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A Goal Directed Transfusion Approach during Urgent CABG Following Full-Dose Clopidogrel Load: A Case Series

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Abstract

Preoperative antiplatelet agent use may incur excess hemorrhage, morbidity, and mortality. A platelet aggregation guided transfusion protocol was developed to deal with profound platelet inhibition in cardiac surgical patients. This retrospective case series tested the hypothesis that utilizing a protocol avoids excessive post-operative bleeding and re-sternotomy in patients receiving a full clopidogrel load before urgent CABG surgery.

Methods: Demographic and laboratory data, operative details and transfusion records were retrieved for CABG surgery procedures performed within 48 hours of receiving a 600 mg clopidogrel loading dose from July 2009 to January 2011. In patients with confirmed clopidogrel effect, restoration of an estimated, postoperative functional platelet count of ~75-100 x10^9/liter was targeted. Adequate surgical hemostasis was confirmed by the surgeon prior to leaving the operating room. Chest tube drainage (CTD) over the first 24 postoperative hours, blood product administration, and surgical re-exploration were described.

Results: Of the 5 patients identified, all presented with acute coronary syndrome requiring CABG surgery. One was clopidogrel resistant and avoided transfusion, others required 11.6 – 19 x 10^{11} (3-6 apheresis units) to achieve hemostasis. Blood product usage ranged from 3-12 units overall and no patients required surgical re-exploration.

Conclusions: An algorithm using early, targeted, allogeneic platelet transfusion could potentially avoid both unnecessary transfusions as well as excessive bleeding in patients presenting for urgent CABG surgery after a full-dose clopidogrel load. Randomized studies are warranted for further investigation.

Keywords

targeted transfusion strategy; Clopidogrel load; platelet inhibition; clopidogrel resistance; and platelet function testing

Introduction

Coronary artery bypass grafting (CABG) surgery, especially with cardiopulmonary bypass (CPB), is more challenging in patients receiving dual antiplatelet therapy (aspirin and a thienopyridine) due to hemorrhagic complications [1,2]. Currently, despite the ubiquitous use of antiplatelet agents in the setting of acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI) [3], few

evidence-based guidelines exist for the reversal of antiplatelet agent effect. To further complicate matters, individual responses to these agents are variable [4].

Clopidogrel, the most commonly used thienopyridine antiplatelet agent, continues to be a key therapy in patients undergoing PCI. Thienopyridines selectively and irreversibly bind to the adenosine diphosphate (ADP) P2Y12 receptor on platelets and inhibit aggregation by preventing the activation of the glycoprotein GP IIb/IIIa complex and release of granules at the site of endothelial injury. Activation of the glycoprotein GP IIb/IIIa receptor results in enhanced platelet degranulation, thromboxane production, and prolonged platelet aggregation [5]. In order for clopidogrel to become functional, the pro-drug must first undergo metabolism by the cytochrome P450 system in the liver. Genetic variation in the cytochrome system (e.g. CYP2C9 and/or CYP2C19) may result in poor metabolism of the pro-drug clopidogrel to an active compound, leading to high on-treatment platelet reactivity [6]. The majority of patients are responders to clopidogrel and they pose an increased risk of perioperative bleeding, including resternotomy to control hemorrhage.

The aim of this retrospective case series was to present a multi disciplinary transfusion strategy that combines platelet function testing, to determine individual responsiveness to antiplatelet agents, with appropriate platelet dosing. This standardizes our approach to coagulopathy management in the setting of CABG surgery with concurrent, dual antiplatelet agent therapy. We tested the hypothesis that early, goal-directed allogeneic platelet transfusion, based on platelet function assays sensitive to clopidogrel effect, is associated with avoidance of excessive post-operative bleeding and re-sternotomy in patients receiving a full clopidogrel load before urgent CABG surgery.

