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Research Article

IMPACT OF PREOPERATIVE CLOPIDOGREL AND ASPIRIN ON BLEEDING COMPLICATIONS IN OFF PUMP CORONARY ARTERY BYPASS GRAFTING

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A B S T R A C T

Introduction: Clopidogrel in isolation or as dual antipatelet threrapy (with aspirin) has been the mainstay of antiplatelet therapy for critical coronary artery disease and interventions. Guidelines recommend stoppage of clopidogrel at about 5 days prior to any major surgical procedure. In the clinical setting however more often than not we may need expedited surgery where antiplatelets may not be optimally discontinued. We share our experience in a similar setting to compare bleeding complications in the above subset of patients undergoing off pump coronary artery bypass grafting

***Patients and methods*:** Retrospective data collected from July 2018 to March 2020. Patients who underwent off pump coronary artery bypass grafting were included and divided in two groups ,group I with clopidogrel aspirin discontinued just 24 hours pre surgery and group II where the same dual antiplatelets were discontinued 5 days prior to off pump CABG.. The groups were demographically matched and their perioperative data compared.

***Results*:** Fall in platelet count, total drainage, units of blood transfusion were higher in group I and was statistically significant (p value 0.004).. There was no significant difference in left ventricular ejection fraction, number of grafts ,ICU and hospital stay and operative mortality in these groups.

Conclusion: Optimally patients on clopidogrel+ aspirin subjected to elective surgery are best served by discontinuation of these drugs atleast 5 days prior to surgery .However in conditions requiring expedited surgery, Off pump CABG can be safely carried out with a minimally increased risk of increased blood transfusion.

INTRODUCTION

Clopidogrel in isolation or in combination with Aspirin has been in use for long time to reduce platelet aggregation and therefore lessen the risk of myocardial infarction in critical coronary artery disease as well as before and after coronary artery bypass grafting (CABG) and coronary stenting[1, 2, 3]. Clopidogrel is a thienopyridine derivative and it inhibits the adenosine di phosphate (ADP) induced platelet aggregation without directly affecting archidonic acid metabolism[4]. Most patients diagnosed with critical CAD and recommended surgical revascularization are on continued dual antiplatelet therapy in the form of clopidogrel-aspirin combination. Major bleeding complications (pericardial tamponade, reoperation, blood transfusion) are increased when CABG is performed within 24 hours of clopidogrel discontinuation[5,6]. Conversely, no increase in bleeding or transfusions is noted when CABG is performed 5 days after clopidogrel has been stopped. The magnitude of bleeding risk when CABG is performed 1 to 4 days after the discontinuation of clopidogrel is less certain[7,8].

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In our institutional practice approximately two thirds of patients undergo CABG less than 5 days after clopidogrel-aspirin discontinuation. The reasons are driven largely by concerns for patient stability, resource utilization, financial implications (fixed duration of package), patient preference, and the confidence of the surgical team in managing hemostasis.

Off pump CABG (OPCABG) has gained popularity in the last decade. This study aimed at assessing the effect of continuation of clopidogrel prior to CABG (off pump) in preoperative period 24 hours prior to surgery and comparison with the patients where clopidogrel was stopped 5 days prior to surgery.

Patients and methods- This study was conducted at Department of cardiothoracic and vascular surgery, Mahatma Gandhi hospital Jaipur. Retrospective data collected from July 2018 to March 2020.

All patients undergoing elective OPCABG were divided in two groups. Group I where dual antiplatelets (clopidogrel and

aspirin) was stopped 24 hours prior to surgery and group II where both drugs stopped 5 days prior to surgery.

