Title

National trends in intraoperative red blood cell transfusion practice: a report from the Multicenter Perioperative Outcomes Group.

Authors

Fiona Linton, MBBCh

Paul Picton, MD

Elizabeth Jewell MS

Michelle Morris MS

Other collaborators

Sachin Kheterpal, MD

Introduction

Approximately 15 million red blood cell units are transfused across the USA annually (AABB guidelines) and it has recently been estimated that 25-40% or greater of these transfusions are medically unnecessary (Taylor M, 2012..). This represents a vast waste of an expensive and invaluable resource. Furthermore blood transfusion has potential serious side effects, causing substantial morbidity and even mortality, which may be avoidable.

There has been a wealth of literature published over the past 10-15 years assessing the risk benefit profile of red blood cell transfusion. There has been an evolution in the evidence, beginning with the landmark TRICC study in 1999, which showed that utilizing a restrictive transfusion trigger (7 g/dL) was at least as effective as a more liberal measure (10g/dL) in anemic patients in an ICU setting (TRICC). This has been corroborated with extensive work including further trials and systematic reviews, largely conducted in intensive care and postoperative surgical settings (ABC, CRIT, FOCUS, vascular 2013 paper, GI 2013 paper). This evidence base showed that a restrictive transfusion policy was equivalent or superior to a more liberal use of red cell transfusion in terms of patient morbidity and mortality. This has resulted in the AABB guidelines (Carson, 2012), which recommended use of a 7-8g/dL Hb (restrictive) threshold for hospitalized, stable patients. Results in patients with known cardiovascular disease have been more varied and the resultant AABB guidelines reflect this. The recommendations are that in these patients transfusion should occur at 8g/dl Hb or when symptomatic, whereas in acute coronary syndrome the risk benefit ratio is still unclear. (AABB guidelines).

The paucity of literature regarding intraoperative blood transfusion practices and outcomes stands in stark contrast to the general medical, critical care, and postoperative literature. Randomized control trials have focused upon patients in ICU or postoperative patients. Observational papers in ICU settings assessing current practice have shown mixed results. Some studies have suggested that there have been substantial improvements in the use of appropriate transfusion triggers and others that clinical practice has been slow to change with higher transfusion thresholds being used than those suggested in their contemporary literature (TRICC 2005 investigators, CRIT, Chohan et al, Walsh et al, French et al).

A number of papers in largely single center and single surgical specialty or operation specific patient populations have demonstrated significant reductions in perioperative transfusion triggers over recent years (Mayo clinic papers, Robinson, 2012). However there has yet to be a multi-center intraoperative review of red cell transfusion conducted over a range of surgical specialties anywhere in the world.

In this study we will aim to fill this gap in the literature. We will describe the patterns of change, if any, in clinical practice surrounding intraoperative red blood cell transfusion over the past six years. In addition the differences between the management of patients in different surgical specialties will be examined. Furthermore a sub group analysis will also be performed, looking at patients with known ischemic heart disease, given the literature specific to this group.

We hypothesize that over the time period studied there will have been significant changes in transfusion practice across the United States, with a decrease in transfusion trigger utilized alongside a reduction in the proportion of patients receiving red cell transfusions. Moreover we also hypothesize that we may detect important differences between surgical specialties and in the management of patients with ischemic heart disease.

Materials and methods

To address this question a multi-center, retrospective, observational study will be performed using the MPOG database. This extensive database contains electronic health record data inputted pre, intra and post operatively. All protected health information within this data set has been removed, with the exception of procedure date. Owing to this and as no interventions being performed patient consent was waived.

Institutional Review Board approval has already been obtained for all MPOG projects involving the University of Michigan, Ann Arbor, Michigan.

Centers contributing preoperative history and physical data and postoperative laboratory result data were included for analysis (University of Michigan, Oregon Health and Sciences University, University of Colorado, University of Tennessee, University of Oklahoma, University of Vermont, and Vanderbilt University).Procedures performed between the dates of January 1st 2007 and January 1st 2013 will be reviewed. Cases involving outpatient care will be excluded due to the low risk of significant bleeding or transfusion during these procedures.

Patient population

All adult patients undergoing orthopedic, general , vascular, gynecology, urologic, otolaryngology, neurologic, and thoracic surgery with an inpatient stay will be included.

To allow a basic description of the patient population, descriptive variables from the preoperative history and physical examination will be recorded. These include ASA status, age, and operation being undertaken and major comorbidities.

Patient exclusion criteria

All pediatric patients <18 years old

All patients undergoing cardiac surgery

All patients undergoing outpatient operations

All patients who received massive transfusion, defined for this study as recipients of more than 4 units of red blood cells intraoperatvely.