Methods

Study Design: Following Institutional Review Board approval, we retrieved data for all non-emergent CABG surgery procedures performed at this single University Center between July 2009 and January 2011. Patient demographics, operative details, and postoperative outcomes data were available from the electronic medical record. Medical record numbers were used to query transfusion records to determine blood product unit numbers of the units transfused from the day of surgery through postoperative day one. Ninety six records were reviewed to obtain the five patients that had the same loading dose given within 48hours of surgery. Inclusion criteria for the retrospective review also included having a complete set of data regarding the platelet function testing. Several records were excluded for missing data.

Patient Selection: Data were only collected on patients receiving a 600 mg clopidogrel loading dose up to 48 hours before undergoing CABG surgery. Assessment of platelet function was performed with either LTA or Verify Now P2Y12 assay (Accumetrics Inc., San Diego, CA) with ADP agonist. The cases included in the review all had documentation of an a baseline platelet function test after the 600mg clopidogrel load as well as a note to document a plan for an individualized transfusion strategy based on evidence of clopidogrel effect on aggregometry and the assumption that most platelets would be dysfunctional after a 600mg loading dose.

Laboratory Assessments: Pre-bypass platelet reactivity was determined using light transmission aggregometry (AggRAM®, Helena Laboratories, Beaumont, TX) or Verify Now P2Y12 assay (Accumetrics Inc, San Diego, CA) with testing performed at 37°C. After calibration of the aggregometer with platelet

rich plasma, a platelet agonist was added to the sample while stirring to facilitate activation and aggregation of platelets [8]. Results were reported as a percentage of control aggregation. The Verify Now P2Y12 assay utilizes whole blood while light transmission aggregometry (LTA) uses platelet rich plasma to evaluate and quantify antiplatelet drug effects thereby identifying non-responders [8]. By incorporating tests to determine the qualitative function of platelets in after antiplatelet therapy, platelet transfusion may be dosed accordingly or avoided entirely, thereby decreasing overall allogeneic blood product utilization.

We reported the optical signal as P2Y12 reaction units (PRU) with a range of 194-418 to estimate platelet function after receiving clopidogrel.

Intervention: Briefly, restoration of a functional platelet count of ~75-100 $x10^9$/liter was targeted by transfusion of an appropriate dose (typically 2-3 apheresis units) of allogeneic platelets following separation from CPB,provided clopidogrel-related platelet dysfunction had been demonstrated on preoperative testing, described above, and coagulopathic bleeding was observed after protamine administration. Such subjective assessment of bleeding has actually been shown to be associated with abnormal laboratory testing confirming a coagulopathic state, increased bleeding and transfusion [9].

Patient management: All 5 patients received balanced, general anesthesia using isoflurane with invasive hemodynamic monitoring and standardized CPB. Non-pulsatile, hypothermic (28-34C) CPB was conducted while maintaining an activated clotting time of > 480 seconds using porcine heparin. During CPB, temperature adjusted flow rates of 2.5l/min/m^2 were used, and the goal mean arterial pressure range was 50-70 mmHg. Anesthesia was maintained with isoflurane (0.5%–1.0%) vaporized via the oxygenator. The arterial blood gas sampling technique consisted of alpha stat management for maintenance of normal pH, $_PO_2$, and $_PCO_2$ values. A hematocrit of greater than 0.20 was maintained during CPB; after separation from CPB, red blood cells were transfused per protocol based on the patients preoperative condition, volume status, and hemoglobin concentration, as outlined in our transfusion algorithm. (Appendix 1) Protamine sulfate was administered after separation from CPB to reverse heparin anticoagulation. A ratio of 1mg protamine for each 100 units of the initial dose of heparin was administered with additional doses (25-50mg) given if the activated clotting time (ACT)did not return to baseline; an abnormal ACT was not pursued in the absence of bleeding. In each case, satisfactory hemostasis was documented by the surgeon at the completion of operation prior to closure. Standard practice included intra-operative administration of anti-fibrinolytic therapy with epsilon-aminocaproic acid, administered as a 10-g bolus followed by a 1-g/h infusion. The return of washed, shed red blood cells (BRAT II blood cell salvage machine; Cobe Cardiovascular Inc., Arvada, CO) to the patient was used in all patients.

