Effect of Fresh Frozen Plasma Transfusion On International Normalized Ratio

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Abstract

Importance: Fresh frozen plasma (FFP) serves as a crucial intervention in managing bleeding, surgical, and elevated international normalized ratio (INR) scenarios within medical settings. This research delves into the relationship between FFP administration and the reduction of INR, with a specific focus on the influence of pre-INR values on this connection.

Objective: The primary aim of this study is to investigate the correlation between the administration of FFP and the subsequent reduction of INR levels, particularly emphasizing the impact of pre-INR values on this association.

Design: This study adopts a retrospective cohort design. Data from 271 patients at King Fahad Medical City were included and analyzed. The investigation is focused on discerning the connection between pre-INR values and the resultant change in INR levels following FFP administration. The data for this study were collected and analyzed between [January 2021–October 2021], with the analysis being conducted in [June 2023].

Setting: The study was conducted at King Fahad Medical City, providing insight into a specialized clinical setting catering to various medical conditions and scenarios requiring FFP interventions.

Participants: The study involved patients with various clinical disorders requiring FFP administration, with eligibility determined based on necessity and sociodemographic characteristics. Consecutive sampling ensured all eligible individuals were included.

Results: A total of 1000 units of FFP were transfused to 271 patients, with 46.5% receiving FFP for surgery, 40.9% for bleeding, and 12.5% for high INR. Median pre-transfusion INRs were 1.25 for surgical, 1.65 for bleeding, and 1.9 for high INR patients. Post-transfusion INRs showed significant decreases, especially in the high INR group. Pearson correlation showed strong positive relationships between pre-transfusion INR and INR improvement (r=0.78 for surgical, r=0.89 for bleeding, r=0.92 for high INR), indicating greater efficacy of FFP at higher pre-transfusion INR levels.

Conclusion: FFP administration effectively reduces INR levels, with the greatest improvement observed in patients with higher pre-transfusion INR values.

Keywords: Fresh Frozen Plasma; reduction of INR levels; impact of pre-INR values; Association.

Introduction

Patients who are bleeding or scheduled to undergo high-risk surgery with a prolonged INR may require correction of their INR to reduce the risk of bleeding prior to any procedure. There are several methods that can be used to correct for a prolonged INR. One of the most common methods is transfusing fresh frozen plasma (FFP). FFP prepared from a whole blood or apheresis collection and frozen at less than or equal to -18ºC, has a shelf life of 1 year [1]. It contains all the coagulation factors, plasma proteins, fibrinogen, electrolytes, and anticoagulant factors. It is used to treat conditions in which there are low blood clotting factors (INR>1.5), or as replacement fluid in plasma exchange [2]. There are many indications for FFP such as liver failure with a deficiency of clotting factors, active bleeding and Thrombotic Thrombocytopenic Purpura (TTP) [3]. However, there are contraindications to FFP transfusion such as volume replacement, albumin replacement and replacement of single or multiple coagulation-specific factor(s) when an effective alternative is available such as factor VIII concentrate in hemophilia or prothrombin complex concentrate for warfarin reversal [1].

In addition to FFP, it contains antibodies capable of causing complications for the patient, such as hemolytic transfusion reaction, and also transmitting infectious diseases such as Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) [4]. A unit of FFP has an average of INR 1.1 [2]Overall, some studies have found that there was a significantly greater decrease in INR when the pre-FFP INR was higher, specifically when the pre-transfusion INR was above 2. For example, a study by Holland and Brooks found significant changes in INR at levels above 1.7, with only 50% of patients with an INR of 1.7 showing a significant change [5]. Another study by Shinagare et al. [2] reported that the mean improvement in INR per unit of FFP was more substantial at higher pre-transfusion INR levels, with a linear relationship (r=0.89) noted between pre-transfusion INR and improvement (Shinagare et al., 2010). Additionally, Sezik et al. (2014) demonstrated a very strong positive correlation (r = 0.957) between higher pre-transfusion INR levels and greater decreases in INR, particularly significant above INR 2 [6].

