Coagulopathy and plasma transfusion in critically ill patients

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Clinicians’ attitude towards prophylactic transfusion of fresh frozen plasma – an evaluation of a multicenter randomized clinical trial

Marcella C.A. Müller, Rob J. de Haan, Margreeth B. Vroom, Nicole P. Juffermans

Submitted for publication
Abstract

**Background:** Prophylactic use of Fresh Frozen Plasma (FFP) to prevent bleeding in critically ill patients with a coagulopathy is widespread practice, while evidence of efficacy is lacking and detrimental effects of FFP in this population have clearly been demonstrated. This has led to a call for randomized trials on the risks and benefit of FFP in the non-bleeding critically ill patients with a coagulopathy. However, to date, conducting a trial on this subject has not been successful. Recently a multicenter randomized trial was stopped prematurely due to slow inclusion.

**Aim:** To examine clinicians’ attitude towards correction of coagulopathy with FFP in non-bleeding critically ill patients undergoing an intervention and to assess clinicians’ opinions regarding a trial on prophylactic administration of FFP in critically ill patients with a coagulopathy prior to undergoing an intervention.

**Methods:** A survey in 55 critical care physicians working at 4 intensive care departments which participated in a randomized trial on the risks and benefits of FFP in critically ill patients.

**Results:** Response rate was 84%. Of all respondents, 61% stated a need to assess International Normalized Ratio (INR) before placement of a central venous catheter. Before insertion of a chest tube (89%) or tracheostomy (91%), nearly all respondents indicated that INR should be assessed. Reasons to withhold transfusion of FFP to non-bleeding critically ill patients are risk of TRALI (46%), fluid overload (39%) and allergic reaction (24%). Although the majority of respondents expressed the opinion that the trial was clinically relevant and had a clear protocol, up to 56% of them indicated that one or more patient subgroups should have been excluded from participating in a trial on prophylactic administration of FFP.

**Conclusion:** Critical care physicians express the need for more evidence on the prophylactic use of FFP in critically ill patients with a coagulopathy. However, the majority expressed reluctance to include patients in a trial on the effectiveness of FFP due to their personal beliefs about the preferable transfusion strategy in certain patient categories. Results suggest that trials on FFP, at least in the Netherlands, are not feasible.
Background

The prevalence of coagulopathy as detected by prolonged coagulation tests in critically ill patients is high [1]. In order to prevent bleeding complications, fresh frozen plasma (FFP) is frequently administered prophylactically to critically ill patients with prolonged prothrombin times (PT) or elevated International Normalized Ratio (INR) values [2-4]. However, evidence that prophylactic transfusion of FFP reduces bleeding risk in these patients is limited [5,6]. On the other hand, it has well been demonstrated that FFP transfusion in the critically ill contributes to adverse outcome [3,7]. This has resulted in a call for randomized trials evaluating the benefit of prophylactic FFP in patients with a coagulopathy [8-12]. However, to date only small trials [13,14], cohort studies [15] or retrospective studies have been reported [16-18].

Conducting a successful trial on the efficacy of FFP transfusion in critically ill patients is likely to encounter several difficulties. First, critically ill patients are often not able to give consent to participate in a trial [19] and permission from a legal representative is warranted. However, most substitute-decision makers are unaware of patients wishes regarding research and are anxious to make a decision to participate or not [20]. Furthermore, time is limited in decision making about participation in a trial conducted on the Intensive Care Unit (ICU). Besides issues on informed consent there may be factors related to clinical practice which hamper performing transfusion trials. It has been reported that clinicians have strong beliefs about the ability of FFP to influence bleeding risk in coagulopathic patients [21-23]. Altogether, this may have contributed to a lack of successfully conducted large randomized trials on the effectiveness of prophylactic FFP transfusion in critically ill patients. In line with this, results of two randomized trials have not been completed (NCT00953901) or published [24].

We carried out a multicenter randomized clinical trial to assess risks and benefits of FFP to prevent bleeding in coagulopathic critically ill patients undergoing an invasive procedure (TOPIC trial) [25]. However, despite a proactive screening approach at all trial sites, the trial was stopped early due to slow inclusion. In order to give directions that help to improve conduction and subject enrolment in future transfusion trials, we conducted a survey among the ICU physicians who participated in this trial.
Methods

Setting
In June 2013, a questionnaire was sent to staff physicians and fellows of the ICU departments of two university hospitals and two large teaching hospitals in the Netherlands just after ending enrolment of patients in the TOPIC trial. The TOPIC trial randomized critically ill patients with a coagulopathy prior to undergoing an intervention to administration of a fixed dose of FFP (12 ml/kg) or to no transfusion [25]. At each research site, a local investigator was responsible for active screening of eligible patients, and at two sites, research nurses supported the trial. Medical staff of participating sites was informed and updated on relevant aspects of the trial by regular presentations by the main or local investigator and a digital newsletter. All involved medical staff members were provided with pocket cards containing essential information of the trial and for inclusion and randomization 24/7 phone assistance was available.

