Comparison of Intensity of Platelet Aggregation between Patients Receiving Low and High Aspirin Dosage in Post CABG Patients

Wanchai Wongkornrat, M.D.*, Somchai Sriyoscharti, M.D.*, Pansak Laksanabunsong, M.D.*, Teeravit Phanchaipetch, M.D.*, Thaworn Subtaweesin, M.D.*, Punnarerk Thongchareon, M.D.*, Pranya Sakiyalak, M.D.*, Worawong Slisatkorn, M.D.*, Nisarat Opartkiattikul, M.D.**

**Department of Surgery, **Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Background: Aspirin used after coronary artery bypass graft surgery (CABG) improved patient survival and reduced graft thrombosis. However, individual variations in the antiplatelet effect of aspirin have been reported among CABG patients.
Objective: To compare the intensity of platelet aggregation between patients receiving low and high aspirin dosage in post CABG patients.
Methods: We prospectively studied the effect of aspirin dosage on platelet aggregation in 100 CABG patients. Oral aspirin was discontinued prior to CABG and re-started within 12 hours after CABG. Blood samples were collected and transferred to a laboratory prior to surgery then again on postoperative days two and eight for platelet aggregation test and platelet count within three hours after venipuncture.
Results: One hundred patients (sixty five male and thirty five female patients) post coronary artery bypass graft (CABG) were evaluated for eligibility to enter the trial. The percentage of platelet aggregation was compared between low dose (<100 mg/day), and high dose (>100 mg/day) aspirin, at postoperative CABG days 2 and 8, which showed no significant difference for the platelet aggregation ($p = 0.161$ post CABG day 2 and $p = 0.098$ post CABG day 8).
Conclusion: Low dosage aspirin should be used in post CABG patients because the intensity of platelet aggregation between patients post CABG receiving low and high aspirin dosage were not different, while the prophylactic effect of the low aspirin dosage in reducing the risk of cardiovascular events proved equally as effective as the high aspirin dosage.

Keywords: Aspirin dosage, platelet aggregation, post CABG patient

Siriraj Med J 2011;63: 187-190
E-journal: http://www.sirirajmedj.com

Coronary Artery Bypass Grafting "CABG" surgery is the most common major cardiac surgery performed at Siriraj Hospital (500 cases/yr). CABG is indicated for the relief of symptoms as well as the prolongation of life. Aspirin is given to minimize the incidence of early and late graft occlusion while improving long-term cardiovascular outcomes.[1-2] Prospectively controlled trials have demonstrated a graft patency benefit when aspirin was started within 24 hours after the operation.[3-5] Dosage regimens ranging from 100 to 325 mg daily appear to be efficacious. The early postoperative use of aspirin is associated with a reduced risk of death, renal failure and ischemic complications involving the heart, brain, and gastrointestinal tract.[6]

The benefit of aspirin in cardiovascular disease relates to its ability to irreversibly inhibit platelet aggregation through acetylation of the platelet cyclooxygenase enzyme. Cyclooxygenase is required for the production of thromboxane A2, a promoter of platelet aggregation. This effect is so pronounced that higher doses of aspirin appear to yield no additional benefit and greatly increased doses may actually be damaging due to concomitant inhibition of endothelial cell synthesis of prostacyclin (a vasodilator and inhibitor of platelet aggregation). Low doses of aspirin may selectively inhibit platelet synthesis of thromboxane, while maintaining endothelial cell synthesis of prostacyclin.[7]

Correspondence to: Wanchai Wongkornrat
E-mail: siwanchai@mahidol.ac.th
Received 18 October 2010
Revised 10 June 2011
Accepted 16 June 2011

The policy for aspirin dosage in post CABG patients at Siriraj Hospital depends on the individual surgeon's experience (i.e. 60 mg, 80 mg, 120 mg and 325 mg) and is administered 12 hours after surgery and continued for a minimum of one year. Unfortunately there are inconclusive results regarding platelet aggregation in various aspirin dosages, although increase dosages of aspirin appear to be of no additional benefit and greatly increased dosages could have adverse effects.

