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Original Article / Özgün Makale

Frequency of development of aspirin resistance in the early postoperative period and inadequate inhibition of thromboxane A2 production after coronary artery bypass surgery

Koroner arter bypass cerrahisi sonrası erken dönemde aspirin direnci gelişme sıklığı ve tromboksan A2 üretiminin yetersiz inhibisyonu

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ABSTRACT

Background: This study aims to investigate the frequency of the development of aspirin resistance, whether or not this resistance was reversible, and to evaluate the efficiency of the mechanism of incomplete inhibition of thromboxane A2 in development of aspirin resistance in the early postoperative period in patients who had undergone coronary artery bypass grafting.

Methods: Eighty patients (55 males, 25 females; mean age 63.1±9.2 years; range 51 to 75 years) who underwent coronary artery bypass grafting between February 2009 and March 2010 at our clinic were prospectively evaluated. Venous blood samples were collected from all patients and evaluated by a platelet function analyzer in the preoperative period and on postoperative days 7 and 15. Aspirin resistance diagnosis was defined as collagen-epinephrine closure time less than 186 seconds. The urine levels of 11-dehidro thromboxane B2 were also measured on postoperative day one.

Results: Aspirin resistance was found in 23 patients (28.75%) in the preoperative period, in 31 patients (38.75%) on the postoperative seventh day and in 25 patients (31.25%) on the postoperative 15th day. The urine levels of 11-dehidro thromboxane B2 in patients with aspirin resistance on the postoperative seventh day were significantly higher than those in patients without aspirin resistance ($p<0.001$). The mean aortic cross-clamping time ($p=0.003$) and cardiopulmonary bypass time ($p=0.029$) in the patients with aspirin resistance on the postoperative seventh day were significantly higher than those in patients without aspirin resistance.

Conclusion: The results of this study suggest that aspirin resistance develops within the first seven days after coronary artery bypass grafting and is highly reversible, and that the mechanism of inadequate inhibition of thromboxane A2 by aspirin has a role in the development of aspirin resistance in the early postoperative period.

Keywords: Aspirin resistance; coronary artery bypass graft; platelet function analyzer-100; thromboxane A2.

ÖZ

Amaç: Bu çalışmada koroner arter bypass greft cerrahisi uygulanan hastalarda ameliyat sonrası erken dönemde aspirin direnci gelişme sıklığı ve bu direncin geri dönüşümlü olup olmadığı araştırıldı ve ameliyat sonrası erken dönemde aspirin direnci gelişmesinde tromboksan A2 üretiminin yetersiz inhibisyonu mekanizmasının etkinliği değerlendirildi.

Çalışma planı: Şubat 2009 - Mart 2010 tarihleri arasında kliniğimizde koroner arter bypass greft cerrahisi yapılan 80 hasta (55 erkek, 25 kadın; ort. yaş 63.1±9.2 yıl; dağılım 51 to 75 yıl) prospektif olarak değerlendirildi. Ameliyat öncesi ve ameliyat sonrası yedinci ve on beşinci günlerde hastalardan alınan venöz kan örnekleri trombosit fonksiyon cihazı ile değerlendirildi. Aspirin direnci tanısı kollajen-epinefrin kapanma zamanının 186 sn'den düşük olması durumu olarak tanımlandı. Ameliyat sonrası birinci gün alınan idrar örneklerinde 11-dehidro tromboksan B2 düzeyleri ölçüldü.

Bulgular: Ameliyat öncesi dönemde 23 hastada (%28.75), ameliyat sonrası yedinci günde 31 hastada (%38.75) ve 15. günde 25 hastada (%31.25) aspirin direnci saptandı. Ameliyat sonrası yedinci günde aspirin direnci olan hastalardaki 11-dehidro tromboksan B2 düzeyi, aspirin direnci olmayan hastalardaki düzeylere göre anlamlı derecede daha yüksekti ($p<0.001$). Ameliyat sonrası yedinci günde yeni aspirin direnci gelişen hastaların ortalama aort kross-klemp süresi ($p=0.003$) ve kardiyopulmoner bypass süresi ($p=0.029$) aspirin direnci olmayan hastalardaki sürelere göre anlamlı derecede daha yüksekti.

