Algorithmic and Consultative Integration of Transfusion Medicine and Coagulation: A Personalized Medicine Approach with Reduced Blood Component Utilization

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Abstract. Background. Therapy customized for the individual patient defines personalized medicine. Current transfusion therapy is performed primarily using general guidelines such as keeping the platelet count at >100,000/µL, the INR at ≤1.7 and fibrinogen at >100mg/dL for patients undergoing surgery.

Objective: The purpose of this report is to provide an algorithmic and consultative approach for the delivery of personalized and targeted blood component, blood derivative, and recombinant therapies in order to minimize unnecessary exposure to such therapies and to deliver an optimal risk-benefit ratio for a particular patient.

Methods: The initiative involved a step-wise process that included: 1. establishing “triggers” to alert and permit the clinical pathologist to intervene in the utilization of blood components for a given patient in the context of the blood bank inventory; 2. developing algorithms for the assessment of the patient’s procoagulant/anticoagulant status so that appropriate blood component, derivative, and/or recombinant therapies could be instituted while minimizing the risk of thrombophilia; 3. a real time assessment and interpretation of the coagulation data so that dialogue between the pathologist and the patient’s clinical team could be effected 24 hours a day, 7 days a week; and 4. monitoring the outcome of these efforts by comparing blood component utilization prior to or during development, early implementation and following full implementation of the program.

Results: “Triggers” (i.e., administration of six units of fresh frozen plasma [FFP] or ten units of cryoprecipitate or two single donor [apheresis] platelets in a 24-hour period) were approved. A diagnostic and therapeutic algorithm was constructed, with multidisciplinary input to assist in defining the coagulopathy contributing to the patient’s microvascular bleeding in the adult cardiac surgery/cardiac intensive care unit (CICU) and the adult intensive care unit (AICU). Monitoring of utilization, prior to or during development, early implementation and following full implementation of this initiative, revealed a decline in the number of units of FFP, cryoprecipitate and single donor (apheresis) platelets administered. Conclusion: We report on the successful development of a model - based on the algorithmic and consultative integration of transfusion medicine and coagulation - that customizes blood component, derivative, and recombinant therapies appropriate for an individual patient’s need, resulting in targeted transfusion therapy and associated with reduced blood component utilization.

Introduction

In a recently published analysis of the frequency and outcomes of blood product transfusions from the Nationwide Inpatient Sample database for 2004, Morton and colleagues reviewed data from an estimated 38.66 million hospital discharges in the United States, of which 2.33 million (5.8%) were associated with blood product transfusions [1].

Moreover, they reported a statistically significant increase (p<0.0001) in the following in those who received transfusions: the average length of stay was 2.5 days longer and charges were $17,194 more; the odds of infection and death were 1.9 and 1.7 times higher, respectively. The authors opined that such findings might “encourage the adoption of novel approaches to minimize intraoperative and early postoperative bleeding, reduce transfusion requirements and most important, improve patient-level postoperative outcomes and health-related quality of life”[1]. Having realized this same need earlier, in 2002 the Transfusion Committee at Geisinger Medical Center endorsed a policy of striving to ensure that blood component and blood derivative therapies were specific to the individual patient’s need, as determined by clinical and...
laboratory parameters, and were administered in a dosage and unit type that had been shown to be appropriate and efficacious, while minimizing the risk of transfusion-associated reactions and adverse effects. To that end, we developed a comprehensive strategy that essentially integrated transfusion medicine and coagulation and applied a consultative, algorithmic approach involving the laboratory medicine and clinical care teams in an effort to customize blood component, blood derivative, and recombinant therapies for the individual patient.

This report details the essential elements of the model for this personalized medicine approach to transfusion therapy and provides comparative outcomes data as proof of concept.

Materials and Methods and Patient Study

Population

Establishment of Blood Utilization “Triggers” Authorizing Dialogue between the Clinical Pathologist and the Patient’s Physician. To ensure blood component utilization appropriate to the patient’s need and available based on existing blood bank inventories, the Transfusion Committee recommended to the Medical Executive Committee, for its approval, guidelines authorizing intervention by the clinical pathologist. These included the administration of six (6) units of fresh frozen plasma or ten (10) units of cryoprecipitate or two (2) single donor (apheresis) platelets to any individual patient within a 24-hour period.

