Preoperative Point-of-Care Platelet Function Testing in Cardiac Surgery

Seema Agarwal, BM, BS, MA, FRCA,* Robert Ian Johnson, PGDip,† and Matthew Shaw, MA*

Objective: To investigate if the use of preoperative platelet function testing (PFT) as part of a transfusion algorithm reduced blood product usage in coronary artery bypass surgery (CABG).

Design: Prospective, randomized, controlled trial.

Setting: A cardiothoracic hospital.

Participants: 249 patients having CABG surgery.

Interventions: The patients were allocated randomly to PFT preoperatively with Multiple Electrode Aggregometry (MEA, Group A), TEG PlateletMapping (PM, Group B) or none (control, Group C). Post-bypass bleeding management was determined by a transfusion algorithm.

Measurements and Main Results: The primary outcome measure was blood product transfusion in the first 48 hours post-surgery. There was a significant reduction in all blood product transfusion between Groups A (MEA) and B (PM) and Group C (control) (median number of units transfused, 2 (A)/2 (B)/ 4(C), $p = 0.02$). Those in A and B received fewer units of red cells (median number of units, 0 (A)/1 (B) /2 (C), $p = 0.006$) and fresh frozen plasma than the control Group C (median number of units, 0 (A)/0 (B)/2 (C), $p < 0.001$), without receiving significantly more units of platelets (median number of units, 1 (A)/1 (B)/0 (C), $p = 0.11$). In those who had taken an adenosine disphosphate (ADP)-receptor antagonist within 5 days ($n = 173$), these results were amplified, and additionally, there was a significant cost saving (median cost, A = £1738.53, B = £1736.96, C= £3191.80 $p = 0.006$).

Conclusion: Preoperative PFT as part of a point-of-care testing-based transfusion algorithm led to a reduction in blood transfusion. There is a potential cost saving in those who have taken an ADP-receptor antagonist within 5 days.

KEY WORDS: *point-of-care technology, platelet mapping, multiple electrode aggregometry, antiplatelet therapy, transfusion, CABG, ADP-receptor antagonist*

CARDIAC SURGERY always has been associated with a large blood loss and transfusion requirement; indeed, it is estimated that approximately 15% of all donated blood in the UK is used in cardiac surgery.[1] Over the past 5 years, the blood and blood product usage in the authors' hospital, at which approximately 1,800 cardiac surgeries per year are performed, has increased, with more than 50% of patients presenting for first-time coronary artery surgery now requiring red cell transfusion. At the same time, the number of patients presenting for surgery either electively taking an anticoagulant drug (usually an antiplatelet drug) or in a nonelective manner (when it usually is not possible to delay surgery to wait for drugs to be stopped) has risen; at present, more than 33% of all cardiac surgeries in the authors' hospital are nonelective, and more than 70% of patients are taking an antiplatelet drug (usually aspirin, often with an adenosine disphosphate (ADP)-receptor antagonist).

It is accepted widely that the use of allogeneic blood products is associated with increases in mortality and morbidity,[2] as is resternotomy for bleeding.[3] Point-of-care testing in cardiac surgery has been shown to reduce transfusion and blood loss.[4,5] Shore-Lesserson et al first published their algorithm in 1999,[6] yet while this algorithm is deservedly well known, there have been developments in platelet function testing that were not included.

The Multiplate (MEA, Roche Verum GmbH, Munich, Germany) is a multiple-electrode aggregometer that has been validated against both flow cytometry and optical light aggregation in studies looking at platelet inhibition by clopidogrel.[7] In the only published study to date, an ADP-induced aggregation of fewer than 31 units (U) was found to be associated independently with an increased risk of bleeding and transfusion in cardiac surgery.[8]

The thromboelastograph (TEG, Haemonetics, Braintree, MA) is a point-of-care coagulation monitor, the use of which has been associated with a reduction in inappropriate transfusion;[6] however, it is not able to detect the platelet defects that occur with aspirin[6,9,10] or demonstrate ADP-receptor blockade. The TEG PlateletMapping (PM, Haemonetics, Braintree, MA) assay, however, allows the measurement of the degree of platelet inhibition resulting from aspirin or ADP-receptor antagonists. This technique has been shown to have good agreement with light transmission aggregometry.[11]

Recently, Gorlinger et al[12] and Weber et al[13] published algorithms that included the use of point-of-care platelet function testing using multiple electrode aggregometry (MEA). However, both of these algorithms use factor concentrates such as prothrombin complex and fibrinogen complex, which are not licensed for use in the perioperative setting. Neither algorithm uses TEG PlateletMapping (PM).

