı gibi herhangi bir klinik semptom tespit edilmemiştir. Kistik lezyonun lokal anestezi altında mukoperiosteal flep kaldırılarak enükle edilmesiyle elde edilen örnekler Gazi Üniversitesi Diş Hekimliği Fakültesi Oral Patoloji Anabilim Dalı'na gönderilmiştir. Histopatolojik incelemede yüzeyi parakeratinize, retesiz, bazal tabaka hücreleri çit tarzında dizilim gösteren odontojenik çok katlı yassı epitel ile döşeli kistik lezyona parakeratinize odontojenik keratokist tanısı konmuştur [Resim 2].

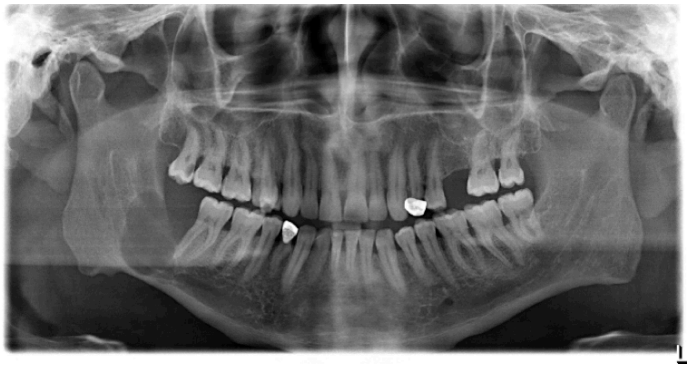


Resim 1. Hastanın ilk operasyondan önceki panoramik radyografisi

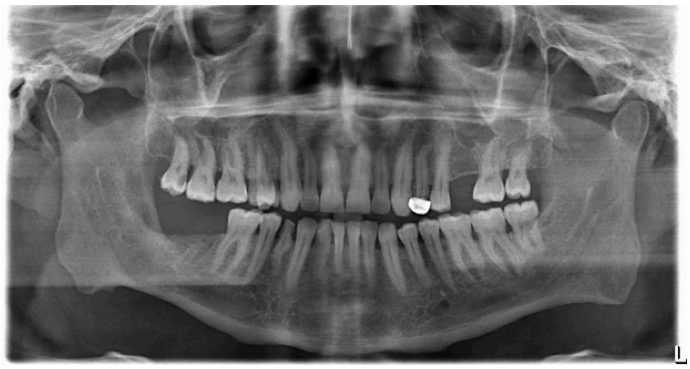


Resim 2. Yüzeyi parakeratinize (*) bazal tabaka hücreleri ters polarizasyona sahip (ok), retesiz odontojenik çok katlı yassı epitel ile döşeli kistik lezyon (HE x400)

Operasyon sonrası kontrole gelmeyi ihmal eden hasta, ilgili bölgesinde ağrı meydana gelmesi nedeniyle 2 sene sonra kliniğimize yeniden başvurmuş ve alınan kontrol filminde lezyonun nüks ettiği ve boyutunun eskiye nazaran daha da büyüdüğü tespit edilmiştir [Resim 3]. Lokal anestezi altında gerçekleştirilen ikinci operasyonda; lezyona komşu 47 numaralı dişin çekiminin ardından ilgili bölgeden mukoperiosteal flep kaldırılarak,enükleasyon ve küretaj ile beraber nervus alveolaris inferioru koruma maksadıyla kist kavitesinin tabanı hariç yalnızca duvarlarınalikit nitrojen kriyoterapisiuygulanmıştır.İkinci ameliyat materyali de parakeratinize OK tanısı alan hastadan 9 ay sonra alınan kontrol filminde sağlıklı yeni kemik oluşumu gözlenmiş olup herhangi bir semptom saptanmamıştır [Resim 4].