ASA 5 or 6

Primary outcome

Trend in percentage of patients receiving intraoperative transfusion during the specified time period

Secondary outcome

Other outcomes include:

Trend in lowest intraoperative hematocrit/hemoglobin (inferred as the transfusion trigger) and reported for each year of the study, across all specialties studied.

Trend in mean units of blood administered per patient.

Trend in percentage drop in hemoglobin from the pre-operative baseline to the lowest intraoperative value.

Other outcomes observed will include incidence of post-operative myocardial infarction and 30 day mortality observed.

An analysis will also be performed to compare the surgical specialties.

Data source

The MPOG database will be used for retrieval of the data. This data will be both structured inputs and free text. The free text is with respect to preoperative history and examination, which will need to be categorized prior to analysis, in the centers which provide this.

From the intraoperative electronic record for each participating institution, data will be collected regarding red cell transfusion and the measurement of hemoglobin and hematocrit. The lowest recorded intraoperative hemoglobin/hematocrit will be taken as the transfusion trigger for the case. This is the same assumption taken by previous observational work in the same area. (ref Mayo clinic papers). The first post-operative hemoglobin and the peak 7-day postoperative serum troponin laboratory values will also be collected each case.

Mortality will be derived from the social security administration's master death file (United States Department of Commerce, Springfield, Virginia). This is a publicly available database and although it does not include specific cause of death, the date of death and social security number of the patient allows calculation of the 30 day mortality.

Statistical Analysis

Statistical analysis will be performed utilizing the statistical programs STATA (STATACORP LP, College Station, TX) and RSTudio. The main thrust of the statistical assessment will be detection of secular trends amongst the outcome variables. Initially the data will be graphically displayed as time-series data, looking at general shape and direction of the lines plotted as well as the presence of any outliers. Non-parametric smoothers can be used to suggest the type and degree of any secular trends, while the existence of such a secular trend in non-parametric data can be confirmed by applying the Mann-Kendall test. If appropriate, a parametric linear regression model can also be used to test whether trends are significantly different from 0.

A statistical process control chart may also be a possible option depending upon the trends observed and if there is a possibility to use a distinct cut off point. This could be hinged around a time period, for example using the year published of a high impact paper or comparing practice before and after the implementation of a unit specific transfusion policy.

The primary hypothesis regarding the proportion of patents receiving an intraoperative transfusion will be assessed using a one tailed test at a p value of 0.05. Secondary outcome trends, as detailed above, can also be tested in the same way or where appropriate with a two tailed test. It should be noted that some outcomes are expressed as proportions, so will probably need to be transformed - for example, using a logit model.

While the initial purpose is to seek to identify secular trends in the various outcome measures, it will also be necessary to look for differences in the trends due to certain factors or co-variates. An important question concerns whether the hypothesized trend in the outcome measures is uniform across specialties (factors). This can be investigated by comparing time-series data across the subgroups defined (surgical specialties, centers and ischemic heart disease patients). This could be performed either by using an ANCOVA model (or, equivalently, a multiple linear regression model with dummy variables for specialties) to test for factor-related differences between trend values, or - if this is not possible - by equivalent non-parametric methods.

It is proposed that the techniques envisaged as relevant will be trialed initially in a smaller pilot study using sub groups of patients sampled from the data before applying the methodology to the complete data set.

If the data was sufficient with adequate numbers of patients we plan to do a sub analysis of the patients with ischemic heart disease, utilizing the same tests mentioned above. This should allow assessment of trends in the outcomes and then, study of whether the underlying risk can go some way in explaining any such results.

Regarding mortality, transfusion patients will be included who died up to 30 days post surgery and inference can be derived. This also holds true for the known ischemic heart disease patients where we will look at the incidence of post-operative MI (from the troponin rise) and see if there is any relationship between the two. Obviously we understand that possible conclusions from this will be limited unless a full adjusted risk model is utilized.

Power analysis

Although this study is a retrospective observational analysis, not involving recruitment of patients, it is still vital to perform a power analysis to ensure the MPOG database has the capability of detecting a statistically significant change in trends.

This will be performed retrospectively after an initial data retrieval using N Query to assess if an adequate population and sub groups are present to demonstrate significance. It is worth noting that we are anticipating the data set to be very large and easily sizeable enough to address this question. A statistically significant difference may be detectable, but discussion regarding a clinically meaningful effect size needs to occur as well. We recommend that an effect size difference of 20% (ie, 20% fewer

patients transfused) or a transfusion hematocrit trigger difference of 1.5% be established as initial effect size measures.

Management of missing data

Some data regarding preoperative details may not be present in every institute and therefore, although intraoperative data from these cases can be utilized, a full analysis of these cases cannot be made. Their exact use will be summarized in the initial figure outlining the study population, inclusion and exclusion criteria and the further breakdown detailing the cases analyzed in each group.