Exclusion criteria included

1. All emergent CABG cases
2. Deranged liver function tests preoperatively
3. Patient with chronic renal disease or those on dialysis,
4. Patient with known bleeding disorders, thrombocytopenia
5. Those on supplemental anticoagulants like oral anticoagulants, heparin or loading of antiplatelets in cath lab within one week or patients on alternative antiplatelets like ticagrelor.
6. MICS CABG or OPCABG with other concomitant procedures.
7. Reoperations

Preoperative assessment - Patients of both groups were investigated identically with standard radiological and hematological investigations. Particular note of Hemoglobin, RBC counts, Peripheral smear morphology, Platelet counts, coagulation parameters like BT, CT, PT/INR were initiated. A comparative parameter was assessed in the immediate (within 24 hours) and postoperative period

Operative procedure- Both groups underwent off pump CABG with standard techniques and protocols. Left internal mammary artery (LIMA) and saphenous vein graft were harvested in all patients. Once LIMA was harvested heparin was given at 4 mg/kg, activated clotting time kept above 400. Once grafting was completed heparin effect was reversed with protamine which was given 1.3 times of heparin dose as per our protocol. Standard stabilizer equipment-Maquet acrobat octopus and starfish systems are used for grafting. Our mainstay for inotropy was norepinephrine, dobutamine and nitroglycerin and epinephrine only if there was severe left ventricular or RV dysfunction. We rarely use milrinone in our cases and excluded cases where milrinone was used because of its ant platelet effect on prolonged use. All intraoperative blood loss was assessed using volume indicator on external suction device container. Exact quantification was however impossible due to additional volumes of heparinised saline or blood used procedurally. Cell saver was not routinely used in our elective CABGs.

Transfusion protocol- Blood transfusion as determined by our departmental protocol was carried out only in cases of Hemoglobin less than 8g%. Intra operatively we rely on ABG reports for transfusion indication, while postoperatively the ABG reports are confirmed with simultaneous sample sent to our Hematology laboratory

Postoperative protocol

We prefer fast tracking for all our patients of OPCABG (extubation rate 70% within first 6 hours) unless we are dealing with bleeding, low cardiac output or any neurological issue. Post operatively clopidogrel and aspirin are restarted on day one irrespective of hemoglobin or platelet counts in addition to the routine combinations of other cardiac and non cardiac drugs.

METHODS

Data collection included preoperative and postoperative hemoglobin(day 1) platelet counts, left ventricular ejection fraction (echo based), number of graft, intra operative blood loss, postoperative drain within 24 hour and 48 hours, need for blood transfusion (during first 24 hour and during overall hospital stay), extubation time, intensive care unit stay duration, re-exploration rate and death rate. Univariate analysis was used to evaluate differences in the rates for study outcomes occurring between groups I and II .Student t test performed to compare continuous variables between both groups (presented as mean±SD). P value <0.05 was considered significant.

RESULTS

Total patients in group I and group II were 53 and 46 respectively. Demographic assessment of groups I and II reveal age and sex matched populations. Preoperative laboratory parameters of both groups are also consistently comparable in age, gender, preoperative hemoglobin, preoperative platelet count and left ventricular function (table 1). In group II five patients had ejection fraction ≤30%, while in group I only one patient had severe LV dysfunction. There was no significant difference was there in total number of grafts in both groups.

Table 1

Baseline characteristics	Group I	Group II	
Number of patients	53	46	
Male	44(83%)	39(84.7%)	
Age (mean± SD)	62±7.4	60±7.5	P value1.8
LV EF (mean± SD)	45±4%	45±5.1%	
Number of grafts (Mean)	3.4±0.65	3.3±0.65	
Pre operative hemoglobin	13.1± 1.63	13.04±1.68	
Pre operative platelets	2.59±0.95	2.62±0.753	

Demographic and preoperative data in patients where clopidogrel aspirin discontinued 24 hours (group I) and clopidogrel aspirin stopped 5 days prior (group II).

Blood loss in all cases was assessed during surgery (intraoperative), at 24 hour and 48 hours in Millilitres (mean±SD). There was significant blood loss in group I compared to other group. Intraoperative blood loss was significantly higher in group I compared to group II.There was significantly higher number of blood transfusion in group I. 24 patients in group I and one patient in group II received blood transfusion during first 24 hours. Twelve patients in group I received ≥2 units of blood transfusion while in group II only one patient received two units. In group I, two patients received FFP and platelet transfusion while in group II only one patient received FFP and platelet transfusion. All patients extubated as per our protocol and mean extubation time was lesser in group II .In group II , 36 patients took 6 hours or less for extubation after transfer to intensive care unit (ICU) while in group I eighteen patients were extubated within 6 hours of transfer..

Table 2 Blood parameters and hemorrhagic complication in both groups.

