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Off-pump coronary artery bypass grafting under clopidogrel treatment

Klopidogrel tedavisi altında atan kalpte koroner arter baypas greftleme

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ABSTRACT

Background: This study aims to compare the myocardial damage, inflammation and early postoperative morbidity and mortality following coronary artery bypass grafting in patients receiving and not receiving clopidogrel preoperatively.

Methods: Between April 2008 and May 2014, 91 patients who underwent isolated off-pump coronary artery bypass grafting due to acute coronary syndrome were included. Of these patients, 48 (13 females, 35 males; mean age 65.3±8.3 years; range, 52 to 79 years) received clopidogrel (clopidogrel group) and 43 (10 females, 33 males; mean age 63.1±7.7 years; range, 49 to 76 years) did not use clopidogrel before surgery (control group). Levels of creatine phosphokinase-myocardial band, troponin I, C-reactive protein, and the amount of intraoperative blood loss, transfusion requirements, postoperative chest tube output, the length of hospital and intensive care unit stay, postoperative ejection fraction, and the incidence of postoperative atrial fibrillation of both groups were analyzed.

Results: Postoperative troponin I and C-reactive protein levels were significantly lower in the clopidogrel group ($p<0.01$). A significantly lower number of patients in the clopidogrel group developed postoperative atrial fibrillation (13% vs 30%; $p<0.05$). However, postoperative chest tube output was significantly higher in the clopidogrel group, than the control group (883.2±256.9 mL vs 766.7±218.4 mL; $p<0.02$).

Conclusion: Although preoperative clopidogrel use increases chest tube output after emergency off-pump coronary artery bypass grafting, this increase is tolerable. During and after surgery, protective effects of clopidogrel can be achieved, such as reduced postoperative troponin levels and reduced postoperative atrial fibrillation development. Preoperative clopidogrel use does not preclude early coronary artery bypass grafting.

Keywords: Atrial fibrillation; clopidogrel; ejection fraction; myocardial protection; off-pump coronary artery bypass grafting.

ÖZ

Amaç: Bu çalışmada cerrahi öncesi klopidogrel kullanan ve kullanmayan hastalarda koroner arter baypas greftleme sonrası miyokard hasarı, enflamasyon ve ameliyat sonrası erken dönem morbidite ve mortalite karşılaştırıldı.

Çalışma planı: Nisan 2008 - Mayıs 2014 tarihleri arasında, akut koroner sendrom nedeniyle atan kalpte izole koroner arter baypas greftleme yapılan 91 hasta çalışmaya alındı. Bu hastaların 48'i (13 kadın, 35 erkek; ort. yaş 65.3±8.3 yıl; dağılım, 52-79 yıl) cerrahi öncesinde klopidogrel kullanmış (klopidogrel grubu) ve 43'ü (10 kadın, 33 erkek; ort. yaş 63.1±7.7 yıl; dağılım, 49-76 yıl) klopidogrel kullanmamıştı (kontrol grubu). Her iki grubun kreatin fosfokinaz-miyokard bandı, troponin I, C-reaktif protein düzeyleri ve ameliyat sırası kan kaybı, transfüzyon gereksinimi, ameliyat sonrası göğüs tüpü drenajı, hastanede ve yoğun bakım ünitesinde kalış süresi, ameliyat sonrası ejeksiyon fraksiyonu ve ameliyat sonrası atriyal fibrilasyon gelişme oranları incelendi.

Bulgular: Ameliyat sonrası troponin I ve C-reaktif protein düzeyleri klopidogrel grubunda anlamlı düzeyde düşüktü ($p<0.01$). Klopidogrel grubunda anlamlı düzeyde daha az sayıda hastada ameliyat sonrası atriyal fibrilasyon gelişti (%13'e karşın %30; $p<0.05$). Ancak, ameliyat sonrası göğüs tüpü drenajı, kontrol grubuna kıyasla, klopidogrel grubunda anlamlı düzeyde yüksekti (766.7±218.4 mL'ye kıyasla 883.2±256.9 mL; $p<0.02$).

Sonuç: Ameliyat öncesi klopidogrel kullanımı, acil atan kalpte koroner arter baypas greftleme sonrasında göğüs tüpü drenajını artırsa da, bu artış kabul edilebilir düzeydedir. Cerrahi sırasında ve sonrasında, klopidogrelin ameliyat sonrası troponin düzeylerinde düşüş ve ameliyat sonrası atriyal fibrilasyon gelişiminde azalma gibi, miyokard koruyucu etkileri elde edilebilir. Ameliyat öncesi klopidogrel kullanımı, erken dönemde koroner arter baypas greftleme yapılması önünde engel teşkil etmemektedir.