Survey
The questionnaire comprised multiple-choice questions regarding the need to assess coagulation status in non-bleeding patients, factors influencing the decision to administer FFP, factors affecting patient inclusion, and overall evaluation of our TOPIC trial. In addition, data on hospital setting, previous training and age of participants were collected.

Statistical analysis
Descriptive statistics were used to summarize respondents’ characteristics. Categorical data were presented in percentages and analyses were carried out with SPSS version 20.0 (SPSS, Inc, Chicago IL, USA) and Prism version 5.0 (Graphpad Software, San Diego, USA).

Results
A fully completed survey was obtained in 46 of 55 participants (84%). The majority of respondents worked at an ICU in a university hospital, however other character-
Clinicians’ attitude towards FFP transfusion in the critically ill

Characteristics of the respondents are summarized in table 1.

**Table 1: Characteristics of respondents**

<table>
<thead>
<tr>
<th>N=46</th>
<th></th>
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<tbody>
<tr>
<td><strong>Medical specialty</strong></td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>62%</td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>28%</td>
</tr>
<tr>
<td>Cardiology</td>
<td>10%</td>
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<tr>
<td><strong>Qualification</strong></td>
<td></td>
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<tr>
<td>Critical care specialist</td>
<td>72%</td>
</tr>
<tr>
<td>Fellow training in intensive care</td>
<td>28%</td>
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<tr>
<td><strong>Type of ICU</strong></td>
<td></td>
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<tr>
<td>University hospital</td>
<td>83%</td>
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<tr>
<td>Teaching hospital</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>20-35 year</td>
<td>24%</td>
</tr>
<tr>
<td>36-50 year</td>
<td>63%</td>
</tr>
<tr>
<td>51-65 year</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>65%</td>
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</tbody>
</table>

Need to assess coagulation status

The most commonly performed invasive procedures in critically ill are placement of a central venous catheter (CVC), a chest tube, a tracheotomy and drainage of fluid/abscess collections. 61% of respondents indicated that INR should be assessed before placement of a CVC. For placement of a chest tube or tracheostomy, nearly all respondents indicated that INR should be assessed (89% and 91% respectively to CVC). According to 75% of the respondents, there is a need to assess INR before fluid or abscess drainage (figure 1).

Decision to administer FFP and inclusion of patients

Respondents were asked to indicate which factors determine the decision to prophylactically administer FFP prior to an invasive procedure. Reducing risk of bleeding is the main reason to administer FFP prophylactically. However, risk of bleeding was a concern in only a minority of respondents (15%). In addition, 60% indicated to have no concerns about the occurrence of bleeding complications after an intervention.
**Figure 1**: Percentage of respondents indicating that INR should be assessed before placement of a central venous catheter, chest tube, tracheostomy or abscess or fluid drainage.

CVC = central venous catheter

**Figure 2**: Factors reported by respondents to omit transfusion of fresh frozen plasma in critically ill patients with a coagulopathy needing to undergo an intervention.

TRALI = transfusion related acute lung injury
Factors determining the decision to withhold FFP were more frequently reported. The risk of inducing a transfusion related acute lung injury (TRALI) was the most frequently reported factor to omit administering FFP. Participants also reported risk of fluid overload, an allergic reaction or loss of coagulation status as a marker of disease severity as reasons not to administer FFP before an intervention in non-bleeding critically ill patients with a coagulopathy (figure 2).

**Overall evaluation of the TOPIC trial**
The majority of the respondents had no objection towards the conduct of research in incapacitated patients (76%) or intervention studies in critically ill patients (91%). Nearly all physicians (98%) indicated that it was ethically justified to study the effect of FFP on prevention of bleeding and correction of INR in critically ill patients. Clinicians indicated to have a need for more evidence with respect to the treatment of coagulopathy (80%) and administration of FFP in critically ill (76%). In addition, the majority judged the trial to be well designed with a clear protocol and 87% stated that the chosen endpoint of the trial, major bleeding complication after an intervention, was clinically relevant.

Of respondents, 89% had no objection towards requesting informed consent of critically ill patients or relatives. However, 15% considered asking patients consent to be complex for the TOPIC trial, moreover 24% indicated that asking consent of patients’ relatives was complex. Indeed, declined consent rate for the TOPIC trial was 25%.

Three quarters of participants indicated that the chosen range of INR (1.5-3.0) for inclusion was appropriate. However, 30% classified a FFP dose of 12 ml/kg as too high, whereas 11% indicated that the trial had interference with prevailing treatment protocols. In contrast to these answers, only 41% stated that the trial was widely supported by the medical staff in their department. Furthermore, the majority of respondents had the opinion that certain patient groups should have been excluded from the trial (table 2). Altogether, 56% of respondents indicated one or more clinical conditions to exclude a patient from participating in the TOPIC trial.
The current survey demonstrates that the majority of critical care physicians requires assessment of INR before commonly performed invasive procedures in critically ill patients. In addition, they indicated a need for more evidence regarding the treatment of coagulopathy and administration of prophylactic FFP. Nevertheless, a randomized trial on the efficacy of prophylactic FFP transfusion, which was judged to be ethical and well designed, was not widely supported by the medical staff of participating centers. Moreover, the majority of physicians were reluctant to include all patients in this trial, indicating a lack of knowledge and the presence of strong personal beliefs regarding FFP administration in the critically ill. These personal beliefs were major contributors to a lack of sufficient inclusion in a trial on the efficacy of prophylactic FFP transfusion.

