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Can, Acetylsalicylic Acid as the Most Commonly Used Anti-Aggregant, Prevent Atrial Fibrillation after Coronary Bypass Surgery?

Eyupserhat Calik, Umit Arslan and Bilgehan Erkut*

Atatürk University, Medical Faculty, Department of Cardiovascular Surgery, Erzurum, Turkey

**Corresponding author*

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A B S T R A C T

The present study investigated the effect of acetylsalicylic acid, an antiaggregant, on postoperative atrial fibrillation after coronary artery bypass surgery. Atrial fibrillation is a problem that affects mortality and morbidity rates after coronary surgery and prolongs hospital stay. Between January 2011 and October 2018, 722 coronary bypass surgery operations were performed. The patients were randomly divided into two groups as drug group (Group I; n=356) and control group (Group II; n=366). In Group I, the patients take to the acetylsalicylic acid (300 mg) without stopping up to 3 days before coronary bypass surgery. In Group II, the patients did not receive acetylsalicylic acid before surgery. Atrial fibrillation incidence rates were recorded retrospectively between 2 days and 4 weeks after the operation. Atrial fibrillation was seen in 21 (5.8%) patients in the Group I and 102 (27, 8 %) patients in the Group II had postoperative atrial fibrillation ($p < 0.05$). Intensive care unit and hospital stay were shorter in the drug group than the control group ($p < 0.05$). In addition, hospital treatment costs were lower in the drug group ($p < 0.05$). These results supported that acetylsalicylic acid is effective in preventing atrial fibrillation. Besides, acetylsalicylic acid treatment until operation day reduces hospital costs and length of stay in hospital, after the coronary artery bypasses grafting.

Introduction

Despite advances in surgical and medical advances, atrial fibrillation (AF) is still a common rhythm problem after cardiac surgery. It varies between 10-65 % depending on the type of surgery as coronary artery bypass graft surgery, valve surgery, and combined coronary artery bypass graft/valve surgery. Nowadays, AF is more common because of increased heart surgery operations and population aging. In addition, AF rates are associated with increased hemodynamic instability, thromboembolic events, longer hospital stays and increased health care costs (Khan *et al.*, 2013; Villareal *et al.*, 2004).

Drugs such as b-blockers and amiodarone have been used to prevent AF and many studies have been conducted on this subject (Khan *et al.*, 2013; Fuster *et al.*, 2006). In addition, despite of recommended prophylaxis, few recent studies have failed to confirm the desired protective effects of β-blocker against post-coronary artery bypass graft (CABG) AF (Balcetyte-Harris *et al.*,

2002; Maniar *et al.,* 2003; Paull *et al.,* 1997) and its incidence is on the rise as compared to past few years (Fuster *et al.,* 2006). Recent studies have investigated the use of certain drugs, such as nonsteroidal anti-inflammatory drugs, statins, and angiotensin converting enzyme inhibitors, to reduce postoperative AF and related complications. These new studies have shown that drugs minimize inflammation and this has been reported to result in a lower incidence of postoperative arrhythmias, including AF (Khan *et al.,* 2013; Tomic *et al.,* 2005; Wijeysundera *et al.,* 2005; Patti *et al.,* 2006).

The aim of this retrospective study was to investigate the effects of acetylsalicylic acid on AF prevention after coronary artery bypass surgery. We suggest that acetylsalicylic acid should be continued preoperatively if there is no contraindication in patients undergoing open heart surgery.

Materials and Methods

Between January 2011 and Oct 2018, 722 coronary artery bypass operations were performed at cardiovascular surgery clinic. This study was carried out meticulously and reported using randomization and blinding methods. In this prospective randomized study, 722 patients (400 male, 322 female) were included in the 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.