The study aims to assess the effect of fresh-frozen plasma (FFP) transfusion on INR levels in relation to pre-INR levels at King Fahd Medical City.

Several studies have investigated the effect of FFP transfusion on the INR, which is an important measure of coagulation status. The available evidence suggests that FFP transfusion is effective in reducing INR levels in patients with coagulopathies, particularly those with liver disease or undergoing liver transplantation. The effect of FFP transfusion on INR levels varies depending on the initial INR level and the amount of FFP transfused. Some studies also suggest that FFP transfusion can be effective in achieving INR reversal in patients taking warfarin, an oral anticoagulant. However, further studies are needed to investigate the optimal dose and timing of FFP transfusion in different patient populations and the effect of FFP transfusion on clinical outcomes, such as bleeding and mortality.

Kim et al [7] presented a retrospective study that investigated the clinical outcomes of prothrombin complex concentrate (PCC) for the treatment of coagulopathy in patients with liver cirrhosis. The study found that PCC effectively reduced INR levels in these patients and was associated with a lower risk of bleeding complications compared to fresh frozen plasma (FFP) transfusion. However, the study also found that PCC was associated with a higher risk of thromboembolic events. The authors suggest that PCC should be used with caution in patients with liver cirrhosis, and further studies are needed to determine the optimal dose and timing of PCC administration in this patient population.

The study conducted by Franchini and Lippi [8] provides an updated review of the use of prothrombin complex concentrates (PCCs) for reversing anticoagulation. The authors discuss the benefits of PCCs compared to fresh frozen plasma (FFP), including their faster onset of action, lower volume requirements, and reduced risk of transfusion-related complications. The study emphasizes the effectiveness of PCCs in reducing INR levels and highlights the potential for PCCs to be a viable alternative to FFP in various clinical scenarios. However, the authors emphasize the need for further research to determine the optimal dosage and timing of PCC administration, as well as the long-term safety and efficacy of PCCs.

The systematic review conducted by Stanworth and colleagues [9] examines the effectiveness of recombinant factor VIIa (rFVIIa) for preventing and treating bleeding in non-hemophilic patients. The study's analysis of randomized controlled trials indicates that rFVIIa may be beneficial in reducing bleeding and transfusion needs in specific clinical scenarios, such as cardiac surgery and trauma. However, the study also emphasizes the lack of conclusive evidence regarding the long-term safety and efficacy of rFVIIa, calling for more research in this area. The authors recommend that rFVIIa should be used judiciously, considering individual patient characteristics, and closely monitoring for any adverse reactions.

The study by Shinagare et al. [2] is an audit of fresh frozen plasma (FFP) usage and its effect on the pre-transfusion international normalized ratio (INR). The authors reviewed the medical records of 301 patients who received FFP transfusions in a tertiary care hospital and found that the most common indications for FFP transfusion were bleeding and coagulopathy. The study also demonstrated a statistically significant decrease in pre-transfusion INR following FFP transfusion, suggesting that FFP can effectively correct coagulopathy in patients. The authors conclude that judicious use of FFP, based on appropriate indications and dosing, can help manage bleeding and coagulopathy in patients, and also emphasize the need for regular audits of FFP usage to ensure appropriate and effective use.

Material and Methods

All records of patients who received FFP between (January 2021–October 2021) were reviewed. Patients with Therapeutic plasma exchange or Post INR not analyzed were excluded. Only patients with pre- and post-INR were included in this study 271 patients met the inclusion criteria. All demographic data and clinical and laboratory data were collected from patients' records. 1000 units of FFP were received by these patients.

The study was carried out at King Fahad Medical City Riyadh following Internal Review Board approval. The pre-and post-transfusion INRs were calculated and analyzed by ACL TOP 550.