Sonuç: Bu çalışmanın sonuçları koroner arter bypass greft cerrahisi sonrası ilk yedi gün içinde aspirin direnci geliştiğini ve bu direncin büyük oranda geçici olduğunu ve erken dönemde aspirin direnci gelişmesinde tromboksan A2 üretiminin aspirin tarafından yetersiz inhibe edilme mekanizması etkili olduğunu desteklemektedir.

Anahtar sözcükler: Aspirin direnci; koroner arter baypas grefti; trombosit fonksiyon analizörü-100; tromboksan A2

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Aspirin is a strong antiaggregant used to prevent atherothrombotic cardiovascular events. However, the level of antiaggregant activity of aspirin is not the same in all patients and even some patients don't benefit at all. These patients are clinically known as aspirin-resistant patients or aspirin-naive patients.[1]

Shantsila et al.[2] described aspirin resistance as an inability to suppress thromboxane production with appropriate doses of aspirin. Weber et al.[3] classified aspirin resistance based on three main categories: Type 1: Pharmacokinetic, Type 2: Pharmacodynamic, Type 3: Pseudoresistance.

Incidence of the aspirin resistance is reported as 28% in a meta-analysis by Krasopoulos et al.[4] Aspirin resistance can be identified using various methods and devices, including bleeding time, optic aggregometry, platelet function analyzer (PFA-100), Ultegra rapid platelet-function assay (Ultegra-RPFA; Accumetrics, Inc., San Diego, California, USA), active coagulation time, whole blood aggregometry, platelet aggregation rate, flow cytometry, blood or urine thromboxane A2 level, and platelet surface proteins.[3] However, the most commonly used reliable and rapid methods are the verifynow system (bedside - photometric agregometric system) and PFA-100 laboratory test. The mechanism of development has not yet been fully clarified, and a number of studies have been conducted on this matter.[5,6]

The aim of the current study was to investigate the frequency of aspirin resistance development in the early postoperative period in patients who had undergone coronary artery bypass grafting (CABG) surgery, to learn whether or not this resistance is reversible, and determine the role of inadequate inhibition of thromboxane A2 production on the development of aspirin resistance in the early postoperative period.

PATIENTS AND METHODS

Prior to the commencement of the study, approval was obtained from the Ethics Committee of University (27.07.2009/ 2989). A total of 80 patients (55 males, 25 females; mean age 63.1±9.2 years; range 51 to 75 years) who were diagnosed with coronary artery disease (CAD) and scheduled for CABG were included in the study. All of the patients were informed on the study protocol and methodology, and signed written informed consent forms.

The exclusion criteria of patients were as follows: contraindication to aspirin, taking antiplatelet/ anticoagulant medication other than aspirin, undergoing of platelet transfusion within the first postoperative week, not being extubated within the postoperative 24 hours, and chronic renal insufficiency, thrombocytopenia (<100,000 platelets), or thrombocytosis (>500,000 platelets).

The operations were performed under a moderate systemic hypothermic cardiopulmonary bypass (CPB) in all patients. The hematocrit value was maintained around 20-25 mg/dL. Venous blood samples were obtained from the antecubital vein on the preoperative, postoperative seventh and fifteenth days from all patients and placed into citrated tubes. A maximum of four subjects were evaluated per day using the PFA-100 system.

The PFA-100 system is a cartridge-based device in which the adhesion and aggregation process of platelets is stimulated just like intracellular conditions after vascular injury to assess primary hemostasis. The platelet dysfunction detected by the PFA-100 system may be acquired, congenital or induced by agents that inhibit platelets such as aspirin. This system uses Collagen/Epinephrine (Col/Epi) and Collagen/ adenosine diphosphate (Col/ADP) cartridges. Each cartridge has a chamber that can hold up to 800 µL of blood absorbed through a capillary tube at a high shear rate. The absorbed blood passes through an aperture, the center of a membrane coated with fibrillar type 1 collagen. The membrane also contains epinephrine in the Col/Epi cartridge and ADP in the Col/ADP cartridge. The platelets adhere to the type 1 collagen as they pass through the aperture and are activated by an additional stimulant. This aperture is closed by the formation of the aggregate and the platelet plug. The period between the start of absorption and the end of blood flow is reported as closure time and the results are given in seconds. The system can measure up to 300 seconds, with any result above 300 is indicated as >300 sec.

