Targeted Bleeding Management Reduces the Requirements for Blood Component Therapy in Lung Transplant Recipients

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Objective: **Lung transplantation is associated with high rates of bleeding and frequent blood transfusion. The authors aimed to determine if point-of-care coagulation testing (POCCT) reduced transfusion requirements.**

Design, Settings, and Participants: **A before-and-after cohort analysis conducted at a single tertiary referral center. Ninety-three sequential adult patients between January 2010 and January 2014 undergoing isolated lung transplant without preoperative extracorporeal support were analyzed.**

Intervention: **ROTEM and multi-plate POCCT were introduced on July 1, 2012, with an associated algorithm based on the results.**

Measurements and Main Results: **Statistically significant decreases in the proportion of patients receiving PRBCs (87% *v* 65%; p = 0.015), FFP (72% *v* 30%; p < 0.0001) and platelets (70% *v* 37%; p = 0.002) were found after the intervention. There were small decreases in median chest tube blood loss at 2 hours (300 mLs *v* 215 mLs; p = 0.03) and 4 hours (440 mLs *v* 350 mLs; p = 0.050) but not at 12 hours postoperatively. There were no changes in reoperation for bleeding (9% *v* 4%; p = 0.158) or in-hospital mortality (6% *v* 2%; p = 0.617). The cost of blood products administered decreased from a median of $3,935.00 to $991.00 (p < 0.001).**

Conclusions: **Use of POCCT in lung-transplant surgery is associated with significant reductions in blood product use and cost. There were no detectable changes in outcome aside from a small decrease in early postoperative bleeding.**

KEY WORDS: point-of-care coagulation testing, blood transfusion, lung transplantation

THE RATE of allogeneic blood transfusion to treat bleeding complications in the bilateral sequential lung transplant (BSLT) population is poorly reported.[1–3] Managing bleeding with a liberal transfusion approach, particularly in this patient group, may negatively impact outcome. Cohort studies have demonstrated a dose-dependent association of worse outcomes including transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and transfusion-related immunomodulation (TRIM)[4–8] related to blood component therapy. TRIM increases the frequency and severity of viral and bacterial sepsis in an already immunosuppressed population, with sepsis being a direct cause of acute lung injury.[6] Primary graft dysfunction (PGD) is a significant manifestation of acute lung injury and is the greatest risk factor for death during the first year post-transplantation.[9] Large-volume blood product use is associated with both increased rate and severity of PGD and is, therefore, an important modifiable risk factor.[10] Furthermore, blood transfusion may lead to the generation of anti-human lymphocyte antibodies, which may impact acute and chronic graft rejection, prospects for future re-transplantation, and survival.[3]

The benefits of transfusion are not well quantified. The ability of transfused packed red blood cells (PRBCs) to carry and deliver oxygen to tissues is impaired due to acquired structural and functional changes developing during storage.[11] Transfused platelets do not function normally, contributing less to hemostasis than anticipated.[12] The use of other pro-hemostatic agents, including recombinant activated factor VII (rVIIa), prothrombin complex concentrates, and tranexamic acid may increase the risk of thromboembolic events.[13,14]

The authors aimed to minimize unnecessary transfusion by implementing evidence-based hemostasis management supported by point-of-care coagulation testing (POCCT). This study compared blood product use, patient outcomes, and cost before and after implementation of this change in practice in lung-transplant patients.

METHODS

A retrospective before-and-after cohort analysis was performed on 93 patients over the age of 15 who underwent primary BSLT between January 2010 and January 2014 at a single-center tertiary referral hospital, the Prince Charles Hospital, in Brisbane, Australia. This study was approved by the institutional ethics committee (HREC/13/QPCH/310). The change in blood management practice commenced on July 1, 2012, with 47 patients receiving a lung transplant before the change and 46 after. A power analysis revealed that a baseline 80% rate of transfusion dropping to 50% transfusion would need a sample size of 39 in each arm to achieve a power of 80% at a significance level of 0.05. Exclusion criteria were limited to patients having concurrent procedures (eg, valve or coronary surgery), multi-organ transplant, re-transplantation, or pre-transplant extracorporeal support. No single-lung transplants were performed in the study period, and all transplants were conducted on cardiopulmonary bypass.

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The primary endpoint of the study was the incidence of transfusion of autologous blood products. Secondary endpoints included the number of units of each blood product type, acquisition cost of blood products, unplanned re-exploration for bleeding, chest tube output, and primary graft dysfunction. Data for mortality, ventilation time, and length of intensive care also were recorded along with the frequency of other hemostatic therapies including prothrombin complex concentrate (Prothrombinex VF, CSL Behring, Melbourne, Victoria Australia), recombinant factor VIIa use (rFVIIa; NovoSeven: Novo Nordisk, Bagsvaerd, Gladsaxe Denmark), and tranexamic acid (Cyklokapron, Pfizer, Pty Ltd, Perth, Australia).