Anahtar sözcükler: Atriyal fibrilasyon; klopidogrel; ejeksiyon fraksiyonu; miyokard koruma; atan kalpte koroner arter baypas greftleme.

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Several reports have shown that clopidogrel reduces the risks of cardiovascular death, myocardial infarction (MI), cerebrovascular accidents, and recurrent ischemic events in patients with acute coronary syndrome (ACS).[1,2] Clopidogrel have been established, in combination with aspirin, as the gold standard for stent thrombosis prophylaxis.[2] Many emergency physicians, internists, and cardiologists aggressively prescribe clopidogrel for prophylactic antiplatelet therapy.[1,2] A proportion of these patients will subsequently need urgent surgical revascularization, and this has become a concern for both cardiac surgeons and anesthesiologists in patients requiring coronary artery bypass grafting (CABG).[1,3]

A number of studies have reported that patients exposed to clopidogrel experience markedly increased postoperative bleeding and transfusion requirements after CABG surgery.[1-3] The timing of surgery in this subgroup of patients still remains controversial. Compared to coronary surgery under cardiopulmonary bypass (CPB), off-pump coronary artery bypass grafting (OPCABG) is associated with a reduced frequency of inflammatory and hemorrhagic disorders.[4] We believe that clopidogrel may possibly reduce these advantages of OPCABG by increasing perioperative hemorrhagic complications.

In this study, we aimed to compare the myocardial damage, inflammation and early postoperative morbidity and mortality following OPCABG in patients receiving and not receiving clopidogrel preoperatively.

PATIENTS AND METHODS

This observational, prospective study was approved by the local Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Between April 2008 and May 2014, a total of 91 patients who underwent urgent OPCABG due to ACS were included. The clopidogrel group included 48 patients (13 females, 35 males; mean age 65.3±8.3 years; range, 52 to 79 years) who were on a daily oral regimen of 75 mg clopidogrel within the past seven days of surgery. The control group consisted of 43 patients (10 females, 33 males; mean age 63.1±7.7 years; range, 49 to 76 years) who did not use clopidogrel. Patients with recent preoperative exposure to coumadin, platelet glycoprotein inhibitors, or thrombolytics were excluded from the study. Demographic characteristics, levels of creatine phosphokinase-myocardial band (CK-MB), troponin I, C-reactive protein (CRP), and the amount of intraoperative blood loss, transfusion requirements, postoperative chest tube output, the length of hospital and intensive care unit (ICU) stay, postoperative ejection fraction (EF), and the incidence of postoperative atrial fibrillation (AF) of both groups were compared.

Surgical technique

All procedures were performed using standard anesthetic and surgical techniques. A median sternotomy was performed in all patients. The left internal mammary artery, radial artery, and saphenous vein were harvested using standard techniques. Hypothermia was avoided. Partial anticoagulation was accomplished with 1 to 2 mg/kg body weight of heparin, until a target activated clotting time (ACT) of ≥250 sec was achieved. Both groups underwent OPCABG and Octopus 4 (Medtronic Inc., MN, USA) was used as a cardiac stabilizer in all patients. After arteriotomy, to obtain a blood-free anastomotic field in both groups, intracoronary shunts of sizes 1.5, 2.0 or 2.5 (Clearview Intracoronary Shunt, Medtronic Inc., MN, USA) were inserted according to the diameter of the coronary artery and were revomed before the last suture knotting. An 8-0 polypropylene suture was used for the left internal mammary artery-to-left anterior descending artery anastomosis. 7-0 polypropylene sutures were used for other distal anastomoses. The duration of each distal anastomosis was noted in both groups. Proximal anastomoses were created using a side-bite clamp. Heparin was neutralized by protamine sulfate (750 IU/1000 IU heparin) at the end of the operation. The chest was closed in a standard fashion. For postoperative myocardial infarction follow-up, all daily electrocardiograms were examined for the presence of signs of new Q waves, loss of R wave progression, or a new ST elevation >2 mm, or T-wave changes. The CK-MB/CK ratios were also evaluated to find an increase of >5%. The need for inotropic support was defined as a requirement of inotropic administration for more than 30 min.

