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The Effect of Aspirin as an Irreversible COX_1 Inhibitor in Preventing Non-Valvular Atrial Fibrillation After Coronary Bypass Surgery

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ABSTRACT

Background: We investigated whether the use of aspirin (irreversible COX1 inhibitor) in the preoperative period may prevent non-valvular atrial fibrillation, which is the most common rhythm problem in the postoperative period. Non-valvular atrial fibrillation after coronary surgery may lead to an increase in hospital costs due to excessive drug use and long-term hospitalization.

Methods: More than 1000 coronary artery bypass grafting operations were performed between January 2011 to and Nov 2018. The 572 patients were included in this study. Patients were divided into two groups as medication (n=292) and medication-free group (n=280). In the medication group, while patients received aspirin (300 mg daily) therapy (up to 5 days) before the operation, the other group did not receive any anti-aggregan treatment. The patients were followed up for the occurrence of atrial fibrillation from the early postoperative period up to 3 months.

Results: While non-valvular atrial fibrillation was developed in 16 patients (5,5 %) in medication group, this rate was 24,3 % with 68 patients in medication-free group 3 month after operation ($P < .05$). In addition to the intensive care unit and hospital stay, there was a significant difference between the groups in terms of hospital costs ($P < .05$).

Conclusions: According to the results of our study, we found that the aspirin used in preoperative period may prevent non-valvular atrial fibrillation in the postoperative period. In relation to these results; we found that hospital stay and hospital expenses decreased.

INTRODUCTION

Non-valvular atrial fibrillation (NVAF) is still the most common rhythm problem after cardiac surgery, despite worldwide surgical innovations and improvements in hospital facilities. It also remains the most common complication after coronary heart surgery. Although the cardiac functions, the surgical application, the patient's clinical pathology and parameters, and age-related incidence vary, it is now reported that it can still be seen in 10% to 65%. Nowadays, NVAF is more frequent because of the increasing number of cardiac surgeries, cardiac surgery for more comorbid patients and aging of the population. This increase in NVAF incidence; postoperative hemodynamic instability, thromboembolic events and longer hospital stays and health care costs can lead to an increase [Khan 2013; Villareal 2004].

Several pharmacological agents such as β-block, calcium channel blockers and amiodarone have been tested over the years to prevent or reduce NVAF after coronary bypass surgery [Khan 2013; Fuster 2006]. In spite of the studies on these medications, in recent studies, it was determined that the protective or preventive effects of these agents were insufficient for postoperative NVAF [Balcetyte-Harris N 2002; Maniar 2003; Paull 1997; Fuster 2006]. In addition to many trials with drugs over the years, different agents have been recently used to prevent this complication (such as anti-aggregating agents, non-steroidal anti-inflammatory drugs, statins, and angiotensin converting enzyme inhibitors). Many of these new agents have been shown to inhibit not only NVAF but many postoperative arrhythmias due to their anti-inflammatory effects [Khan 2013; Tomic 2005; Wijeysundera 2005; Patti 2006].

The aim of this prospective study was to investigate the effects of aspirin on the prevention of NVAF in patients undergoing coronary artery bypass grafting. According to the results, we advocate that aspirin should be continued in the preoperative period to patients undergoing coronary bypass surgery if there are no contraindications.

METHODS

Patient Population

More than 1000 coronary bypass operations were performed in cardiovascular surgery clinics (Atatürk University and Regional Training and Research Hospital) in our province between Jan 2011 Nov 2018. The 572 patients were included in this study. This study was carried out meticulously, and reporting was done on the randomization and blinding methods employed. The 572 patients (288 male, 284 female) were studied in this prospective randomized study. Ethical permission was given by the Erzurum Regional Training and Research Hospital ethics committee, and informed written consent was obtained from all participants and/or parents or guardians. Furthermore, all procedures were carried out in accordance with

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Table 1. Preoperative Data in Patients Undergoing CABG

	Treatment Group	%	Control Group	%	*P*
Sex (M/F)	154/138		148/132		.549
Age (mean)	63.2 ± 5.2		63.4 ± 5.8		.431
Hypertension	187	64	181	64.6	.877
Smoker habits	204	69.8	190	67.8	.752
Diabetes Mellitus	91	31.1	91	32.5	.654
Hypercholesterolemia	179	61.3	155	55.3	.901
CVD	17	5.8	16	5.7	.890
PVD	43	14.7	42	15	.766
Preoperative PTCA	80	27.4	85	30.3	.642
Preoperative IABP	20	6.8	17	16.8	.977
Unstable angina	31	10.6	38	13.6	.510
LA antero-posterior diameter	4.1 ± 1.1		4.0 ± 1.0		.105
LVEF (mean %)	45.9 ± 4.5		48.7 ± 4.7		.330