Data were collected prospectively within the routine audit of the center with a dedicated audit team, which did not include any clinicians or any of the authors, and were not associated with the point-of-care testing program. A search was conducted within medication charts, anesthetic charts, and admission clerking documentation, as relevant, for preoperative and intraoperative use of anticoagulants and pro-hemostatic agents. Blood product information and laboratory values were sourced from the electronic blood banking/laboratory software and cross-checked against anesthetic or intensive care charts. Chest tube drainage was sourced from the intensive care computerized information system recorded contemporaneously by ICU nursing staff. Return-to-operating-room events were sourced from the notes and cross-checked against computerized operating room records for each patient. In-hospital mortality was sourced from the notes and the associated discharge summary for each patient. Where necessary, additional or missing information was checked by study authors by individual chart review.

Clinical Management

During the 2 comparison periods, the lung-transplant program was supported unchanged by 3 surgeons and 10 anesthesiologists. All BSLTs at the authors' institution are performed on cardiopulmonary bypass with a beating heart. The technique is standardized across all patients. Donor selection complies with international practice. The surgical technique includes a midline sternotomy with central cannulation, cooling to 34 degrees, and a pulmonary arterial vent. Weaning from bypass was achieved with a low inspired oxygen concentration (~30%) after lung recruitment with a protective ventilation strategy.

POCCT

Whole-blood coagulation assays rotational thromboelastometry (ROTEM®; Tem International GmbH, Munich, Germany) and impedance platelet aggregometry (Multiplate®; Verum Diagnostica GmbH, Munich, Germany), in conjunction with treatment algorithms, increasingly are being used to guide bleeding management decisions in the surgical setting. Neither test utilizes serum, avoiding delays for blood centrifugation. ROTEM is a viscoelastic citrated whole-blood coagulation assessment using a stationary cup and a moving pin. Changes in rotational forces between the pin and cup occur with coagulation. Time to initiation of coagulation, acceleration of coagulation, maximum clot strength, and presence of fibrinolysis all can be detected within minutes in the presence of different activators. The Multiplate uses thrombin-inhibited whole blood in an impedance aggregometry test. An electrical current is passed between 2 pairs of electrodes, and as platelets adhere, resistance rises. Both these tests provide clinicians with rapid and comprehensive information for diagnosing and targeting specific hemostatic defects and can be performed in the operating room.[15,16]

Hemostatic Management

ROTEM assays were performed at various time points. In the event of continued bleeding after protamine administration, a ROTEM was standard of care. Multiplate and ROTEM also were conducted at the discretion of the anesthesiologist after induction of anesthesia and on rewarming in high-risk patients. Tests were repeated after administration of products if bleeding continued.

The heparin was reversed with protamine with an initial dose of approximately 0.8 mg per 100 units of total heparin administered with further doses of approximately 0.2 mg per 100 units of total heparin during administration of residual circuit blood. If bleeding continued after protamine administration, a treatment plan, following the authors' previously described bleeding management treatment algorithm, was followed (Fig 1).[15] An abnormal ROTEM was not treated unless there was active bleeding. Prothrombinex complex concentrate was utilized to correct bleeding diathesis due to warfarin after rewarming. Dosing remained at the discretion of the anesthesiologist but was guided by EXTEM results in the second cohort.

Cost Analysis

The costs of blood products were calculated from the National Blood Authority of Australia website (all prices in Australian dollars) current from July 1, 2015.[17] The current costs are $374.00, $304.00, $387.00, and $177.00 for packed red blood cells, fresh frozen plasma, platelet concentrate, and cryoprecipitate per unit respectively. Factor concentrates costs included prothrombine complex concentrate at $274.00 per 500 IU and recombinant factor VIIa at $1,283.00 per mg. All costs were considered as acquisition only and did not include any costs of storage, cross-matching, thawing, administration, or complications. Other costs included ROTEM and Multiplate testing at $15.16 and $11.23 per test of testing. The cost of tranexamic acid is $5.81 per 1-gram ampoule at the authors' hospital.

Statistical Analysis

Data are presented as means (± standard deviation [SD]), medians (with interquartile ranges [IQRs]), and percentages as appropriate. Statistical calculations were performed in R version 2.15.2 for Windows (R Development Core Team, 2008, Vienna, Austria). The Wilcoxon signed-rank test was used to test for differences (before perioperative bleeding management compared to after perioperative bleeding management) for continuous nonparametric variables. Fisher's exact test was used to perform analysis of frequencies, and the binomial test was used to determine differences in proportions before perioperative bleeding management