The intention of this research was to collect data regarding relationships between aspirin dosage and platelet aggregation, while trying to search for the minimal effective dosages of aspirin and which provide maximum effectiveness.

MATERIALS AND METHODS

Methods

This study was approved by the Ethical Committee on Research Involving Human Subject, Faculty of Medicine Siriraj Hospital, Mahidol University on January 14th 2003. The procedure was performed after informed written consent was obtained from patients.

Patients

Between October 2003 and July 2004, a total of 100 patients who were treated in our facility by CABG, for coronary artery disease, were screened for participation in the study. The subjects received aspirin (ranging from totals of 60 mg to 325 mg) within 12 hours following CABG. The patients were excluded if they displayed contraindications to aspirin or if they were a re-operative case, an emergency case or had preexisting hematologic disease. There were a number of pre-existing diseases in these patients. Diabetes Mellitus was defined as fasting plasma glucose that was higher than 126 mg/dl and/or history of diabetes mellitus documented in medical records and/or on insulin/oral hypoglycemic drugs. Dyslipidemia was defined as cholesterol higher than 200 mg/dl or triglyceride higher than 150 mg/dl and /or on lipid lowering drugs. Hypertension was defined as systolic BP >140 mmHg, diastolic BP >90 mmHg and/or on antihypertensive drugs. Renal insufficiency was defined as creatinine greater than 2.0 mg/dl.

Blood samples to assess the extent of platelet aggregation were taken at three different time points. First after admission, but before operation then on post-operative day 2, because during peri-operative and immediately post-operative periods they still have the effect of cardiopulmonary bypass (such as thrombocytopenia, platelet dysfunction and fibrinolysis).[8] The final post-operative sample was taken on day 8 because the patient would be discharged if there were no complications. The blood samples were transferred to the laboratory within three hours after venipuncture. Platelet aggregation was evaluated considering the maximum percentage of platelet aggregation. This evaluation was performed by using a Lumiaggregometer (Model 1020B) and chart recorder (Model SPH5P), Payton scientific Inc. Buffalo, N.Y. Platelet aggregation was measured using a turbidometric approach after the addition of an aggregating agent into the platelet suspension. The baseline was set automatically for platelet aggregation. The percentage of platelet aggregation at five minutes after the addition of aggregating agent was 80-90% of normal (arachidonic acid) and the percentage of spontaneous platelet aggregation at 5 minutes (i.e. aggregation without any aggregating agent) was 10-20% of normal. Arachidonic acid must be converted by the platelets into prostaglandin, endoperoxides and thromboxanes for aggregation. If the enzyme has been inhibited by aspirin, then there will be no aggregation.

Statistical analysis

The baseline demographic was presented as mean +/-SD for the continuous variables and as the absolute number (percentage) for the categorical variables. Categorical variables were compared using Chi-square tests, and for continuous variables, student's t test was used. For data analysis, SPSS software was used. The statistical method used the Mann-Whitney test to compare the percentage of platelet aggregation at days 2 and 8 following surgery, between low and high dosage groups, and were considered statistically significant if the p-value was less than 0.05.

RESULTS

One hundred patients, sixty five male and thirty five female patients who received coronary artery bypass grafts (CABG), were evaluated for eligibility to participate in the trial. Their ages ranged from 32 years old to 88 years old (mean 63.83 ± 10.04), the body weight ranged from 40 to 108 kilograms (mean 64.42 ± 13.25), and the height ranged from 140-180 centimeters (160.02 ± 7.95). The preexisting diseases were diabetes mellitus in 49 patients (49%), hypertension in 77 patients (77%), hyperlipidemia in 22 patients (22%), and renal insufficiency (creatinine >2 mg/dl) in 9 patients (9%). Eighty six patients (86%) received the low dosage of aspirin (<100 mg/day), 12 patients (12%) received the high dosage of aspirin (>100 mg/day) and 2 patients (2%) were inconclusive. The baseline characteristics of the patients were comparable in the two groups. No difference was observed in the patient demographic characteristics. The characteristics of patients with low and high dosages of aspirin have been shown in Table 1.