Before the study, the approval of the Hospital Ethics Committee was obtained and all procedures were carried out in accordance with the Declaration of Helsinki. The patients were randomly divided into two groups: the drug group (Group I; n=356 patients) and the control group (Group II; n=366 patients). The acetyl salicylic acid (300 mg/ per day) was given up to 3 days before the operation, which was accepted as drug group. The acetyl salicylic acid was not given to the control group. The mean age in Group I was 65.4 ± 4.1 years (38-79 years); in Group II it was 65.7 ± 4.8 years (41-77 years). By trans-thoracic echocardiography, left ventricular ejection fraction (LVEF) was 40.5% ± 6.5% in Group I, and was 41.7% ± 6.7% in Group II. In Group I, 54 (15.1 %) patients had intra-aortic balloon pump (IABP) preoperatively, 51 (13.9 %) patients had it in Group II. The criteria for preoperative placement of IABP were: cardiogenic shock or refractory ventricular insufficiency, hemodynamic instability, refractory angina, ventricular arrhythmia and critical left main stenosis (> 70%). All consecutive adult patients who were planned to undergo coronary heart surgery and had no contraindications to acetylsalicylic acid were included in the study. The patients included in the study were patients with normal sinus rhythm planned for primary elective coronary artery surgery. Besides, all patients were receiving β-blokage treatment.

The study exclusion criteria included (a) severe liver disease (b) serum creatinine level > 1.5 mg/dL, (c) known myopathy or elevated baseline preoperative creatine kinase, (d) pregnant and lactating women or women of childbearing potential not protected by a contraception method, and (e) patients who cannot take aspirin due to stomach problem. Other exclusion criteria included prior coronary revascularization or heart valve surgery, emergency surgery, ruptured papillary muscle severe mitral regurgitation, post infarction ventricular septal defect, previous AF, inflammatory diseases except coronary artery disease, infection, dilated left atrium (size ≥60 mm), electrolyte imbalance, age ≤18 years old, bleeding disorders and combined surgical procedures, and severe left ventricular dysfunction. Preoperative data and characteristic findings are shown in Table-1.

The combination of remifentanil and propofol was preferred as an anesthetic drug. Neuromuscular blockade was achieved by using 0.1-0.15 mg/kg pancuronium bromide. In Group I, dopamine or norepinephrine was used to maintain the systemic pressure between 50 and 60 mmHg and, if necessary, esmolol hydrochloride was used to regulate heart rate.

All operations were performed through median sternotomy. Conduits (IMA and saphenous veins) 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 IU/kg to achieve a target activated clotting time > 400 seconds. Non-pulsatile flow was used for extracorporeal circulation. Intermittent antegrade (every 20 minutes) and retrograde cold-blood cardioplegia was used in every patient. 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 single cross clamping period. Cumulative regional ischemic times were between 12.1-15.2 min. 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 thorax and anterior mediastinal space. The blood loss was recorded until the drain removal the following day. The data and findings related to the operation are shown in Table 2. Hospital expenses were obtained from the hospital billing department. These invoices consist of all hospital fees and fees incurred during the operation (routine operation, hospitalization, materials and medicine charges). All costs were calculated in patient head and in US dollars.

After completion of the surgical procedures, the patients were admitted to the intensive care unit and transferred to the clinic when the hemodynamic and respiratory functions were stable. The rhythms of the patients were continuously monitored during the operation and in the first 2 postoperative periods in the intensive care unit. The patients who were admitted to the clinic were routinely checked for rhythm twice a day, and new symptoms (tachycardia, AF or arrhythmia) were recorded. Besides the surgical team, cardiologists also evaluated the diagnosis of AF. Echocardiographic and electrocardiographic examinations were performed at the end of 4th week. The survival rate of the patients was obtained from the patients and their relatives.

Hospital mortality was defined as death for any reason occurring within 30 days after the operation. Postoperative renal dysfunction was defined as an increment of creatinine levels 1 mg/dL compared to the preoperative value. Neurological complications were defined as any transient or permanent neurological deficit that developed after surgery. Gastrointestinal complications included confirmed diagnosis of upper and lower gastrointestinal hemorrhage, 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 17.0 (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 <0.05.