Serum CK and CK-MB levels were determined using the Roche/Hitachi Automated Clinical Chemistry Analyzer, Modular P-800 using commercial Roche kits (Roche Diagnostics GmbH, Mannheim, Germany). Reference values were as follows: men: 39-308 U/L, women: 26-192 U/L for CK, and 7-25 U/L for CK-MB. The diagnosis of myocardial infarction was made using the combination of CK and CK-MB activity: CK_{men} >190 U/L, CK_{women} >190 U/L and CK-MB >24 U/L. Troponin I (cTnI) plasma concentrations were measured by commercial Pathfast™ cTnI kits (Pathfast™ cTnI, Compact immuno-analyzer, Mitsubishi Kagaku latron, Inc., Tokyo, Japan) using chemiluminescent enzyme immunoassay (CLEIA). Reference values of cTnI were 0.00-0.02 ng/mL.

Statistical analysis

Statistical analysis was performed using SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed as mean + standard deviation or number of patients and percentage. The difference between the groups for nominal data was analyzed using the chi-square test. Continuous variables were assessed using the student t and Mann-Whitney U tests. Repeated measures were compared by paired t-test and Bonferroni correction. A *p* value of <0.05 was considered statistically significant.

RESULTS

Both groups were similar with respect to gender, age, presence of hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), congestive heart failure, previous MI, and preoperative (EF) values. Also, there was no significant difference in the preoperative troponin I, CK, CK-MB, and CRP levels between the groups (Table 1). The amount of intraoperative bleeding and fluid resuscitation was also similar between the two groups (p>0.05). In addition, postoperative transfusion requirements (packed red blood cell (PRBC) (3.56±0.72 packs vs 3.86±0.83 packs) and the need for fresh frozen plasma (FFP) (3.83±0.97 packs vs 3.95±0.72 packs) were similar (p>0.05). However, chest tube output was significantly higher in the clopidogrel group (883.2±256.9 mL vs 766±218.4 mL, p<001). Furthermore, the length of ICU stay was significantly longer in the clopidogrel group (Table 2). At the postoperative third month, EF rates

Table 1. Preoperative patients data

	Clopidogrel group (n=48)			Control group (n=43)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			65.3±8.3			63.1±7.7	NS
Gender							
Female	13	27		10	23		NS
Congestive heart failure	6	13		5	12		NS
Previous myocardial infarction	21	44		17	39		NS
Previous cerebrovascular accident	5	10		4	9		NS
Chronic obstructive pulmonary disease	6	13		5	12		NS
Diabetes mellitus	22	46		16	33		NS
Hypertension	28	58		24	56		NS
Previous cardiac operation	2	6		1	5		NS
Ejection fraction			42.9±5.8			43.8±7.0	NS
Previous percutaneous coronary intervention	27	56		11	26		NS
On aspirin	35	73		32	74		NS
Priority	11	23		11	26		NS
Unstable angina pectoris	25	52		21	49		NS
Myocardial infarction	12	25		11	26		NS
EuroSCORE			8.6±11.3			8.3±11.5	NS
Hemoglobin (g/dL)			13.1±1.9			12.2±1.8	NS
Hematocrit (%)			36.3±5.2			37.1±4.9	NS
Platelets (1000/L)			218±7			225±6	NS
Prothrombin time (s)			14.7±1.2			15±2.1	NS
International normalized ratio			1.1±0.4			1.2±0.9	NS
Partial thromboplastin time (s)			73±3			67±1	NS
Digoxin use (within 2 weeks)	11	23		9	21		NS
B-blocker usage	25	52		22	51		NS
Calcium antagonists	16	33		14	33		NS
Amiodarone	3	6		2	5		NS
Angiotensin converting enzyme inhibitors use	7	15		6	14		NS
Angiotensin receptor blocker use	4	8		5	12		NS
Aldosterone inhibitors use	3	6		2	5		NS
Statin use	22	46		20	47		NS
Atrial fibrillation	2	4		2	5		NS

SD: Standard deviation; NS: Not significant; EuroSCORE: European system for cardiac operative risk evaluation.

were significantly increased in both groups, while this increment was higher in the study group than the control group (p<0.06). The duration of distal anastomoses was also longer in the clopidogrel group (26.1±9.24 sec vs 23.5±7.8 sec, p<0.01). At the postoperative sixth hour (0.517±0.367 vs 0.674±0.195, p<0.01) and 24th hour (0.353±0.237 vs 0,712±0.179, p<0.001), troponin I levels and postoperative AF incidence were significantly lower in the clopidogrel group (p<0.01). Postoperative immediate (60.96±40.32 vs 91.1±43.54, p<0.01), sixth (66.72±38.42 vs 88.23±41.43, p<0.01) and 24th hour (72.22 ±36.21 vs 85.13±31.43, p<0.01) CRP levels were significantly lower in the clopidogrel group (Table 3).

