Postoperative Venous Thrombosis: Frequency and Risk Factors in Patients Undergoing Isolated Coronary Artery Bypass Graft Surgery

İzole Koroner Arter Baypas Greft Cerrahisi Uygulanan Hastalarda Postoperatif Venöz Tromboz: Sıklık ve Risk Faktörleri

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ABSTRACT Objective: In this study, we investigated whether there was any difference between the extremity that was used for harvesting saphenous vein and the contralateral one with regard to frequency of venous thrombosis (VT) and the risk factors in patients who underwent coronary artery bypass graft (CABG) procedure. **Material and Methods:** This prospective study included 102 patients who underwent isolated CABG operation. Frequency of VT was investigated in extremity that was used for harvesting saphenous vein and the contralateral one. A total of 102 patients (86 males and 16 females; mean age: 63 ± 9.99 years, ranging between 39 - 79 years) underwent CABG operation in our clinic between July 2013 and December 2014. The patients were examined with Doppler ultrasonography on postoperative day 5 to investigate development of VT. **Results:** VT was detected in the extremity from which saphenous vein was harvested in 4 (3.92%) of 102 patients. No VT was detected in contralateral extremities. There was no statistically significant difference in terms of VT between the extremity from which saphenous vein is harvested and the contralateral extremity ($p>0.05$). In 24 (23.5%) patients, acute thrombosis was detected at great saphenous vein (GSV) stump in the saphenous vein-harvested extremity, and it was statistically significant ($p<0.001$). Male sex, body mass index and smoking were statistically significant parametes ($p <0.05$). **Conclusion:** In CABG patients, thrombosis showed statistically significant associations with being male, BMI, and being a smoker. We recommend the use of color venous Doppler USG as a non-invasive test in the postoperative period since subclinical VT may develop in the CABG patients.

Key Words: Coronary artery bypass; venous thrombosis; venous thromboembolism

ÖZET Amaç: Bu çalışmada izole koroner arter baypas greft (KABG) operasyonu uygulanan hastalarda safen ven grefti (SVG) alınan ve alınmayan ekstremiteler arasında venöz tromboz (VT) sıklığı ve risk faktörleri açısından fark olup olmadığı araştırıldı. **Gereç ve Yöntemler:** Çalışmaya izole KABG ameliyatı yapılan 102 hasta alındı. SVG alınan ekstremite ve alınmayan ekstremitede VT sıklığı ve risk faktörleri araştırıldı. Temmuz 2013 - Aralık 2014 tarihleri arasında, kliniğimizde KABG operasyonu uygulanan 102 hasta (86 erkek, 16 kadın; ortalama 63 ± 9,99 yıl; dağılım 39 – 79 yıl) prospektif olarak incelendi. Hastalara VT taraması amacı ile postoperatif 5. günde renkli Doppler ultrasonografi yapıldı. **Bulgular:** KABG yapılan 102 hastanın 4'ünde (%3,92) SVG hazırlanan ekstremitede VT tespit edildi. SVG çıkarılmayan kontralateral ekstremitede VT saptanmadı. SVG çıkarılan ve çıkarılmayan ekstremiteler karşılaştırıldığında istatistiksel olarak anlamlı fark yoktu ($p>0.05$). Yirmi dört hastada (%23,5) SVG çıkarılan bacakta vena safena magna güdüğünde akut tromboz tespit edildi. Bu sonuç istatistiksel açıdan anlamlıydı ($p<0,001$). Erkek cinsiyet, vücut kitle indeksi ve sigara içiciliği ile VT arasında istatistiksel olarak anlamlı ilişki saptandı ($p<0,05$). **Sonuç:** KABG uygulanan hastalarda VT gelişimi ile erkek cinsiyet, vücut kitle indeksi ve sigara içiciliği arasında istatiksel açıdan anlamlı ilişki saptandı. CABG hastalarında subklinik VT gelişebileceği için, postoperatif dönemde noninvazif bir test olan renkli venöz Doppler ultrasonografi yapılmasını öneriyoruz.