	Group I	Group II	P value
Intraoperative blood loss	743±219	488±114	0.0001
Chest tube drain first 24 hour	270±118	187±120	0.0009
Chest tube drain in 48 hour	383±152	282±195	0.05
Hemoglobin at 24 hours	10.27± 1.43	10.3±1.41	0.8
Platelets at 24 hours	2.03±0.82	2.22±0.76	0.03
Extubation time (Hours)	8.02±2.56	6.87±1.97	0.0195
Blood transfusion in first 24 hour	0.54±0.66	0.086±0.35	0.015
Total unit of blood transfused (mean ±SD)	1.16±0.47	0.65±0.45	*P value 0.0001*
2 units transfused	N=12 (23%)	N=1 (2%)	

Blood parameters and hemorrhagic complication in both groups

There was no difference in ICU stay and hospital stay and none of the patient in our study underwent re exploration for bleeding. Overall reexploration rate at our center is less than 1% and we are performing approximately. 700 cases per year on an average inclusive of pediatric cases.

DISCUSSION

As per AHA guidelines[9] in patients referred for elective CABG, clopidogrel should be discontinued for at least 5 days before surgery (Level of Evidence: B) to limit blood transfusions. In patients referred for urgent CABG, clopidogrel should be discontinued for at least 24 hours to reduce major bleeding complications. (Level of Evidence: B).

Our study has demonstrated that continuation of clopidogrel (till 24 hour prior to surgery) increased the risk of bleeding and blood transfusion supported by studies done by Hongo *et al*[10] and yende *et al*[11]. Hongo *et al* found that clopidogrel in combination with aspirin was associated with significant higher bleeding and reoperation rate. But in this study surgery was done on cardiopulmonary bypass so hemorrhagic complication associated with cardiopulmonary bypass added the overall bleeding complications. Herman *et al*[12] showed that there was increased hemorrhagic complications (bleeding, blood transfusion and exploration) in patients where clopidogrel was not stopped. They concluded that patients receiving clopidogrel with in 24 hour of surgery were at increased risk for hemorrhagic complication. Potent inhibition of platelet function with these drugs leads to prolong bleeding time and major hemorrhagic complications[13].

Englberger *et al*[14] showed increased platelet and FFP (fresh frozen plasma) transfusion in patients where clopidogrel was continued 3 days prior to surgery. However few studies showed no increase in blood loss and significant blood products requirement[15].

In some studies prophylactic platelet transfusion was advised in cases where CABG cannot be delayed although there is currently little evidence that this is of benefit [10, 11]. Aprotinin has some role in hemostasis in patients receiving aspirin but lack of evidences in clopidogrel exposure[16].

Studies have showed that the combination of clopidogrel and aspirin produces a synergistic effect on platelet inhibition and increases bleeding postoperatively[18]. Yende *et al* and Yusuf *et al* showed, this combination significantly increase the risk of postoperative bleeding and blood transfusion if continued prior to surgery[11,18].

In our study, the two study groups were evenly matched in demographics, male predominance, number of grafts and left ventricular ejection fraction. Left internal mammary was harvested in all cases. Group I (where clopidogrel+ aspirin was stopped 24 hours prior) showed significant fall in post operative platelet counts but warranting few RDP (random donor platelet) transfusions and a higher need of blood transfusion., Approximately 23% patients received two or more than 2 units of blood transfusion. ICU stay for both groups remained comparable. In our study there was no mortality and all patients were discharged without any complications. But overall need of blood transfusion and ICU stay is acceptable in both groups. The main reason behind this could be because of all surgery done without cardiopulmonary bypass and added injury caused by CPB could be avoided.

CONCLUSION

In conclusion, we recommend that if the clinical situation allows, for patients receiving clopidogrel aspirin, undergoing cardiac surgery should be delayed at least for 5 days. But in case of conditions warranting expedited surgical revascularisation, off pump CABG is a good option with marginally increased risk of blood or blood products transfusion without increasing morbidity or mortality or hospital stay.

We acknowledge several limitations to this study. Firstly, it is retrospective in nature .Secondly number of patients were low and a prospective study on large scale will certainly shed more light.

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Conflict of interest- dr ajay meena has nothing to disclose.

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