Resim 3. Hastadan 2 sene sonra alınan panoramik radyografi



Resim 4. Hastanın enükleasyon sonrası kriyoterapi uygulanarak yapılan ikinci operasyondan sonraki panoramik radyografisi

Tartışma

OK birçok benzersiz klinik ve histolojik özelliğe sahip; iyi huylu, gelişimsel bir odontojenik kisttir[7]. OK'nin genişbir görülme yaş aralığı vardır, ancak çoğunlukla yaşamın ikinci ve dördüncü dekatlarında görülür.Bu lezyonlar erkeklerde daha sık görülür[8]. Vakaların %70'inden fazlası, özellikle mandibuler molar, ramus ve angulus bölgelerinde görülür[9]. Mandibulada görülme oranı maksillaya göre daha fazla olmakla beraber, mandibulada ortaya çıkan OK vaka yüzdesi % 65-83 civarındadır. Bu lezyon, mandibulada herhangi bir bölgede meydana gelebilir; ancak lezyonların çoğu posterior bölgede, angulusta ve yükselen ramusta görülür[10]. Maksilla anterior, maksiller sinüs ve maksiller posterior gibi diğer bölgelerde görüldüğü de bildirilmiştir[9].OK'ler ve diğer çene kistleri arasındaki temel farklardan biri, OK'nin medüller kemik içinde sinsice büyümesi ve klinik semptomlara neden olmamasıdır[7]. Sunulan bu çalışmadaki hasta 46 yaşında erkektir ve lezyon mandibula sağ ramusta tespit edilmiştir. İlk operasyondan sonra kontrole gelmeyen hasta, ağrısının olmasından dolayı hastanemize 2 sene sonra tekrar başvurmuş ve lezyonun nüks ettiği tespit edilmiştir.

OK, dental lamina hücrelerinden gelişir. Histopatolojik olarak OK, tipik olarak tek parça halinde kemikten enükleasyonu zor olan ve lifli, içinde küçük uydu kistleri bulunan, ince ve fibröz bir kist epitel duvarı içerir. Bu nedenle OK'ler genellikle tedaviden sonra nüks etme eğilimindedir[11]. Bu lezyonların nüks oranlarının %2.5 ile %62.5 arasında olduğu ayrıca multiple odontojenik keratokistlerin Nevoid Bazal Hücreli Karsinoma Sendromu (NBHKS) ile ilgili olabileceği de literatürlerde sunulmuştur[12]. Yapılan histopatoloik inceleme sonucu lezyona parakeratinize odontojenik keratokist tanısı konmuştur.

OK'ler; epitelyal kökenli kistler olup, çenelerde görülen kistlerin yaklaşık %11'ini oluşturmaktadır. Bu kistler çenelerde görülen birçok kist ve tümör gibi çenelerde ekspansiyon yapmadan ve bulundukları bölgede enfeksiyona sebebiyet vermeden hastalar tarafından farkedilmezler. Ekspansiyon konusundaki en kritik belirteç, kemikte yaptığı ekspansiyonun, alınan radyograflarda tespit edilen boyutlarına göre çok daha az miktarda olmasıdır[13]. Radyografik olarak OK, düzgün ve sıklıkla kortikal kenarlara sahip iyi izlenebilen uniloküler veya multiloküler görünüm sergiler[11]. Bu lezyonlar, kemiğin medüller kavitesi içinde hastanın rahatsızlık duyacağı herhangi bir semptoma sebebiyet vermeden, çoğu kez dışardan gözlenebilecek ekspansiyona sebep olmadan, antero posterior yönde büyüme eğilimindedirler[7,11,14]. Bizim vakamızdan alınan panoramik radyografilerde lezyon uniloküler ve iyi sınırlı olarak tespit edilmiştir. Ekspansiyon ve enfeksiyon bulgusu yoktur. Lezyonun nüksü tespit edilene kadar geçen sürede anetro posterior yönde genişlediği tespit edilmiştir.

OK'ler için çeşitli tedavi seçenekleri tanımlanmıştır. Walid Ahmed Abdullah 2011 yılında bir çalışmasında,OK'lerin cerrahi tedavisini; dekompresyon ve marsupyalizasyon, tek başına ya da başka yardımcı uygulamalarla enükleasyon, enükleasyon ve Carnoy solüsyonu ile kemik defektinin tedavisi, enükleasyon ve sıvı nitrojen kriyoterapisi, çenenin devamlılığını koruyarak ya da bozarak uygulanan blok rezeksiyon olarak sınıflandırmıştır[11]. Tedavi; lezyonun ilgili bölgede ortaya çıkmasından itibaren geçen süre, yeri ve büyüklüğü gibi bazı faktörlere ve lezyonun primer olması veya nüks etmesi durumuna bağlıdır. "Periferik ostektomi" ile total enükleasyon, lezyon tekrarlamadıkça veya önemli yumuşak doku invazyonu olmadıkça, çoğu OK için tercih edilen tedavi yöntemidir[15]. Sunduğumuz hastanın tedavisinde enükleasyon ve likitnitrojen kriyoterapisi yönemini tercih ettik ve 9 ay sonra alınan kontrol filminde başarılı sonuç aldığımızı kaydettik.

