

Effect of Anti-Platelet Therapy on Peri-Operative Blood Loss in Patients Undergoing Off-Pump Coronary Artery Bypass Grafting

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ABSTRACT

Purpose: The purpose of this study was to review the effect of the pre-operative use of clopidogrel and aspirin on peri-operative bleeding, blood product transfusion, and resource utilization after coronary artery bypass grafting (CABG).

Materials and Methods: A total of 1200 patients who underwent off-pump CABG (OPCABG) between 2010 and 2012 were retrospectively studied. Patients were divided into three groups: group 1: discontinued aspirin and clopidogrel 6 days prior to surgery (n = 468), group 2: discontinued both drugs 3 to 5 days prior to surgery (n = 621), and group 3: discontinued both drugs 2 days prior to surgery (n = 111). The bleeding pattern and blood product transfusion were studied and compared between the groups. Patients having history of other drugs affecting the coagulation profile, other organ dysfunction, on-pump CABG, and the combined procedure were excluded from the study.

Results: Group 2 patients had a higher rate of bleeding and a reduced mean value of hemoglobin (Hb) as compared to other groups. The same results were seen in blood and blood product transfusion. Patients of group 2 and group 3 were associated with higher blood loss in terms of drainage at 12 and 24 hours. Post-operatively, this was statistically significant. Re-exploration was statistically significant in group 3 patients (9.01%) than in group 2 (2.58%) and group 1 (1.07%) patients.

Conclusion: The pre-operative use of clopidogrel and aspirin in patients undergoing OPCABG showed limited clinical benefits; however, its use significantly increased the risk of bleeding and blood transfusion, thus increasing morbidity and resource utilization. Hence, clopidogrel and aspirin should be stopped at least 6 days prior to surgery.

Keywords: Anti-platelet, aspirin, blood transfusion, clopidogrel, off-pump CABG, post-operative bleeding

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INTRODUCTION

Coronary artery bypass grafting (CABG) is highly effective in relieving the symptoms of ischemic heart disease (IHD) and improving the life expectancy. Platelet-rich intra-coronary thrombi are central to the pathogenesis of acute coronary syndromes. The use of

anti-platelet drugs is of great clinical importance in both pre- and post-revascularization states.^[1,2]

Bleeding and the need for transfusion of red blood cells are associated with an increased risk of morbidity and prolonged intensive care unit (ICU) stay. The need

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for peri-operative transfusion is one of the significant predictive factors for the risk of subsequent post-operative morbid events.^[3] Platelet inhibition is paramount in the management of coronary artery disease. Anti-platelet drugs reduce mortality and the incidence of major vascular events in patients with a wide variety of vascular occlusive pathologies.^[4] First discovered in 1897, aspirin irreversibly inhibits platelet cyclooxygenase-1, thereby eliminating the production of thromboxane A₂, a potent activator of platelet aggregation. Clopidogrel is an irreversible adenosine 5 diphosphate receptor antagonist that provides potent anti-aggregant effects on platelets.^[5] The enhanced anti-platelet therapy provided by clopidogrel has led to its use in combination with aspirin as the gold standard for prevention of intra-coronary stent thrombosis (ST).^[5]

Clopidogrel is often given before angiography and percutaneous coronary interventions (PCIs). The multi-national GRACE registry showed that 7% of non-ST elevation myocardial infarctions (NSTEMIs) and 4% of STEMI patients receive CABG surgery during their hospital admission.^[6] Most of these patients receive clopidogrel upon the first presentation of their acute coronary syndrome in the emergency department. Many patients receive long-term clopidogrel with or without aspirin and present for surgical coronary revascularization.

Compared to aspirin, which has been studied extensively in the post-operative period, another important issue is the use of clopidogrel in CABG patients. Studies have shown that treatment with clopidogrel before CABG is associated with increased post-operative bleeding, transfusion, re-exploration rates, overall lengthier hospital stays, and increased mortality.^[7-9]

Post-operative bleeding is a significant cause of morbidity and mortality, requiring transfusion of blood and blood products and sometimes requiring surgical re-exploration for control of bleeding. Re-operation for bleeding may occur in as many as 2% of patients. The main causes of bleeding include incomplete surgical hemostasis, defective coagulation, and platelet dysfunction.