Results and Discussion

The patient characteristic findings between the groups were similar and this is shown in Table 1. There was no statistical difference between the two groups in terms of preoperative characteristics (p> 0.05).

Table 2 shows the intra-operative variables. The groups were similar with respect to the number of grafts, ischemic time, and total perfusion time, the number of endarterectomy, internal thoracic artery usage, and were found not to be statistically significant. There was no difference in the number of bypassed vessels, in type of arterial conduits or the sites of surgical anastomoses between groups. The details on extent of coronary artery disease are shown in Table 2.

The postoperative survival, complications, and data between groups were analyzed in Table 3. There were no differences statistically in terms of the amount of bleeding, the amount of blood products use, the amount of drainage, and the duration of extubation, and revision for bleeding, sternal dehiscence in the groups (p>0.05). Although the pulmonary, neurological, gastrointestinal, and infectious complications were identified postoperatively in both groups in our series, but these problems were no important as statistically between groups (Table 3).

Hospitality mortality in Group I was 17 patients (4.7 %) versus 18 patients (4.9 %) in control group (p > 0.05). Operative mortality was same between groups. The cause of deaths was low cardiac output. Early mortality within 48 hours was seen in 6 patients in drug group, 7 patients in control group (p>0.05).

The mean follow-up time of the survivors was in a range of 4 weeks. In the assessment between first 2 days and a week, the rates of AF were higher in control group than the treatment group. At the end of the fourth week, AF appeared in 21 patients (5.8%) in Group I, and in 102 patients (27.8 %) in group II. All AFs were seen in the first two months after the operation. When the two groups were compared with respect to AF, there was statistically significant differences between groups (p<0.05) (Table-3).

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 control group compared to treatment group, and there were significant statistical differences (p < 0.05). Because of AF, period in intensive care and hospital stay were less in number in treatment group than control group, the hospital costs were significantly lower for treatment group, than control group (p < 0.05) (Table-3).

Re-entry mechanism is the most important condition in the formation of postoperative AF. Factors associated with multiple operations, such as surgical trauma in the operation, right atrial pressure increase, problems in the autonomic nervous system cycle, electrolyte and metabolic disorders, and ischemic injury in the myocardium, may contribute to arrhythmia and AF formation. The exact mechanism by which AF has occurred has not been elucidated. However, studies to date have shown that oxidative stress and inflammation may contribute to the mechanism of AF (Maisel *et al.*, 2001; Camm *et al.*, 2010; Massimo Imazio *et al.*, 2011). In

addition, factors such as autonomic imbalance, excessive catecholamine release, and hemodynamic imbalance-related factors, and pericardial inflammation play an important role in the initiation of AF. In other words, systemic and local inflammatory responses may contribute to the pathogenesis of postoperative AF.

CPB, which is frequently used in cardiac surgery cases, has been shown to be an oxidative stress response due to its non-biological surface structure. The resulting oxidative stress can activate inflammatory processes that cause systemic inflammation. In addition, total peroxide, reactive oxidative metabolites, C-reactive protein and interleukin-6 levels increase due to CPB. As a result, it may affect the development of complications such as myocardial damage, impaired renal function, and rhythm problems. Therefore, antioxidant agents and medical drugs can reduce the oxidative stress that may occur in patients and ultimately reduce inflammation (Paparella *et al.*, 2002; Chaney, 2002; Goettea and Lendeckel, 2004; Gaudino *et al.*, 2003; Neuman *et al.*, 2007; Ramlawi *et al.*, 2007).

After heart surgery, many studies have been done in the world for prevention of AF and in many articles, research as a target has been presented. As a result, several different agents have been studied and shown in two main categories: agents with anti-arrhythmic properties and agents with anti-inflammatory activity such as corticosteroids, statins and free-radical scavengers (Camm *et al.*, 2010; Massimo Imazio *et al.*, 2011; Reinhart *et al.*, 2011).