Discussion

The data derived will be used to describe trends in transfusion practice across multiple centers using a number of descriptive analyses. This will give the most accurate reflection of current, modern transfusion practice in the United States yet performed. These results will show the impact of recent studies and describe variation between sub specialties and where future randomized control trials should be concentrated.

Areas for PCRC discussion/limitations

- Should the primary outcome be proportion of patients receiving an intraoperative transfusion, or hemoglobin
- Is the absence of postoperative transfusion data such a strong limitation that the project is not impactful enough for publication in *Anesthesiology*
- What are effect size measures valid for trend analysis
- Should the “unit of analysis” be year, month, or 6 month period for SPC analysis
- Should we focus on discretionary RBC usage – ie, just 1 or 2 units, as opposed to including patients with 3 or 4 units?
- Should emergency cases be a separate subgroup analysis?
- Manual review of many cases potentially required
- Classification of preoperative details from the History and Physical may be time consuming (?how to classify IHD, looking at risk factors separately from those patients with proven IHD)
- Difficulty of producing a model that corrects for sufficient input factors to allow a sensible and useful conclusion to be derived regarding outcome with post operative MI and 30 day mortality, without fully examining all outcome data? Comorbidity risk adjusted model something we should undertake?
- Assumption of the “lowest intraoperative Hb” as the transfusion trigger, although as noted above has been used in previous work.
- Consistency between form Hb/hematocrit recorded in as inaccuracy may occur if they are recorded in different ways between institutes and anesthesia providers?

- Utilizing trend analysis may allow trends to be identified but will not provide much insight in attributing a shown trend to a particular cause

Variables to be collected/specific data columns required for analysis

<table>
<tr><td>Source</td><td>Data Column</td><td>Data Type</td><td>Source table, column and concept</td></tr>
<tr><td>MPOG preop data</td><td>Age in years</td><td>Numeric, 0-150</td><td>Aims_intraopcaseinfo.AIMS_age_in_years</td></tr>
<tr><td></td><td>ASA status</td><td>Numeric, 1-4</td><td>Preoperative descriptions. MPOG concept ID 70233</td></tr>
<tr><td></td><td>Surgical procedure</td><td>Free text</td><td><table><tr><td>18101</td><td>Column Mapping - AIMS_Procedure_Room_Name</td><td>Extraction Preferences</td><td>100</td></tr><tr><td>18107</td><td>Column Mapping - AIMS_Scheduled_Procedure_Text</td><td>Extraction Preferences</td><td>100</td></tr><tr><td>18108</td><td>Column Mapping - AIMS_Actual_Procedure_Text</td><td>Extraction Preferences</td><td></td></tr></table>Possible data sources. Billing data also a possibility.</td></tr>
<tr><td></td><td>Coronary artery disease</td><td>Free text/pick list</td><td>Preoperative descriptions. MPOG concept ID 70027</td></tr>
<tr><td>Laboratory data</td><td>Peak postoperative troponin (within 7 days)</td><td>Numeric, 0-500</td><td>Aims_labvalues, MPOG concept 5011</td></tr>
<tr><td></td><td>Most recent preoperative haemoglobin</td><td>Numeric, 0-20</td><td rowspan="3">Aims_labvalues, MPOG concept<table><tr><td>5005</td><td>Formal lab - Hemoglobin</td><td>Laboratory or Testing Observations</td><td>90</td></tr><tr><td>3440</td><td>POC - Coulter counter - Hemoglobin</td><td>Laboratory or Testing Observations</td><td>90</td></tr><tr><td>5080</td><td>Formal lab - Blood gas - Hemoglobin</td><td>Laboratory or Testing Observations</td><td>90</td></tr><tr><td>5081</td><td>POC - Blood gas - Hemoglobin</td><td>Laboratory or Testing Observations</td><td>90</td></tr></table></td></tr>
<tr><td>MPOG Intraoperative data and laboratory data</td><td>Lowest intraoperative haemoglobin</td><td>Numeric, 0-20</td></tr>
<tr><td></td><td>Initial postoperative hemoglobin</td><td>Numeric, 0-20</td></tr>
</table>

			3435 POC - hematocrit spun Laboratory or Testing Observations 81 3450 POC - Coulter counter - Hematocrit Laboratory or Testing Observations 81 5006 Formal lab - Hematocrit Laboratory or Testing Observations 81
	Number of red blood cell units administered between anesthesia start and anesthesia end	Numeric,	Aims_intraopphysiologic, MPOG concept 10489, 10490 “intraoperative blood products in” autologous/homologous
	Estimated blood loss	Numeric, 0-10000	Aims_intraopphysiologic, MPOG concept 10499
Social security	Mortality at 30 days	Binary	-

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