Design of a Diagnostic and Therapeutic Algorithm for Microvascular Bleeding. A team comprised of perfusionists, surgeons, intensivists, clinical pathologists, and blood bank and coagulation laboratory staff, with input from the clinical hematologist-coagulation specialist, designed such a diagnostic and therapeutic algorithm for microvascular bleeding in adult cardiac surgery and the intensive care settings. The main components of the algorithm included: thromboelastography, platelet count and fibrinogen. Later, a soluble fibrin monomer and quantification of the patient’s antithrombin III level were added to either confirm suspected cases of disseminated intravascular coagulation (DIC) with utilization depletion of procoagulants or to provide therapeutic direction.

Figure 1. Algorithm using thromboelastographic (TEG) parameters combined with platelet count and quantitative fibrinogen to identify basis and suggest treatment for microvascular bleeding to include: residual heparin, mild to moderate and severely decreased platelet function and thrombocytopenia and moderate or severe hypofibrinogenemia versus surgical bleeding. Also in cases of suspected intravascular consumption coagulopathy (DIC), TEG parameters to be combined with antithrombin (AT) III, soluble fibrin monomer complex (SFMC) assay, fibrinogen level (mg/dL) and platelet count (K/µL). TEG parameters are detailed in Figure 2.
to the replacement of anticoagulants such as antithrombin III in order to minimize the risk of a thrombotic event in states of suspected hypercoagulability or when rFactor VIIa was administered (Figure 1).

**Laboratory Methods.** Thromboelastography mechanically measures the viscoelastic properties of a clot over time, as related to the functionality of initiating plasma clotting factors, fibrinogen levels, and platelets and also the impact of factors responsible for clot lysis [2, 3]. It is performed on whole blood at point of care settings in the operating room or on citrated whole blood in the clinical laboratory using the thromboelastograph (TEG5000(R) Haemonetics, Braintree, MA). The principal parameters of thromboelastographic analysis are detailed and illustrated in Figure 2 [2]. Hemoglobin (Hb), hematocrit (Hct) and platelet count were performed on EDTA whole blood using a Coulter (R) LH750 analyzer (Beckman Coulter, Inc., Brea, CA). Quantification of plasma fibrinogen utilized citrated whole blood and was determined using a STA Evolution instrument (Diagnostica Stago, Inc., Parsippany, NJ). Additionally, a prothrombin time (PT) and activated partial thromboplastin time (aPTT) were performed on citrated blood using the STA Evolution instrument (Diagnostica Stago, Inc., Parsippany, NJ) with Hexasorb pretreatment (Inotech Biosystems International Inc.), if indicated. When available, data from the PT and aPTT were utilized in conjunction with the “triggers” and blood bank inventory in the dialogue between the clinical pathologist and the ordering physician. In cases of suspected disseminated intravascular coagulopathy, both the soluble fibrin monomer and antithrombin III levels were determined on citrated plasma. Assessment of soluble fibrin monomer complexes (SFMC), which are found to be increased at the initial phase of disseminated intravascular coagulation syndrome [4], employed a manual latex agglutination technique; antithrombin (AT) III percentages were determined on a STA Evolution instrument (both from Diagnostica Stago, Inc., Parsippany, NJ). Parenthetically, the decision to submit specimens for ATIII and SFMC determinations was based largely on the suspicion of the surgeon and included clinical observations associated with DIC such as renal, hepatic, respiratory, and/or central nervous system dysfunction, shock and thromboembolic phenomena. Additionally, the ordering physician also took into consideration predisposing factors including active endocarditis, blunt trauma, and aortic disruption or dissection.

**Criteria for Recombinant Factor VIIa Administration to Meet the Algorithmic Indications.** A rationale with criteria was developed for the use of recombinant, activated Factor VII (rFVIIa) in accordance with the established algorithm. It was presented to the members of the Pharmacy and Therapeutics Committee for their consideration and recommendations.

**Laboratory Support and Review of the Algorithmic Data by the Clinical Pathologist in a Real Time Fashion.** Policies and procedures were developed to provide logistical direction for delivery of the patient specimens and 24/7 generation of the technical data pertinent to the algorithms. A corresponding call schedule for the clinical pathologists was implemented so that the data could be reviewed in a real time fashion and a call initiated to the physician or perfusionist attending to the transfusion needs of the patient.

