Proposed Manuscript Title: Understanding Intra Operative Blood Use: a retrospective procedure-specific analysis of MPOG data

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Introduction:

The goal of appropriate intraoperative transfusion support of scheduled surgical procedures is to ensure patient safety, and efficient use of resources. By having an awareness of which procedures will be associated with large intraoperative blood losses, testing and identification of compatible blood products can be prepared in advance and be ready for immediate use on day of surgery. This also includes avoiding over utilization by preparing blood or performing type and screen testing only for procedures that are predicted to require transfusions, while simultaneously avoiding under-utilization, by preparing sufficient quantities when there is a high likelihood of a procedure being associated with heavy blood loss. For this reason, many hospitals have created a file that cross-references different procedures with the standard amount of blood that would be required, vs. only a type and screen to be performed, vs. no Blood Bank support is anticipated nor should be ordered. Often this file is referred to the maximum blood ordering schedule (MSBOS). If the MSBOS is used properly, it allows for the Blood Bank staff to review the operating room schedule in advance for the next several days, and prepare blood or request patient samples in advance to properly support the next day's surgical procedures. Being able to predict intraoperative transfusion use allows for a steadier and more leveled workflow, where patients who may need transfusions are assessed in advance, allowing for time to identify compatible RBC units when compatibility issues are identified in advance of the day of surgery. In contrast, the lack of an anticipatory strategy of predicted intraoperative blood use would lead to bottle necks in testing and possibly an avoidable massive bolus of stat laboratory testing, insufficient blood component availability and rushed compatibility searching on the morning of surgery for patients.

The MSBOS was proposed over 30 years ago (Friedman (1979)) through the analysis of blood use from approximately 300 hospitals for various procedures. It identified median and mean blood use, and suggested default Blood Bank orders to support the various specific procedures. However, it is unclear whether hospitals have updated their own institutions' MSBOS file over time, whether the "default" levels set for amount of blood or testing to be performed in advance of surgery was appropriate, or that the MSBOS was even in use. Recent and past studies suggest poor compliance with its use (Friedberg (2003); Hall (2013)), and delays in patients starting their surgery cases associated with incomplete testing due to same day submission of samples to the Blood Bank (McWilliams (2012)). Frank et al (2013) attempted to revise their MSBOS at a single academic medical center and found that among patients who did not require preoperative blood orders by the MSBOS, 32.7% had a type and screen, 9.5% had a crossmatch order. Of patients who required only a type and screen, 32.5% had an additional crossmatch order. The first part of the proposed study will be to analyze the multi-center database of current intraoperative blood use in MPOG and to generate a revised data-based version of the MSBOS that would help facilitate better utilization of transfusion services. However, we are

anticipating significant variation in intraoperative blood use when we analyze this data. Selected review of certain procedures (total hip replacement, colectomy, and pacreaticoduodenectomy) by others has already demonstrated this (Qian 2013). Therefore, our primary research hypothesis for this study is that transfusion support across different institutions will not be uniform, even when accounting for differences in procedure and patient demographics. Nonetheless, the gathering of such data is important to better understand and improve intraoperative transfusion support.

In selected areas of surgery, mostly in cardiac surgery, there has been additional research towards predicting those patients most at risk for receiving a blood transfusion (Litmathe (2003); Alghamdi (2006); Ranucci (2009)). In cardiac surgery, some attempt has been made in developing models for predicting the quantity of blood needed (Simeone (2011); Cevenini (2013)). However, these studies do not address other non-cardiac surgery procedures with regards to risk of needing intraoperative transfusions, nor with the exception of the study by Simeone et al, do they attempt to predict the quantity that should be anticipated. Simeone et al. were able to assign a certain quantity of blood to be prepared base on the whether the patient had renal failure requiring preoperative dialysis (4 units of RBC), low hematocrit less than 20% at bypass (2 RBC unit), and low preoperative hematocrit less than 40% (1 RBC unit), for example. The second part of the proposed study will be to identify preoperative risk factors for blood use and compare these with those previously identified in cardiac surgery patients to determine if they are relevant outside of cardiac surgery. As a novel approach, we will also attempt to identify consistent risk factors associated with outlier cases that had exceeded 90th percentile of blood use from the data we gathered in the first part of our study.