Subsequent transfusion decisions in the perioperative period were aided by local guidelines combining chest tube output, hemoglobin concentration, activated clotting time, platelet count, fibrinogen level, thromboelastography, prothrombin time, and partial thromboplastin time, as recommended by the American Society of Anesthesiologists published guidelines [10].

Postoperatively, inotropic agents and vasoactive agents were used to maintain a cardiac index of > 2.0 l/min/m^2, a mean arterial pressure of > 60 mmHg, and a systolic arterial pressure < 140 mmHg. Patients were extubated if hemodynamically stable, including minimal mediastinal bleeding, with

neurological and respiratory status either normal or at baseline.

Outcome measures: Chest tube drainage (CTD) over the first 24 postoperative hours, total blood product administration, and the occurrence of re-sternotomy for hemorrhage were described.

Statistical analysis: A formal statistical analysis was not performed due to the small sample size; data for our five patients are expressed as median [overall range].The primary outcome measure aimed to determine whether aggressive, early platelet transfusion, to achieve an estimated functional ~75 $x10^9$/liter platelet count, would prevent excessive bleeding as evaluated by crude comparison of 24 hour CTD to that of a historical dataset expressed as median [interquartile range/IQR].

Results

There were five patients included in this case series. Between July 2009 and January 2011 at a single site, these subjects met the inclusion criteria by receiving 600mg of clopidogrel up to 48 hours before CABG surgery. Patients were young (median age 50, range 43-62 years), two were women and their median weight was 84, range 56-108 kilograms. Smoking (80%), dyslipidemia (100%) and hypertension (100%) were common, but there were no diabetics. No patients had a history of congestive heart failure or prior CABG. One suffered a myocardial infarction and one underwent PCI prior to urgent CABG surgery, with a drug eluting stent implanted in both the left anterior descending and left circumflex arteries. Initially, the subjects suffering from acute coronary syndrome or non-ST elevation myocardial infarction received the clopidogrel loading dose and underwent coronary angiography with the intent of performing a PCI. Due to the severity or location of the stenotic lesion(s), it was determined that CABG surgery using cardiopulmonary bypass (CPB) would be the optimal therapeutic intervention.

Hemoglobin levels and platelet counts were measured pre- and post-CPB in the operating room, ICU, and 24 hours after surgery (Figures 1 and 2). As expected, the platelet counts decreased from 219 [184-263] x 10^9 per liter (median and range) to 160 [118-199] x 10^9 per liter, despite transfusion, and hemoglobin concentration decreased from 11.8 [9.8-14.8] g/dL to 8 [5.6- 10.4] g/dL post-CPB.The individual platelet function test results are provided in (Table 1). After evaluating the platelet function test results, one non-responder to a 600 mg clopidogrel loading dose was identified, this subject expressed only a 9% platelet inhibition and was described as a control. All other subjects were clopidogrel responders, demonstrating inhibition of platelet aggregation as a result of their clopidogrel load. Loss of aggregation in response to arachidonic acid agonist demonstrated aspirin effect in those tested. The reduced response to collagen agonist is consistent with a more marked clopidogrel effect in subjects 2 and 3 and the preserved response to ristocetin agonist is expected despite aspirin and clopidogrel effect.

Each plateletpheresis/apheresis unit contained 3.3- 4.1 $x10^{11}$ platelets and the estimated dose needed to increase the platelet count by approximately 75 x 10^9 per liter was 8 x 10^{11} or 2- 4 apheresis units. The clopidogrel non-responder (control) demonstrated minimal qualitative platelet dysfunction in laboratory testing and did not display coagulopathic bleeding, therefore was not given allogeneic platelet transfusion. It is important to note that both the platelet counts (Figure 2) and postoperative bleeding (Table 2) were lower in this control subject. Following allogeneic platelet transfusion, bleeding (range 760 -1130 milliliters over 24 hours) was not excessive in the clopidogrel group. This was comparable to a historical cohort of cardiac surgery patients at our institution, without clopidogrel use, with 24 hour

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chest tube drainage of 781 [420-1130] milliliters. The majority of the transfusions were administered in the operating room, while the surgical field could be directly observed for coagulopathic bleeding. None of the patients required resternotomy for bleeding postoperatively.