Anahtar Kelimeler: Koroner arter baypas; venöz tromboz; venöz tromboembolizm

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Open cardiac surgery is associated with numerous risk factors for deep vein thrombosis (DVT) development (e.g. general anesthesia, long duration of surgery, high number of manipulations in vascular structures during surgery, long hospital stay, immobilization, need for intensive care, etc.).[1-4] In coronary artery bypass grafting (CABG), risk factors for DVT development include obesity, hyperlipidemia, heavy smoking, cardiac failure, advanced age, female sex, pregnancy, oral contraceptive or hormone replacement therapy use and surgical operation performed in the lower extremities (e.g., saphenous vein harvesting).[1-5] Similar to other surgical procedures, DVT following cardiac surgery may lead to significant complications.[6] Venous thromboembolism (VTE) and pulmonary embolism (PE) are leading causes of mortality following cardiac surgery, and together are the fifth-most frequent cause of readmission to hospital following CABG.[7,8] Although DVT remains silent in most cases, its signs usually manifest within a few weeks of surgery.[5] The incidence of PE following cardiac surgery is 0.5–3.9%.[1,5,9] Despite aggressive prophylactic anticoagulant treatment, asymptomatic DVT was detected in 13% of the patients who underwent cardiac surgery.[10]

There are a few studies related to the incidence of DVT in the extremity used for harvesting saphenous vein and the contralateral one in patients who have undergone CABG.[6,7] However, to the best of our knowledge, this is the first prospective study that has investigated presence of any difference between the extremity used for harvesting saphenous vein and the contralateral one with regard to frequency of venous thrombosis (VT) and the risk factors in patients who underwent CABG operation.

MATERIALS AND METHODS

The present study was approved by the local Ethics Committee. Informed consents were obtained from all patients. The study was conducted in accordance with the principles of the Helsinki Declarationand all patients were willing to participate. We included 102 consecutive patients with coronary artery disease who underwent isolated CABG in our clinic between July 2013 and December 2014. None of the patients were given VTE prophylaxis. The risk factors and frequency of VT was investigated in the extremity used for harvesting saphenous vein and the contralateral one. Two groups were established in relation with development of VT: venous thrombosis group, and non-venous thrombosis group. Exclusion criteria were history of DVT or malignancy, and long-term use of oral anticoagulants or low-molecular-weight heparin for any other reason. The patients that developed postoperative atrial fibrillation and required prophylaxis were not included in the study.

All patients were evaluated for coagulation profile [activated partial thromboplastin time, partial thromboplastin time, international normalized ratio (INR), and thrombocyte count] prior to surgery. Surgery was postponed in patients who had abnormal coagulation profiles (INR > 1.5; thrombocyte count < 100,000) until the results returned to normal. No conditions causing hypercoagulability were detected in any of the patients.

The age and sex of the patients were recorded. Additionally, comorbidities (e.g. diabetes mellitus, smoking, chronic obstructive pulmonary disease, or chronic renal failure), intensive care unit (ICU) time, mobilization time, and the number of great saphenous vein (GSV) grafts used were analyzed.

Color flow duplex ultrasonography was done to all patients prior to surgery to confirm the preexistence of venous thromboemboli, and, it was done 5 days after CABG to determine VT development. The GSV stump and its tributaries at the saphenofemoral junction (SFJ) were examined in detail. Duplex ultrasonography was performed in supine position using an ultrasonographic scanner (Logiq E9; GE Healthcare, Little Chalfont, UK) and an 11–15 MHz linear probe by the same physician and at the same laboratory. The criteria used to detect thrombosis were non-compressibility of the vein on B-mode scanning and/or a filling defect on color flow imaging. Low-molecular-weight heparin was administered to the patients with thrombosis.

SURGICAL TECHNIQUE

The legs and groin were shaved, prepared, and draped in the operating room to avoid the skin preparation solution touching the diathermy plate, resulting in diathermy burns. All surgical procedures were performed by the same two cardiovascular surgeons. One surgeon harvested the saphenous vein graft while the other harvested the left mammarian artery and performed cannulation of the heart.