Statistical Analysis Procedure

All categorical variables such as gender are presented as frequency and percentage. Continuous variables such as age were expressed as Mean ± SD and PRE INR, and Post INR were presented as Median [IQR]. The Kolmogorov-Smirnov test was used to confirm the assumption of normal distribution. If the data was biased, a nonparametric test was used. The Pearson correlation coefficient test was used to determine the significant correlation between PRE INR and change in INR. Furthermore, regression analysis was applied and a scatter diagram with a regression line was drawn to develop a relationship between PRE INR and change in INR. A two-sided p-value less than 0.05 was considered statistically significant. All data were entered and analyzed using the ACL TOP 550 and Medcalc (18.11.11).

Results:

A total of 1000 units of FFP were transfused to 271 patients. The analysis of collected data showed that 45.5% (121) of patients were males and 54.5% (150) were females. The mean age of patients in the study's sample was 44.53 years in the range of (1-88 years). According to the diagnosis to receive FFP, the patients were divided into three groups, 126 (46.5%) patients received 462 FFP units for surgical procedures, 111 (40.9%) patients received 419 FFP units due to bleeding injuries, and 32 (12.5%) patients received 119 FFP units for High INR injuries. The median number of FFP units was 3 units per patient with a range around from 1 unit to 18 units per patient. These percentages are displayed in Table 1:

Table 1: FPP units' distribution according to the diagnosis

Requested distribution	Number of Patients	Number of FFP units
Surgical	126 (46.5%)	462 (46.2%)
Bleeding	111 (40.9%)	419(41.8%)

High INR	34 (12.5%)	119(11.9%)
Total	271	1000

The pre-and post-transfusion INRs for the 271 patients were analyzed according to the patient's needs, for the surgical purpose the median pre-transfusion INR was 1.25 (range: 0.87 to 6.98) and the median post-transfusion INR was 1.25 (range: 0.65 to 2.91). For bleeding patients, the median pre-transfusion INR was 1.65 (range: 0.86 to 10), and the median post-transfusion INR was 1.39 (range: range 0.78 to 3.53). In the third group of patients with high INR, the median pre-transfusion INR was 1.9 (range: 1.35 to 10), and the median post-transfusion INR was 1.54 (range: 1.11 to 3).

The results of the Pearson correlation test indicate that the net improvement in INR was greater with higher pre-transfusion INR values. In contrast, the low values of the Pre-INR for patients showed a slight improvement in the INR change values, and therefore the high INR group showed the greatest improvement and the largest correlation between FFP units and the change in the INR, among the three groups of patients, where the value of the change in the INR values was equal to 0.586 for which this change was statistically significant ($P < 0.001$).

Regression analysis results showed a linear relationship between the pre-transfusion INR and the change in INR (pre and post) of the three groups (surgical, bleeding, high INR). Pearson's correlation coefficient (r) in the surgical group was 0.78, in the bleeding group was 0.89 and the high INR was 0.92. The following table shows the results of regression analysis between change in INR and pre-INR values for the surgical group:

The correlation test between pre-INR and change in INR for this group is shown in Table 3:

Table 2: Correlation test between pre-INR & change in INR for all groups

Variables	**Correlation (r)**	**P – value**
Surgical Group		
PRE INR	0.887	<0.001
Change in INR		
Bleeding Group		
PRE INR	0.944	<0.001
Change in INR		
High INR Group		
PRE INR	0.959	<0.001
Change in INR		
For All Patients		
PRE INR	0.956	<0.001
Change in INR		

As Table 3 showed, there was a direct and positive correlation between pre-transfusion INR and improvement in INR per unit of FFP for the surgical group, with Pearson linear correlation factor (r=0.89) and with a p-value less than 0.001.