The percentages of platelet aggregation were compared between low and high dosages of aspirin at postoperative CABG days 2 and 8 and have been shown in Table 2, Fig 1 and 2. In post CABG day 2, the patients who received the low dosages of aspirin had a mean platelet aggregation of 14.16% (median 5%) and a mean platelet aggregation of 13.13% (median 2.5%) for the high dosages of aspirin. In comparison, post CABG day 8, the patients who received the low dosages aspirin had a mean platelet aggregation of 12.06% (median 5%) and a mean platelet aggregation of 2.72% (median 2.5%) for the high dosages

TABLE 1. Baseline characteristics of patients.

Variable	Low dose aspirin (<100 mg) n = 86	High dose aspirin (>100 mg) n = 12	P value
Male	55 (63.6)	9 (75)	0.67
Age (years)	64.49 ± 9.94	59.67 ± 12	0.55
Body weight (Kg)	63.79 ± 13.12	69.45 ± 14.49	0.70
Height (cm.)	160 ± 8.36	160 ± 5.178	0.07
Diabetes mellitus	40 (46.5)	8 (66.7)	0.32
Hypertension	67 (77.5)	9 (75)	1.00
Dyslipidemia	45 (52.5)	7 (58.3)	0.35
Renal insufficiency	7 (8.1)	2 (16.7)	0.67
Platelet count average	213790	209666	0.70

Data are presented as mean ± SD or number (%)

TABLE 2. The percentage of platelet aggregation between low and high dose aspirin at post-operative CABG day 2, day 8.

	Low dose				High dose				P
Day	N	Mean ± SD	Min	Max	N	Mean ± SD	Min	Max	
2	77	14.16 ± 23.67	0.0	90.0	12	13.13 ± 26.07	0.0	70.0	0.16
8	68	12.06 ± 23.17	0.0	95.0	11	2.72 ± 2.36	0.0	5.0	0.10

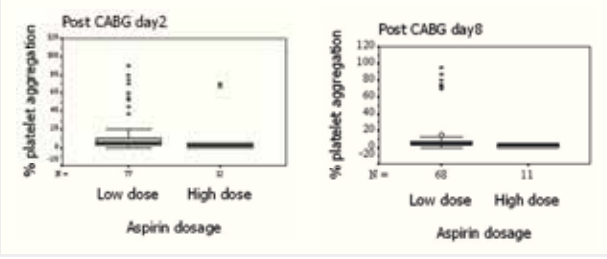

Fig 1. The percentage of platelet aggregation in low/high dose aspirin post CABG day 2 and day 8.

of aspirin. An insignificant difference for the platelet aggregation (p = 0.161 post CABG day 2 and p = 0.098 post CABG day 8) occurred. However, ten patients could not be assessed for the results of platelet aggregation due to a malfunction of the Lumiaggregometer.

The Siriraj protocol had advised discontinuation of aspirin 7-10 days prior to CABG. Thirty three patients received the low dosage aspirin prior to CABG and 67 patients received the high dosage aspirin. The revelation of this research was about the durations of aspirin, the patients who discontinued aspirin more than four days prior to surgery (65 patients) had a mean platelet aggregation of 65% (median 75 %), while the patients who discontinued aspirin less than or equal to four days prior had a mean platelet aggregation of 12.4% (median 5%). A significant difference (p <0.001) has been shown in Table 3 and 4, Fig 3.

DISCUSSION

Coronary artery bypass grafting (CABG) has been performed for more than 40 years. One year after the first CABG with a saphenous vein graft was performed in 1964,[9] the use of the internal thoracic artery was initiated. In an attempt to reduce the incidence of coronary restenosis, the risk factors of atherosclerosis should be controlled, such as smoking cessation, control of hypertension, blood sugar, cholesterol and antiplatelet therapy.