Although the majority of respondents deemed it necessary to obtain an INR before performing an invasive procedure in a critically ill patient, evidence supporting that increased INR or PT values predict bleeding risk is scarce [27]. Despite the limited value of INR to predict bleeding risk, increased values are an important trigger for clinicians to administer FFP [21]. In the current survey, respondents indicated that the TOPIC trial was clinically relevant. This is in line with the call in the medical community for trials on this subject [6,8]. Moreover, the design of the TOPIC trial was in line with a proposal done by a committee of experts on clinical trial opportunities in transfusion medicine [28]. Therefore, the TOPIC trial was expected to be widely supported by involved physicians.

Table 2: Reasons to exclude a patient from participating in a trial on the effectiveness of fresh frozen plasma.

<table>
<thead>
<tr>
<th>Medical condition</th>
<th>Percentage indicating that patient should be excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>24</td>
</tr>
<tr>
<td>State of fluid overload</td>
<td>33</td>
</tr>
<tr>
<td>Liver failure</td>
<td>24</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>33</td>
</tr>
<tr>
<td>Reduced P/F ratio</td>
<td>13</td>
</tr>
</tbody>
</table>

P/F = PaO$_2$ divided by the fraction of inhaled oxygen
The survey indicated several barriers for inclusion of patients in the TOPIC trial. A general well-known problem is the difficulty of obtaining informed consent in critically ill patients. A substantial amount of respondents indicated that obtaining informed consent of substitute decision maker was complex. In a quarter of eligible patients, consent was declined which is in line with other intervention studies in critically ill patients [29]. However, a more important barrier for patient inclusion in our FFP trial turned out to be physician-driven. Physicians involved in the TOPIC trial indicated to be reluctant to include certain patients. The reasons were bidirectional. Physicians who wanted to correct increased INR with FFP before the planned invasive procedure did not want to take the risk of randomization to no FFP, although this concerned a minority. The majority of physicians felt no need for FFP transfusion and did not want to risk having to administer FFP. Nearly half of the surveyed physicians indicated to be concerned about possible detrimental effects of FFP, with TRALI being the most frequently mentioned. This is consistent with reported increased awareness of TRALI [30]. Reluctance to include patients was also reflected by a relatively low percentage reporting support by the medical staff for the trial. Taken together, despite the recognition that a trial on the efficacy of FFP is highly warranted, reasons for slow inclusion with subsequent early stopping the TOPIC trial, are, at least in part, physician-driven.

The strong beliefs among physicians about the administration of FFP are in line with surveys reporting high rates of inappropriate use of FFP [22,23]. Moreover, in line with previous reports [22], involved clinicians demonstrate a lack of knowledge about appropriate dosing of FFP, as 30% indicated that the dose of 12 ml/kg FFP used in the TOPIC trial was too high, while the recommended dose is 12 to 15 ml/kg [31] or even as high as 35 ml/kg to obtain full normalization of factor levels [13]. When designing future trials on the efficacy of FFP in critically ill patients with a coagulopathy, abovementioned obstacles need to be addressed in order to obtain improved cooperation of involved ICU physicians.

The current survey has some limitations. First, the questionnaire was not formally tested for reliability and validity. Furthermore, we did not address potential improvements of the design and protocol of the TOPIC study. Modifiable factors in enhancing enrolment of critically ill patients in clinical trials are research culture, support of the clinical team and the consent procedure [29]. Also, it has been reported
that passive dissemination of research information does not affect clinicians’ attitudes [32]. Therefore, we actively informed medical staff at all sites throughout the whole study period by repeated presentations, digital newsletters and pocket cards. Although we did not ask respondents for potential improvements on this information strategy, the majority indicated that enrolment criteria of the trial were clear. Therefore, we do not think that a lack of information or knowledge about the trial by involved physicians has contributed to the disappointing inclusion rates. Of note, in line with previous reports [29], the presence of dedicated experienced research personnel contributed to improved enrolment of subjects and minimized potential additional workload for the bedside staff. In our opinion, exclusion of certain patient categories, although desired by the respondents, should be avoided because this will limit generalizability of results. However, in future trials these barriers should be specifically addressed, so they can be overcome.

**Conclusion**

Despite that critical care physicians express a need for trials on the use of FFP in patients with a coagulopathy, strong preferences of treating physicians about the use of FFP were major constraints to the conduction a successful clinical trial. We feel that results indicate that future trials on the efficacy of FFP may not be feasible to conduct, at least in the Netherlands. Thereby, further knowledge on the efficacy of FFP should be gathered from prospective cohort studies or retrospective studies.
References


27. Segal JB, Dzik WH: Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. Transfusion 2005;45: 1413-25