Unfortunately, two patients died in the clopidogrel group. Of these patients, one stayed more than 48 hours in mechanical ventilation, while the other had a low cardiac output syndrome. In the control group, only one patient with a preoperative EF of 30% died due to chronic renal failure in the fourth day of surgery. Overall, perioperative MI incidence was found to be 1.2% (1/82). Myocardial infarction was detected in ECG records during the ICU stay in only one patient. As it was attributed to the graft failure, the patient underwent re-do surgery and the diagonal graft was re-anastomosed.

DISCUSSION

In this study, we compared the myocardial damage, inflammation and early postoperative morbidity and mortality following OPCABG in patients receiving and not receiving clopidogrel preoperatively. Our study results showed protective effects of clopidogrel including reduced postoperative troponin levels and reduced postoperative AF development.

It has been shown that clopidogrel improves the outcome of non-ST segment elevation myocardial infarction (NSTEMI) or ACS.[5] In the multi-center Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial, more than 12,000 patients with NSTEMI or ACS were randomized either to clopidogrel plus aspirin or aspirin alone.[6]

Table 2. Perioperative and postoperative patients data

	Clopidogrel group (n=48)			Control group (n=43)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Mean distal anatomosis			2.8±0.7			2.7±0.7	NS
Operative blood loss			394.8±84			373±83	NS
Operative fluid use			1245.2±241.2			1148.9±122.6	NS
Left internal mammary artery use	44	91		40	92		NS
Radial artery	3	6		2	5		NS
Total duration of distal anastomosis (min)			26.1±9.2			23.5±7.8	NS
Intra-aortic balloon pump	9	19		7	16		NS
Chest tube blood loss			883.2±256.9			766.7±218.4	0.02
Packed blood red cell			3.6±0.7			3.4±0.8	NS
Fresh frozen plasm			3.5±1.0			3.4±0.7	NS
Reexploration for bleeding	2	4		1	2		NS
Length of stay in the intensive care unit			1.5±0.5			1.2±0.4	0.05
Length of stay in the hospital			5.7±0.9			5.7±0.9	NS
Postoperative stroke			0			0	NS
Protamine after C-reactive protein			61.0±40.3			91.1±43.5	0.01
Postoperative 6th h C-reactive protein			66.7±38.2			88.2±41.4	0.01
Postoperative 24th h C-reactive protein			72.2±36.2			85.1±31.4	0.01
Renal failure or dialysis	1	2		1	2		NS
Gastrointestinal complications			0			0	NS
Postoperative renal failure	2	4		1	2		NS
Inotropic support	13	27		11	26		NS
Reexploration	2	4		1	2		NS
Postoperative atrial fibrillation	6	13		13	30		0.01
Postoperative ejection fraction			51.1±8.6			47.8±6.8	0.06
Intra-aortic balloon pump in intensive care unit	1	2		1	2		NS
In hospital mortality	1	2		1	2		NS

SD: Standard deviation; NS: Not significant.

Table 3. Preoperative and postoperative cardiac enzeyms

	Clopidogrel group (n=48)	Control group (n=43)	
	Mean±SD	Mean±SD	*p*
Preoperative troponin I	0.341±0.264	0.396±0.403	NS
Preoperative CK	83.5±71.7	78.1±33.6	NS
Preoperative CK-MB	1.9±11.3	25.4±8.8	NS
Postoperative 6th h CK	727.2±485.6	617.9±468.5	NS
Postoperative 6th h CK-MB	44.8±16.5	50.6±19.5	NS
Postoperative 6th h troponine I	0.517±0.367	0.674±0.195	0.014
Postoperative 24th h CK	550.6±408.7	552.9±424.3	NS
Postoperative 24th h CK-MB	38.9±15.4	43.8±16.8	NS
Postoperative 24th h troponin I	0.353±0.237	0.712±0.179	0.000

SD: Standard deviation; CK: Creatine phosphokinase; CK-MB: Creatine phosphokinase myocardial band; NS: Not significant.