These proposed analyses have a number of potential follow up projects or studies. A potential future application of these analyses would be to create a process whereby certain preoperative values or conditions would generate alerts to surgical and anesthesia teams of such high risk cases, to warn them of the potential need for greater transfusion support. Given the recent findings from a multi-center retrospective study of an increased risk of death (odds ratio of 1.29) with intraoperative transfusions (Glance et al. 2011), there is an opportunity to also look at patient outcomes associated with intraoperative transfusions More specifically, it would be useful to know if the findings from the proposed studies would address the gap in recent knowledge of procedure-specific intraoperative blood use at the local level (to assist with predicting who would need blood and how much), and whether it would improve outcomes due to better preparedness for bloodier cases. Finally, by generating this data at the inter-institutional level, benchmarking between those institutions with lower blood utilization vs. those with higher blood utilization for the same procedures may allow for identification of the most effective local measures or initiatives that have reduced the need for intraoperative transfusions. We anticipate that there will be significant inter-institutional variation in blood use observed. Our proposed analyses will determine if these differences are accounted for by differences in patient-specific risk factors for transfusions that are identified or if they are institution-specific, laying down the necessary foundation for these future studies or projects.

Methods and Statistical Analyses

The proposed study will be a multicenter retrospective study of cross-sectional de-identified data from the MPOG database. Data on procedures performed from January 1st 2010 to January 1st 2013 will be reviewed. Patient inclusion criteria: All patients undergoing elective and urgent surgery. Patient exclusion criteria: All pediatric patients < 18 years old, all patients undergoing trauma surgery. The primary outcome for the proposed studies is intraoperative blood use (all blood components including autologous blood use). Specific methods and statistical analyses (to be conducted by Peter Callas, a PhD level statistician) are further described below.

Proposed Study Part 1: Identification and classification of surgical procedures associated with intraoperative blood transfusions.

To simplify the study, a Pareto analysis will be performed, whereby surgical procedures associated with 80% of intraoperative blood transfusions will be identified. This will be performed for red blood cells, platelets, and plasma. These procedures will then be combined into broader groupings based on similarity of procedure to simplify subsequent surgical procedure-specific analyses. The method for aggregating the various surgical procedures will follow the method as described by Frank et al. (2013), meaning surgical procedures with very similar surgical procedure codes. We will use anesthesia CPT codes because they are already broader than the much more detailed surgical CPT codes. In addition, the median, 10th percentile to 90th percentile range of blood use per broader grouping of similar procedures will be determined by institution. Finally, the median, 10th to 90th percentile range for each procedure will be determined among the institutions collectively. For this aggregate analysis, results from each institution will be volume-adjusted, so that each institution will have an equal contribution to the calculation of the range of variation for each procedure.

For the determination of the degree of inter-institutional vs. intra-institutional variation for surgical procedures (to test the primary hypothesis), the distribution width of 10th to 90th percentile blood use within an institution for a given broad group of similar procedures will be compared against that of the aggregate of institutions to determine if there are significant differences. In addition, repeated measures analysis of variance will be used to compare the variance in blood use associated with each procedure within each institution to the variance in the mean blood use for each procedure among institutions. As an additional evaluation, we will determine if 10th-90th percentile intraoperative blood use as determined by the MPOG data for the various groupings of surgical procedures will generate a similar assignment of default blood component orders as that developed by Frank et al (2013).

Finally, it would be useful to identify procedures that never require blood transfusions (and therefore would not even need a Type and Screen). Therefore, all procedures identified by anesthesia CPT codes that used no RBC transfusions intraoperatively will be identified. Additionally, it will be determined if outpatient procedures all do not require RBC transfusions as if this is true, then identification of procedures as outpatient-based may be a means of recognizing procedures that would not require unnecessary laboratory testing such as the Type and Screen.

Proposed Study Part 2: Determination of risk factors associated with greater blood use

Multivariate linear regression will be used to analyze the following: patient variables (age, gender, weight, preoperative hemoglobin and platelet count (within 7 days of surgery), creatinine, ~~pre-existing diabetes, pre-existing liver disease, pre-existing bleeding disorder, pre-operative anticoagulation medication),~~ surgical procedure variables (~~complex surgery, repeat surgery~~, emergent/urgent vs. elective), and anesthesia technique; as independent factors, and quantity of blood used (RBC units) as the dependent factor. Of interest will be the determination of the relative effect of preoperative hemoglobin relative to other factors in predicting blood use. In addition, a logistic regression to compare cases with greater than 90th percentile blood use vs. less will be performed, where independent factors are as defined in the multivariate linear regression analysis. Risk factors that are associated with high volumes of transfusion support (massive transfusions, multiple blood product types) will be also be identified.