OK tedavisi için enükleasyondan sonra kemik duvarlarına kriyoterapi uygulanması ilk olarak 1975 yılında Bradley ve Fisher tarafından tanımlanmıştır[16]. Yapılan bir çalışmada 139 OK vakasının %25'inin uydu kisti içerdiği bildirilmiştir[17]. Kriyoterapi uygulanarak kemik doku içerisinde kalan epitel artıklarının ve uydu kistlerinin dondurularak öldürülmesi amaçlanmaktadır[12].

Zhou ve arkadaşlarının 2006 yılında yaptıkları bir çalışmada, rekürrens gösteren 10 hastaya, enükleasyon yöntemi ile birlikte likit nitrojen içeren kriyoterapi yapıldığı ve 5 yıllık hasta takiplerinde hiçbir vakada nüks görülmediği rapor edilmiştir[18].

Schmidt ve Pogrel'in 2001 yılında yayınladıkları bir çalışmada, OK'i olan 26 hastayı enükleasyon ve likit nitrojen kriyoterapisi ile tedavi ettikleri ve rekürrensin yalnızca 3 hastada (%11.5) görüldüğü bildirilmiştir[19].

Ayrıca Eduardo Luis de Souza Cruz ve arkadaşları 2017 yılında yayınladıkları bir çalışmada; propan, bütan ve izobütan gaz karışımına sahip kriyoterapiyi, sıvı nitrojene alternatif olarak göstermişler ve OK tanısı alan 10 hastanın 8'inde başarılı sonuç aldıklarını ve nüks gözlemediklerini bildirmişlerdir. Hastaların hiçbirinde patolojik fraktür ve enfeksiyon görülmemiştir[20].

Sonuç

Mandibula ramus bölgesinde lokalize, nüks göstermesi nedeni ile iki sene üç ay sonra enükleasyonun ardından kriyoterapi uygulanan odontojenik keratokist vakası sunulmuştur. Nüks sonrası enükleasyon ile birlikte kriyoterapi kullanılarak opere edilen hastadan 9 ay sonra alınan panoramik radyografide yeni kemik oluşumu gözlenmiş ve nükse dair bir semptom saptanmamıştır.

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Letter To Editor

Is yoga style crossed leg sitting position best for neuraxial analgesia and/or anaesthesia for delivery?

Yoga tarzı bağdaş oturuşu, nöroksiyal analjezi ve / veya doğum anestezi için en iyi pozisyon mudur?

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The patient's position including standard traditional sitting position (TSP) or lateral position during insertion of the epidural catheter plays a major role in the success of labour epidural analgesia [1-3]. Recently, crossed-legged sitting position (CLSP) has been recommended as an alternative for the administration of regional analgesia for labour [4].The authors compared the cross-legged sitting position (CLSP) with traditional sitting position (TSP) in performing epidural analgesia for labor to elucidate which is an easier option for placing an epidural catheter. The rate of successful epidural insertion at the first attempt was higher in CLSP group than that of TSP group (88% vs 44%). The landmark, needle-bone contact and comfort during positioning were comparable between the groups [4]. In an earlier study, maternal and neonatal effects of either TSP or lateral decubitus position to perform combined spinal epidural (CSE) anaesthesia in otherwise healthy parturients underwent elective caesarean section (CS) were investigated [2]. Rate of performing CSE at the 1st attempt was higher in the TSP than that of lateral decubitus position (73.3% vs 40%). Incidence of paresthesia due to Whitacre spinal needle used for CSE was less in the TSP than that of lateral decubitus (3.3% vs 20%) [2]. Thus, choice of CLSP over TSP for epidural block during labor analgesia and TSP over lateral decubitus for CSE for CS seem to be better in terms of ease of insertion [2,4]. In a study including 60 pregnant women with lumbopelvic pain practicing yoga in CLSP had lower pain compared to standard posture exercise [5].