CVD: Cerebro-vascular disease; PVD: Peripheral vascular disease; PTCA: Percutaneous transluminal coronary angioplasty; IABP: Intra-aortic balloon pulsation; LVEF: Left ventricle ejection fraction (*P* values < 0.05) important statistically

Table 2. Operative Data

Variables	Treatment Group	%	Control Group	%	*P*
CPB time (min)	54 ± 11		51 ± 12		NS
XCL time (min)	31 ± 9		32 ± 10		NS
Number of distal anastomosis	3.3 ± 0.5		3.1 ± 0.5		NS
LAD bypass	281	96.2	277	98.9	NS
Diagonal branches	196	67.1	201	71.8	NS
Cx bypass	202	69.2	211	75.3	NS
RCA bypass	256	87.7	241	86.1	NS
Coronary endarterectomy	61	20.9	59	21.1	NS
Retrograde cardioplegia usage	261	89.4	255	91.1	
Details of coronary artery disease					
Left main disease	56		62		NS
Three vessel disease	101		110		NS
Two vessels disease	98		108		NS
Complete revascularization	292		280		NS

CPB: Cardiopulmonary bypass; XCL: Aortic cross-clamping; LAD: Left anterior descending artery; Cx: Circumflex artery; RCA: right coronary artery, ITA: Internal thoracic artery (*P* values < .05; important statistically, NS: non-specific statistically)

the Declaration of Helsinki. Surgical and systemic complications, amount of bleeding, cardiovascular status, mortality rate, infection, ICU and hospital stay and hospital costs were compared between groups. In addition, NVAF was observed during the 3-month period from the early postoperative period.

The patients were randomly divided into two groups: the medication group (N=292 patients) and the medication-free (N=280 patients). The aspirin therapy (300 mg/ per day) was given up to 5 days before operation, which was accepted as medication group. The aspirin therapy was not given to the medication-free group. The both groups received low molecular weight heparin (factor Xa inhibitor) therapy until the morning of the operation. The mean age in medication group was 63.2 ± 5.2 years (44-79 years); in medication-free group it was 63.4 ± 5.8 years (45-77 years). By trans-thoracic echocardiography, left ventricular ejection fraction (LVEF) was 45.9% ± 4,5% in medication group, medication-free group was 48.7% ± 4.7%. In medication group, 20 (6.8%) patients had intra-aortic balloon pump (IABP) preoperatively, 17 (6,1 %) patients had it in medication-free group. The criteria for pre-operative insertion of an IABP were as follows: cardiogenic shock or refractory ventricular failure, hemodynamic instability, refractory angina, ventricular arrhythmia, and a critical left main stenosis (>70%).

Inclusion Criteria

All patients who were included in the study and who underwent primary elective coronary bypass surgery had no contraindications to aspirin. In addition, all of these patients had normal sinus rhythm preoperatively and all were receiving β-blokage therapy.

Exclusion Criteria

The study exclusion criteria included (1) known severe liver disease or current transaminases 1.5 times the upper normal limit, (2) current serum creatinine 2.5 mg/dL, (3) known myopathy or elevated baseline preoperative creatinine kinase, (4) known blood dyscrasias or gastrointestinal disease, (5) pregnant and lactating women or women of childbearing potential not protected by a contraception method, and (6) not use aspirin patients with stomach problem. Add exclusion criteria included prior coronary revascularization or heart valve surgery, emergency surgery, ruptured papillary muscle severe mitral regurgitation, post infarction ventricular septal defect, New York Heart Association Class III or IV congestive heart failure, history of AF, hyperthyroidism, inflammatory disease except coronary artery disease, infection, a left atrium size ≥70 mm, electrolyte imbalance, age ≤18 years old, bleeding disorders and combined surgical procedures, and severe left ventricular dysfunction. All preoperative data are depicted in Table 1.

