Transfusion-related acute lung injury in the critically ill: a translational approach
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A survey of physicians’ reasons to transfuse plasma and platelets in the critically ill

A prospective single center cohort study

A.P. Vlaar, A.L. in der Maur, J. Binnekade, M. J. Schultz, N.P. Juffermans
Abstract

Background: Data on the rationality of transfusion practice of FFP and platelets in the critically ill are sparse and may contribute to efforts to reduce transfusion rates. To provide insight into determinants of the decision of ICU-physicians to transfuse a survey study on the reasons of ICU-physicians to transfuse FFP and platelets was performed.

Methods: In a survey study, the reasons of ICU-physicians to transfuse FFP and platelets were determined during a 10-week period. Transfusion triggers were assessed, as well as correction of prolonged coagulation test results. Normal PT is 12.3 [9.8 - 14.7]

Results: Of 310 admissions, 44 patients (14%) received a transfusion of FFP and 35 patients (11%) received a platelet transfusion. In 67% patients, FFPs were transfused in bleeding patients and in 33% in non-bleeding patients. FFP was transfused at a pro-thrombin time (PT) of 19 sec [17-22]. After FFP transfusion, PT levels of 15-18, 18-20 and 20-26 seconds decreased with a median of 0.7, 1.9 and 3.5 seconds respectively. On average, 3.2 FFP units were ordered, of which 28% was not transfused. The major reason to transfuse platelets was bleeding. Platelets were transfused at a platelet count of 95 [36-116] x10^9/L in bleeding and 13 [10 - 18] x10^9/L in non-bleeding patients. On average, 1.4 platelet units were ordered, of which 20% was not transfused. The agreement between physicians reporting a major bleeding and a definition of bleeding was poor (κ < 0.10 for FFP and 0.20 for platelets).

Conclusions: One-third of FFP transfusions was given to non-bleeding patients. FFP transfusion failed to normalize prolonged coagulation test results in the majority of the patients. Transfusion of platelets was restrictive in non-bleeding patients and liberal in bleeding patients. Education on indications of FFP transfusion and improved identification of bleeding may reduce transfusion rates.
Introduction

Fresh frozen plasma (FFP) and platelets are frequently prescribed in intensive care unit (ICU)–patients. In particular, the use of FFP has risen over the past decades.\(^1\)\(^-\)\(^3\) Although guidelines for transfusion of FFP and platelets have been published,\(^4\)\(^5\) there is a reluctance to adhere to these guidelines in the critically ill.\(^6\)\(^7\) In these patients, FFP is frequently administered in the absence of active bleeding, to correct prolonged coagulation test results or given before performing an invasive procedure.\(^7\)\(^8\) For platelets, half of the transfusions in critically ill patients is administered in the absence of significant bleeding. Also, a higher pre-transfusion platelet count then recommended in general guidelines is applied in these patients.\(^8\) Presumably, it is thought that guidelines may not apply to critically ill patients, in whom co-morbidity, coagulopathy and the need for invasive procedures may be considered to contribute to an increased risk of bleeding.

As transfusion of FFP and platelets is associated with the development of acute lung injury, circulatory overload and allergic reactions,\(^3\)\(^9\)\(^-\)\(^12\) the risk–benefit ratio of transfusion may not be favorable in a number of clinical situations, including prevention of bleeding by correction of prolonged coagulation test results or given before an invasive procedure.\(^9\) Efforts to reduce transfusion rates may benefit from insight into determinants of the decision of ICU–physicians to transfuse. Data on transfusion practice of FFP and platelets in the critically ill are limited. To gain insight into transfusion practice, a prospective cohort study was performed with the use of questionnaires. We investigated the reasons of ICU-physicians to transfuse FFP and platelets in a cohort of critically ill patients in the Netherlands. In the case of suspected bleeding, a comparison was made with a definition of bleeding. Triggers for transfusion of FFP and platelets and outcome of transfusion were assessed.

Methods

Setting

The study was performed in a 30–bed mixed medical–surgical ICU of a university hospital in The Netherlands. This ICU is a “closed format” department in which patients are under the direct care of the ICU–team consisting of 10 full–time intensivists, 8 subspecialty fellows and 12 residents.
Population
The population consisted of all patients on the ICU receiving a first transfusion of FFP or platelets, ordered by an ICU-physician, from March till June 2007.