The linear relationship between the change in INR (Δ INR) with the value f pre-INR ($\mathrm{INR_{pre}}$) to the surgical group according to the results in Table 2, can be fitted through the following equation: $\Delta\mathrm{INR}_{\mathrm{surgical}} = -0.928 + 0.748 * \mathrm{INR_{pre}}$

Figure 1 shows the representation of this relationship:

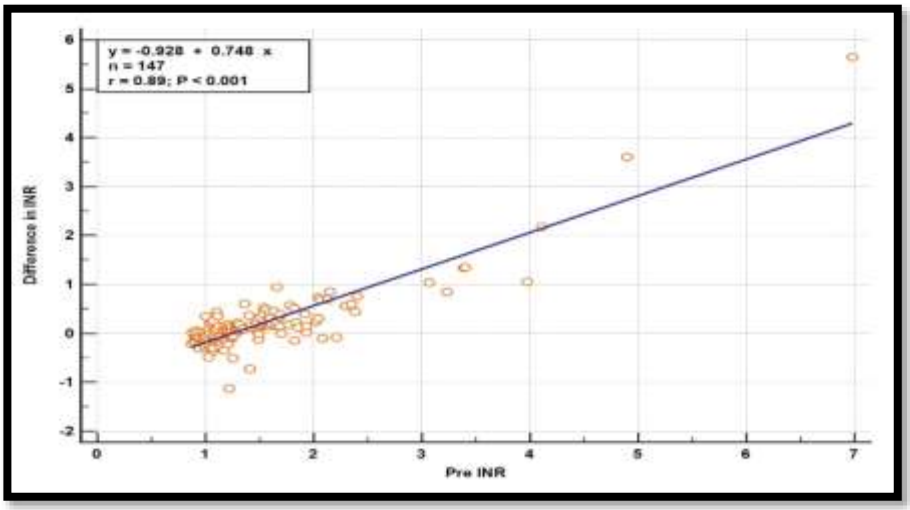

Figure 1: Relationship between pre-INR & change in INR for Surgical Group

The correlation test between pre-INR and change in INR for this group is shown in Table 3 (above). As the Table showed, there was a direct and positive correlation between pre-transfusion INR and improvement in INR per unit of FFP for the bleeding group, with Pearson linear correlation factor (r=0.944) and with a p-value less than 0.001.

The linear relationship between the change in INR (Δ INR) with the value of pre-INR (INR_{pre}) to the bleeding group according to the results in Table 4, can be fitted through the following equation:

$$\Delta INR_{\ surgical} = -1.194 + 0.834 * INR_{pre}$$

Figure 2 shows the representation of this relationship:

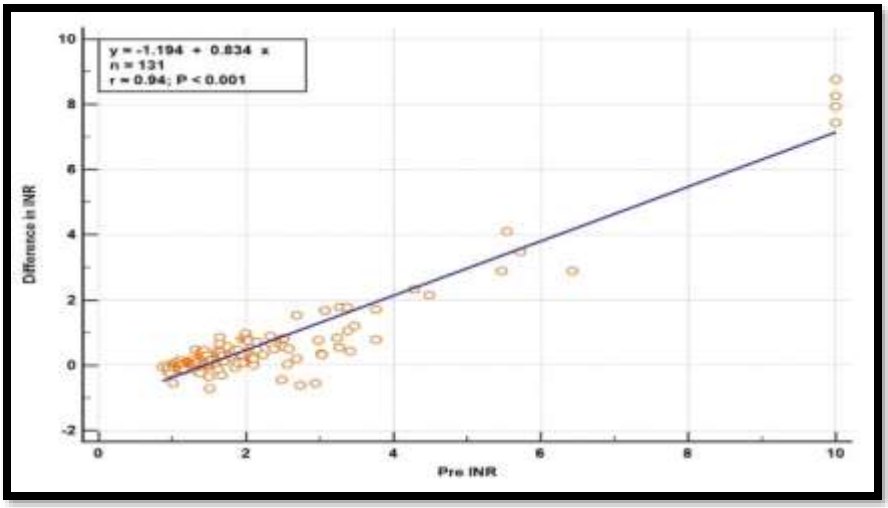

Figure 2:Relationship between pre-INR & change in INR for bleeding group

As Table 3 showed for high INR group, there was a direct and positive correlation between pre-transfusion INR and improvement in INR per unit of FFP for the bleeding group, with Pearson linear correlation factor (r=0.959) and with a p-value less than 0.001.