The aim of this study was to investigate if a proposed algorithm that incorporates recent developments in point-of-care platelet function testing (using MEA or PM) reduced blood product usage in patients having coronary artery bypass grafting.

METHODS

This study was approved by the hospital review board and regional ethics committee (NREC number 12/NW/0127). From May 2011 to April 2012, adult patients presenting for coronary artery surgery (including emergent and urgent procedures regardless of preoperative

*From the Departments of *Anaesthesia and Critical Care, and †Perfusion, Liverpool Heart and Chest Hospital, Liverpool, United Kingdom.*

Disposables and reagents for Multiplate analysis were received from Verum Diagnostica. Disposables and reagents for TEG and PlateletMapping were received from Haemonetics. There was no direct financial aid and the authors did not receive honoraria from either manufacturer.

Address reprint requests to Seema Agarwal, BM, BS, MA, FRCA, Department of Anaesthesia and Critical Care, Liverpool Heart and Chest Hospital, Thomas Drive, Liverpool, L14 3PE, United Kingdom. E-mail: Seema.Agarwal@lhch.nhs.uk

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antiplatelet and anticoagulant medication) were approached to be included. This was a prospective, randomized, controlled trial aiming to recruit 80 patients in each arm—240 in total. Patients presenting with significant hepatic disease (ALT ×2 normal) renal disease requiring dialysis or patients requiring preoperative inotrope support were excluded. Written informed consent was obtained for all participants by investigators trained in Good Clinical Practice and following the Declaration of Helsinki guidelines.

After informed consent was obtained and before anesthesia, patients were assigned randomly by the investigators into 1 of 3 groups. Randomization was performed by block randomization technique with 80 blocks of 3 treatments using an SAS algorithm. At the onset of surgery, all patients received tranexamic acid, 5 mg/kg bolus, followed by an infusion of 5 mg/kg/hour until the end of surgery, as is the usual practice. Cardiopulmonary bypass was conducted in the standard fashion, and anticoagulation was accomplished with heparin sulphate, 300 U/kg, with additional increments as needed to maintain an activating coagulation time of 400 seconds or above. Protamine reversal of heparin was performed at the end of surgery at a dose of 1 mg/100 U of total heparin dose.

Baseline laboratory tests were conducted on all patients; these included full blood count, prothrombin time, activated partial thromboplastin time, and Clauss fibrinogen. All patients had arterial blood gas analysis and activating coagulation time measurement on induction of anesthesia, half hourly during bypass and after administration of protamine. Those in Groups A and B had platelet function analysis (both MEA and PM), a kaolin-activated TEG, and a functional fibrinogen TEG (FF TEG) performed on induction of anesthesia, and TEG kaolin and kaolin heparinase and FF TEG performed 10 minutes after completion of administration of protamine. All tests were carried out by the investigators. Those in the control arm (Group C) had no preoperative testing, with only a kaolin and kaolin heparinase TEG performed 10 minutes after completion of administration of protamine as per institutional practice.

All instruments had quality control performed daily, and the tests were performed following manufacturer specification. All tests were performed by staff fully trained in their use, with regular assessments on their ability to perform the tests.

In the case of microvascular bleeding (defined as bleeding from a nonsurgical cause, which normally would have prompted transfusion of blood and blood products, as agreed by the operating surgeon and anesthesiologist), the operating team was informed of the results of the point-of-care testing (they were unaware of these results until this point). Patients in Groups A and B were transfused according to the study algorithm (Fig 1). Group A had bleeding management determined by preoperative platelet function testing with MEA, as well as post-protamine TEG (kaolin, kaolin heparinase, and FF TEG), Group B had management determined by preoperative platelet function testing with TEG PlateletMapping as well as post-protamine TEG (kaolin, kaolin heparinase, and FF TEG). Group C had routine management with a post-protamine TEG (kaolin and kaolin heparinase) only, with management decided by the authors' usual algorithm (Fig 2, based on the algorithm by Shore-Lesserson et al) and the clinicians.