In all of the patients, the saphenous vein graft (SVG) was harvested via a a sufficient-length linear incision, made as long as the length of the saphenous graft, from the medial malleolus along with the course of the saphenous vein. Both the graft and venous collaterals at the side of the leg were tied with 4/0 silk sutures. Bleeding was controlled only by ligation along the dissection line. In all cases, the SVG was harvested from the right or left lower extremity. Following closure, the leg was wrapped with a sterile elastic bandage. After CABG, the extremity from which the saphenous vein had been harvested was compressed with an elastic bandage and the patient was mobilized early, and both lower extremities were compressed with compression stockings on the first postoperative day. We use antiaggregant (antiplatelet) agents to treat idiopathic patients with CABG.

STATISTICAL ANALYSIS

The data were recorded and analyzed using SPSS for Windows software (ver. 21.0; SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was accepted as statistically significant. Continuous variables were expressed as medians and interquartile range (25th - 75th percentile), and categorical variables were expressed as numbers and percentages. Mann-Whitney U-test and Chi-square test were performed to compare the thrombosis groups. Binary Logistic Regression was used to determine the risk factors for trombosis. Using the data obtained in our study, power analysis showed a 95% confidence interval and 94% power.

RESULTS

Between July 2013 and December 2014, 102 patients (86 males and 16 females with a mean age of 63 ± 9.99 years; age range: 39–79 years) underwent CABG in our clinic. In four (3.92%) of 102 patients, asymptomatic VT was detected at the extremity from which the saphenous vein was harvested ($p>0.05$). There was acute thrombosis in the popliteal vein in two patients, but only in the crural veins in the other patients. The first patient was 58 years old one who underwent bypass surgery in four vessels and harvesting of the saphenous vein (ICU stay time was 56 hours). The second patient was 58 years old, and underwent bypass surgery in three vessels and harvesting of the saphenous vein above the level of the knee (ICU stay time was 41 hours). The third one was a 64-year-old patient who underwent bypass surgery in four vessels and harvesting of the saphenous vein (ICU stay time was 38 hours). The final patient was 77 years old, and underwent bypass surgery in four vessels and harvesting of the saphenous vein (ICU stay time was 74 hours). No VT was detected in their contralateral extremities. In 24 (23.5%) patients, acute thrombosis was detected in the GSV stump in the leg from which the saphenous vein was harvested ($p<0.001$). In the thrombosed segments, the mean distance of the GSV stump from the harvest site was 35 mm. There was no thrombus extension from the sapheno-femoral junction to the common femoral vein in any of the cases.

There was no PE development or mortality in any of the patients who had stump thrombosis or VT. The demographic data of the patients are listed in Table 1, and the post-operative data are given in (Table 2).

The logistic regression analysis revealed that the BMI and cigarette smoking had statistically significant effects on the presence of thrombosis. It was realized that an increase in the BMI by one degree increased the risk for the presence of thrombosis by 1.44 times. It was identified that the risk for the presence of thrombosis was 4.4 times higher in smokers than it was in non-smokers. It was evident that other risk factors such as age, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, dyslipidemia, chronic kidney failure, Pulmonary arterial hypertension, malignity, duration of stay in intensive care unit, time of mo-

TABLE 1: Demographic and clinical characteristics of the patients.

	Thrombosis found (n = 28)	%	Thrombosis not found (n = 74)	%	P-value
Male	28	100	58	78.4	0.005*
Female	0	0	16	21.6	
DM	14	50	44	59.5	0.389
HT	14	50	50	67.6	0.069
Smoking	22	78.6	36	48.6	0.005*
COPD	4	14.3	22	29.7	0.11
Dyslipidemia	18	64.3	34	45.9	0.098
CRF	0	0	4	5.4	0.573
PAD	4	14.3	6	8.1	0.456

DM: diabetes mellitus; **HT:** hypertension; **COPD:** chronic obstructive pulmonary disease; **CRF**: chronic renal failure; **PAD:** peripheral arterial disease.

bilization, and the number of saphenous vein grafts used had no significant effects on the risk for thrombosis (Table 3).