Questionnaires
Questionnaires were given to ICU-physicians within 24 hours after prescribing FFP or platelets either by person or by e-mail. For patients receiving multiple transfusion episodes, only the first order per type of blood product was evaluated. This was done to prevent bias in the results of the questionnaire due to patients with recurrent bleeding episodes, resulting in over-representation of bleeding as the transfusion reason. For each blood product, a separate questionnaire was provided. If the ICU-physician did not respond to the questionnaire within 24 hours, it was defined as a non-response. When a non-response occurred, the first following transfusion of the same blood product was taken as the first new transfusion.

Physicians were asked to point out the most important reason of transfusion: treatment of bleeding, prevention of bleeding by correction of prolonged coagulation test results or prevention of bleeding before an invasive procedure.

The level of experience of the physician was recorded (staff, fellow or resident). The physicians were also asked whether the need for transfusion was noticed by him/herself or whether it was noticed by an ICU-nurse or his/her supervisor.

Data collected
Data on patient history, APACHE II score, anti-coagulant medication, coagulation tests and platelet count were prospectively collected from the electronic patient file. In non-transfused patients, the highest pro-thrombin time (PT) and lowest platelet count during admission were collected to compare with the pre-transfusion PT and platelet count in transfused patients. Patients receiving a transfusion were screened by the physicians for major bleeding. Major bleeding was diagnosed as a drop in Hemoglobin of 1.6 g/dl per hour (after correction for transfusion with red blood cells; 0.8 g/dl Hb per unit transfused) combined with clinical evidence of bleeding (rectal blood loss, melena, blood in gastric tube, loss of blood in thoracic or abdominal drains, or hemoptoe). The normal mean PT value is 12.3 with a range of [9.8 - 14.7] seconds. Change of coagulation test results was determined for three levels; a pre-transfusion PT of 15-18, 18-20 and 20-26 seconds. Increment of platelet count was defined as an increase of the pre-transfusion platelet count.

Statistical analysis
Descriptive statistics were performed with SPSS 12.0.1. Normal distributed data are presented as means with standard deviation and compared using a Student-t
test. Not normal distributed data are presented as medians and interquartile ranges and compared with a Mann Witney U-test. A Wilcoxon signed ranks test was used for paired data. Relative agreement between suspicion of major bleeding by the physician and the definition of major bleeding was calculated using weighed kappa.

**Results**

During a 10–week period, from March until June 2007, 310 ICU–admissions were screened, of which 79 (26%) patients received a FFP and/or a platelet transfusion. In this cohort, 70 questionnaires were obtained from physicians ordering 40 FFP and 30 platelets transfusions. Patient characteristics are shown in Table 1.

**Table 1. General patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>FFP transfused (n=40)</th>
<th>Platelet transfused (n=30)</th>
<th>Non-transfused (n=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61 ±16.0</td>
<td>60 ±16.5</td>
<td>60 ±15.6</td>
</tr>
<tr>
<td>Male</td>
<td>70%</td>
<td>76%</td>
<td>69%</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>2.5 [0.8-10.9]</td>
<td>2.9 [0.9-9.7]</td>
<td>1.8* [0.9-3.9]</td>
</tr>
<tr>
<td>Surgical</td>
<td>27.5%</td>
<td>16.7%</td>
<td>33%</td>
</tr>
<tr>
<td>Medicine</td>
<td>35.0%</td>
<td>46.7%</td>
<td>34%</td>
</tr>
<tr>
<td>Cardio-surgery</td>
<td>37.5%</td>
<td>36.7%</td>
<td>33%</td>
</tr>
<tr>
<td>APACHEII score</td>
<td>18 ±7.4</td>
<td>18 ±7.8</td>
<td>16* ± 6.4</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or as median with inter quartile range [IQR] or as percentage (%).* p<0.05 transfused groups compared to non-transfused groups, student t-test.