Yet to our knowledge, there is no study that primarily compares the three positions (TSP, CLSP or lateral decubitus) altogether to demonstrate the ease of insertion of epidural catheter for vaginal and caesarean delivery to provide analgesia and/or anesthesia. If CLSP could have been one of the competitors of the two studies [2,4], we would be able to suggest one position over another without any hesitation. Despite aforementioned concerns, either conventional lumbar epidural or CSE particularly for delivery in CLSP for a term parturient might be considered as advantageous due to mainly ease of performing and comfort of the parturient in the CLSP.

Keywords: cross leg sitting position; neuraxial analgesia; epidural; yoga

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TURKISH JOURNAL of CLINICS and LABORATORY

Türk Klinik ve Laboratuvar Dergisi

Turkish Journal of Clinics and Laboratory - Türk Klinik ve Laboratuvar Dergisi

Tıp dergilerine gönderilecek makalelerin standart gereksinmeleri ile ilgili tüm bilgileri www.icmje.org internet adresinde bulabilirsiniz

Amaç ve kapsam: "Turkish Journal of Clinics and Laboratory", hakemli, açık erişimli ve periyodik olarak çıkan, DNT Ortadoğu Yayıncılık A.Ş. ye ait bir dergidir. Hedefimiz uluslararası bir tabanda hastalıkların teşhis ve tedavisinde yenilikler içeren yüksek kalitede bilimsel makaleler yayınlamaktır. Yılda dört kez çıkan bir bilimsel bir tıp dergisidir. Hakemli bir dergi olarak gelen yazılar konsültanlar tarafından, öncelikle, biyomedikal makalelere ait Uluslararası Tıp Dergileri Editörleri Komitesi (www.icmje.org adresinden ulaşılabilir) tarafından tanımlanan standart gereksinimler ile ilgili ortak kurallara uygunluğu açısından değerlendirilir. Tıbbın her dalı ile ilgili retrospektif/prospektif klinik ve laboratuar çalışmalar, ilginç olgu sunumları, davet üzerine yazılan derlemeler, editöre mektuplar, orijinal görüntüler, kısa raporlar ve cerrahi teknik yazılarıları yayımlayan bilimsel, uluslar arası hakemli bir dergidir. Başka bir dergide yayımlanmış veya değerlendirilmek üzere gönderilmiş yazılar veya dergi kurallarına göre hazırlanmamış yazılar değerlendirme için kabul edilmez.

On-line makale gönderimi: Tüm yazışmalar ve yazı gönderimleri dergipark üzerinden http://dergipark.gov.tr/tjcl yapılmalıdır. Yazı gönderimi için detaylı bilgi bu internet adresinden edinilebilir. Gönderilen her yazı için özel bir numara verilecek ve yazının alındığı e-posta yolu ile teyid edilecektir. Makalelerin "full-text" pdf formuna http://dergipark.gov.tr/tjcl linkinden ulaşılabilir.

Açık erişim politikası: Turkish Journal of Clinics and Laboratory açık erişimi olan bir dergidir. Kullanıcı lar yazıların tam metnine ulaşabilir, kaynak gösterilerek tüm makaleler bilimsel çalışmalarda kullanılabilir.

Aşağıdaki rehber dergiye gönderilen makalelerde aranan standartları göstermektedir. Bu uluslararası format, makale değerlendirme ve basım aşamalarının hızla yapılmasını sağlayacaktır.

Yazarlara Bilgi: Yazıların tüm bilimsel sorumluluğunu yazar(lar)a aittir. Editör, yardımcı editör ve yayıncı dergide yayınlanan yazılar için herhangi bir sorumluluk kabul etmez.

Dergi adının kısaltması: Turk J Clin Lab

Yazışma adresi: Yazılar e-mail yoluyla sorumlu yazar tarafından, Dergipark ta yer alan Turkish Journal of Clinics and Laboratory linkine girip kayıt olduktan sonra gönderilmelidir.