Discussion

Following confirmation of a therapeutic clopidogrel effect with platelet function testing, an algorithm using early, targeted, allogeneic platelet transfusion is capable of avoiding excessive bleeding in patients presenting for urgent CABG surgery after a full-dose clopidogrel load. As illustrated by our non-responder/control patient, if clopidogrel effect is not identified by platelet function testing, avoiding platelet transfusion in this setting is feasible.

The five patients included in this case series displayed varying degrees of platelet inhibition ranging from nine to ninety nine percent. Given the limited number of patients, data interpretation is limited; however, the chest tube drainage we observed was within an expected range at our institution and within a 500-1,200 milliliter “normal range" described after routine CABG [11]. Similarly, the bleeding we describe was classified as only “moderate” by recently proposed definitions [12]. Based on all these metrics, the five patients in this series demonstrated acceptable postoperative chest tube drainage not indicative of excessive bleeding after following our strategy of laboratory directed platelet transfusion to restore a functional platelet pool.

As there is a paucity of literature on this topic, physicians typically rely on local expert opinion and personal experience to manage these complex patients. However, Sarode and Vilahur et al [13,14] described a protocolized reversal of antiplatelet agents based on in vitro studies. Briefly, platelet aggregation studies were used to measure the effects of adding normally functioning donor platelets (in vitro) to functionally impaired platelets that had been exposed to clopidogrel. Based on these experimental observations, they proposed that a transfusion plan can be predicated upon percent platelet inhibition and that platelet function studies should be serially followed during the perioperative period, with an estimated equivalent of 2 apheresis platelet units being required to achieve hemostasis [13]. This contrasts to the 3-6 unit platelet transfusions we used to achieve hemostasis. While theirs is a logical approach, it may not always be feasible to repeat these complex assays in the dynamic setting of urgent, high-risk surgery, especially outside of routine laboratory hours, and it does not account for additional CPB related platelet dysfunction. Furthermore, our first patient underwent postoperative platelet function testing (data not shown) yet, despite adequate hemostasis, the platelet aggregometry was still read as minimal. This is to be expected following mixing native with allogeneic platelets in vivo rather than in vitro [13,14]. It demonstrates residual inhibition of the largest platelet population, namely those inhibited by clopidogrel, which are still circulating because they were not consumed achieving hemostasis. Therefore, we elected not to test postoperatively, as proposed [13,14], but to use bleeding as our treatment end-point.

What is clear in the literature, is the increased transfusion requirement and associated morbidity resulting from the excessive bleeding seen with preoperative clopidogrel use [2,5,15,16]. For example, an average twelve unit transfusion requirements and a 15% reoperation rate was reported for patients with only regular dose clopidogrel within 4 days of CABG surgery [17]. Our approach intended to rapidly arrest bleeding and avoid the development of anadditional, dilutional coagulopathy, which may develop while

administering only RBCs and volume replacement. By rapidly reversing platelet dysfunction, we aimed to avoid the excessive transfusion and re-sternotomy rates described above [17], which may be of increased value when encountering more potent anti-platelet agents such as prasugrel or ticagrelor.

While platelet transfusion thresholds have been described in the perioperative setting [10], the selection of an appropriate platelet dose to achieve these targets requires extrapolation from the hematology literature. Even in the more stable setting of prophylactic transfusions to non-refractory, non-bleeding patients, a dose of $3x10^{11}$ platelets (the American Association of Blood Banks {AABB} mandated minimum for a single apheresis platelet unit) only achieved a post-transfusion platelet increment of 15-20 x 10^9 per liter; 18 our average platelet dose in an apheresis unit was 3.8 x 10^{11} Consistent with this, a dose of > 8 x 10^{11} was required to achieve an average increase of > 60 x 10^9 per liter [19]. The presence of on-going bleeding, male gender or larger patient size will reduce this increment [20] possibly increasing the platelet requirement beyond the 2-4 apheresis units initially estimated to approximate a 75 x 10^9 per liter increase in functional platelets. Two of our patients indeed received additional platelet units and the totals of 5 and 6 units would have achieved approximate increments of ~ 100 -180 x 10^9 per liter, which is not excessive in the setting of on-going bleeding. This heavy burden on the transfusion service should, ideally, be recognized and discussed early, to ensure the capability of providing sufficient platelet units.

