SHORT COMMUNICATION

Effect of FFP Transfusion on International Normalized Ratio in Liver Disease Patients

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Abstract Fresh frozen plasma (FFP) is widely used in liver diseases to rectify coagulation derangements. In this study we have analysed the pattern of FFP usage in liver diseases and its effect on International normalized ratio (INR). A retrospective study of liver disease patients who received FFP transfusions from January 2016 to June 2016 was done. FFP used for liver transplant surgeries and plasma exchange procedures were excluded from the study. A total of 1935 units of FFP were transfused to 576 patients. We found a high linear correlation between pre transfusion INR and change in INR per unit of FFP. Patients receiving 6 units or more FFP have shown significant INR improvement. Improvement was more in acute liver failure and acute on chronic liver failure cases compared to chronic liver disease. FFP is not effective in correcting mild to moderate coagulation defects in liver diseases. Large volumes are required to cause significant INR improvement. Considering the risks associated with FFP transfusion, decision of transfusion should be carefully weighed. Future prospective randomized control trails are required for understanding the risk benefit ratio better and formulating plasma transfusion guidelines in liver diseases.

Keywords FFP · INR · ALF · CLD

Introduction

Fresh frozen plasma (FFP) is transfused in liver diseases both therapeutically and prophylactically to correct deranged coagulation [1]. However the aetiology of coagulation defects in liver disorders is highly complex and coagulation tests alone have a low predictive value of bleeding risk [2]. Available literature has reported the inability of FFP transfusion to cause significant improvement in INR in chronic liver disease [3, 4]. Considering the potential side effects and unknown efficacy, prophylactic transfusion of FFP in liver disease based on raised PT/INR values is not advisable [5]. A more appropriate plasma transfusion strategy is one that emphasizes its use in the presence of active bleeding or prior to invasive procedures. Though various studies in literature have reported effects of FFP transfusion on deranged coagulation profile, very few of these have been done on patients with liver diseases. In this study done exclusively on liver disease patients; we have analysed the pattern of FFP usage in liver diseases and its effect on international normalized ratio (INR).

Materials and Methods

The study was done at the Institute of Liver and Biliary sciences, New Delhi. Medical records of patients who received FFP transfusions from January to June 2016 were retrospectively reviewed and analysed. Patient's age, sex, diagnosis, indication for FFP transfusion, number of unit's transfused, pre and post transfusion INR values were recorded from the blood requisition forms and the hospital information system. The relation between pre-transfusion INR and change in INR per unit of FFP was studied using linear correlation. The magnitude of change in INR was

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Fig. 1 Relation between pre transfusion INR and change in INR following FFP transfusion

determined using linear regression analysis. Patients who received FFP during liver transplant surgeries and plasma exchange procedures were excluded.

Statistical Analysis

Categorical variables were presented as proportion while continuous variables were either presented as mean or median. Comparison of continuous variables was done by one way ANOVA with post hoc by Kruskal–Wallis test and categorical variables by Fischer's exact test or Pearson's Chi square test. All statistical tools were 2 tailed and significance level (p) of < 0.05 was used.

Results

A total of 1935 units of FFP were transfused to 576 patients. Among them, 86.3% (497) were males. The mean age was 47.12 ± 12.36 years. 86.9% received 2–4 units and 9% received 6 or more units of FFP per episode.

The commonest category of liver disorder was chronic liver disease (CLD) (80.7%) followed by acute on chronic liver failure (ACLF) (13%), hepatic abscess (2.6%), malignancy (2.6%), acute liver failure (ALF) (0.7%) and post LDLT (0.3%). The commonest indication for transfusion was coagulopathy with deranged INR (55.2%). 27.4% transfusions were given before invasive procedures and 17.4% were given to patients with active bleeding.