Anesthesia

In the operations performed under general anesthesia remifentanil (0.5-1 g/kg per min) and propofol (3 mg/kg per

Table 3. Postoperative parameters between groups

Variables	Treatment Group	Control Group	*P*
Hospital mortality (within 30 days)	26	24	>.05
Early mortality (48 hours)	4	6	
Pre-operative AMI	11	9	>.05
New IABP insertion	22	19	>.05
Duration of inotropic support (days)	6.2 ± 4.3	6.1 ± 4.1	>.05
LCOS	16	14	>.05
Atrial fibrillation (patients)			
First one week	32	85	<.05
One month	25	71	<.05
3 months	14	68	<.05
Postoperative renal dysfunction (Cr>1,5 mg/dl)	9	10	>.05
Post-operative hemodialysis	7	5	>.05
Pulmonary complications	10	8	>.05
Neurological complications	9	9	>.05
Gastrointestinal complications	9	5	>0.05
Sternal dehiscence	14	16	>.05
ICU stay	3.2 ± 2.1	7.3 ± 4.3	<.05
Hospital stay	8.5 ± 3.7	13.7 ± 3.4	<.05
Time to extubation (h)	41.2 ± 15	33.2 ± 14	>.05
Infectious complications	7	5	>.05
DSWI	2	3	>.05
Surgical revision for bleeding	11	12	>.05
Postoperative bleeding > 1000 mL	17	16	>.05
Charge (as dollar) > $5000	28	101	<.05
LVEF increase (>35 %)	19	18	>.05
LVEDD decrease (< 60 mm)	32	30	>.05

AMI: Acute myocardial infarction; LCOS: Low cardiac output syndrome; IABP: intra-aortic balloon pump; ICU: Intensive care unit; DSWI: Deep sternal wound infection; LVEF: left ventricle ejection fraction; LVEDD: Left ventricle end-diastolic diameter.

hour) were used. Neuromuscular blockage was performed with pancuronium bromide or vecuronium at a dose of 0.1-0.15 mg/kg. All operations were done by cross-clamp with cardiopulmonary bypass and systemic blood pressure was maintained between 50 mmHg and 60 mmHg. Dopamine, nor adrenaline or nitroglycerin infusions were used to adjust systemic pressure if necessary.

Surgical Techniques

Operations were performed through median sternotomy. Conduits were harvested and prepared. CPB was instituted by using ascending aortic cannulation and a two-stage venous cannulation in the right atrium. In both groups, heparin was given at a dose of 300 lU/kg to achieve a target activated clotting time > 450 seconds. A standard circuit was used, including a Bard tubing set, which included a 40-m filter, a roller pump, and a hollow fiber membrane oxygenator. The extracorporeal circuit was primed with 1000 mL of Hartmann's solution, 500 mL of gelofusine, 0.5 g/kg of mannitol, 7 mL of 10% calcium gluconate, and 60 mg of heparin. Non-pulsatile flow was used. Systemic temperature was kept between 30°C and 32°C (middle hypothermic). The aorta was cross clamped, and myocardial protection was achieved with intermittent antegrade and retrograde blood cardioplegia. The distal anastomoses were constructed with running sutures of 7-0 or 8-0 polypropylene, and the proximal anastomoses were connected to the ascending aorta with 5-0 or 6-0 polypropylene sutures during a side clamping period. Cumulative regional ischemic times were between 9.1 – 14.2 minute for each anastomosis during cross clamping. After the patient was weaned from CPB and decannulated, the heparin was reversed with protamine infusion (1/1.5 rate). In all patients, two drainage tubes were inserted into to the space of a 32 F drainage left thorax and a 30 F drainage anterior mediastinal. The blood loss was recorded until the drain removal the following day. The average 20mm Hg continuous absorbing pressure was applied for drainage. Chest tubes were removed the following day when the drainage was less than 20 ml/h for a consecutive 4 h. The data and findings related to the operation are shown in Table 2.

Charges Data

Hospital expenses were obtained from hospital billing department considering hospital records. The hospital costs consisted of the following parameters: routine charges, operating room facility use, operating room supply use, pharmaceutical charges, laboratory charges, radiology charges, physical therapy charges, etc. Disposable supply costs are based on actual acquisition costs. The labor costs for nurses, technicians, fellows, residents, secretaries, orderlies, and other personnel are derived directly from actual salaries and include benefits. All hospital expenditures were calculated as per patient and presented as US dollars.

Monitoring of NVAF after discharge and postoperative period

After the completion of the surgical procedure, the patients were admitted to the intensive care unit and were closely monitored for hemodynamic and respiratory functions. In the intensive care unit and clinic, patients were followed up for rhythm problems (by 12-lead electrocardiography). Electrocardiographic recording was obtained twice a day on a routine basis, when the patient developed a new symptom or on physical examination, when tachycardia or irregular rhythm occurred. These electrocardiographic recordings were evaluated by cardiologists. All patients were followed up for up to 3 months following surgery.

