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Pre-Operative Use of Aspirin May Reduce Atrial Fibrillation Development Rate during Coronary Bypass Surgery

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Abstract

Objective: We sought to determine whether the administration of aspirin reduces the incidence of postoperative atrial fibrillation in coronary arterial bypass grafting surgery. Atrial fibrillation leads to an increase in morbidity and mortality as well as a increase in length of hospital stay due to an excess of medication usage.

Methods: From January 2012-May 2015, 550 patients undergoing coronary artery bypass surgery at our hospital were randomly assigned to two groups-treatment and control. In the treatment therapy group, the patients took acetylsalicylic acid (300 mg) without stopping before coronary bypass surgery. In the control group, the patients did not receive any anti-aggregant therapy before surgery. The rate of atrial fibrillation was retrospectivel evaluated between first 3 days, one week, and 4 weeks after surgery.

Results: While atrial fibrillation developed in 14 patients (5.1%) in treatment group, this rate was 24.2% with 68 patients in control group 4 weeks after operation (p<0.05). Between the groups there was an significant difference in terms of intensive care unit and hospital stay. In the treatment group, the ICU and hospital stay was shorter compared with the other group (p<0.05). Hospital charges were less in the treatment group (p<0.05).

Conclusion: These results suggest that aspirin is a useful drug for prevention of atrial fibrillation. Besides, aspirin treatment until operation day reduces hospital costs and length of stay in hospital, after the coronary artery bypasses grafting.

Keywords: Coronary artery bypass grafting; Atrial fibrillation; Anti-aggregant treatment; Cardiac surgery

Introduction

Despite surgical and pharmacological developments atrial fibrillation (AF) can often be observed undergoing cardiac surgery. Postoperative AF is the most common complication after cardiac surgery; it is reported in 10% to 65% of cases, depending on the surgery type (coronary artery bypass graft surgery (CABG), valve surgery, or combined coronary artery bypass graft/valve surgery), patient features, definition of arrhythmia, and surveillance [1,2]. Currently, AF is becoming more common because of the increasing number of cardiac surgery operations and the aging of the population. Besides, it is associated with increased incidence of hemodynamic instability, thromboembolic events, longer hospital stays, and increased health care costs [1,2].

A variety of pharmacological and non-pharmacological strategies have been employed to prevent AF after CABG such as adrenergic blocking agents and amiodarone [1,3]. In addition, despite of recommended prophylaxis of AF, few recent studies have failed to confirm the desired protective effects of β-blocker against post-CABG AF [4-6] and its incidence is on the rise as compared to past few years [3]. Recent evidence has suggested judicious use of certain perioperative medications like anti-aggregant agents, nonsteroidal anti-inflammatory drugs, statins, and angiotensin converting enzyme inhibitors to decrease the risk of postoperative complications. Some of these new measures have been independently shown to minimize inflammation resulting in lower incidence of postoperative arrhythmias including AF [1,7-9]. The goal of this prospective study was to examine the effects of acetyl salicylic acid on prevention of AF after coronary arterial bypass grafting.

Material and Methods

Patient population

Between January 2012 and May 2015, 721 coronary artery bypass operations were performed at our clinic. 550 of these patients (270 male, 280 female) were included in this randomized study due to detected exclusion criteria. Ethical permission was given by the our hospital ethics committee, and informed written consent was obtained from all participants and/or parents or guardians. The Hospital Ethical Committee Permission was obtained prior to commencement of the study. Furthermore, all procedures were carried out in accordance with the Declaration of Helsinki.

The patients were randomly divided into two groups: the aspirin therapy group (treatment group; n=270 patients) and the no aspirin therapy group (control group; n=280 patients). Aspirin (acetyl salicylic acid; 300 mg/perday) was given until the morning of the operation, which was accepted as treatment group. Aspirin was not given to the 280 patients in control group. Firstly, surgical and systemic complications, parameters associated with hemorrhage, cardiac status, mortality rate, infections, ICU and hospital length of stay and hospital costs compared between groups, postoperatively. Besides, the rate of postoperative AF was retrospectively evaluated between first 3 days, one week, and 4 weeks after surgery. The asymptomatic AF episodes can not be detected and self-terminating in the first 3 days could not be determined and

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taken into consideration.