**Patient Study Population and Comparative Utilization Outcomes.** Patients admitted to adult cardiac surgery, the cardiac intensive care unit (CICU), and the adult intensive care unit (AICU) of Geisinger Medical Center comprised the main patient study population. Blood component, blood derivative, and recombinant therapies were compiled as part of the routine data collection for the purposes of monitoring utilization and for the generation of the previously approved blood bank scorecards. These utilization outcomes were reported to the Transfusion Committee and on occasion, to the Medical Executive Committee. As part of the analysis of utilization outcomes, comparisons of the utilization of units of single donor (apheresis) platelets, fresh frozen plasma, and cryoprecipitate in cardiac surgery/CICU and the AICU prior to or during development versus the early-implementation phase and following full implementation of this integrated consultative
and algorithmic approach were made. Reporting of the utilization outcomes data in this study was approved by the Institutional Review Board of Geisinger Medical Center.

Results

Blood Component "Triggers". Following approval of the blood component "triggers" by the Medical Executive Committee, the blood bank developed a PATH COAG NOTIFICATION form that included: patient name, medical record number, ordering physician and his contact information, blood component trigger and current inventory of the corresponding component, laboratory data from the past 24 hours (Hb, platelet count, fibrinogen, PT with international normalized ratio [INR] and aPTT, when available), and a means to document both the notification of the pathologist-on-call by the blood bank staff (with date and time) and the action taken by the clinical pathologist. These completed reports were retained in the blood bank files and were available for review as part of the blood utilization report to the Transfusion Committee. The results of this effort and dialogue between the clinical pathologist and patient’s physician included: 1. relative prioritization of existing inventory; 2. an increased awareness on the part of the ordering physician of the availability of consultative services using either the algorithmic approach or the clinical hematologists on the coagulation service; and 3. a better understanding on the part of the laboratory team and the ordering physician of the patient’s underlying coagulopathy and the options available to specifically address the need.

Implementation of Diagnostic and Therapeutic Algorithm for Microvascular Bleeding in Adult Cardiac Surgery/CICU and the AICU. Policies and procedures were developed regarding the logistics of laboratory notification, specimen transport, and the communication of coagulation testing results 24/7 to the pathologist-on-call, along with the ordering physician’s contact information. The pre-algorithm and developmental phases of this study were carried out prior to January 2004 and from January 2004 through July 2004, respectively. The early implementation phase took place from August 2004 through December 2004, while the post-implementation phase began in January 2005.

Impact of the Diagnostic and Therapeutic Algorithm for Microvascular Bleeding on Blood Component and Blood Derivative Therapies in Adult Cardiac Surgery/CICU and The AICU. The numbers of units of fresh frozen plasma (FFP), single donor (apheresis) platelets and cryoprecipitate (hemostatic blood components and derivatives) were tallied for the Adult Cardiac Surgery/CICU and AICU prior to and during the developmental phase of the microvascular bleeding algorithm and compared with the utilization during the implementation phases. Subsequent utilization data, generated by the Division of Perfusion Services, showed a graphic decline in the number of units of single donor (apheresis) platelets, FFP, and cryoprecipitate as calculated on a per patient basis in the Adult Cardiac Surgery/CICU population. This was evident in the developmental and implementation phases of the diagnostic and therapeutic algorithm when compared with the pre-implementation time periods (Figure 3). Similarly, major reduction in blood component therapy use were noted in the
AICU patient population when the developmental/early implementation phase was compared with the post-implementation phase: apheresis single donor platelet transfusions (303 versus 77 [74% decrement]); FFP units (1596 versus 1092 [31% decrement]); and units of cryoprecipitate (53 versus 14 [74% decrement]). This occurred even during a time when the AICU admissions were showing a slight upward slope (575 versus 649, respectively; Table 1). The decrease in transfusions of these hemostatic elements coincided with the full implementation of the algorithmic approach to the management of microvascular bleeding (10 microvascular bleeding profiles performed and algorithmic consults rendered in the period from January ’04 through August ’04 [the developmental and early implementation phases] versus 32 in January 05 through August 05 [the full, post-implementation phase]; Table 1).