Makale dili: Makale dili Türkçe ve İngilizcedir. İngilizce makaleler gönderilmeden önce profesyonel bir dil uzmanı tarafından kontrol edilmelidir. Yazıdaki yazım ve gramer hataları içerik değişmeyecek şekilde İngilizce dil danışmanı tarafından düzeltilebilir. Türkçe yazılan yazılarda düzgün bir Türkçe kullanımı önemlidir. Bu amaçla, Türk Dil Kurumu Sözlük ve Yazım Kılavuzu yazım dilinde esas alınmalıdır.

Makalenin başka bir yerde yayımlanmamıştır ibaresi: Her yazar makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, editöre sunum sayfasında belirtmelidirler. 400 kelimeden az özetler kapsam dışıdır. Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal, vb.) yazarlara aittir.

Değerlendirme: Dergiye gönderilen yazılar format ve plagiarism açısından değerlendirilir. Formata uygun olmayan yazılar değerlendirilmeden sorumlu yazara geri gönderilir. Bu tarz bir zaman kaybının olmaması için yazım kuralları gözden geçirilmelidir. Basım için gönderilen tüm yazılar iki veya daha fazla yerli/yabancı hakem tarafından değerlendirilir. Makalelerin değerlendirilmesi, bilimsel önemi, orijinalliği göz önüne alınarak yapılır. Yayıma kabul edilen yazılar editörler kurulu tarafından içerik değiştirilmeden yazarlara haber verilerek yeniden düzenlenebilir. Makalenin dergiye gönderilmesi veya basıma kabul edilmesi sonrası isim sırası değiştirilemez, yazar ismi eklenip çıkartılamaz.

Basıma kabul edilmesi: Editör ve hakemlerin uygunluk vermesi sonrası makalenin gönderim tarihi esas alınarak basım sırasına alınır. Her yazı için bir doi numarası alınır.

Yayın hakları devri: http:/www.dergipark.ulakbim.gov.tr/tjclinlab adresi üzerinden online olarak gönderilmelidir. 1976 Copyright Act'e göre, yayımlanmak üzere kabul edilen yazıların her türlü yayın hakkı yayıncıya aittir.

Makale genel yazım kuralları: Yazılar Microsoft Word programı (7.0 ve üst versiyon) ile çift satır aralıklı ve 12 punto olarak, her sayfanın iki yanında ve alt ve üst kısmında 2,5 cm boşluk bırakılarak yazılmalıdır. Yazı stili Times New roman olmalıdır. "System International" (SI) unitler kullanılmalıdır. Şekil tablo ve grafikler metin içinde refere edilmelidir. Kısaltmalar, kelimenin ilk geçtiği yerde parantez içinde verilmelidir. Türkçe makalelerde %50 bitişik yazılmalı, aynı şekilde İngilizcelerde de 50% bitişik olmalıdır. Türkçede ondalık sayılarda virgül kullanılmalı (55,78) İngilizce yazılarda nokta (55.78) kullanılmalıdır. Derleme 4000, orijinal çalışma 2500, olgu sunumu 1200, editöre mektup 500 kelimeyi geçmemelidir. Özet sayfasından sonraki sayfalar numaralandırılmalıdır.

Yazının bölümleri

1. Sunum sayfası: Yazının Turkish Journal of Clinics and Laboratory 'de yayınlanmak üzere değerlendirilmesi isteğinin belirtildiği, makalenin sorumlu yazarı tarafından dergi editörüne hitaben gönderdiği yazıdır. Bu kısımda makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, maddi destek ve çıkar ilişkisi durumu belirtmelidir.

2. Başlık sayfası: Sayfa başında gönderilen makalenin kategorisi belirtilmedir (Klinik analiz, orijinal çalışma, deneysel çalışma, olgu sunumu vs).

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir. Tüm yazarların ad ve soyadları yazıldıktan sonra üst simge ile 1'den itibaren numaralandırılıp, unvanları, çalıştıkları kurum, klinik ve şehir yazar isimleri altına eklenmelidir.

Bu sayfada "sorumlu yazar" belirtilmeli isim, açık adres, telefon ve e-posta bilgileri eklenmelidir.

Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir.