The purpose of this study was to review the effect of the pre-operative use of clopidogrel and aspirin on clinical outcomes, bleeding-related complications, and resource utilization after off-pump CABG (OPCABG) in our institution.

AIMS AND OBJECTIVES

1. The primary objective of the study was to determine the effects of anti-platelet drug usage on peri-operative bleeding.
2. To assess the morbidity and mortality associated with the use of anti-platelet drugs prior to surgery.

MATERIAL AND METHODS

All the patients who underwent OPCABG between January 2010 and December 2012 were retrospectively studied. A total of 1200 patients were studied and were divided into three groups, namely, group 1: patients who discontinued both anti-platelet drugs (aspirin and clopidogrel) 6 days prior to surgery (n = 468), group 2: patients who discontinued both anti-platelet drugs 2 to 5 days prior to surgery (n = 621), and group 3: patients who discontinued both drugs 2 days prior to surgery (n = 111). Baseline demographics, standard comorbidity factors, and pre-operative medications were collected for all patients. The approval of ethics committee was taken. Date of approval from Institutional Ethical Committee: 30.09.2012.

Anesthetic and surgical techniques

Anesthetic techniques and heparin and protamine management were standardized for all patients. Intravenous heparin was given 1 mg/kg after the internal mammary artery harvesting. All patients underwent OPCABG. Anti-coagulation was maintained with the activated clotting time (ACT) twice the normal value or above 250 seconds for all patients. Heparin was then completely reversed at the end of surgery by protamine to obtain an ACT less than 125 seconds.

Post-operative management

Patients were transferred to ICU for elective post-operative ventilation and managed according to unit protocols. Patients were extubated as they met the extubation criteria. Hematocrit was targeted greater than 24% in all patients. Aspirin 150 mg and clopidogrel 75 mg were given on the first post-operative day.

On arrival in ICU, all patients underwent a routine coagulation screening. In the case of excessive bleeding (more than 150 ml/hr, for longer than 2 consecutive hours) or derangement of the coagulation profile, patients were treated with a diagnosis-directed therapy. Elevation of ACT of more than 30 sec. above the baseline was treated with an additional dose of protamine. The values of PT, aPTT, and INR of more than 1.5 times the control (suggesting factor deficiency) were treated with fresh frozen plasma (FFP). A platelet count of less than 80,000 was an indication for platelet transfusion. A hematocrit of less than 24% was corrected by transfusion of red blood cells. The total blood loss was measured starting immediately after closure of the chest in the operating theater until the chest drains were

removed, provided the drainage was less than 20 ml/hr for 3 consecutive hours. The indications for re-exploration were blood losses greater than 500 ml over the first hour, more than 300 ml for 2 consecutive hours, more than 200 ml for 3 consecutive hours, and more than 1 liter over the first 8 hours.

Exclusion criteria

Patients having history of previous cardiac surgery, emergency surgery, pre-operative exposure to warfarin sodium (Coumadin), platelet glycoprotein IIb/IIIa inhibitors or thrombolytics, end stage renal failure, and liver dysfunction were excluded from the study. Patients needing conversion to on-pump surgery or combined procedures (valve surgery along with CABG) were also excluded.

Source of data

Data were prepared from the history taken and pre-operative out-patient department prescription taken from the record file of the patients for a period of 3 years, that is, from January 2010 to December 2012. Data were collected according to the performa which had patient details, investigation details, and any events recorded during hospital stay. Intra-operative and peri-operative findings were noted from operative reports.

Statistical analysis

Quantitative data were described in mean and standard deviation, and group values were compared using analysis of variance (ANOVA). Categorical data were described by absolute and percentage frequencies and were compared using the Chi-square test. Differences were considered significant when $P \leq 0.05$.

OBSERVATIONS AND RESULTS

We included a total of 1200 patients in our study of different age groups from 31 years to 70 years. There was no statistically significant difference in age among all three groups. Among the three groups, the male and female ratio was similar and statistically insignificant (a total of 945 males and 255 females). There were four main major risk factors as noted from the past history of all patients, which included hypertension, diabetes mellitus, smoking, and dyslipidemia. All these four factors were distributed similarly in the three groups with no statistical difference. As a standard protocol, the assessment of Hb was performed in all patients at five points of time at different time intervals as listed in Table 1. We found that the value of Hb on post-op. day 1 was statistically significantly lower in all groups (p value < 0.001). There

was no significant difference in mean Hb value on other four points of observations.