The small sample size and retrospective design are both major limitations to this report. Also it lacks a true control, as we used historical data and one clopidogrel non-responder, as a basis for comparison. However, the patients we described are rarely encountered, making enrollment for a prospective study logistically burdensome. This report therefore represents a valuable discussion of the approach to managing these difficult cases.

Conclusion

In summary, we demonstrate that a targeted platelet transfusion approach, with preoperative platelet function testing to confirm significant platelet inhibition, can rapidly repopulate a functional platelet pool and avoid excessive bleeding after urgent CABG surgery in the setting of dual antiplatelet therapy. Whether this strategy is effective at improving patient outcomes will require further prospective study.

Figures

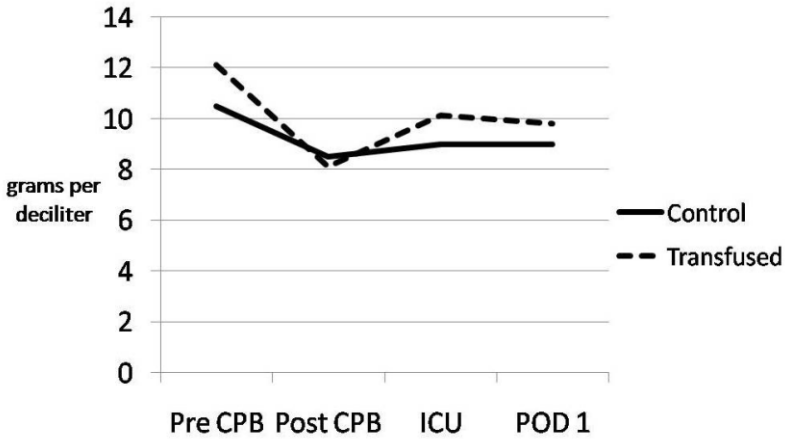


Figure 1: Hemoglobin levels (grams per deciliter on the y-axis) from the control patient and the average of the four transfused patients.

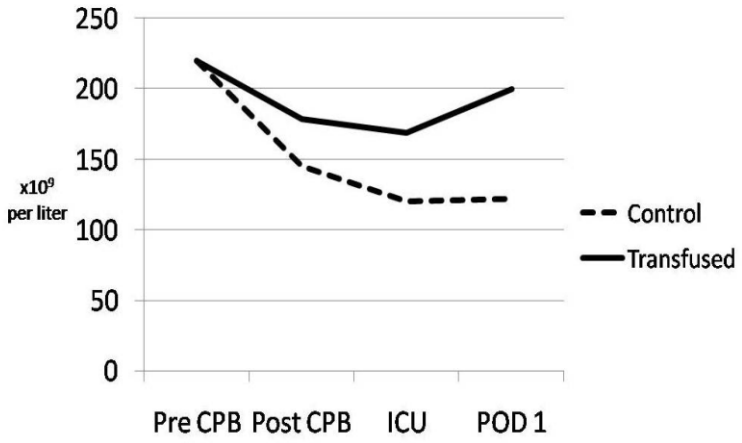


Figure 2: Platelet counts (x 10^9 per liter on the y-axis) from the control patient and the average of the fourtransfused patients.