Hospital mortality was defined as loss of patients for any reason occurring within 30 days after the operation. Postoperative renal dysfunction was defined as creatinine levels with a 50% increase compared to preoperative values.

Neurological complications were defined as temporary or permanent neurological deficits after surgery. Gastrointestinal complications included a confirmed diagnosis of upper and lower gastrointestinal bleeding, intestinal ischemia, acute cholecystis and pancreatitis. Generally, mortality, per-operative acute myocardial infarction, IABP usage, incidence of low cardiac output syndrome (LCOS), renal failure, use of inotropic agent, intensive care unit and hospital stay, cardiac hemodynamic changes, bleeding, revision rates, gastrointestinal, pulmonary and neurological complications, infections, and survive rates were determined.

Statistical Analysis

Statistical analysis was performed with SPSS software version 18.0 (SPSS Inc., Chicago, IL). Clinical data was determined as the mean ± SD. Student *t* test, χ^2 test, and the Fisher's exact test were used as indicated. The differences were considered to be significant for *P* values < .05.

RESULTS

Basic patient characteristics were similar between two study groups and reported in Table 1. There was no difference between the two groups in the characteristics of preoperative patients, and no statistical difference (*P* > .05).

The groups were similar with respect to the number of grafts (including the use of internal thoracic), ischemic time, cumulative regional ischemic times and total perfusion time, retrograde cardioplegia usage, the number of endarterectomy, internal thoracic artery usage, and were found not to be statistically significant. The mean overall number of distal anastomoses was 3.3 ± 0.5 versus 3.1 ± 0.5 (p>0.05). There was no difference in the number of bypassed vessels, in type of arterial conduits or the sites of surgical anastomoses between groups. The data related to the operation are shown in Table 2.

Postoperative survival, complications and data between groups were analyzed in Table 3. There were no differences between the groups in terms of bleeding amount, blood product type and amount of use, duration of inotropic support, amount of drainage, extubation time, revision rates and number of sternal revisions.

Hospitality mortality in medication group was 26 patients (8,9 %) versus 24 patients (8.5 %) in medication-free group (*P* > .05). Operative mortality was same between groups. The cause of deaths was low cardiac output. Early mortality within 48 hours was seen in 4 patients in medication group, 6 patients in medication-free group (*P* > .05). There was no pleural effusion requiring intervention in both groups. We did not encounter pericardial tamponade between patients.

Survivors are followed up to 3 months from the early period. In the first week, first month and third month follow-up, NVAF rates were higher in the medication-free group. There was a statistically significant difference between two groups in terms of NVAF (*P* > .05) (Table 3).

The echocardiography examination within a month revealed improvement of left ventricle function. EF increase and left ventricular end-diastolic diameter decrease were higher in both groups. However, these differences between the groups were not statistically significant (*P* > .05).

Between the groups there was an important difference in terms of ICU and hospital stay. The duration in the ICU and in hospital was higher in medication-free group compared to medication group, and there were significant statistical differences (*P* > .05). Because of NVAF, period in intensive care and hospital stay were less in number in medication group than medication-free group, the hospital costs were significantly lower for medication group (*P* > .05) (Table 2).

DISCUSSION

The generally accepted reason for the postoperative NVAF mechanism is the re-entry event. Several factors have been reported to be effective in arrhythmia, such as dilated or increased pressure in the atria, disturbances in the autonomic nervous system, metabolic and electrolyte imbalances, and myocardial ischemic injury. Recent research has shown that oxidative stress and inflammation also contribute to arrhythmia formation [Maisel 2001; Camm 2010; Imazio 2011]. Nevertheless, the mechanism is not fully illuminated. In the postoperative period, autonomic imbalance, excessive catecholamine production and hemodynamic factors as well as pericardial inflammation are triggering. In other words, systemic and local inflammatory responses may contribute to the pathogenesis of postoperative NVAF.