Inclusion criteria

All consecutive adult patients undergoing cardiac surgery and without contraindications to acetylsalicylic acid were accumulated. To be included in the study, patients needed to be referred for primary elective coronary artery and in normal sinus rhythm. Besides, all patients were receiving β-blokade 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 creatine 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 diseases 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.

Anesthesia

Anesthesia consisted of propofol (3 mg/kg per hour) combined with remifentanyl (0.5-1 g/kg per min). Neuromuscular blockade was achieved by using 0.1-0.15 mg/kg pancuronium bromide or vecuronium. In the first Group, which is the treatment group, metaraminol or phentolamine was used to maintain the systemic pressure between 50 and 60 mmHg and, if necessary, esmolol hydrochloride (11 mg/kg) was used to slow the heart rate.

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. Intermittent antegrade and retrograde cold-blood cardioplegia and moderate hypothermia were applied in all Group I patients. CPB was established with aortic cannulation and bicaval venous drainage. 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 9.1-14.2 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 space of a 32 F drainage left thorax and a 30 F drainage anterior mediasten. The blood loss was recorded until the drain removal the following day. The average 20 mm 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. Per-operative data one is depicted in Table 1.

Charges data

Hospital charges are obtained through the hospital billing department as reported to our hospital authorities. The charges data is divided into the following categories: 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 costs were calculated per patient and presented in U.S. dollars.

Definition and follow-up for postoperative atrial fibrillation

After completion of the surgical procedure, patients were admitted to the intensive care unit and when their hemodynamic and respiratory functions were stable, they were transferred to the wards. Rhythm was monitored continuously during the operation and during the first 2 postoperative days in the intensive care unit. In the wards, patients were monitored with a 12-lead electrocardiography. An electrocardiography was obtained two times a day routinely and when the patient developed new-symptom or if physical examination revealed a tachycardia or irregular rhythm. All occurrences of AF were confirmed by diagnostic findings on 12-lead electrocardiography. Two blinded cardiologists assessed the electrocardiography. The rhythm was monitored during hospitalization. All surviving patients underwent a postoperative echocardiography and electrocardiography examination within 4 weeks after the surgical procedure. Survival status was determined by contacting all patients or next of kin by telephone.

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 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

Baseline patient characteristics were similar between the 2 study groups and are reported in Table 2. The mean age in treatment group was 62.1 ± 5.5 years (48-79 years); in control group it was 63.4 ± 5.8 years (45-77 years). By transthoracic echocardiography, LVEF was 45.6% ± 4.5% in treatment group, control group was 48.7% ± 4.7%. There were no differences between two groups in preoperative patients' characteristics. There was no statistical distinction in terms of preoperative features (p>0.05). In treatment group, 41 (15.2%) patients had IABP preoperatively, 47 (16.8%) patients had it in control 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%).

Table 1 shows the intra-operative variables of the patients. The groups were similar with respect to the number of grafts (including the use of internal thoracic), ischemic time, and total perfusion time, retrograde cardioplegia usage, the number of endarterectomy, internal thoracic artery usage, and were found not to be statistically significant (Table 1). 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 details on extent of coronary artery disease are shown in Table 1.

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, duration of inotropic support, the amount of drainage, the duration of extubation, revision for bleeding, sternal dehiscence in the groups. The post-operative use of IABP, per-operative acute myocardial infarction, postoperative renal dysfunction and LCOS was similar between 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 treatment group was 26 patients (9.6%) versus 24 patients (8.5%) 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 4 patients in treatment group, 6 patients in control group (p>0.05).

Early and late pericardial effusion detected by the echocardiography. There was no pleural effusion requiring intervention in both groups. We did not encounter pericardial tamponade between patients.