Tables

Table 1: Platelet function testing

Platform	Agonist	Normal Range	Subject 1	Subject 2	Subject 3	Subject 4	Control
Light Transmission Aggregometry	ADP 5 microM	>60%	31	4	1	5	
	ADP 20 microM		N/A	N/A	N/A	11	
	Collagen 0.01mg/ml	>60%	66	22	6	N/A	
	Arachidonic Acid 0.5mg/ml	>60%	6	5	3	N/A	
	Thromboxane A2 1.0 microM	>60%	96	15	54	N/A	
	Ristocetin 1.5mg/ml	>80%	83	87	84	N/A	
Verify Now	P2Y12 reaction units (PRU)	194-418	N/A	N/A	N/A	N/A	307
	% Platelet inhibition	40-60%					9*
Interpretation Aspirin Clopidogrel			 + +	 +++ +++	 +++ +++	 Not done +++	 Not done Minimal

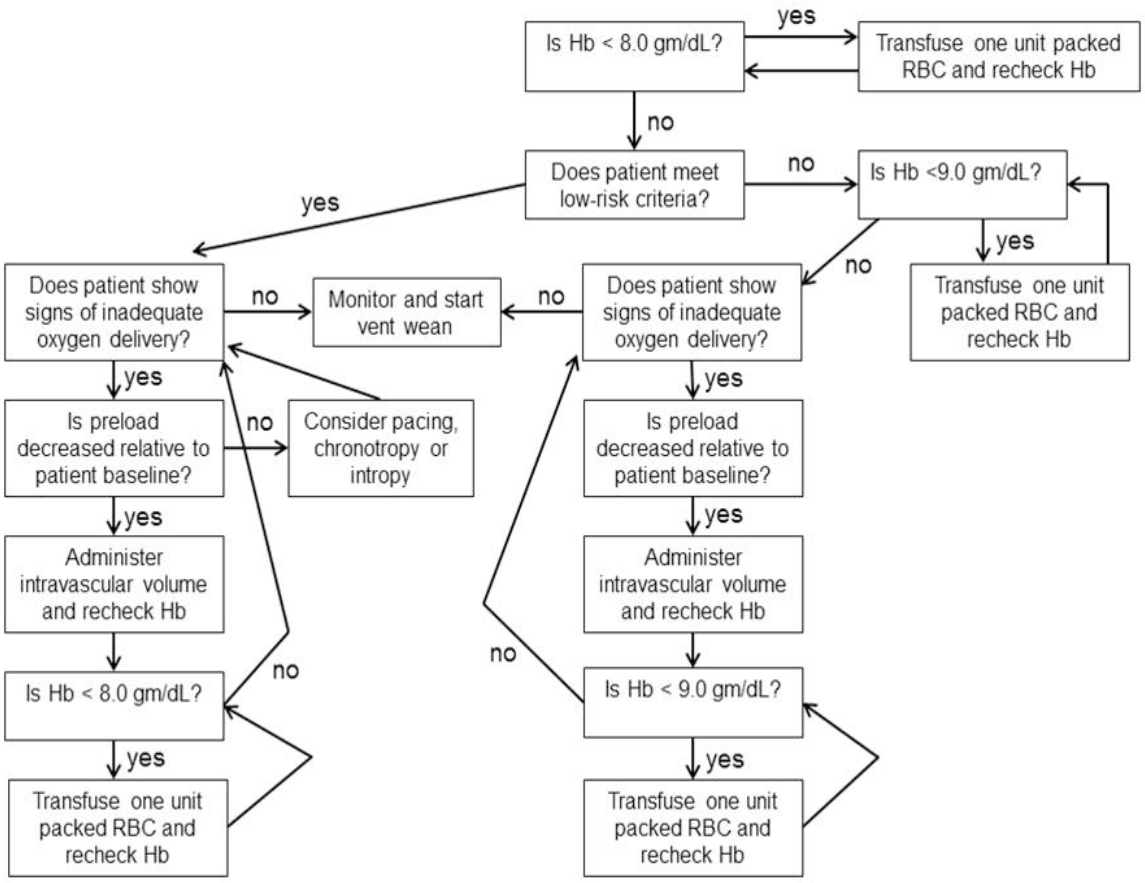
* 40-60% consistent with clopidogrel effect

Table 2

SUBJECTS	24 HOUR CHEST-TUBE DRAINAGE (ml)
1	1130
2	760
3	815
4	780
Control	420

Appendix 1

Approach to transfusion: In the appendix is a flow diagram depicting our approach to a targeted transfusion strategy aimed at repopulating an adequate functional platelet count without exposing the patient to unnecessary transfusions and wasting of resources.



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