Fresh frozen plasma is ineffective for correcting minimally elevated international normalized ratios

We read with interest the recent article by Wallis and Dzik1 regarding the number of potentially inappropriate transfusions of fresh frozen plasma (FFP) in the United States. Like most institutions, we constantly strive to minimize the number of inappropriate FFP transfusions. We find, however, that the blood bank staff flags 25 to 30 percent of transfused FFP units as not meeting transfusion guidelines. Other institutions have reported similar percentages of inappropriate FFP transfusions.2 Although the significance of a minimally elevated prothrombin time (PT)-international normalized ratio (INR) has not been definitively proven,3 many clinicians will prophylactically order FFP for a patient with a minimally elevated PT-INR.

Although guidelines published by the AABB and others define appropriateness of FFP administration based on PT (or partial thromboplastin time) greater than 1.5 times normal, we find that defining the transfusion guidelines in terms of INR makes it easier for our clinicians to quickly evaluate the coagulation status of patients. Our guidelines suggest that FFP be considered only when the patient’s INR is equal to or greater than 1.6. We use thromboplastin with an international sensitivity index of 1.01 in our PT assay and so the reported INR is essentially the ratio of the patient’s PT to the normal value. At a glance, the clinicians can gain the same information from the INR that they would obtain by performing a calculation on the PT. Furthermore, because the PT reference range for each new batch of reagents may change slightly, we avoid the potential problem of clinicians applying a previously calculated PT transfusion cutoff to a new reference range.

During an audit of monthly FFP utilization, we identified 22 nontrauma patients, receiving a total of 68 units of apheresis FFP (500 mL), who did not meet criteria for receipt of FFP. Some patients received FFP on more than one occasion. All received appropriate dosages of FFP, at least 10 mL per kg, with a mean of 1.9 units of FFP per transfusion (range, 1 to 6 units). The INR values around the time of the transfusion were recorded with pretransfusion INRs available at a median time of 6.3 hours before transfusion (range, 0.7-21 hr) and posttransfusion INRs available at a median of 3.9 hours after initiation of transfusion (range, 0.5-21 hr). The mean pretransfusion INR was 1.37 (range, 1.1-1.6), and the mean change was a decrease of 0.03 INR per unit of FFP infused. The changes in INR from transfusion of these 68 units and 10 control patients receiving FFP transfusions that did meet criteria are summarized in Fig. 1.

We also calculated INRs for 20 units of apheresis FFP (500 mL). The mean INR of these FFP units was 1.1 (range, 0.9-1.3) (Fig. 2). These values are in agreement with those presented in other studies.4,5 Given that the INR of FFP units can be as high as 1.3 (Fig. 2), it is not surprising that transfusion of FFP will have little effect on minimally elevated INRs. In this situation, the difference in coagulation activity between FFP and the patient’s plasma is so small that there will be little effect on the INR. In the short term, FFP will only affect the INR when there is a relatively large difference between the coagulation activity of the FFP and the patient’s plasma.

Taken together these findings provide evidence of the limited efficacy of FFP for correcting minimally elevated INRs. Even patients with minimally elevated INRs receiving supernormal doses of FFP (as high as 30 mL/kg) showed minimal changes in their INRs. Therefore, regardless of their possible clinical significance, minimally ele-
vated INRs cannot be corrected with FFP administration at currently accepted dosages.

Lorne L. Holland, MD, MS
Tisha M. Foster, MD
Department of Pathology
University of Oklahoma Health Science Center
1100 N. Lindsay
Oklahoma City, OK 73104
Richard A. Marlar, PhD
Jay P. Brooks, MD, MBA
Department of Pathology
University of Oklahoma Health Science Center
Oklahoma City VA Medical Center
921 NE 13th Street
Oklahoma City, OK 73104

REFERENCES

Independent association of massive blood loss with mortality in cardiac surgery

With much interest we read the article by Karkouti and coworkers1 on the independent association of massive blood loss (MBL) with mortality in TRANSFUSION. As they stated in their abstract, “. . . it is unclear whether MBL is an independent risk factor or, instead, simply a marker for other adverse events . . .” Especially important, but notoriously difficult to distinguish, are the effects of MBL (hypovolemia, hypotension, compensatory mechanisms of the patient) on the one hand and the effects of massive transfusion therapy (stored blood, allogeneic contact, additive solution) on the other hand.