Antiplatelet agents, such as aspirin, are given to minimize the incidence of early graft occlusion. The 2008 American College of Chest Physicians (ACCP) guideline on the primary and secondary prevention of coronary artery disease recommended administrating aspirin (75 to 100 mg/day) following CABG.[10] It should be given immediately or within 24 hours following CABG, assuming there was no contraindications. Recent studies have demonstrated the prophylactic effect of low dosage aspirin (100 mg) in reducing the risk of cardiovascular events is equally as effective as high dosage aspirin by clinical comparison, but laboratory comparisons have not been considered. There was no significant differences in systemic embolisms, vascular deaths, total death rates, or total number of hemorrhagic events between the low and high dosage aspirin treatment groups (0.5 and 1.1, 1.2 and 0.5, 4.6 and 2.5, and 7.9 and 13.4 per 100 patients/year, respectively).[11]

The revelation of this research is that low dosage (<100 mg) and high dosage (>100 mg) of aspirin can inhibit platelet arachidonate-induced aggregation at postoperative CABG days 2 and 8. The results showed no significant difference for the platelet aggregation.

Based on the results from this research, the aspirin dosages in post CABG patients at Siriraj Hospital are

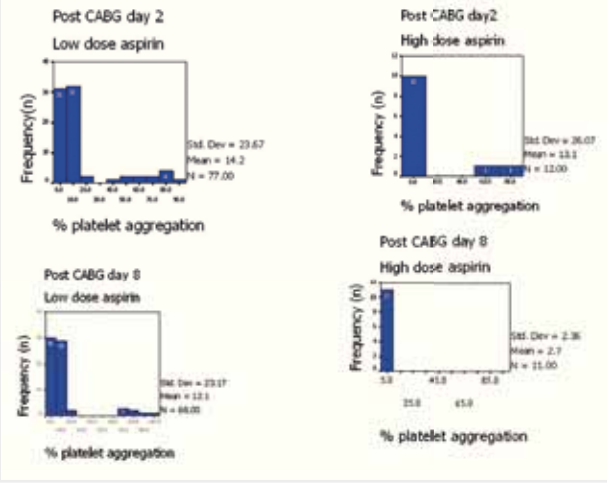

Fig 2. The percentage of platelet aggregation in low/high dose aspirin post CABG day 2 and day 8.

TABLE 3. The percentage of platelet aggregation after discontinued aspirin before surgery among CABG patients.

Discontinued aspirin pre-op (day)	Mean %plt agg	N	Std. deviation
1	5.625	4	6.2500
2	16.429	7	22.8609
3	4.000	5	1.3693
4	16.944	9	26.0342
5	60.000	11	29.9166
6	52.500	3	40.2337
7	62.656	16	26.4649
8	66.313	8	28.5206
9	68.214	7	30.0595
10	53.125	4	35.9035
11	80.000	2	7.0711
12	82.500	3	15.6125
13	72.500	1	.
14	80.000	1	.
16	45.000	1	.
17	70.000	1	.
19	75.000	1	.
26	87.000	1	.
30	40.000	2	49.4975
39	95.000	1	.
45	85.000	1	.
100	87.500	1	.
Total	50.389	90*	34.7276

TABLE 4. The percentage of platelet aggregation of patients discontinued aspirin before CABG.

Discontinued aspirin	N	Platelet aggregation (%)				
		Median	Mean	Standard deviation	Minimum	Maximum
< / = 4 day	25	5.00	12.40	19.91	2.50	80.0
>4 day	65	75.00	65.00	27.35	0.00	107.5
Total	90*	68.75	50.39	34.73	0.00	107.5

*Ten patients cannot be assessed the result of pre-operative platelet aggregation due to malfunction of Lumiaggregometer.