The limits used for triggering platelet transfusion as a result of platelet inhibition shown by MEA and TEG PM were based on the results of an audit of the authors' own practice (Appendix).

Surgical re-exploration occurred as per institutional practice; for hemodynamic instability, chest tube drainage of greater than 500 mL in the first hour or greater than 1000 mL in the first 4 hours or evidence of tamponade (TEE-guided). At resternotomy, it was noted if a definitive surgical cause was found or not (noted as "definitive surgical cause" or "no definitive surgical cause"). Red cell transfusion was indicated if the hemoglobin concentration fell below 65 g/L on cardiopulmonary bypass or 80 g/L at any time in all patients. Postoperatively, patients were discharged from the intensive care unit (ICU) if they met institutional discharge criteria (including requiring no ongoing organ support.)

The primary outcome measure was blood product transfusion in the first 2 postoperative days (total number of units of any type and total number of each particular type of product). Secondary outcome measures were postoperative blood loss in mediastinal drains in the first 12 hours after surgery, the requirement for re-exploration for bleeding, length of time to extubation, and length of stay in the intensive care unit. A cost analysis also was planned.

As estimations of study effect were unavailable, no formal power calculation was possible (the data that were used for deciding the transfusion triggers assessed the blood loss with platelet inhibition but did not assess the effect of administering platelets on blood loss). Baseline characteristics are reported as medians and interquartile ranges for non-normally distributed continuous variables and as frequencies and percentages for categoric variables. Costs are shown as medians ± ranges. Groupwise comparison of normally distributed variables were tested by means of one-way ANOVA, non-normally distributed variables were tested with the Kruskal-Wallis test. In all cases, a p value of <0.05 was considered statistically significant. Statistical analyses were performed using SAS for Windows Version 9.2 (SAS Institute, Cary, NC). An interim analysis was planned to take place after 100 patients had been randomized. A subgroup analysis was performed of those patients who had taken an ADP-receptor antagonist within 5 days, comparing the same variables; this originally was not planned.

The authors' institution uses the Patient Level Costing Information System (PLICS) and Service Level Reporting system to enable detailed microcosting. Service Level Reporting allows the hospital to analyze cost and profitability, at the patient level, of each service provided rather than just overall profitability. Costs of resources can be attributed directly to particular patient episodes. The use of sophisticated consumables dispensing and supply tracking technologies assigns costs and allows precise tracing of resource use to the patient and episode in which they were used. Staff time is allocated with reference to employment contracts and the proportion of the time that is to be dedicated to each duty. That is, the cost of a particular surgeon for a given procedure is a function of the surgeon's salary, the proportion of the employment contract that the surgeon is to operate, and the time the procedure takes. The ward costs of the clinician can be allocated in a similar way. These costs are then allocated based on the observed values of time for each patient episode. Indirect costs such as utilities and hospital overhead are allocated/absorbed, although some of them are not directly attributable to any particular episode/service line; they are divided up and shared among all episodes.

RESULTS

Table 1 shows the baseline characteristics for the subjects. There was no significant difference between the age, sex, body mass index, surgery, baseline hemoglobin (Hb), platelet count, international normalized ratio, or drug history among the 3 groups. Importantly, there was no significant difference among the 3 groups in terms of recent ADP-receptor antagonist use (A *v* B *v* C, 72.6% *v* 67.9% *v* 67.9%, respectively). There was a statistically significant difference between Groups A and C in the length of cardiopulmonary bypass, with Group A undergoing a slightly longer time than the control group, although there was not a statistically significant difference in the duration of the aortic cross-clamp.

Table 1 also shows the results of the primary outcome measure—transfusion. It can be seen that there was no significant difference between the proportion of patients who received a transfusion in the first 2 days post-surgery (77.4% (A) *v* 77.4% (B) *v* 79.0% (C), $p = 0.96$). However, there was a significant difference between the median numbers of units they received (2 [A] *v* 2 *v* [B] *v* 4 [C], $p = 0.02$). When this was broken down into the individual blood components, there were significant