Knowing the problems of collecting reliable data on perioperative blood loss, we were interested in the method used to collect these data. To our surprise, the authors had neither data on blood loss nor a definition of MBL for data collection. Their definition of “5 or more units of RBC within 1 day of surgery” was chosen as “most appropriate cutoff.” Thus, the mortality rate among patients with MBL “was markedly higher than the mortality rate among patients without MBL.” Besides coming close to circular reasoning, this definition created a serious flaw in their main conclusion.

The objective of this study was to demonstrate whether MBL is an independent risk factor or, simply, a marker of other adverse events. In answering this question, it is unacceptable to define MBL with the number of RBC units transfused “as a surrogate measure.” One must distinguish between effects of MBL and effects of massive transfusion therapy to prove the independence of the effect of MBL. Therefore, if any conclusions can be drawn from this study, they are not about MBL, but about transfusing 5 or more units of RBCs within 1 day of surgery.

Leo van de Watering, MD, PhD
Anneke Brand, MD, PhD
Sanquin Blood Bank Southwest Region
Plesmanlaan 1a
2333 BZ Leiden, the Netherlands

REFERENCE

The above letter was sent to Karkouti et al.: Dr Karkouti and colleagues offered the following reply.

We thank Drs Van de Watering and Brand for their interest in our study and appreciate the opportunity to discuss these issues.

One of their questions relates to our use of “number of RBC units transfused” as a substitute measure for “estimated perioperative blood loss” and whether or not this is a valid surrogate measure. Recognizing that both these measures are actually surrogate measures for the clinical outcome of interest, which is “actual amount of perioperative blood loss,” we would argue that, in the setting of massive blood loss (MBL), the former is a better surrogate measure than the latter because clinical estimates of perioperative blood loss are inherently unreliable even in more controlled settings.1 They are presumably even less reliable when carried out as part of routine clinical care in the setting of MBL. Thus, in the setting of MBL, “actual amount of perioperative blood loss” is probably more strongly and consistently associated with “number of RBC
units transfused” than with “estimated perioperative blood loss,” which means that it should be a better surrogate measure. It is therefore not surprising that the preferred outcome in randomized clinical trials assessing the efficacy of perioperative hemostatic agents is reductions in “number of RBC units transfused” (at least based on our experience with peer review for publication or funding support).

Drs Van de Watering and Brand also wonder if we used “circular reasoning” by first defining MBL based on the relationship between number of units of RBC transfused and mortality and then finding that mortality is increased among patients defined as having MBL. It is important to note that we defined MBL based on the unadjusted relationship between number of units of RBCs transfused and mortality and then measured the adjusted relationship between this variable and mortality by using multiple logistic regression analysis to control for the effects of multiple confounders. In other words, instead of using the interval variable “number of RBC units transfused” as a continuous variable, we transformed it into a dichotomous variable for inclusion in the multivariable analysis. This is standard method for multiple logistic regression analysis.

Finally, we disagree with the premise that “one must distinguish between effects of MBL and effects of massive transfusion therapy to prove the independence of the effect of MBL.” Massive transfusion therapy is an integral part of MBL therapy, which is why it is a good surrogate measure. One may assume, without benefit of a randomized clinical trial, that MBL unaccompanied by massive transfusion therapy is likely to result in unfavorable outcomes. Although identifying which components of MBL therapy are harmful is an important objective, one must first demonstrate that MBL is harmful, which our study has done.

Keyvan Karkouti, MD
W. Scott Beattie, MD
Duminda N. Wijeyasurya, MD
Terrence M. Yau, MD
Department of Anesthesia
Division of Cardiovascular Surgery
University Health Network
Toronto, Ontario, Canada

REFERENCES

Compensating for iron loss in regular blood donors using ferrous gluconate and ascorbic acid

In a previous placebo-controlled double-blind study,1 we demonstrated that an oral dose of 20 mg of elemental iron daily for 8 weeks compensated for iron loss after whole-blood donations in men, but the same dose for 12 weeks increased iron stores in women. In contrast, iron stores decreased significantly in men and women without iron supplementation. Whether a lower dose of elemental iron and/or a shorter duration of iron replacement will compensate for iron loss remains an open question. In this communication, we present the results of an open study in which regular male and female donors received 20 mg of elemental iron and 400 mg of ascorbic acid daily for only 30 days. The investigational product was identical to that used in our first study.