Table 1 shows the packed cell volume (PCV) count of all patients of our study on five points of time. No statistically significant difference was observed in total PCV count in all groups except on post-op. day 1 (p value < 0.001). The platelet count of all patients of our study on five points of time is shown in Table 1. We found no significant difference in total platelet count in all groups except the statistically significant difference on post-op. day 1 (p value < 0.001). There was a significant difference in chest tube drainage at 12 hours and 24 hours in the post-op. period but no significant difference on 48 hours and 72 hours in the post-op. period [Table 2]. Table 3 shows a statistically significant difference observed in requirement of total blood transfusion in patients of all three groups. A total of 636 patients needed blood transfusion in the post-op. period. Out of these, 375 patients were in group 2, 197 patients were in group 1, and 64 patients were in group 3. Table 3 suggests a statistically significant difference in total platelet requirement in all groups. A total of 245 patients required < 2 units of platelet transfusion, whereas 14 patients needed > 2 units of platelet transfusion. Also, there was a statistically significant difference in requirement of total FFP in patients of all three groups. A total of 164 patients needed FFP in the post-op. period. Out of 164, group 2 had the maximum number of patients who required FFP ($n = 123$), followed by group 1 ($n = 26$) and then group C ($n = 15$). This difference was statistically significant. Out of total 1200 patients analyzed, overall total 31 patients required re-exploration in all three groups [Table 4]. 9.01% patients of group 3 ($n = 10$) needed re-exploration, whereas only 2.58% patients of group 2 ($n = 16$) and 1.07% patients of group 1 ($n = 5$) required re-exploration. This difference in re-exploration rate between the three groups was statistically significant (p value < 0.001).

DISCUSSION

The inhibition of platelet functions, through the administration of aspirin and clopidogrel, is the mainstay of treatment for patients with documented coronary artery disease.^[10] Nevertheless, controversy remains regarding the optimal type and timing of anti-platelet therapy to prevent peri-operative ischemic episodes and graft occlusions and at the same time minimize bleeding complications.

Aspirin has been shown to reduce the risk of stroke, myocardial infarction (MI), and vascular death in patients with ischemic heart disease.^[4] Some patients may show that

Table 1: Distribution of Hb, PCV, and platelet count in different points of observation

Hb	Group 1	Group 2	Group 3	Total	P
Hemoglobin					
Pre-operative	12.404±1.8	12.427±1.953	12.61±1.604	12.435±1.864	0.573
Post-op. Day 1	11.97±1.563	9.26±2.38	11.71±1.20	10.54±2.40	< 0.001
Post-op. Day 3	10.285±1.515	10.505±5.049	10.218±1.788	10.393±3.792	0.561
Post-op. Day 5	10.468±1.33	10.335±1.366	10.262±1.177	10.38±1.336	0.164
On discharge	10.857±1.299	10.785±1.734	10.661±1.078	10.801±1.524	0.444
Packed Cell Volume					
Pre-operative	36.757±5.584	36.159±6.153	37.458±5.173	36.512±5.861	0.050
Post-op. Day 1	35.05±5.70	28.84±6.61	34.78±3.89	31.81±6.79	< 0.001
Post-op. Day 3	30.853±4.953	31.419±15.27	30.762±5.321	31.137±11.525	0.679
Post-op. Day 5	31.419±4.006	31.009±4.206	30.786±3.532	31.148±4.073	0.159
On discharge	32.57±3.897	32.362±5.199	31.984±3.233	32.408±4.57	0.449
Platelet Count					
Pre-operative	223.13±71.914	226.035±81.621	221.261±83.694	224.461±78.133	0.751
Post-op. Day 1	202.05±98.85	189.04±72.455	185.207±69.732	188.253±83.566	0.021
Post-op. Day 3	171.699±72.694	176.823±71.89	171.748±70.294	174.355±72.045	0.470
Post-op. Day 5	180.481±69.931	191.448±81.559	195.234±83.179	187.521±77.537	0.038
On discharge	212.244±83.441	221.953±93.66	239.018±103.941	219.745±91.093	0.014