The patients who received clopidogrel with aspirin within 24 hours after the event had significantly reduced mortality and cardiovascular morbidity, compared to the patients who received aspirin alone. In our study, troponin I, an indicator of ischemia, was significantly lower in the clopidogrel group in the postoperative period. This finding supports the recent studies suggesting that clopidogrel prevents recurrent ischemia.[4,6,7]

On the other hand, the main and well-studied side effect of clopidogrel is postoperative bleeding.[2-4] As reported, OPCABG yields two-fold reduction in postoperative bleeding, lower surgical reexploration rates, and a 20 to 25% decrease in transfusion requirements.[8] In 2001, Yende and Wunderink[3] analyzed 247 patients undergoing CABG grafting surgery. Of these patients, 51 used clopidogrel. The authors reported that clopidogrel significantly increased the amount of blood products to be transfused after surgery. This data was also confirmed by Mehta et al.[5] who performed a multi-center study including patients with NSTEMI or ACS who underwent CABG. The authors reported a significant increase in the blood transfusion requirement in the patients receiving clopidogrel recently, compared to those who underwent CABG more than five days after clopidogrel discontinuation. Similar results were also presented by Hongo et al.[1] who analyzed a series of 224 patients undergoing CABG [clopidogrel exposure within seven days, (n=59), and no clopidogrel exposure, (n=165)]. The authors showed a 10-fold increase in the rate of reoperation for bleeding in clopidogrel-treated patients (6.8%). On the other hand, Karabulut et al.[9] analyzed a series of 1,628 patients undergoing CABG under CPB [clopidogrel exposure within seven days (n=48) and no clopidogrel exposure (n=1580)]. The authors reported that preoperative use of clopidogrel was not associated with increased bleeding rates and need for surgical exploration, and the risk of blood and blood product transfusion after CABG. In another study, Erdem et al.[10] compared clopidogrel doses and demonstrated that 600 mg and higher doses of clopidogrel increased bleeding after surgery. Consistent with these findings, in our study, we found an increased chest tube output and transfusion requirement in the clopidogrel group; however, no increase in the re-exploration rates was observed.

While most of the benefits of clopidogrel have been attributed to the inhibition of platelet activation, blockade of the P2Y12 receptor has been also suggested to have pleotropic effects with respect to endothelial cell function, leukocyte activation, and inflammation.[11] The expression of P-selectin and CD40 ligand as well as increased CRP levels after revascularization may all be blunted by clopidogrel.[12]

Furthermore, AF is the most frequent arrhythmic complication after CABG with an incidence ranging from 25 to 35%.[13] To date, several risk factors for postoperative AF have been elucidated.[13] However, the etiology of postoperative AF remains unclear, although a multiplicity of factors such as surgical trauma contributes to the development of postoperative AF.[8] Many pre- and postoperative factors have been also suggested to increase the incidence of postoperative AF after CABG, such as advanced age, hypertension,[14] withdrawal of β-blocker drugs,[15] right coronary artery stenosis,[16] respiratory complications,[17] and bleeding.[18] In a meta-analysis of 46 studies involving 2,613 patients, Sedrakyan et al.[19] reported a substantial risk reduction associated with OPCABG. Postoperative AF causes a significant increase in mortality and hospitalization.[20] In our study, of all factors reportedly causing AF, only CRP levels differed between the two groups. Ronnier et al.[21] reported that CRP was not

only associated with the presence of AF, but could be also predictive for an increased risk for further AF development. In addition, Aronson et al.[22] also showed that there was a graded positive correlation between increased CRP levels and new-onset AF in a large cohort of patients with acute MI. Moreover, inflammation may contribute to the development of AF in the setting of acute MI. In our study, C-reactive protein levels were found to be significantly lower in the clopidogrel group after protamine at six and 24 hours. These mechanisms may contribute to the postoperative increased reduction in AF in patients using clopidogrel.

In conclusion, although preoperative clopidogrel use increases chest tube output after emergency off-pump coronary artery bypass grafting, this increase is tolerable and does not increase the need for surgical exploration. Based on our study findings, we believe that this increase does not constitute a risk factor for mortality and morbidity. Positive impacts of clopidogrel on postoperative troponin I and ejection fraction levels suggest that clopidogrel has also cardioprotective effects. As reduced C-reactive protein levels indicate an anti-inflammatory effect of clopidogrel, the reduction of postoperative atrial fibrillation development can be explained by this mechanism. Considering its positive effects, we recommend using clopidogrel in acute coronary syndrome early as possible. We believe that preoperative clopidogrel use does not preclude early coronary artery bypass grafting.

Declaration of conflicting interests

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