A total of 165 regular blood donors (83 men and 82 women) were enrolled in this study, which was approved by the Ethics Committee of Charité University Hospital. Written informed consent was obtained from all volunteers. In accordance with German guidelines for blood donor selection, all donors were healthy volunteers with hemoglobin concentrations of 13.5 (men) or 12.5 g per dL (women). At the initial visit, 1 unit of whole blood (495 + 25 mL for test samples) was collected, and each volunteer received 30 capsules of the investigational product (20 mg of elemental iron in the form of ferrous gluconate, 400 mg of ascorbic acid, 1.5 mg of pyridoxal-phosphate, 2.25 µg of cyanocobalamin, 200 µg of folic acid, and 75 µg of biotin). Serum ferritin and soluble transferrin receptor (TfR) levels were measured before the first blood collection (Visit 1) and at a follow-up visit (Visit 2) 2 (men) or 3 months later (women). Evaluation of compensation for iron loss was determined by calculating the base 10 log of the ratio of TfR to ferritin concentration [log(TfR/F)] for each visit (outcome variable). The log(TfR/F) shows an inversely linear correlation to the content of iron stores and is a valid indicator of the body iron storage.2

Of 165 volunteers (18-65 years old) enrolled in the study, 53 men (64%) and 46 women (56%) were included in the analysis. The overall dropout rate was 34 percent (56/165), and 6 percent (10/165) were excluded in the analysis because one or more laboratory tests could not be performed. The mean interval between the two visits was 69 (men) and 101 (women) days.

The mean serum ferritin concentration in men and women increased by 2.6 µg/L between visits. The number of men and women with depleted iron stores (ferritin level, <12 µg/L) decreased, and the mean log(TfR/F) decreased by 0.10 in men and 0.11 in women, reflecting a slight increase of stored iron (Table 1; Fig. 1). Mean log(TfR/F) levels were equivalent and did not increase between Visit 1 and Visit 2 (p<0.001; paired t test).
LETTERS TO THE EDITOR

TABLE 1. Serum ferritin concentrations, number of donors with depleted iron stores, TfR levels, and log(TfR/F), by sex

<table>
<thead>
<tr>
<th>Gender</th>
<th>Visit</th>
<th>Ferritin level (µg/L)*</th>
<th>Number (%) of donors with depleted iron stores (ferritin level &lt;12 µg/L)</th>
<th>TfR (mg/L)*</th>
<th>Log(TfR/F)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1</td>
<td>31.6 ± 46.0</td>
<td>12/53 (22.6)</td>
<td>1.72 ± 0.56</td>
<td>1.91 ± 0.42</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>21.0 ± 17.2</td>
<td>13/46 (28.3)</td>
<td>1.49 ± 0.46</td>
<td>1.93 ± 0.34</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>23.6 ± 20.6</td>
<td>6/46 (13.0)</td>
<td>1.35 ± 0.35</td>
<td>1.82 ± 0.28</td>
</tr>
</tbody>
</table>

* Data are reported as mean ± SD.

Log(TfR/F), however, increased in 26 percent (14/53) of men and 26 percent (12/46) of women, reflecting a decrease of stored iron. In the previous study, 135 and 36 percent of men with iron supplementation (40 and 20 mg daily, respectively) over 8 weeks showed a decrease of storage iron. Similarly, stored iron decreased in 22 and 30 percent of women with iron supplementation (40 and 20 mg daily, respectively) over 12 weeks. A possible explanation for this phenomenon could be poor compliance.

The prevalence of iron deficiency in the population is relatively high and may exceed 40 percent in menstruating female blood donors. Iron deficiency may decrease work and cognitive capacities, even if anemia is absent. 3,4 In contrast, iron supplementation may aggravate undiagnosed hemochromatosis or obscure diseases with blood loss. 5 Whether low iron stores may favorably impact the incidence of cancer 6 and coronary heart disease 7 remains an open question. Therefore, iron supplementation in blood donors should compensate iron loss and avoid overcompensation. In this study, we used the same investigational product, but reduced the duration of treatment. The results of the present study indicate that 20 mg of elemental iron and 400 mg of ascorbic acid daily for 30 days adequately compensates for iron loss in the majority of male and female whole-blood donors. Also, the fixed duration of replacement and the lower total dose (600 mg of iron) are unlikely to obscure the diagnosis of an underlying blood loss disease or aggravate undiagnosed hemochromatosis.

