

Transfusion of Fresh Frozen Plasma in Critically Ill Patients: Effective or Useless?

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Abstract

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BACKGROUND: Fresh frozen plasma (FFP) is widely used in critically ill patients to correct the deficiency of coagulation factors or increased INR.

AIM: In the present study we aimed to evaluate the outcome of the freshly frozen plasma use as prophylaxis in ICU patients before an invasive procedure.

METHODS: The study was conducted at Central Anaesthesiology and Intensive Care Service UHCT "Mother Theresa", Tirana. 136 patients were enrolled with coagulopathy with no bleeding before the invasive procedure, from June 2016 to December 2016. A group of 75 patients underwent a median volume of 12.5 ml/kg FFP given, and 61 had no transfusion. Data were collected on demographics, the severity of illness measured by APACHE III scores, INR, medication use, hemodynamic data.

RESULTS: From 136 patients with coagulopathy with no bleeding who underwent planned invasive interventions, 75 [55%] received FFP, vs 61 [45%] p = 0.04 who did not receive. Overall, the median FFP dose was 12.5 ml kg⁻¹. Median INR level in FFP and non-FFP groups was respectively 3.1 (1.9-4.8) and 3.5 (1.8-5.2). INR was corrected in 24 of 75 (32%) of those who received a transfusion. The frequency of minor bleeding episodes was 9.3% in transfused patients vs 4.9% in the non-transfused group. Patients who developed an onset of acute lung injury were more frequent in the FFP group. No allergic transfusion complications were observed. Also, the median length of hospital stay [LOS] was 3.05 days vs 2.91 days and mortality rate 8.2% vs 6.5% with no significant difference between two groups.

CONCLUSIONS: Freshly frozen plasma transfusions are often unnecessarily administered during an inadequate correction of the deficiencies of coagulation factors. When comparing a liberal FFP transfusion strategy vs restrictive other clinical trials are required to assess which one is the best to adopt in intensive care settings.

Introduction

The use of FFP has significantly increased in the past 10 years, and its usage continues to increase. There are certain situations where FFP is indicated, such as in patients with coagulopathy resulting from DIC who are undergoing invasive procedures or having active bleed, in patients with liver failure with active bleed and patients with thrombotic thrombocytopenic purpura (TTP) [1].

Fresh frozen plasma is widely used in ICU patients and prescribed for the treatment of bleeding or the prevention of bleeding in critically ill patients. However, there are few detailed, prospective, descriptive data from large studies describing these patterns of use in the critically ill and clinical evidence to help aid the critical care clinician make decisions on whether to transfuse or not is at present limited [2] [3].

It is now usually used in cases of excessive bleeding or to prevent bleeding in those patients with abnormal coagulation tests that are undergoing an

invasive procedure. Its use has been extended to patients with a coagulopathy but who are not bleeding (for instance, in the ICU) [4].

In the last decade, use of FFP has expanded to include prophylactic administration of FFP. However, there are concerns about the efficacy of FFP to prevent bleeding. Evidence from randomised controlled trials that support FFP transfusion to correct coagulopathy before an invasive procedure is limited, including commonly performed procedures on the ICU, such as insertion of a central venous catheter, a chest drain or a percutaneous tracheotomy [5]. Moreover, retrospective studies suggest that the risk of bleeding after an invasive procedure is low and relevant bleeding requiring blood transfusion or intervention is less than 1% [6].

Furthermore, FFP contains antibodies capable of causing complications like hemolytic reactions and transfusion-related acute lung injury. It is also capable of transmitting viruses like human immunodeficiency virus, hepatitis B virus, and C virus [7]. Hence, the use of FFP is not without potential danger, and it should be used only if indicated.

Most clinical uses of FFP, currently recommended by practice guidelines, are not supported by evidence from randomised trials. In particular, there is little evidence for the effectiveness of the prophylactic use of FFP [5].

Material and Methods

This prospective observational study was conducted at Central Anaesthesiology and Intensive Care Service UHCT "Mother Theresa", Tirana. Data were collected prospectively from 136 patients admitted to ICU with coagulopathy with prolonged International Normalized Ratio (INR) ≥ 1.5 at any time during their ICU stay; with no bleeding before the invasive procedure, from June 2016 to December 2016.

Inclusion criteria were: > 18 years old, prolonged International Normalized Ratio (INR) ≥ 1.5 , and undergoing any invasive procedure.