Col/Epi is the main cartridge and is used first. If closure time is close to the upper limit of the normal values, the Col/ADP cartridge is applied. If the closure time of Col/ADP is normal, the result is attributed to aspirin use since the antithrombotic effect of aspirin prolongs the closure time of Col/Epi cartridge but does not change that of the Col/ADP. The limits were set as 85-165 sec for the former and 71-118 sec for the latter. In cases when Col/Epi closure time was less than 186 sec, aspirin resistance was diagnosed.[7]

The first urine sample was taken from the patients on the morning of postoperative day 1. For the tests, the 11-dehydrothromboxane B2 EIA kit (catalog no. 519501) manufactured by Cayman Chemical

Table 1. Demographic and clinical characteristics of the patients

	n	%	Mean±SD	Comorbidities	n	%
Mean age (year)			63.1±9.20			
Gender				PAD	7	8.75
Male	55	68.75				
Female	25	31.25				
Smoker	46	57		HT	64	80
Clinical				DM	37	46.25
Stable angina pectoris	36	45				
Unstable angina pectoris	23	28.75				
Myocardial infarction	21	26.25				
Stroke/transient ischemic attact	5	6.25		Hyperlipidemia	39	48.75

SD: Standard deviation; PAD: Peripheral artery disease; HT: Hypertension; DM: Diabetes mellitus.

for laboratory (Cayman Chemical, Michigan, USA) analyses was used.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 13.0 statistical program (SPSS Inc., Chicago, IL, USA). Data was presented as arithmetic mean ± standard deviation. The Fisher exact test and Chi-square test were used to compare the patients with and without aspirin resistance according to age, gender, and smoking status. The t-test and Mann-Whitney U test were used to compare the independent samples in the patient and control groups. The correlation between the independent samples within the patient and control groups was evaluated based on Pearson and Spearman coefficients with $p<0.05$ being considered as significant in all statistical tests.

RESULTS

The demographic and clinical characteristics of the patients are shown in Table 1. The patients who died within the first 24 hours of the operation were excluded from the evaluation.

The mean aortic cross-clamping (ACC) time was 58.56±25.99 min, the mean CPB time was 98.22±33.83 min, the mean extubation time was 9.79±4.48 hours, and the mean intensive care unit stay was 2.3 days. Four patients required an intra-aortic balloon pump due to

Table 2. Previous surgical interventions

	n	Mean±SD
Isolated coronary artery bypass graft	74	
Coronary artery bypass graft + aortic valve replacement	3	
Coronary artery bypass graft + mitral valve replacement	1	
Coronary artery bypass graft + mitral valve repair	2	
Average cross-clamping time (min)		58.6±26.0
Cardiopulmonary bypass time (min)		98.2±33.8
Use of intra-aortic balloon pump	4	
Renal dysfunction	16	
Amount of drainage (mlt)		908.8±491.7
Duration of extubation (hour)		9.8±4.5
Stay in intensive care unit (day)	2.3	

SD: Standard deviation.

Table 3. Aspirin resistance and patient data in the preoperative period

	Aspirin resistance				
	Resistant		Non-resistant		
Characteristics	n	Mean±SD	n	Mean±SD	*p*
Age (year)		63.9±9.2		61.2±9.1	0.205
Gender					0.334
Male	9		16		
Female	14		41		
Clinical manifestation					0.720
Stable angina pectoris	9		27		
Unstable angina pectoris	8		15		
Myocardial infarction	6		15		
Stoke					0.655
Present	1		4		
Absent	22		53		
Pulmonary arterial disease					0.376
Present	1		6		
Absent	22		51		
Hypertension					0.711
Present	19		45		
Absent	4		12		
Diabetes mellitus					**0.008**
Present	16		21		
Absent	7		36		
Hyperlipidemia					0.697
Present	12		27		
Absent	11		30		
Smoker					0.910
Yes	13		33		
No	10		24		

SD: Standard deviation.

low cardiac output syndrome and 16 patients developed renal dysfunction, which was defined as the creatinine level being above 1.2 mg/dL. The perioperative and postoperative data is shown in Table 2.