Table 2: Distribution of drainage among the study groups

Drainage	Group 1	Group 2	Group 3	Total	P
12 hours	232.107±223.063	314.994±240.081	289.919±142.343	280.389±229.309	< 0.001
24 hours	216.475±188.928	333.939±258.845	283.682±191.915	283.408±234.498	< 0.001
48 hours	136.261±114.386	161.32±152.371	142.921±99.089	149.938±134.918	0.011
72 hours	93.309±88.982	100.637±89.418	93.488±80.649	97.232±88.322	0.690

Table 3: Distribution of total blood transfusion among the study groups

Total transfused blood units	Group 1		Group 2		Group 3		Total	
	No.	%age	No.	%age	No.	%age	No.	%age
No	271	57.91	246	39.61	47	42.34	564	47.00
1-2	141	30.13	273	43.96	48	43.24	462	38.50
3-6	56	11.97	96	15.46	15	13.51	167	13.92
>6	0	0.00	6	0.97	1	0.90	7	0.58
P	< 0.001							

'aspirin resistance' may adversely impact post-operative saphenous vein graft patency.^[11,12] In this context, more intense anti-platelet therapy, including the use of clopidogrel, has been proposed as a means to improve post-operative outcomes and graft patency.

Combining aspirin therapy with clopidogrel has potent synergistic anti-thrombotic effects. Following the publication of the CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) and CREDO (Clopidogrel for the Reduction of Events During Observation) studies, the number of patients referred for surgical revascularization after having recently received clopidogrel has dramatically increased.^[8] The association of aspirin with clopidogrel in the pre-operative setting is a cause for concern because complete inhibition of platelet functions causes serious bleeding.

The proportion of patients undergoing CABG may have post-operative issues, namely, re-exploration for

bleeding (incidence of 2% and 6%). The re-exploration may result in post-operative morbidity, for example, deep and superficial wound infections, and hemodynamical instability and may require a greater number of blood and blood product transfusion.^[13]

This study was undertaken to assess the effect of aspirin and clopidogrel in OPCABG surgery. OPCABG surgery differs from standard on-pump CABG because patients receive less heparin and are not exposed to cardiopulmonary bypass complications, which has known documented deleterious effects on platelet activation and coagulation system regulation. American Heart Association (AHA) guidelines suggest that patients should discontinue clopidogrel for 5 days prior to CABG.^[7] We reviewed the literature related to peri-operative anti-platelet therapy and designed this study. We divided our patients into three groups according to their medication history.

Ferraris *et al.*^[14] reported that patients randomized to receive pre-operative aspirin had significantly greater chest tube drainage, significantly increased requirements for post-operative blood product transfusion, and a greater need for re-exploration. Similar results were reported by Kallis and Ghaffarnejad in randomized controlled trials.^[15,16] In one of the largest controlled trials to address the hemorrhagic effect of pre-operative aspirin, Sethi *et al.*^[17] randomized 772 patients to one of five regimens

Table 4: Distribution of platelet and FFP transfusion and incidence of re-exploration among the study groups

	Group 1		Group 2		Group 3		Total	
	No.	%age	No.	%age	No.	%age	No.	%age
RDP transfusion								
No	401	85.68	450	72.46	90	81.08	941	78.42
1-2	64	13.68	162	26.09	19	17.12	245	20.42
>2	3	0.64	9	1.45	2	1.80	14	1.17
FFP transfusion								
No	442	94.44	498	80.19	96	86.49	1036	86.33
1-2	26	5.56	91	14.65	14	12.61	131	10.92
>2	0	0.00	32	5.15	1	0.90	33	2.75
Re-exploration								
No	463	98.93	605	97.42	101	90.99	1169	97.42
Yes	5	1.07	16	2.58	10	9.01	31	2.58
<i>P</i>								<0.001

involving aspirin, dipyridamole, sulfinpyrazone, and placebo. Compared to patients who were administered placebo, aspirin patients received significantly more blood transfusions and more frequently required re-operations for bleeding (6.6 with aspirin versus 1.7% no aspirin, $P = 0.002$).