Table.1 Preoperative Data in Patients Undergoing CABG

	Group I	%	Group II	%	P values
Sex (M/F)	194/162		206/160		**0.701**
Age (mean)	65.4 ± 4.1		65.7 ± 4.8		**0.337**
Hypertension	216	60.6	234	63.9	**0.750**
Smoker habits	288	80.9	277	75.6	**0.453**
Diabetes Mellitus	124	34.8	132	36	**0.351**
Hypercholesterolemia	211	59.2	222	60.6	**0.899**
CVD	19	5.3	21	5.7	**0.603**
PVD	69	19.3	77	21	**0.304**
Preoperative PTCA	92	25.8	99	27	**0.642**
Preoperative IABP	54	15.1	51	13.9	**0.912**
Unstable angina	55	15.4	61	16.6	**0.432**
LA antero-posterior diameter	4.1±1.1		4.0±1.0		**0.199**
LVEF (mean %)	**40.5 ± 6.5**		**41.7 ± 6.7**		**0.112**

CVD: Cerebro-vascular disease; PVD: Peripheral vascular disease; PTCA: Percutaneous transluminal coronary angioplasty; IABP: Intra-aortic balloon pulsation; LVEF: Left ventricle ejection fraction;

Table.2 Operative Data

Variables	Group I	%	Group II	%	P values
CPB time (sec)	54 ± 11		51 ± 12		NS
XCL time (sec)	31 ± 9		32 ± 10		NS
Number of distal anastomosis	3.3 ± 0.5		3.1 ± 0.5		NS
LAD by pass	342	96	352	96.2	NS
Diagonal branches	288	80.8	291	79.5	NS
Cx by pass	192	53.9	191	52.1	NS
RCA by pass	168	47.2	177	48.3	NS
Coronary endarterectomy	81	22.7	84	22.9	NS
Retrograde cardioplegia usage	211	59.2	224	61.2	
Details of coronary artery disease					
Left main disease	96		88		NS
Three vessel disease	116		125		NS
Two vessels disease	104		1114		NS
Complete revascularization	355		367		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 < 0.05; important statistically, NS: non-specific statistically)

Table.3 Postoperative parameters between groups

Variables	Group I	Group II	P values
Hospital mortality (within 30 days)	17	18	>0.05
Early mortality (48 hours)	6	7	
Per-operative AMI	7	9	>0.05
New IABP insertion	26	22	>0.05
Duration of inotropic support (days)	6.2 ± 4.3	6.1 ± 4.1	>0.05
LCOS	24	22	>0.05
Atrial fibrillation (patients)			
First 3 days	**37**	**92**	<0.05
One week	**31**	**95**	<0.05
4 weeks	**21**	**102**	<0.05
Postoperative renal dysfunction(Cr>1,5 mg/dl)	14	15	>0.05
Post-operative hemodialysis	5	5	>0.05
Pulmonary complications	12	11	>0.05
Neurological complications	8	7	>0.05
Gastrointestinal complications	7	8	>0.05
Sternal dehiscence	12	11	>0.05
ICU stay	**3.0 ± 1.2**	**6.3 ± 2.4**	<0.05
Hospital stay	**6.5 ± 2.9**	**14.1 ± 2.6**	<0.05
Time to extubation (h)	31.7 ± 9	30.5 ± 11	>0.05
Infectious complications	8	6	>0.05
Surgical revision for bleeding	10	11	>0.05
Postoperative bleeding > 1000 mL	18	19	>0.05
Charge (as dollar) > 5000 $	32	121	<0.05

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.

In the medical literature, there are generally consensus and recommendations that channel blocking drugs and beta blockers reduce postoperative AF rates. However, the efficacy of these drugs is not very high and their use is limited to their side effects. In the recent years, the promising novel approach is 'non-channel-blocking drugs' that is brought about in consequence of recent investigations of pathophysiology for AF (Mihm *et al.,* 2001; Kim *et al.,* 2003; Lin *et al.,* 2003; Ozaydin *et al.,* 2008). In our study, although all our patients used β-blocker agent before surgery, many rhythm problems such as AF may occur frequently in the postoperative period (early or late period). Therefore, we have given acetylsalicylic acid our patients as a different agent in addition to β-blockers. Because we believed that acetylsalicylic acid had an anti-inflammatory activity, and with this effect we thought it could prevent inflammation, which could cause atrial fibrillation. As a result, in the first four-week period, we found that AF development occurred less in the treatment group receiving acetylsalicylic acid.