Aspirin resistance was detected in 23 patients during the preoperative period (28.75%). The prevalence of diabetes mellitus diagnosis in patients with aspirin resistance in the preoperative period was statistically significantly higher than that of the non-resistant patients ($p<0.01$) (Table 3).

On postoperative day 7, aspirin resistance was detected in 31 patients (38.75%). Among them, eight patients had no aspirin resistance in the preoperative period. The mean CPB and ACC time of the patients with aspirin resistance were significantly higher than that of the non-resistant patients ($p=0.003$, $p=0.029$, respectively). The urinary 11-dehydrothromboxane B2 levels in patients with aspirin resistance were significantly higher than the patients without aspirin resistance (10.96±1.66 vs 4.90±1.62, $p=0.000$). The results obtained on postoperative day 7 are given in Table 4. The comparison of the results of the blood analysis with the patients with and without aspirin resistance revealed a statistical significant difference in hemoglobin and platelet count on postoperative day 1, 7, and 15 ($p<0.05$), (Table 5).

Aspirin resistance was present in 23 patients in the preoperative period, 31 patients on postoperative day 7, and 25 patients on postoperative day 15. In brief,

Table 4. Aspirin resistance and surgical data on postoperative day 7

	Aspirin resistance				
	Resistant (n=31)		Non-resistant (n=49)		
	n	Mean±SD	n	Mean±SD	*p*
Coronary artery bypass graft					0.709
One	3		4		
Two	6		15		
Three	16		20		
Four	6		10		
Use of left internal mammary artery					0.747
Yes	27		44		
No	4		5		
Additional surgical intervention with CABG					0.383
Aortic valve replacement	2		1		
Mitral valve replacement	0		1		
Mitral repair	1		1		
Reoperation					
Yes	3		0		7.724
No	28		49		0.005
Use of intra-aortic balloon pump					
Yes	3		1		4.397
No	28		49		0.036
Development of renal dysfunction					
Yes	10		6		4.409
No	21		43		0.036
Aorta cross-clamping time		66.4±29.4		50.7±18.8	**0.003**
Pump time		105.2±42.2		89.3±28.7	**0.029**
Duration of extubation		10.3±5.3		9.3±3.6	0.991
Amount of drainage		937.0±545.9		880.7±437.6	0.737
11-dehydro thromboxane B2		11.0±1.7		4.90±1.6	**0.000**

SD: Standard deviation; CABG: Coronary artery bypass graft.

aspirin resistance developed in eight patients from the preoperative period to postoperative day 7, but six patients of these patients became responsive to aspirin by postoperative day 15, and aspirin resistance persisted in the remaining two patients.

DISCUSSION

In this study, aspirin resistance was shown to develop within the first seven days after CABG with a CPB; however, this resistance was mostly temporary. The findings that support this result are: *(i)* Aspirin resistance was detected in 23 patients in the preoperative period, 31 patients on postoperative day 7, and 25 patients on postoperative day 15; and *(ii)* six of the eight patients who had newly developed aspirin resistance by postoperative day 7 became responsive to aspirin by postoperative day 15, and aspirin resistance only persisted in the remaining two patients. In addition, our results suggest that the mechanism of inadequate aspirin inhibition of thromboxane A2 production is effective in the development of aspirin resistance in the early postoperative period and following CABG with a CPB. This finding is supported by the fact that the urinary 11-dehydrothromboxane B2 levels in the patients that had aspirin resistance on postoperative day 7 were significantly higher than in the non-resistant patients.