**FFP transfusion**

The result of the questionnaires showed that the major reason to administer FFP was suspected bleeding (Table 2). In 33% of patients, FFP was administered in the absence of bleeding. The agreement between physicians reporting a major bleeding (n=27) and the definition (n=9) we used was poor (weighed $\kappa < 0.10$). FFP was given on a median PT of 19 [17 - 22] seconds (Table 2), which was higher then the PT in non-transfused patients (p<0.01). Of the transfused patients, there was no difference in PT level between bleeding and non-bleeding patients or between patients receiving an invasive procedure and not receiving an invasive procedure. FFP transfusion on a pre-transfusion of PT 15-18, 18-20 and 20-26 seconds resulted in a median decrease of 0.7 [0.7 [0.1-1.1], 1.9 [0.4-2.6] and 3.5 [0.5-5.2], respectively (Table 2), but did not correct prolonged PT values to normal values (PT <14.7
seconds) in 95% of the transfusions. The mean number of transfused FFPs was 3.2 ± 1.9 units, 28% of these products were not transfused and returned to the Blood Transfusion Center or wasted. For FFP, transfusion need was pointed out by the physician or the supervisor. In less then 5% of patients, the nurse drew attention to transfusion need.

**Platelet transfusion**

The questionnaires showed that the main reason to transfuse platelets was suspected bleeding (Table 3). 58% of bleeding patients were cardio-surgical, 11% surgical and 31% medical. The agreement between physicians reporting a major bleeding (n=19) and the definition (n=12) we used was poor (weighed κ 0.20). Platelets were given on a median platelet count of 59 [IQR 13 to 126] x 10^9/L. In the patients using aspirin or clopidogrel, platelets were transfused on a median platelet count of 214 [IQR 111 to 332] x 10^9/L. In patients not using aspirin or clopidogrel, platelet transfusion threshold was 20 [IQR 13 to 99] x 10^9/L. When corrected for bleeding and non-bleeding, median platelet transfusion threshold was higher in bleeding compared to non-bleeding (95 [IQR 36 to 116] vs. 13 [IQR 10 to 18] x 10^9/L, p<0.01). The median increment in platelet count was 41 x 10^9/L

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### Table 2. Reasons and triggers of FFP transfusion

<table>
<thead>
<tr>
<th></th>
<th>Transfused (n=40)</th>
<th>Non-transfused (n=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT pre-transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>19 [17-22]</td>
<td>17† [16-20]</td>
</tr>
<tr>
<td>Bleeding</td>
<td>19 [18-22]</td>
<td></td>
</tr>
<tr>
<td>Non-bleeding</td>
<td>20 [17-23]</td>
<td></td>
</tr>
<tr>
<td>PT post-transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>18* [16-20]</td>
<td></td>
</tr>
<tr>
<td>PT correction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-transfusion PT level 15-18</td>
<td>0.7 [0.1-1.1]</td>
<td></td>
</tr>
<tr>
<td>Pre-transfusion PT level 18-20</td>
<td>1.9 [0.4-2.6]</td>
<td></td>
</tr>
<tr>
<td>Pre-transfusion PT level 20-26</td>
<td>3.5 [0.5-5.2]</td>
<td></td>
</tr>
<tr>
<td>Reasons for transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>67.5%</td>
<td></td>
</tr>
<tr>
<td>Correction of coagulation test</td>
<td>17.5%</td>
<td></td>
</tr>
<tr>
<td>Invasive procedure</td>
<td>15.0%</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as median and inter quartile range [IQR] or as percentage (%). PT= prothrombin time. † pre-transfusion PT in all transfused patients compared with PT in the non-transfused group, p<0.01 Mann Withney U test. * PT post-transfusion in all patients compared to pre-transfusion PT, p<0.001 Wilcoxon signed ranks test.
However, 30% of the patients failed to mount a platelet increase after a single transfusion. The mean number of transfused platelets was 1.4 ± 0.7 units. Of these products, 20% was not transfused and returned to the Blood Transfusion Center or wasted. For platelets, transfusion need was pointed out by the physician or the supervisor. In less than 4% of patients, the nurse drew attention to transfusion need.

### Discussion

In this prospective study, we found that in 33% of patients, FFP was given outside current guidelines. The amount of transfused FFP failed to normalize coagulation test results in the majority of patients. For platelets, pre-transfusion count was restrictive for non-bleeding patients and liberal in patients suspected for bleeding or using platelet aggregation inhibitors.