Exclusion criteria: thrombocytopenia $< 5 \times 10^3 \mu\text{L}$, hemodynamic instability, active bleeding; patients on warfarin, heparin and other anticoagulants treatment. All patients are carefully evaluated for next 24 hours from admission time, and all data were collected on demographics, the severity of illness measured by APACHE III scores, INR, medication use, hemodynamic data. The level of INR prompting FFP transfusion was recorded for patients who received FFP transfusion and the highest level of INR during their ICU stay, compared with patients that were not transfused with FFP.

Repeated post-invasive procedure measurements were made after 1 and 24 hours. The outcomes measured are relevant bleeding and correction of International Normalized Ratio. Standard tests were used for comparisons of proportions and means. Acute lung injury was recorded if it developed within 72 hrs after FFP administration or within 72 hrs after the highest recorded INR value in patients who did not receive FFP. Independent variables, such as warfarin or heparin anticoagulation, INR level, RBC transfusion and invasive procedure were used in the final model. Categorical outcome variables were compared between two groups based on the chi-square test. Clinical outcomes including hospital mortality and ICU length of stay among survivors were also recorded. Continuous outcome variables were compared using Student's t-test. To determine the clinical characteristics associated with FFP transfusion, logistic regression analysis was performed with FFP transfusion as the dependent variable. All P values are one-tailed, and the result is significant at $p \leq 0.05$.

Results

From a total of 518 patients that were admitted to the ICU during the study period, 189 patients (36.5%) met our criteria. A total of 53 patients with active bleeding were excluded. In a total of 136 patients with elevated INR, coagulopathy and no bleeding, 75 (55%) received FFP vs. 61 [45%] who had no transfusion. Median INR levels in FFP and non FFP groups was respectively 3.1 (1.9-4.8) and 3.5 (1.8-5.2). INR was corrected in 24 of 75 (32%) of those who received transfusion.

Transfusion was administered before an invasive intervention was required. There was no difference in age, sex, median APACHE III scores, or INR level between the FFP and non-FFP groups. It was a difference seen in patients who developed an onset of acute lung injury which was more frequent in the FFP group: 12% vs. 3% in non-transfused group. No allergic transfusion complications were observed.

In addition, the median length of hospital stay [LOS] was 3.05 days vs. 2.91 days and mortality rate 8.2% vs. 6.5% $p = 0.707$ with no significant difference between two groups.

Discussion

In our study, we saw that exists a significant variation in the use of FFP in critically ill patients with

coagulopathy but with no active bleeding. New bleeding episodes were very rare and did not differ between the groups that took FFP transfusions, and those who did not and the use of FFP was associated with the development of acute lung injury.

In our findings, in only 24 of our 75 (32%) transfused patients was INR corrected after the FFP transfusion. This result confirms some other observations that the standard recommended dose of FFP fails to correct coagulation deficit in a majority of critically ill patients [13]. According to the studies, INR level is a poor predictor of subsequent bleeding in the critically ill patients, and in lots of patients, specific factor concentrations remain adequate to prevent microvascular bleeding [13]. A significant number of patients with coagulopathy received FFP transfusion without any demonstrated efficacy [5] [13]. Other sources, such as Abdel-Wahab OI et al., have concluded that whatever the volume of transfused plasma, plasma transfusions did not correct moderate coagulopathy [8]. In another observational study by Holland et al., authors showed that plasma transfusions did not correct INR levels <2.0–2.5 [9]. So, the current practice of FFP transfusion is likely to expose the patients to transfusion risks with little or no documented benefit. During recent years new guidelines have been promoted to educate the hospital personnel [10].

It is important to emphasise that recommendations in the current guidelines are based on expert opinion, as no randomised studies are available. In the current study, FFP was commonly used before an invasive procedure. Although there is a little evidence for the effectiveness of the prophylactic use of FFP, previous studies have shown that invasive procedures can be done safely in patients with disorders of hemostasis by skilled physicians who frequently perform these procedures [5] [11]. Although some published guidelines currently define an invasive procedure as one of the indications for FFP transfusion, our data do not support this practice for the common critical care procedures [12]. We also found the considerable use of FFP in patients who had recent bleeding but no active ongoing bleeding. FFP transfusion was primarily aimed for reversal of warfarin effect. However, the latest British Society for Hematology guidelines clearly states that FFP should not be transfused for the reversal of warfarin anticoagulation when there is no evidence of severe active bleeding [10]. Previous studies also suggested that FFP may not be particularly effective in replacing coagulation factors [13]. In our study, FFP transfusion remained significantly associated with the development of acute lung injury ($p = 0.05$). However, the present study has some circumstantial limitations, and the reported data need replication.