The incidence of aspirin resistance among the patients of this study was 28.8% (n=23) in the preoperative period. In the literature, there are several studies on the incidence of aspirin resistance. Grundmann et al.[8] used PFA-100 in 35 symptomatic

Table 5. Laboratory findings of patients with and without aspirin resistance on postoperative day 7

	Aspirin resistance		
	Resistant (n=31)	Non-resistant (n=49)	*p*
Preoperative hemoglobin	13.7±1.8	13.6±1.6	0.569
Day 1 hemoglobin	9.4±1.1	8.8±1.1	0.014
Day 7 hemoglobin	10.0±1.1	9.4±0.8	0.010
Day 15 hemoglobin	10.5±1.1	9.7±0.7	0.000
Preoperative platelet	293.8±138.2	252.4±79.8	0.300
Day 1 platelet	152.0±54.5	127.6±53.7	0.023
Day 7 platelet	212.5±51.3	177.3±54.1	0.002
Day 15 platelet	240.2±54.2	191.6±52.1	0.000
Preoperative fibrinogen	363.3±111.1	348.4±79.3	0.832
Day 1 fibrinogen	357.6±111.4	343.2±78.9	0.483
Day 7 fibrinogen	379.8±110.3	343.1±59.8	0.273
Day 15 fibrinogen	382.3±91.5	347.0±75.4	0.089
Activated clotting time	166.2±33.3	159.1±31.8	0.480
Postoperative first activated clotting time	160.9±39.3	147.6±28.3	0.193
Uric acid	6.7±1.1	5.2±1.244	0.000

patients with asymptomatic cerebrovascular disease, who received 100 mg aspirin daily, and found that aspirin resistance developed in 34% of symptomatic patients and 0% of asymptomatic patients. Roller et al.[9] determined the threshold value of Col/Epi closure time as 165 sec for the diagnosis of aspirin resistance and found the percentage of aspirin resistance to PFA-100 as 40%. Macchi et al.[10] reported a threshold value for Col/Epi closure time of 186 sec for the diagnosis of aspirin resistance, and reported that in patients with stable angina pectoris disease, who received 160 mg aspirin daily, 29.2% developed aspirin resistance according to PFA-100.

Hovens et al.[11] found the incidence of aspirin resistance to be 22.4% in CAD, 26% in stroke, and 27.3% in various other diseases. Aspirin resistance acquired after CABG is usually a temporary phenomenon observed during the first postoperative month.[6,12] In a study of patients that underwent CABG, the antithrombotic effect of aspirin was investigated using a complete blood aggregometry test and PFA-100.[10] On postoperative day 10, the aspirin response was found to be poor in 11 patients and non-responsive in four patients. In the first month after surgery, the aspirin response was poor in only one patient and a non-response to aspirin was not detected.

Ballotta et al.[13] compared 30 on-pump and off-pump CABG patients, and found that platelet activation was greater in the early postoperative period after on-pump surgery. During the two hours of the on-pump surgery, platelet aggregation induced by ADP decreased (0.89 versus 10.9%) and P-selectin positivity induced by active platelets increased (6 to 9.1%). Another study reported that the platelet activating factor (PAF)-induced platelet aggregation was significantly reduced by about half of the preoperative value following on-pump CABG but was significantly increased after off-pump surgery.[14]

In light of this data, it could be stated that aspirin is more effective after off-pump CABG rather than after on-pump surgery. Similar to the literature, in the current study, the percentage of aspirin resistance was found to be 38.75% on postoperative day 7 and 31.25% on postoperative day 15.

Acquired aspirin resistance is temporary and not associated with genetic polymorphisms observed in persistent aspirin resistance, such as diabetes mellitus, hypercholesterolemia, and other comorbid diseases. The mechanism of aspirin resistance has not yet been fully elucidated. Therefore, it is necessary to briefly review the interaction of CPB, off-pump CABG, and concomitant medication with

the antithrombotic effect of aspirin. Approximately 80-90% of CABG procedures are performed with the help of CPB. It is known that CPB has various effects including systemic inflammatory response and platelet activation.[15] The development of platelet hyperreactivity after CPB may reduce the antithrombotic effect of aspirin and contribute to the formation of aspirin resistance.