3. Makale dosyası: (Yazar ve kurum isimleri bulunmamalıdır)

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir.

Özet: Türkçe ve İngilizce yazılmalıdır. Orijinal çalışmalarda özetler, Amaç (Aim), Gereç ve Yöntemler (Material and Methods), Bulgular (Results) ve Sonuçlar (Conclusion) bölümlerine ayrılmalı ve 250 sözcüğü geçmemelidir. Olgu sunumları ve benzerlerinde özetler, kısa ve tek paragraflık olmalıdır (150 kelime), Derlemelerde 300 kelimeyi geçmemelidir.

Anahtar kelimeler: Türkçe ve İngilizce özetlerin sonlarında bulunmalıdır. En az 3 en fazla 6 adet yazılmalıdır. Kelimeler birbirlerinden noktalı virgül ile ayrılmalıdır. İngilizce anahtar kelimeler "Medical Subject Headings (MESH)" e uygun olarak verilmelidir. (www.nlm.nih.gov/mesh/MBrowser.html). Türkçe anahtar kelimeler "Türkiye Bilim Terimleri' ne uygun olarak verilmelidir (www.bilimterimleri.com). Bulunamaması durumunda birebir Türkçe tercümesi verilmelidir.

Metin bölümleri: Orijinal makaleler; Giriş, Gereç ve Yöntemler, Bulgular, Tartışma olarak düzenlenmelidir. Olgu sunumları; Giriş, Olgu sunumu, Tartışma olarak düzenlenmelidir. Şekil, fotoğraf, tablo ve grafiklerin metin içinde geçtiği yerler ilgili cümlenin sonunda belirtilmeli metin içine yerleştirilmemelidir. Kullanılan kısaltmalar altındaki açıklamada belirtilmelidir. Daha önce basılmış şekil, resim, tablo ve grafik kullanılmış ise yazılı izin alınmalıdır ve bu izin açıklama olarak şekil, resim, tablo ve grafik açıklamasında belirtilmelidir. Tablolar metin sonuna eklenmelidir. Resimler/fotoğraf kalitesi en az 300dpi olmalıdır.

Etik kurallar: Klinik araştırmaların protokolü etik komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda, "Yöntem ve Gereçler" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklerasyonuna (www.wma.net/e/policy/b3.htm) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm insanların bilgilendirilmiş onam formunu imzaladığı metin içinde belirtilmelidir. Turkish Journal of Clinics and Laboratory gönderilen yazıların Helsinki Deklarasyonuna uygun olarak yapıldığını, kurumsal etik ve yasal izinlerin alındığını varsayacak ve bu konuda sorumluluk kabul etmeyecektir.

Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntemler bölümünde Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır.

Teşekkür yazısı: Varsa kaynaklardan sonra yazılmalıdır.

Maddi destek ve çıkar ilişkisi: Makale sonunda varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve varsa bu kuruluşların yazarlarla olan çıkar ilişkileri belirtilmelidir. (Olmaması durumu da "Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur" şeklinde yazılmalıdır.

Kaynaklar: Kaynaklar makalede geliş sırasına göre yazılmalıdır. Kaynaktaki yazar sayısı 6 veya daha az ise tüm yazarlar belirtilmeli, 7 veya daha fazla ise ilk 3 isim yazılıp ve ark. ("et al") eklenmelidir. Kaynak yazımı için kullanılan format Index Medicus'ta belirtilen şekilde olmalıdır (www.icmje.org). Kaynak listesinde yalnızca yayınlanmış ya da yayınlanması kabul edilmiş veya DOI numarası almış çalışmalar yer almalıdır. Dergi kısaltmaları "Cumulated Index Medicus" ta kullanılan stile uymalıdır. Kaynak sayısının araştırmalarda 25 ve derlemelerde 60, olgu sunumlarında 10, editöre mektupta 5 ile sınırlandırılmasına özen gösterilmelidir. Kaynaklar metinde cümle sonunda nokta işaretinden hemen önce köşeli parantez kullanılarak belirtilmelidir. Örneğin [4,5]. Kaynakların doğruluğundan yazar(lar) sorumludur. Yerli ve yabancı kaynakların sentezine önem verilmelidir.