Variables to be collected

The specific elements to be gathered from the MPOG database are identified below:

Element	**Source**
MPOG case identifier	General_Case_Information
MPOG patient identifier	General_Case_Information
MPOG institution identifier	General_Case_Information
Case Date	General_Case_Information.AIMS_Scheduled_DT
age	Caseinfo.age_in_years
gender	Caseinfo.sex
Height in cm	Anthropometrics.MPOG_height_cm
Weight- kg	Anthropometrics.MPOG_weight_kg
BMI	Anthropometrics.Body_Mass_index
Primary Surgical Service	General_Case_Information. MPOG_Primary_Procedural_Service_Concept_ID

Primary Surgical Service	General_Case_Information. MPOG_Primary_Procedural_Service_Concept_Desc
Procedure Code	General_Case_Information. Charge_Capture_Primary_Anesthesia_Code
Procedure Code	General_Case_Information. Charge_Capture_Primary_Surgery_Code
PACKED RED BLOOD CELLS-AUTOLOGOUS (transfused)	Intraoperative Blood Products In -10489
PACKED RED BLOOD CELLS – HOMOLOGOUS (transfused)	Intraoperative Blood Products In - 10490
WHOLE BLOOD – AUTOLOGOUS (transfused)	Intraoperative Blood Products In - 10491
WHOLE BLOOD – HOMOLOGOUS (transfused)	Intraoperative Blood Products In - 10492
FRESH FROZEN PLASMA (transfused)	Intraoperative Blood Products In - 10493
PLATELETS (transfused)	Intraoperative Blood Products In - 10494
CRYOPRECIPITATE (transfused)	Intraoperative Blood Products In - 10495
SALVAGED BLOOD (CELLSAVER, transfused)	Intraoperative Blood Products In - 10496
Endocrine – Diabetes	Preoperative Observations - 70046
Formal lab- Hemoglobin	Laboratory or Testing Observations - 5005
Formal lab- Hematocrit	Laboratory or Testing Observations - 5006
Formal lab- Platelets	Laboratory or Testing Observations - 5004

POC- Coulter counter - Hemoglobin	Laboratory or Testing Observations - 3440
POC- Coulter counter – Hematocrit	Laboratory or Testing Observations - 3450
POC – Coulter counter – Platelets	Laboratory or Testing Observations - 3445
Formal lab – Blood gas - Hemoglobin	Laboratory or Testing Observations - 5080
POC – Blood gas - Hemoglobin	Laboratory or Testing Observations - 5081
Formal lab –Creatinine, Serum	Laboratory or Testing Observations - 5002
GI – Liver Disease	Preoperative Observations - 70052
Hematologic – Bleeding Disorder	Preoperative Observations - 70064
General- Medications – Anticoagulation	Preoperative Observations - 70073
Formal lab – International Normalized Ratio	Laboratory or Testing Observations - 5008
ASA class	ASA_Class
Emergent	ASA_Class
Block_yn	Anesthesia Technique
Epidural_yn	Anesthesia Technique
General_yn	Anesthesia Technique
Spinal_yn	Anesthesia Technique

Management of missing data

The proposed study will not exclude cases that have missing data unless intraoperative blood use is not reported by the participating MPOG institution. This study is based on intraoperative data already mapped for automatic download to the MPOG database, therefore the expectation of encountering substantial missing data is minimal. Any missing data would likely be sporadic and random in

distribution and would not be expected to affect our study where we are examining overall average blood use for various surgical procedures and the distribution width of the variation (10^{th} to 90^{th} percentile) in intraoperative blood use. At most, the missing data will reduce our confidence intervals in our description of intraoperative blood use, but should not affect our analyses which is based on aggregation of data. Our statistical software (Stata 13, StataCorp LP, College Station, TX) allows for analyses where certain data elements are missing for individual cases. In the event that a hemoglobin laboratory value is missing, but a hematocrit is reported, the hematocrit will be divided by three to generate the equivalent hemoglobin value.

IRB statement

The data to be obtained from MPOG is de-identified and does not constitute human subjects research and therefore may be exempt from IRB approval for our research activities. An application for this determination by UVM IRB has been submitted, accepted, and been determined as exempt from IRB approval.

Reporting of results

The investigators agree to abide by the STROBE guidelines and checklist for observational studies when reporting our findings.

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