DISCUSSION

In this study, we identified a statistically significant associations of thrombosis with being male, the BMI and being a smoker in patients that underwent isolated CABG. The logistic regression analysis revealed that the BMI and smoking had statistically significant effects on the presence of thrombosis. The risk for thrombosis increased by 1.44 times when the BMI increased by one unit, and it was 4.4 times higher in smokers than it was in non-smokers.

Although it was not found statistically significant, we found an increased risk of DVT in our study in the extremity in which saphenous vein harvested in the patients who did not receive VTE prophylaxis following CABG. There was asymptomatic DVT in the extremity in which saphenous vein harvesting was performed in 4 (3.92%) patients, and saphenous vein stump thrombosis (SVST) was observed in 24 (23.5%) of 102 patients who underwent CABG. No DVT was detected in the extremity contralateral to the saphenous vein harvesting site, and none of the patients developed PE. It has been reported that, although intraoperative anticoagulation does not prevent DVT development during the postoperative period, these patients should receive prophylactic DVT treatment during the perioperative period. It has been

TABLE 2: Postoperative data of the patients.

	Thrombosis Found (n=28) *Median (25-75 %)*	**Thrombosis Not Found (n=74)** *Median (25-75 %)*	**P value**
Age	63 (57-70)	66 (56.5-70.25)	0.707
ICU time (h)	45 (41-68)	46 (26-52.75)	0.519
The number of GSV grafts used	3 (2-4)	3 (2-3)	0.372
Mobilization time (h)	16 (9-20)	10 (8-18.25)	0.071
BMI	29.75 (27.685 – 30.63)	25.79 (23.97 – 27.95)	0.0001*

SD: standard deviation; **ICU:** intensive care unit; **GSV:** great saphenous vein; **BMI:** Body mass index.

TABLO 3: Risk factors with significant effects on thrombosis.

	Odds Ratio [Exp (B)]	**Std.Error**	**95% C.I.for EXP(B) Lower**	**Upper**	**p**
BMI	1.446	0.098	1.194	1.752	0.001
Smoking	4.407	0.576	1.426	13.615	0.010

BMI: Body mass index.

stated that, despite aggressive prophylactic treatment, the risk of silent DVT development is approximately 13% following cardiac surgery.[11] Ambrosettia et al. found the incidence of DVT as 17%, the incidence of proximal DVT as 2.6%, and the incidence of pulmonary embolism as 0.74%.[12] Additionally, half of their patients had DVT in the contralateral leg in which the saphenous vein was not harvested. [12] We found no DVT in the leg from which the saphenous vein was not harvested.

Some studies in scientific literature investigated the relationship between DVT and VTE.[13,14] It has been reported that cigarette smoking is an independent risk factor for VTE in middle aged men and women. In the same study, it has also been stated that non-smokers and people that quit smoking had the same VTE risk.[13] It has been suggested that the effect of smoking on VTE is more acute and dose-related. Cigarettes are procoagulants reduce fibrinolysis, and increase inflammation and blood viscosity. Smoking is also associated with increased Factor VIII and high plasma fibrinogen levels which are risk factors for VTE. These are the mechanisms behind the association of cigarettes with risk of VTE.[14] We found statistically significant difference between smoking and thrombus in our male patients ($p \leq 0.05$). All of 28 patients we detected thrombosis (CVST or DVT) were males, and the result was statistically significant ($p \leq 0.05$). In contrary to scientific literature, this finding may be attributed to the fact that most of the male patients (78.5%) were active smokers. In a previous study, the coexistence of smoking and thrombus was found to be significant only among the women who used oral contraceptives (OCS).[9] However, none of our female patients smoked or used OCS pills.