Our findings coincide with similar algorithmic approaches that were based largely but not exclusively on thromboelastography. Shore-Lesserson and colleagues [5] reported on the statistically significant reduction in the use of fresh frozen plasma (FFP) and platelets in complex cardiac surgery with the use of a thromboelastography-guided transfusion algorithm but also incorporating fibrinogen and platelet count into their algorithmic approach. Avidan and co-workers [6] compared the use of algorithms based on point of care testing that included thromboelastography as a guide to the management of bleeding after routine cardiac surgery versus clinical discretion. They observed a decrease in transfusion of packed red blood cells and blood

**Table 1. Hemostatic Blood Component Usage in the AICU: Developmental-Early Implementation Phase (I) versus Post-Implementation Phase (II) of the Consultative and Algorithmic Microvascular Bleeding Profile**

<table>
<thead>
<tr>
<th>Hemostatic Component (Units)</th>
<th>Admissions</th>
<th>Profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP</td>
<td>Platelets (Single Apheresis Donor)</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>I. Developmental-</td>
<td>1596</td>
<td>303</td>
</tr>
<tr>
<td>Early Implementation Phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(January 04- August 04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II. Post-Implementation Phase</td>
<td>1092</td>
<td>77</td>
</tr>
<tr>
<td>Phase (January 05- August 05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference I vs II</td>
<td>504</td>
<td>226</td>
</tr>
<tr>
<td>(% Change)</td>
<td>(-31%)</td>
<td>(-74%)</td>
</tr>
<tr>
<td>Units per Admission I vs II</td>
<td>2.8 vs 1.7</td>
<td>0.52 vs 0.12</td>
</tr>
</tbody>
</table>

Abbreviations: AICU= adult intensive care unit; FFP= Fresh frozen plasma

and reported on such a personalized medicine model for microvascular bleeding in an intensive care setting. The essential components of our model included: 1) an algorithm combining thromboelastography, quantitative fibrinogen, platelet count, and when indicated, assays for antithrombin III levels and soluble fibrin monomer complexes and other coagulation tests that the clinical pathologist deemed appropriate (e.g., PT and aPTT); and 2) real time analysis by laboratory staff and interpretation by the clinical pathologist with communication to and discussion of the results with the clinical team caring for the patient. Moreover, by comparing the utilization of blood components and blood derivatives in the Adult Cardiac Surgery/CICU and AICU patient populations over defined time periods prior to and during development and implementation of this approach, we observed an associated decrease in the transfusion of hemostatic elements including units of fresh frozen plasma, single donor platelets, and cryoprecipitate.

**Discussion**

Personalized medicine is intended to customize therapy for the specific needs of the individual patient while reducing the risk, morbidities, and cost of unnecessary therapies. Transfusion medicine lends itself to such an opportunity. By combining transfusion medicine and coagulation with proactive and timely involvement by the clinical pathologist and the laboratory staff, we have developed
components with the former approach and concluded that “cardiac surgery services should use transfusion guidelines based on laboratory-guided algorithms” [6]. Nuttall and co-authors [7] used a coagulation test-based transfusion algorithm in cardiac surgery patients with abnormal bleeding and noticed a reduction in fresh frozen plasma and platelet units transfused in the operating room. The components of their algorithm included MA by thromboelastography, platelet count and fibrinogen. More recently, Ak, et al. [8] noted a significantly lower transfusion median for units of FFP and platelets after elective coronary artery bypass grafting using a thromboelastography-based transfusion algorithm.

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This personalized medicine approach has implications beyond the cost savings in terms of reduced transfusion of blood components and derivatives. It minimizes the potential risk of an untoward outcome of transfusion. Such adverse effects are well known to those who practice transfusion medicine and include transfusion-related infection, fluid overload, and transfusion-related acute lung injury [7, 8]. Moreover, these can result in increased patient morbidity with prolonged hospitalization and even death, as convincingly demonstrated by Morton and colleagues [1] in their demographic study. Our study brings the perspective that transfusion medicine practice should include a proactive approach for the elimination of the potential risks of transfusion therapy which are known to lead to increased mortality and morbidity. Sustained collaboration with an interdisciplinary team is essential for development and implementation of a paradigm shift from the practice of transfusion medicine based on universal guidelines for each blood component and retroactive evaluation of transfusion risks to an integrated, personalized and proactive component therapy that will optimally prevent them.

In summary, we report on the successful development of a model for individualized and personalized transfusion therapy that: 1. is based on the integration of coagulation and transfusion medicine; 2. provides a "trigger" mechanism to establish a dialogue between the clinical pathologist and the clinical team caring for the patient in the context of the patient’s needs and the blood bank’s inventory; and 3. requires the timely involvement and proactive participation of the laboratory staff and the clinical pathologist in the analysis and reporting of the findings in the microvascular bleeding algorithm, along with therapeutic recommendations specific to the patient’s needs. Additionally, we provide a proof of concept of this approach in the form of reduced transfusion of units of fresh frozen plasma, single donor (apheresis) platelets and units of cryoprecipitate in the cardiovascular surgery/CICU and AICU following its full implementation.

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References