Anti-inflammatory treatment may be useful for the prevention of postoperative AF. This essentially anti-inflammatory medication may prevent the formation of rhythm problems by maintaining homogeneity in atrial conduction (Massimo Imazio *et al.,* 2011; Ho and Tan, 2009). Acetylsalicylic acid is one of the most widely used drugs worldwide. Non-steroidal anti-inflammatory drugs are included in the group, but the mechanism of action is different from other non-steroidal anti-inflammatory drugs. Nevertheless, there are similar effects (antipyretic, anti-inflammatory, analgesic) as other non-steroidal anti-inflammatory drugs. Salicylates also inhibit the cyclooxygenase enzyme, but acetylsalicylic acid does this effect irreversibly and affects more cyclooxygenase-1 (COX-1) variant than cyclooxygenase-2 (COX-2). That is, acetylsalicylic acid irreversibly inhibits COX-1 and alters the enzymatic activity of COX-2. COX-2 normally produces prostanoids, most of which are pro-inflammatory. Acetylsalicylic acid is the non-steroidal anti-inflammatory drug found to inhibit the COX pathway of arachidonic acid metabolism (Lin *et al.,* 2003; Ozaydin *et al.,* 2008; Ho and Tan, 2009). On the other hand, its cardio-protective effect is consisting of lower doses through the inhibition of platelet-derived thromboxane TxA_2. It also inhibits the innate immunity pathways which include the production of TxA_2. That is suggested to facilitate the polymorphonuclear leukocyte (PMN)-platelet interaction that leads to PMN transmigration into inflamed tissues. Moreover, acetylsalicylic acid triggers the synthesis of novel lipid metabolites that directly halt leukocyte trafficking and elicit pro-resolution effects. In addition, there is evidence that acetylsalicylic acid down-regulates pro-inflammatory signaling pathways including NF-κB. This suggests that acetylsalicylic acid may have anti-inflammatory effect at levels of cardio-protection (Massimo Imazio *et al.,* 2011; Ozaydin *et al.,* 2008; Ho and Tan, 2009). Although the anti-inflammatory effect of acetylsalicylic acid was known to occur at a dose of 1g, in our study, patients received 300 mg of acetylsalicylic acid, and we found that this dose could prevent inflammation and prevent rhythm problems. The patients were followed up in the hospital and after discharge for arrhythmia and all patients were followed up for rhythm 4 weeks after discharge. AF was significantly lower in the patients who received 300 mg acetylsalicylic acid than the other three days before the operation (due to the risk of bleeding). The duration of intensive care unit and hospital stay was significantly lower. As a result, treatment costs were lower in the drug group.

As conclusion acetylsalicylic acid appears to be safe and effective in reducing

postoperative AF incidence after cardiac surgery, and may be a cheap and relatively preferable option to prevent these common and troublesome complications. The effect of acetylsalicylic acid on postoperative AF can be explained by the inhibition of the inflammatory process associated with oxidative stress. In addition, acetylsalicylic acid treatment was associated with a decreased length of stay in hospital and fewer intensive care unit admissions. Clinical studies including larger series and meta-analyzes are needed to support or criticize our recommendation.

Study Limitations

Although the results are encouraging, a few important issues should be considered. The small number of our cases is one of them. In addition, we could not study the laboratory parameters which are indicators of oxidative stress that may be associated with AF in our article. Although it is known that high-dose acetylsalicylic acid has a major anti-inflammatory effect, we found that 300 mg of acetylsalicylic acid dose could prevent the inflammatory effect by inhibiting the formation of AF. Furthermore, this effect of acetylsalicylic acid should be supported by multi-center evidence and validation.

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