Hartmut Radtke, MD
Joanna Tegtmeier
Lothar Röcker, MD
Abdulgabar Salama, MD
Holger Kiesewetter, MD
Institute of Transfusion Medicine
Charité–University Medicine Berlin
10098 Berlin, Germany

REFERENCES


Comparison of computerized formulae for determination of platelet recovery and survival

Studies to assess the viability of platelets (PLTs) with autologous reinfusion of radiolabeled PLTs involve numerous calculations leading to the determination of recovery and survival. Recovery is usually taken as the proportion of radiolabeled PLTs that would have been found in circulation at the time of reinfusion if instantaneous mixing could have been achieved; as such, extrapolation of the recovery curve back to $t_0$ provides the parameter. Survival is most
often stated as the mean residual life span; the intersection of a tangent to the curve at the x-axis (that is, 0% recovery) provides this parameter. The mathematical method used to calculate these parameters is of importance, therefore, and comparability of technique between laboratories would serve to minimize unnecessary variation.

The COST program\(^1\) has been in wide use among laboratories engaged in radiolabeled PLT studies because of free distribution and ease of use. Its use, however, has required minor modifications to allow it to be supported on a variety of platforms and operating systems. Although these alterations have not changed the mathematical formulae imbedded in the program instructions, concern has arisen whether all laboratories applying a COST program are performing comparable calculations.

The Biomedical Excellence for Safer Transfusion (BEST) Collaborative undertook a comparison of the output of seven laboratories’ computerized calculations as part of an ongoing effort to establish a universally accepted radiolabeling protocol to support the comparison of fresh and stored PLTs in the same subject.\(^2\) Six sets of PLT recovery data were derived from previously performed reinusions of radiolabeled PLTs. These represented a variety of acceptable and suboptimal recoveries (15%-64%) and survivals (3.8-9.2 days). These timed data points (five to seven per data set) were supplied to participating laboratories with the request that the data be analyzed in their programs, that recovery be reported from the multiple-hit model, and that the survival be reported using the multiple-hit, exponential, and weighted mean models. One participating laboratory performed the same mathematical analyses using a commercially available statistical package (SAS Institute, Inc., Cary, NC). The reported results were then compared to determine their similarity.

All of the recovery and survival results reported (a total of 168 reported values) were exactly identical except for 1 recovery value and 1 survival value (reported from different laboratories using COST). These differed by a single digit in the first decimal place. The values derived with the commercial statistical package agreed entirely with those generated by COST analysis.

This analysis provides reassurance that the COST programs currently in use by these laboratories are yielding equivalent results when presented with the same data and thus are not a source of variance of results between these laboratories. These results have provided necessary assurance to allow COST to be selected as the primary means of interpreting radiolabeled PLT infusion data by BEST in the standardized protocol it is preparing.

Other laboratories wanting to compare their programs for analysis of PLT recovery data may obtain the data set used in this analysis by contacting the primary author.

James P. AuBuchon, MD
e-mail: james.p.aubuchon@hitchcock.org
Louise Herschel, BS, MLT(ASCP), CCRC
Jill Roger, MT(ASCP), CCRC
Department of Pathology
Dartmouth-Hitchcock Medical Center
Lebanon, NH 03756
Larry Dumont, PhD
Gambro BCT
Lakewood, CO
Scott Murphy, MD
American Red Cross Blood Services
Philadelphia, PA
Sherrill J. Slichter, MD
Puget Sound Blood Center
Seattle, WA
Pamela Whitley, MS, MT(ASCP)SBB
Eastern Virginia Medical School and
American Red Cross Blood Services
Norfolk, VA
Edward Snyder, MD
Yale University
New Haven, CT
Raymond P. Goodrich, PhD
Navigant Biotechnologies, Inc.
Lakewood, CO

REFERENCES

SUBMISSION OF LETTERS

Instructions for submission of letters can be found in the Detailed Instructions for Authors published on pages 128 to 133 of the January issue. Submit letters to:

**S. Gerald Sandler, MD**
Department of Laboratory Medicine/M-1306
Georgetown University Hospital
3800 Reservoir Road, NW, Washington, DC 20007
fax (202) 444-2440
e-mail: sandlerg@gunet.georgetown.edu

EDITOR’S NOTE: To permit timely publication of correspondence, the references have not been verified as they are for articles appearing in TRANSFUSION, and, therefore, the accuracy of references cited in Letters to the Editor is the sole responsibility of the authors. Payment is not required for submission of Letters to the Editor.