A meta-analysis of 60 randomized controlled trials involving 94,000 patients assessed the safety of anti-platelet therapy administered to high-risk cardiovascular patients. The incidence of fatal and non-fatal bleeding in patients randomized to aspirin was slightly higher (1.1%, compared to 0.7% in the placebo group).^[4]

Chesebro JH studied placebo versus a combination of aspirin and dipyridamole post-op. periods. They found that chest tube bleeding was similar between the two groups.^[18] In a multi-center study involving 1112 CABG patients, Sanz *et al.*^[19] found similar re-operation rates (average 3.9%) in the groups.

Maltais *et al.*^[20] evaluated the effect of aspirin and clopidogrel (CPDG) on operative bleeding and determined the optimal timing for their discontinuation before surgery. They found that clopidogrel in OPCABG surgery was associated with higher intra-operative and post-operative bleeding. They concluded that discontinuation of clopidogrel 72 hours prior to the operation demonstrated a similar blood loss pattern compared to the no anti-platelet group. Our data indicate a significantly higher rate of bleeding in group 2. We found that the values of Hb, PCV, and platelet count on day 1 of the post-op. period were decreased in all groups, but there was a more significant fall in group 2, followed by group 3.

Shim JK *et al.*^[21] conducted a study to determine the effects of aspirin and clopidogrel therapy in OPCABG patients and found a significant decrease in hematocrit level and

platelet count and prolongation in prothrombin time post-operatively in all groups without any inter-group differences. They concluded that pre-operative clopidogrel and aspirin exposure even within 2 days of surgery does not increase peri-operative blood loss and blood transfusion requirements. Our data suggest that 47% patients did not require any transfusion, whereas 53% required blood transfusion (range 1–6 units). In our study, 60.39% patients of group 2 required transfusion, which was significantly higher than those of the other two groups. Similarly, patients of group 2 had statistically significant higher chest tube drainage than other two groups at 12 hours and 24 hours. In our study, we observed significantly higher transfusion of platelets and FFP in group 2 and group 3 compared to group 1, thus suggesting that stopping anti-platelet medication 6 days prior to surgery is associated with decreased bleeding and less transfusion of blood and blood products.

Young Song *et al.*^[22] conducted a retrospective study on 305 patients who received aspirin and clopidogrel within 7 days prior to OPCABG. Leong JY *et al.*^[23] prospectively collected data from 919 patients who had isolated coronary surgery and observed the effect of clopidogrel versus aspirin versus both versus neither. They concluded that patients on both clopidogrel and aspirin had significantly more post-operative bleeding with limited clinical benefits. Our data are in consonance with the above studies and indicate a significantly higher rate of re-exploration in patients of group 3 (9.01%) in comparison to group 2 (2.58%) and only 1.07% of group 1.

In a meta-analysis involving 1748 patients, Alghamdi *et al.*^[24] reported that compared to no aspirin, pre-operative aspirin was associated with significantly increased chest tube blood loss and a greater need for blood product transfusion, but there was no significant increase in the risk for re-opening. In another meta-analysis involving 805 patients, Sun *et al.*^[25] noted that pre-operative aspirin increased the amount of post-operative bleeding and the incidence of re-operation for bleeding, but there was no increase in the transfusion requirements.

Limitations of the study

Ours was a single-center study, and we need more multi-centric trials to ascertain our results. There are many variables which can affect the analysis, for example, the number of vessels grafted, operative time, reperfusion of the blood collected from cardiectomy sites, pre-operative Hb level, coagulation profile, and bleeding disorders which should have been excluded from the study population.

CONCLUSION

The present study was a retrospective study to evaluate the effect of anti-platelet therapy on peri-operative blood loss in patients undergoing OPCABG. Our observations and analysis of data show that there was statistically significant higher incidence of bleeding in patients who took these medicines up to 2–5 days before surgery. The values of Hb, PCV, and platelet count on day 1 of the post op. period were decreased in all groups, but there was a more significant fall in group 2. We also observed transfusion of blood and blood products in patients of all groups. The requirement of blood products was higher in group 2 compared to the other two groups.

The pre-operative use of clopidogrel and aspirin together in patients undergoing off-pump coronary artery bypass graft surgery showed a significantly increased risk of bleeding and blood product transfusion. The use of clopidogrel and aspirin should be stopped 5 to 6 days prior to surgery, thus reducing the morbidity, length of stay, and resource utilization.

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Conflicts of interest

There are no conflicts of interest.

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