In conclusion, plasma transfusion is a common treatment for critical care patients, and it may bring benefits for those who are massively bleeding. In our study, we concluded that FFP transfusion in

critically ill medical patients with coagulopathy but without active bleeding. Plasma transfusions may be associated with worse outcomes, so the risk-benefit ratio of liberal FFP transfusion strategy may not be favourable.

Therefore, the decision to proceed with plasma transfusion must be based on individualised indications, and most physicians suggest plasma transfusions according to their own experiences while balancing the risks and benefits. Unfortunately, no randomised, controlled trial has yet decided the appropriate plasma transfusion threshold. Freshly frozen plasma transfusions are often unnecessarily indicated because of the inadequate correction of the deficiencies of coagulation factors and so comparing a liberal FFP transfusion strategy vs a restrictive one are required other clinical trials to assess which one is the best to perform to avoid the unnecessarily exposures to the ICU patients.

References

1. Fresh frozen plasma: Indications and risks. National Institutes of Health Consensus Development Conference Statement. Natl Inst Health Consens Dev Conf Consens Statement. 1984; 5(5):4. PMID:6395009
2. Stanworth SJ, Walsh TS, Prescott RJ, Lee RJ, Watson DM, Wyncoll D. Intensive Care Study of Coagulopathy (ISOC) investigators. A national study of plasma use in critical care: clinical indications, dose and effect on prothrombin time. *Crit Care*. 2011; 15(2):R108. <https://doi.org/10.1186/cc10129> PMID:21466676 PMID:PMC3219386
3. Tinmouth AT, McIntyre L. The conundrum of persistent inappropriate use of frozen plasma. *Crit Care*. 2011; 15(3):160. <https://doi.org/10.1186/cc10215> PMID:21635704 PMID:PMC3218970
4. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, Murphy M, Thomas D, Yates S, Williamson LM; British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol*. 2004; 126(1):11-28. <https://doi.org/10.1111/j.1365-2141.2004.04972.x> PMID:15198728
5. Stanworth SJ, Brunskill SJ, Hyde CJ, McClelland DB, Murphy MF. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol*. 2004; 126(1):139-52. <https://doi.org/10.1111/j.1365-2141.2004.04973.x> PMID:15198745
6. Holland L, Sarode R. Should plasma be transfused prophylactically before invasive procedures? *Curr Opin Hematol*. 2006; 13(6):447-51. <https://doi.org/10.1097/01.moh.0000245688.47333.b6> PMID:17053457
7. Walker RH. Special report: Transfusion risks. *Am J Clin Path*. 1987; 88:374-8. <https://doi.org/10.1093/ajcp/88.3.374> PMID:3630978
8. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. *Transfusion*. 2006; 46(8):1279-85. <https://doi.org/10.1111/j.1537-2995.2006.00891.x> PMID:16934060
9. Holland LL, Brooks JP. Toward rational fresh frozen plasma transfusion: The effect of plasma transfusion on coagulation test

- results. *Am J Clin Pathol.* 2006; 126(1):133-9. <https://doi.org/10.1309/NQXHUG7HND78LFFK>
10. Green L, Cardigan R, Beattie C, Bolton-Maggs P, Stanworth SJ, Thachil J, Kallis Y, Zahra S. Addendum to the British Committee for Standards in Haematology (BCSH): Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant, 2004 (*Br. J Haematol* 2004,126,11-28). *Br J Haematol.* 2017; 178(4):646-647. <https://doi.org/10.1111/bjh.14163> PMID:27306832
11. Doerfler ME, Kaufman B, Goldenberg AS. Central venous catheter placement in patients with disorders of hemostasis. *Chest.* 1996; 110(1):185-8. <https://doi.org/10.1378/chest.110.1.185> PMID:8681626
12. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets: Fresh-Frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines Development Task Force of the College of American Pathologists. *JAMA.* 1994; 271(10):777-81. <https://doi.org/10.1001/jama.1994.03510340067036>
13. Chowdary P, Saayman AG, Paulus U, Findlay GP, Collins PW. Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. *Br J Haematol.* 2004; 125(1):69-73. <https://doi.org/10.1111/j.1365-2141.2004.04868.x> PMID:15015971