**FFP transfusions.**

In 33% of patients, FFP was transfused to prevent bleeding. This high use of prophylactic FFP was also found for the general hospital population. Although evidence for the efficacy of FFP to prevent bleeding before an invasive procedure...
or merely to correct a coagulopathy is limited, some guidelines define an invasive procedure as an indication for FFP transfusion. We did not study whether prophylactic use of FFP to prevent bleeding was effective. As a dose was used that did not normalize coagulation test results in the majority of patients, our data may reflect the opinion of ICU-physicians that small amounts of FFP favourably influence risk-benefit ratio in patients undergoing an invasive procedure. However, there are no data to support the use of prolonged coagulations test to predict bleeding during invasive procedures. Transfusion of plasma without decreasing the bleeding risk does not seem rational and may merely increase the risk of adverse effects, such as acute lung injury. Notably, transfused patients had a longer ICU stay when compared to non-transfused patients.

In this study, bleeding was the major reason to transfuse FFP. However, the majority of the cases did not correspond with the definition of major bleeding. Why ICU-physicians overestimate bleeding episodes in patients was not clarified in this study. It may be explained by the fact that coagulation tests may not reflect global haemostasis and are poor predictors of bleeding in the critically ill patients. Thromboelastography has been suggested to give better insight in haemostasis and fibrinolysis of the critically ill patient. However, use of this test needs to be compared with the traditional coagulation tests in patients in the intensive care unit. The poor prediction of a bleeding episode may also explain why almost one third of the ordered FFP products was not administered. Education of physicians in detecting bleeding episodes may reduce the amount of FFP transfusions in the critically ill, as well as the amount of wasted orders. Recently, a hemorrhage measurement tool has been published to assess bleeding in critically ill patients. Implementation of such a tool may improve decision making in transfusion policy in critically ill patients and reduce transfusion of FFP outside current guidelines. Education of physicians on current guidelines has showed to be very effective in general hospital departments to reduce inappropriate FFP use and may also apply to ICU-physicians. Education should be focused on the ICU-physicians and not the nurses as shown by our data.

Platelet transfusions.

We found that non-bleeding critically ill patients were transfused on a platelet count of $13 \times 10^9/L$, which is comparable to the pre-transfusion platelet count recommended in oncology patients. We did not compare different platelet triggers and can not comment on the safety of this transfusion trigger in the critically ill. For bleeding patients, a relatively high platelet trigger of $95 \times 10^9/L$ was applied when compared to other studies in the critically ill and higher then
recommended in guidelines. Medication that inhibits platelet aggregation, such as aspirin or clopidogrel, may contribute to this high trigger. Other explanations may be a presumed impairment of platelet function after cardiopulmonary bypass. In accordance, in our study most bleeding patients who received platelets transfusion were cardiothoracic surgery patients. Also others have found a high pre-transfusion platelet count in cardiothoracic surgery patients. Alternatively, overestimation of bleeding by the physicians may explain the high pre-transfusion platelet count. Again, this is supported by the amount of products returned to the Blood Transfusion Center or wasted. The increment in platelet count was poor. In none of the patients in this cohort, allo-immunization was diagnosed. More likely, factors contributing to reduced platelet responses after transfusion in this cohort include inflammatory conditions or the use of antibiotics.

Study limitations. This study has several limitations. We may have missed cases of important microvascular bleeding, which was not captured in our definition of major bleeding. Also, we did not assess efficacy of blood products to reverse or prevent bleeding, nor did we compare the effect of different transfusion strategies on outcome. Therefore, we can not conclude whether transfusion practice was appropriate. Furthermore, the use of multiple choices might have limited and influenced the physicians’ response, as we may have omitted possible other options. Lastly, this study describes transfusion practice in a single center, which may not be comparable to other centers.

In conclusion, we show that FFP transfusion practice in this cohort of critically ill patients was, at least in part, not rational, as FFPs were administered in absence of bleeding and mostly in amounts that modestly decreased prolonged coagulation test results. Platelet transfusion was restrictive in non-bleeding patients and liberal in bleeding patients. Bleeding may be over-estimated by ICU-physicians, which may have resulted in wasted orders.


Reference List