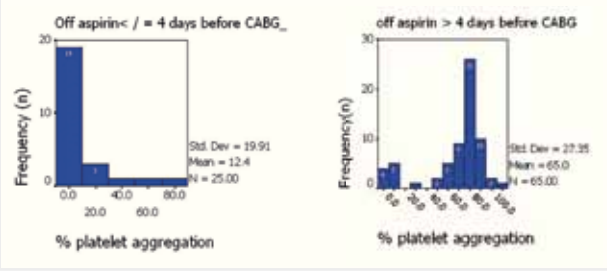

Fig 3. The percentage of platelet aggregation in the patients discontinued aspirin more and less than four days.

recommended as 60 mg or 80 mg due to the fact that there was no significant difference for the platelet aggregation between the two groups. Increased dosages of aspirin appear to have no additional benefit, while greatly increased dosages may have adverse effects.

The limitation of this research was that the sample sizes between the two groups were different, because two of the seven surgeons used high dosage aspirin. However no difference was documented in any of the patient demographic characteristics.

Additionally, the current guideline of the Society of Thoracic Surgeons recommends that for the elective patients who require CABG, it may be reasonable to discontinue aspirin for a few days (2 to 3 days) with the expectation of less peri-operative bleeding and blood transfusion respectively.[12] According to the Society of Thoracic Surgeons recommendation, this research had revealed that the percentage of platelet aggregation in the patients who discontinued aspirin for more than four days had a significant difference when compared to the patients who discontinued aspirin less than or equal to four days.

REFERENCES

1. Sanz G, Pajarón A, Alegría E, Coello I, Cardona M, Fournier JA, et al. Prevention of early aortocoronary bypass occlusion by low-dose aspirin and dipyridamole. Grupo Español para el Seguimiento del Injerto Coronario (GESIC). Circulation. 1990 Sep;82(3):765-73.
2. Gavaghan TP, Gebski V, Baron DW. Immediate postoperative aspirin improves vein graft patency early and late after coronary artery bypass graft surgery. A placebo-controlled, randomized study. Circulation. 1991 May; 83(5):1526-33.
3. Chesebro JH, Fuster V, Elveback LR, Clements IP, Smith HC, Holmes DR Jr, et al. Effect of dipyridamole and aspirin on late vein-graft patency after coronary bypass operations. N Engl J Med. 1984 Jan 26;310(4):209-14.
4. Lorenz RL, Schacky CV, Weber M, Meister W, Kotzur J, Reichardt B, et al. Improved aortocoronary bypass patency by low-dose aspirin (100 mg daily). Effects on platelet aggregation and thromboxane formation. Lancet. 1984 Jun 9;1(8389):1261-4.
5. Koch M, Gradaus F, Schoebel FC, Leschke M, Grabensee B. Relevance of conventional cardiovascular risk factors for the prediction of coronary artery disease in diabetic patients on renal replacement therapy. Nephrol Dial Transplant. 1997 Jun;12(6):1187-91.
6. Mangano DT; Multicenter Study of Perioperative Ischemia Research Group. Aspirin and mortality from coronary bypass surgery. N Engl J Med. 2002 Oct 24;347(17):1309-17.
7. Patrono C, Coller B, FitzGerald GA, et al. Platelet-active drugs, the relationships among dose, effectiveness, and side effects: The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004;126 (3 Suppl):234S-264S.
8. Roque P. Bleeding as a complication of cardiopulmonary bypass: Management of bleeding in cardiovascular surgery. 1st ed. Philadelphia: Hanley & Belfus Inc; 2000. p. 1-7
9. Stephenson LW. History of Cardiac Surgery. In: Cohn LH, Edmunds LH Jr, eds. Cardiac Surgery in the Adult. 2nd ed. New York: McGraw Hill; c2003. p. 18.
10. Becker RC, Meade TW, Berger PB, Ezekowitz M, O'Connor CM, Vorcheimer DA, et al. The primary and secondary prevention of coronary artery disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl): 776S-814S.
11. Altman R, Rouvier J, Gurfinkel E, Scazziota A, Turpie AG. Comparison of high dose with low dose aspirin in patients with mechanical heart valve replacement treated with oral anticoagulant. Circulation. 1996 Nov 1;94 (9):2113-6.
12. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA 2nd, Haan CK, et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. Ann Thorac Surg. 2007 May;83 (5 Suppl):S27-86.