98% of patients had a pre transfusion INR > 1.5 . Median pre transfusion INR was 2.49. We could assess the INR change in response to FFP transfusion in only 86.3% of patients in whom post transfusion reports were available. Out of these patients 92.7% showed improvement in INR 48 h post transfusion. The average improvement was 0.60 (range -2.5 to 5.05). However the improvement was significant in only 20% of these patients who received 6 or more units of FFP per episode ($p < 0.001$) (mean delta INR = 1.3011). 7.2% of patients have shown an increase in INR after 48 h of transfusion. This could be due to deterioration of the underlying disease condition. A high linear correlation has been found between the pre transfusion INR and change in INR per unit of FFP with a significant p value (< 0.001) (Pearson's correlation coefficient = 0.830) (Fig. 1). We have also determined the magnitude of change in INR through linear regression analysis and found that mean change in INR per unit of FFP was 0.27 which was statistically significant ($p < 0.001$). Improvement in INR was more in acute than chronic cases.

Discussion

In this study we have analysed the effect of FFP transfusion on INR in patients with various liver diseases and found that FFP was not effective in correcting mildly elevated INR. Holland and Brooke retrospectively showed that mildly elevated INR's (1.3–1.6) was corrected with supportive care. FFP transfusion had a minimal effect in correcting INR below 1.7 [6]. We have also observed that significant improvement in post transfusion values was seen only in cases where 6 units or more FFP was transfused (Fig. 2). Youssef et al. [3] in his retrospective study in patients with chronic liver disease with prolonged PT found that PT improved minimally by the infusion of 2–6 units of FFP. Improvement of post transfusion INR was more in ALF and ACLF cases compared to CLD in our study (Fig. 3). This may be due to the fact that irreversible damage occurs in chronic liver disease while compensatory mechanisms are still at work in acute cases.

Response to FFP is often unpredictable in liver disease patients and does not completely normalise PT or INR values [5]. Conventional coagulation tests used as a guide to FFP transfusion have a poor predictive value for risk of bleeding in liver diseases [7–9]. Hsieh et al. [10] conducted a study on chronic liver disease patients with oesophageal varices who

Fig. 2 Relation between change in INR and number of FFP units transfused

were given FFP transfusions based on raised INR and concluded that INR is a poor predictor of bleeding and it more likely reflects liver dysfunction than bleeding risk. Recent guidelines of the American Association for the study of liver disease advises against FFP transfusion to correct INR before liver biopsy [11].

Fig. 3 Improvement in INR post transfusion in ALF, ACLF, CLD cases

In our study we have found a high linear correlation between pre transfusion INR and change in INR per unit FFP, similar to the finding of Shinagare et al. [12]. There may be several causes for ineffectiveness of FFP in correcting deranged coagulation in liver diseases. It may be due to an ongoing consumption process of coagulation factors, inadequate dose of FFP, role of several other factors like endothelial dysfunction, portal hypertension, sepsis and renal failure in bleeding in liver diseases [13].

Our study is among the very few in available literature that addresses the effect of FFP transfusion in liver disorders. Our data was analysed retrospectively with its inherent drawbacks in documentation. One drawback of our study is the inability to assess clinical response of patients to FFP transfusion and to assess change in INR based on disease severity. Another drawback of the study is the inability to calculate the adequate dose of FFP transfused to patients based on body weight as the weight of the patients were not available in our records. 86.9% of our patients received 2–4 units of FFP per episode which may be adequate for patients with a body weight less than 60 kg. Hence we have included patients receiving less than 6 units of FFP in our study.

Conclusion

Patients with liver diseases have a complex haemostatic mechanism and the role of FFP in correcting mild to moderate abnormalities of coagulation remains disputed.

Significant improvement in INR may not occur in patients with a high pre transfusion INR even after an adequate dose of FFP.

Considering the known risks associated with FFP transfusion and the lack of evidence of beneficial effects, the need of the hour is to adopt stringent guidelines for appropriate FFP transfusion in liver diseases and focus on global tests of coagulation like thromboelastography to guide transfusion. Further research with prospective randomized control trials is required to arrive at more conclusive evidence and to formulate plasma transfusion guidelines for liver diseases.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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