As a result of the introduction of cardiopulmonary bypass for cardiac surgery, the emergence of a non-biological surface causes oxidative stress response. Oxidative stress can be activated by inflammatory processes that cause systemic inflammation. Inflammatory metabolites such as total peroxide, reactive oxidative metabolites, C-reactive protein and interleukin-6 may increase due to the effect of cardiopulmonary bypass. This process may cause complications such as myocardial damage, renal dysfunction and arrhythmias. On the basis of this mechanism, oxidative stress can be reduced by using antioxidant agents, and it is thought that the inflammatory process will be suppressed and postoperative complications may be eliminated. [Paparella 2002; Chaney 2002; Goettea 2004; Gaudino 2003; Neuman 2007; Ramlawi 2007]. In the post-operative period, a number of researches have been supported by American and European guidelines for the reduction or prevention of NVAF. Many agents have been investigated for this purpose and as a result two main categorical targets have been shown: agents with antiarrhythmic properties and agents with anti-inflammatory activity such as corticosteroids, statins and free radical scavengers [Camm 2010; Imazio 2011; Reinhart 2011].

Conventionally, channel blocking drugs and beta blockers are frequently recommended for reducing the postoperative NVAF rate in current guidelines. However, the effectiveness of these drugs is not very high and their use is limited to their side effects. In recent years, the promising new approach is of non-channel-blocking drugs as a result of pathophysiology studies for AF. Although all patients used β-blocking agent before the operation in this study, many rhythm problems

occurred frequently in the postoperative period. These rhythm problems can be both early and late after surgery. We gave aspirin to the study group before the operation, because we believe that aspirin has an anti-inflammatory activity that prevents inflammation that may cause NVAF. In the first 3-month period, atrial fibrillation development in the aspirin receiving treatment group was found to be less.

Anti-inflammatory treatment may be useful in the prevention of NVAF in the postoperative period. Inflammation that disrupts the homogeneity of atrial conduction and the resulting rhythm problems that may occur as a result of this may be reduced by certain drugs. Due to this accepted fact, anti-inflammatory drugs given to patients have the potential to be effective in preventing or reducing the postoperative NVAF [Imazio 2011; Ho 2009]. Aspirin (acetylsalicylic acid) is one of the most widely used drugs worldwide and is used in the treatment of vascular diseases. Aspirin is part of a group of drugs called non-steroidal anti-inflammatory drugs, but the mechanism of action differs from most of the anti-inflammatory drugs in this group. Aspirin, however, have similar effects (antipyretic, anti-inflammatory, analgesic) as other non-steroidal anti-inflammatory drugs. Aspirin irreversibly inhibits the cyclooxygenase enzyme, but this inhibition is mostly from COX_1 rather than COX_2, and modifies the enzymatic activity of COX_2. It also is the archetypal non-steroidal anti-inflammatory drug found to inhibit the COX pathway of arachidonic acid metabolism [Lin 2003; Ozaydin 2008; Ho 2009]. On the other hand, it may show cardio-protective effect by inhibition of thrombocyte-induced thromboxane TxA_2 at low doses. It also inhibits the innate immunity pathways which include the production of TxA_2. As a result, the polymorphonuclear leukocyte (PMN) -platelet interaction leading to the migration of PMN to inflamed tissues is facilitated. In addition, aspirin triggers the synthesis of new lipid metabolites that directly stop leukocyte migration and induce pro-solubility effects. In addition, there is evidence that aspirin down-regulates pro-inflammatory signaling pathways, including NF-κB. This statement suggests that aspirin may also have an anti-inflammatory effect in cardio-protective doses. Despite the anti-inflammatory effect of aspirin provide with high-dose (1 gr) treatment, we found that 300 mg aspirin can prevent the rhythm problems relation to the inflammation in our study. The incidence of AF was found to be high in patients not receiving aspirin therapy, thus increasing the duration of the intensive care unit and hospital stay. Naturally, the cost of hospital treatment in these patients was also high.

CONCLUSION

These findings may be important for clinical practice because aspirin has been seen as an inexpensive and relatively safe option for the prevention of postoperative NVAF. Despite these positive results, larger studies are needed to demonstrate the efficacy of anti-inflammatory and preventing the rhythm problems at the current dose.

Study Limitations

Although the results are encouraging, important issues need to be considered. The relatively small sample size is the first study limitation. This study shows the first evidence of acetylsalicylic acid treatment efficacy for the prevention of AF, requiring further confirmation and validation in multicenter studies. Besides, we did not evaluate the laboratory parameters of oxidative damage that may associate with post-operative AF. We decided that the dose of 300 mg of acetylsalicylic acid inhibits inflammatory effect according to our study although it is known that the effect of high-dose. This study have shown that this dose acetylsalicylic acid can be correct the rhythm problems with anti-inflammatory effect, but still, additional studies are needed to associated with the this issue.

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