It has been reported that obesity, excessive weight gain, and a high body mass index (BMI) are associated with VTE. The association between the BMI and VTE is unclear in smokers. This is because most smokers have lower body weight than non-smokers. Therefore, the VTE risk is a significant condition in smokers even though they have lower body weight, and weight gain (BMI rise) will increase the risk of VTE.[14]

Symptomatic VTE and PE detection rates are low in patients undergoing CABG. The postoperative breathing difficulties observed in these patients is presumed to be due to atelectasis or left ventricular dysfunction.[16] During the first 30 days after CABG, some patients are lost due to sudden death, without identification of the sites of PE, or due to indeterminate and complex clinical conditions.[16] In patients who have undergone CABG, it may be difficult to identify DVT because complaints such as pain, cramps, tenderness and edema can already be present in the extremity from which the saphenous vein was harvested. Ligation of the proximal part of the saphenous vein after graft harvesting leaves this part of the vein as a stump, in which thrombosis may then develop. Labropoulos et al. [1] found SVST in 15% of patients who showed signs and symptoms of VTE following CABG; furthermore, signs and symptoms of PE were detected in five patients.[6] It has been proposed that the risk of superficial vein thrombosis (SVT) is increased after harvesting of the saphenous vein in CABG, and this, in turn, increases the risk for DVT.[17] SVST occurred in 24 (23.5%) patients in our study. The mean distance between the GSV stumps and the harvesting site was 35 mm in the thrombosed segments, and no VTE, PE or mortality occurred in any of the patients with thrombosis.

Rarely, DVT is suspected when signs are present in the contralateral extremity. DVT does not manifest clinically in many patients, and the incidence of asymptomatic DVT can vary depending on the diagnostic method used, and on whether prophylaxis is administered. VTE prophylaxis in patients undergoing cardiac surgery includes pharmacological and mechanical treatments. Pharmacoprophylaxis involves administration of subcuta neous low-molecular-weight heparin (LMWH), whereas mechanical prophylaxis consists of early mobilization and elastic bandage or medium-pressure (20–30 mmHg) compression stockings to provide external compression.[7] In this study, although all patients used compression stockings in the early phase, DVT still developed in four patients.

In patients who did not receive VTE prophylaxis after vascular surgery, the incidence of post-

operative DVT was found as 21% using venography, and 15% using color Doppler ultrasonography.[18,19] Additionally, Samama et al. reported VTE incidence following aortic surgery as 27% with I^{125} labeled fibrinogen scanning, 4% with ultrasonography, and 18% with venography.[20]

Despite data supporting VTE prophylaxis following extra-cardiac surgery, the significance of post-CABG VTE prophylaxis is unclear.[5] Kolluri R et al. did a randomized double-blind study of fondaparinux versus placebo in 78 patients. They concluded that there was no benefit of prophylactic postoperative fondaparinux.[21] One other study has reported that the data of patients who received VTE prophylaxis and those who did not were compared following CABG, and no significant decrease was found in DVT in the patients who received prophylaxis. Additionally, in that study, 60% of the patients who underwent CABG did not receive prophylactic treatment, and the total incidence of VTE in these patients was less than 1%.[7]

Following recommendation is given in the ACCP guideline published in 2008: for patients undergoing CABG surgery, we recommend the use of thromboprophylaxis with LMWH, low dose unfractioned heparin (LDUH), or optimally used bilateral graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) (Grade 1C).[22] For patients undergoing CABG, we suggest the use of LMWH over LDUH (Grade 2B). For patients undergoing CABG with a high risk of bleeding, it is recommended that the optimal use of mechanical thromboprophylaxis with properly fitted bilateral GCS or IPC (Grade 1C).[22] We perform mechanical prophylaxis in our post-CABG patients in our clinic. Following CABG, the extremity from which the saphenous vein had been harvested was compressed with an elastic bandage and mobilized early, and the lower extremities were compressed with compression stockings on the first postoperative day.

CONCLUSION

In CABG patients, a statistically significant association of thrombosis was found with being male, the BMI and being a smoker and in patients that underwent isolated CABG. Because subclinical DVT occurs in most of these patients, color venous Doppler ultrasonography, which is a non-invasive test, should be used to monitor DVT progression in the postoperative period. We also suppose that patients undergoing CABG surgery should receive prophylactic DVT treatment (LMWH, LDUH, or compression stockings) in the perioperative period.

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This study was approved by the Local Ethics Committee of Pamukkale University Faculty of Medicine. The English in this document has been checked by at least two professional editors, both native speakers of English.

Conflict of Interest

Authors declared no conflict of interest or financial support.

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