Şekil ve tablo başlıkları: Başlıklar kaynaklardan sonra yazılmalıdır.

4. Şekiller: Her biri ayrı bir görüntü dosyası (jpg) olarak gönderilmelidir.

Makalenin basıma kabulünden sonra "Dizginin ilk düzeltme nüshası" sorumlu yazara e-mail yoluyla gönderilecektir. Bu metinde sadece yazım hataları düzeltilecek, ekleme çıkartma yapılmayacaktır. Sorumlu yazar düzeltmeleri 2 gün içinde bir dosya halinde e-mail ile yayın idare merkezine bildirecektir.

Kaynak Yazım Örnekleri

Dergilerden yapılan alıntı;

Özpolat B, Gürpınar ÖA, Ayva EŞ, Gazyağcı S, Niyaz M. The effect of Basic Fibroblast Growth Factor and adipose tissue derived mesenchymal stem cells on wound healing, epithelization and angiogenesis in a tracheal resection and end to end anastomosis rat model. Turk Gogus Kalp Dama 2013; 21: 1010-19.

Kitaptan yapılan alıntı;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Tek yazar ve editörü olan kitaptan alıntı;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams&Wilkins; 1996: 46-60.

Çoklu yazar ve editörü olan kitaptan alıntı;

Schulz JE, Parran T Jr: Principles of identification and intervention. In:Principles of Addicton Medicine, Graham AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams&Wilkins; 1998:1-10.

Eğer editör aynı zamanda kitap içinde bölüm yazarı ise;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag;1988:45-67.

Doktora/Lisans Tezinden alıntı;

Kılıç C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Bir internet sitesinden alıntı;

Sitenin adı, URL adresi, yazar adları, ulaşım tarihi detaylı olarak verilmelidir.

DOI numarası vermek;

Joos S, Musselmann B, Szecsenyi J. Integration of Complementary and Alternative Medicine into Family Practice in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

Diğer referans stilleri için "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References" sayfasını ziyaret ediniz.

Bilimsel sorumluluk beyanı: Kabul edilen bir makalenin yayınlanmasından önce her yazar, araştırmaya, içeriğinin sorumluluğunu paylaşmaya yetecek boyutta katıldığını beyan etmelidir. Bu katılım şu konularda olabilir:

a. Deneylerin konsept ve dizaynlarının oluşturulması, veya verilerin toplanması, analizi ya da ifade edilmesi;

b. Makalenin taslağının hazırlanması veya bilimsel içeriğinin gözden geçirilmesi

c. Makalenin basılmaya hazır son halinin onaylanması.

Yazının bir başka yere yayın için gönderilmediğinin beyanı: "Bu çalışmanın içindeki materyalin tamamı ya da bir kısmının daha önce herhangi bir yerde yayınlanmadığını, ve halihazırda da yayın için başka bir yerde değerlendirilmede olmadığını beyan ederim. Bu, 400 kelimeye kadar olan özetler hariç, sempozyumlar, bilgi aktarımları, kitaplar, davet üzerine yazılan makaleler, elektronik formatta gönderimler ve her türden ön bildirileri içerir."

Sponsorluk beyanı: Yazarlar aşağıda belirtilen alanlarda, varsa çalışmaya sponsorluk edenlerin rollerini beyan etmelidirler:

1. Çalışmanın dizaynı

2. Veri toplanması, analizi ve sonuçların yorumlanması

3. Raporun yazılması

Kontrol listesi:

1. Editöre sunum sayfası (Sorumlu yazar tarafından yazılmış olmalıdır)

2. Başlık sayfası (Makale başlığı/kısa başlık Türkçe ve İngilizce, Yazarlar, kurumları, sorumlu yazar posta adresi, tüm yazarların e-mail adresleri, sorumlu yazarın telefon numarası)

3. Makalenin metin sayfası (Makale başlığı/kısa başlık Türkçe ve İngilizce, Özet/anahtar kelimeler, Summary/keywords, makale metni, kaynaklar, tablo ve şekil başlıkları, tablolar, şekiller)

4. Tablo ve grafikler metin içinde olmalıdır.

5. Şekiller (En az 300 dpi çözünürlükte) ayrı bir veya daha fazla dosya halinde gönderilmelidir.