The mean follow-up time of the survivors was in a range of 4 weeks. In the assessment between first 3 days and one week, the rates of AF were higher in control group than the treatment group. At the end of the fourth week, AF appeared in 14 patients (5.1%) in treatment group, and in 68 patients (24.2%) in control group. 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).

The echocardiographic examination within a month revealed improvement of left ventricle function. EF increase and LVEDD decrease were higher in both groups. However, these differences between the groups were not statistically significant (p>0.05).

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 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).

Variables	Treatment Group	%	Control Group	%	P values
CPB time (sec)	65 ± 10		704 ± 13		NS
XCL time (sec)	26 ± 11		28 ± 110		NS
Number of distal anastomosis	3.3 ± 0.5		3.1 ± 0.5		NS
LAD by pass	270	100	280	100	NS
Diagonal branches	201	74.4	210	75	NS
Cx by pass	177	65.5	181	64.6	NS
RCA by pass	141	52.2	148	52.8	NS
Coronary endarterectomy	65	24.1	71	25.3	NS
ITA usage	268	99.2	277	98.9	NS
Retrograde cardioplegia usage	148	54.8	154	55	
Cumulative regional ischemic times (min.)	8.1 ± 2.2		8.2 ± 2.3		NS
Details of coronary artery disease					
Left main disease	76		78		NS
Three vessel disease	96		102		NS
Two vessels disease	98		100		NS
Complete revascularization	270		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 <0.05; important statistically, NS: Non-Specific Statistically).

Table 1: Operative data.

	Treatment Group	%	Control Group	%	P values
Sex (M/F)	144/126		148/132		0.549
Age (mean)	62.1 ± 5.5		63.4 ± 5.8		0.431
Hypertension	184	68.1	181	64.6	0.877
Smoker habits	196	72.6	190	67.8	0.752
Diabetes Mellitus	88	32.6	91	32.5	0.654
Hypercholesterolemia	165	61.1	155	55.3	0.901
CVD	17	6.3	16	5.7	0.890
PVD	43	15.9	42	15	0.766
Preoperative PTCA	80	29.6	85	30.3	0.642
Preoperative IABP	41	15.2	47	16.8	0.977
Unstable angina	31	11.5	38	13.6	0.510
LA antero-posterior diameter	4.1 ± 1.1		4.0 ± 1.0		0.105
LVEF (mean %)	45.6 ± 4.5		48.7 ± 4.7		0.330

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: Preoperative data in patients undergoing CABG.

Discussion

The usual conception on the mechanism of postoperative AF is reentry. Multiple peri-operative factors, such operative trauma, increased atrial pressure, autonomic nervous system imbalance, metabolic and electrolyte imbalances and myocardial ischemic damage have been contributed to the arrhythmia. Recent investigations have suggested that oxidative stress and inflammation may contribute to the pathophysiology of AF [10-12]. Nevertheless, the electrophysiological mechanisms of postoperative AF are incompletely understood. Post-operative AF is probably initiated by triggers, which are pericardial

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

AMI: Acute Myocardial İnfarction; LCOS: Low Cardiac Output Syndrome; IABP: İntra-Aortic Balloon Pump; ICU: Intensive Care Unit; DSWI: Deep Sternal Wound İnfection; LVEF: Left Ventricle Ejection Fraction; LVEDD: Left Ventricle End-Diastolic Diameter.

Table 3: Postoperative parameters between groups.

inflammation, combined with autonomic imbalance, excessive catecholamine production, and hemodynamic factors, may be significant factors. In other words, systemic and local inflammatory responses can contribute to occur the pathogenesis of postoperative AF.

The using CPB for cardiac surgery has been shown to provoke an oxidative stress response due to the non-biologic surface. Oxidative stress can activate inflammatory processes causing systemic inflammation. Total peroxide, reactive oxidative metabolites, C-reactive protein and interleukin-6 levels can increase because of the CPB. This may contribute to the development of complications such as myocardial injury, renal dysfunction and AF. Thus, agents with antioxidant properties may attenuate the oxidative stress and resultant inflammation seen in patients undergoing potentially reduce postoperative complications [13-18].