In previous studies,[16,17] smoking was found to cause statistically significant increase in resistance to aspirin. This result was attributed to the increased platelet function caused by smoking. In the current study, no statistically significant relationship was observed between aspirin resistance and smoking. Hyperlipidemia may cause aspirin resistance by increasing platelet aggregation and thromboxane A2 levels and Friend et al.[18] showed that in patients with hyperlipidemia, the platelet response to aspirin is reduced. However, in the current study, no statistically significant relationship was found between aspirin resistance and hyperlipidemia. Hyperglycemia leads to platelet reactivity and increases thrombogenicity. Previous studies found that the incidence of aspirin resistance was no different between diabetic and non-diabetic patients,[17-20] This was attributed to good glycemic control in the former patient group. Watala et al.[21] assessed the effect of 150 mg/day aspirin on platelet adhesion and aggregation in diabetic patients and a non-diabetic control group, and reported that the effect of aspirin was lower in the former. Based on the results, the authors suggested that higher doses of aspirin may be required in certain patients, particularly in high-risk diabetic patients. In a study conducted by Abaci et al.,[22] 67% of diabetic patients who received 100 mg aspirin were shown to be responsive to aspirin by the PFA-100 method, and in the aspirin-resistant group (33%), 44% of the patients became responsive when the aspirin dose was increased to 300 mg. Similarly, in our study, the rate of diabetic mellitus diagnosis in patients with aspirin resistance was significantly higher than in the remaining patients. Also consistent with the literature, there was no statistically significant difference between the patients with and without aspirin resistance in terms of age, gender, CAD, stroke, PAD, and hypertension.

No statistically significant correlation was found between aspirin resistance and drugs affecting the cardiovascular system (e.g., ACEI, beta-blockers, statins, calcium channel blockers, and diuretics) used by the patients in this study. In the literature, studies investigating this correlation have found that aspirin resistance only had a high correlation in the patient group that were taking statins. This paradox situation was explained by the possible interaction between statins and aspirin, resulting in reduced antiaggregant effect of the latter, the antithrombotic effects of statins in hyperlipidemic patients that may occur once lipid levels normalize, and increased platelet aggregation due to hyperlipidemia.[23]

Some non-steroidal analgesic antiinflammatory drugs (e.g., indomethacin, ibuprofen, naproxen, and metamizol) temporarily bind to COX-1 in platelets and prevent the irreversible inhibition of platelet thromboxane formation.[24,25] In particular, the globally common use of analgesics such as dipyrone (metamizole) in management of postoperative pain is important in terms of the drug interaction with aspirin in the early period after CABG.

The identification of aspirin non-responsiveness with laboratory tests based on the detection of platelet inhibition caused by aspirin is associated with clinical atherothrombotic events, such as the presence of graft thrombosis, which results in the clinical diagnosis of aspirin resistance. In a meta-analysis of 20 studies involving 2,930 patients, aspirin resistance was found to be 28% in atherosclerotic patients. Cardiovascular events were observed in 33% of the aspirin-resistant patients and 16% of the aspirin-responsive patients, and non-fatal, lethal, cerebrovascular, and vascular events were approximately four times higher (odds ratio 3.85) in patients that were unresponsive to aspirin. The odds ratio was 4.06% for acute coronary syndrome, 4.35% for graft failure, and 3.78% for new cerebrovascular events. In addition, the increased mortality odds ratio in patients with aspirin resistance was 5.99%.[4] A study on the benefits and risks of acetylsalicylic acid on thrombosis was the first prospective multicenter study to investigate the clinical events in aspirin-respondents and non-respondents among CABG patients.[26] In that particular study, aspirin resistance was evaluated in 289 patients based on the measurement of hemorrhage time, including the comparison of the prevalence of preoperative and postoperative aspirin resistance. According to the results, the hemorrhage time was statistically significantly longer in aspirin responders. The prevalence of aspirin resistance before and after surgery, and hemorrhage time was statistically significantly prolonged in aspirin-sensitive patients. Surprisingly, thromboxane synthesis was significantly inhibited in both the resistant and non-resistant groups with no significant difference being observed between the two groups at two-year follow-up in terms of the risk of thrombotic events.

The results of this study support that aspirin resistance temporary and inadequate thromboxane A2 inhibition in the postoperative period. However, there is a need for further experimental and clinical studies to fullyclarify the effects of ECC on aspirin resistance.

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