Prevention of post-operative AF is an important management goal supported by American and European guidelines. Many different agents have been studied to fit this goal and may be grouped into 2 main categories: agents with anti arrhythmic properties and agents with anti inflammatory activity such as corticosteroids, statins, and free radical scavengers [11,12,19].

Classically, channel-blocking drugs and beta-blockers are suggested to decrease the rate of postoperative AF in current guidelines. However, the efficacy of these drugs is not very high and their use is limited by 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. In this regard, previous studies have shown that there is an association between oxidative stress and AF [20-23]. Although all the patients, in this study, used the β-blocking agent before the operation, a lot of rhythm problems as AF were occur often in postoperative term. These rhythm problems may be both in the early and later periods after surgery. We had given acetylsalicylic acid agent up on the morning of the operation, because we believe that the acetylsalicylic acid has an anti-inflammatory activity that this activity prevents inflammation that can cause atrial fibrillation. We compared acetylsalicylic acid treatment group and control group (non-treatment group) in terms of the development of AF. The first four-week period, the development of AF was less in the treatment group receiving acetylsalicylic acid.

Anti inflammatory therapy may be beneficial for the prevention of post-operative AF. Inflammation, in homogeneity of atrial conduction, and the incidence of postoperative AF are decreased by some drugs. On this basis, anti-inflammatory drugs may have potential to be efficacious in preventing postoperative AF [12,24]. Acetylsalicylic acid is one of the most widely used drugs worldwide. It is part of a group of medications called non-steroidal anti-inflammatory drugs, but differs from most other non-steroidal anti-inflammatory drugs in the mechanism of action. Though it, and others called the salicylates, have similar effects (antipyretic, anti-inflammatory, analgesic) like the other non-steroidal anti-inflammatory drugs. Salicylates inhibit the same enzyme cyclooxygenase but the acetylsalicylic acid (not the other salicylates) does so in an irreversible manner and affects more the cyclooxygenase -1 (COX-1) variant than the cyclooxygenase-2 (COX-2). Acetylsalicylic acid irreversibly inhibits COX-1 and modifies the enzymatic activity of COX-2. COX-2 normally produces prostanoids, most of which are pro-inflammatory. Acetylsalicylic acid is the archetypal non-steroidal anti-inflammatory drug found to inhibit the COX pathway of arachidonic acid metabolism. On the other hand, its cardioprotective effect is consisting of lower doses through the inhibition of platelet-derived thromboxane TxA2. It also inhibits the innate immunity pathways which include the production of TxA2. 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 cardioprotection. Despite the anti-inflammatory effect of acetylsalicylic acid provide with high-dose (1 gr) treatment, we found that 300 mg acetylsalicylic acid can prevent the rhythm problems relation to the inflammation in our study. The rates of AF significantly decreased in patients who were treated with 300 mg acetylsalicylic acid until the morning of surgery in the first month. Stay in hospital and intensive care unit was significantly lower. The patients followed in terms of arrhythmia during the hospitalization and all the patients were followed closely throughout the early 4 weeks after discharge. We realized that rhythm problems were not received more in patients who had been given acetylsalicylic acid preoperatively. Incidence of AF, stay in intensive care unit and stay in hospital were higher in group of not used acetylsalicylic acid. Therefore, the treatment costs were higher in this group.

Conclusion

Acetylsalicylic acid seems safe and efficacious in reducing the incidence of post-operative AF after cardiac surgery. Such findings may be particularly important for clinical practice because acetylsalicylic acid might represent a cheap and relatively safe option for the prevention of post-operative AF, common and troublesome complications of cardiac surgery that may increase management costs. The result of this study indicates that acetylsalicylic acid treatment decreases the incidence of post-operative AF. This result supports the idea of the relationship between oxidative stress and AF. In addition, acetylsalicylic acid treatment was associated with a decreased length of stay in hospital and fewer intensive care unit admissions. Large clinical studies are needed to clarify this issue.

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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