The linear relationship between the change in INR (Δ INR) with the value of pre-INR (INR_{pre}) to the high INR group according to the results in Table 6, can be fitted through the following equation:

$$\Delta INR_{\ surgical} = -1.391 + 0.893 * INR_{pre}$$

Figure 2 shows the representation of this relationship:

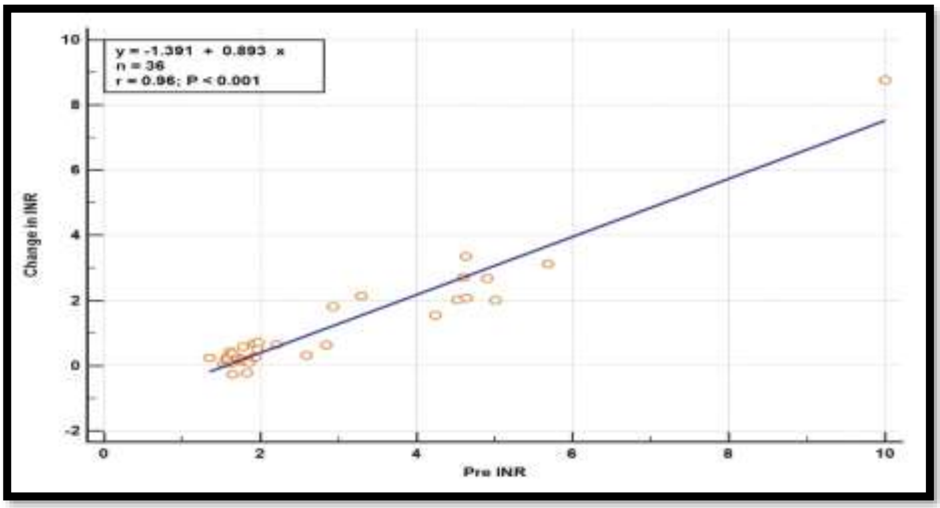

Figure 3: Relationship between pre-INR & change in INR for high INR group

From the foregoing, it can be seen that the strongest correlation and the largest effect of FFP were in the high INR group, then the bleeding group and finally the surgical group. To calculate the effect of FFP on all patients regardless of their group, the correlation coefficient was calculated between pre-INR and change in INR for all Study sample patients, and the result is shown in Table 3. The correlation test for all patients showed a direct and positive correlation between pre-transfusion INR and improvement in INR per unit of FFP, with Pearson linear correlation factor (r=0.956) and with a p-value less than 0.001, which means this correlation is statistically significant.

Discussion:

In our study, we analyzed the effect of FFP transfusion on pre-INR in patients and found that FFP was not effective in correcting mildly elevated INR. Holland and Brooke retrospectively showed that mildly elevated INR (1.3–1.6) was corrected with supportive care. FFP transfusion had a minimal effect in correcting INR below 1.7 [10].

The results of the study demonstrated the effect of FFP transfusion on INR, which is an important measure of coagulation status. Evidence indicated that FFP transfusion is effective in reducing INR levels in patients with coagulopathies, whether as a result of bleeding, surgery, or even due to some diseases.

The results also showed that the effect of FFP transfer on INR levels differed depending on the initial INR level and the amount of FFP transferred. The results of our study agree with the previous literature, which showed that FFP transfusion can be effective in achieving a reversal of INR in patients with high pre-INR values, such as those taking warfarin. Where the effect of FFP was greater in the high INR group, and this agrees with the results of the study of Shinagare et al. [2], the results of their study showed a statistically significant decrease in pre-transfusion INR after FFP transfusion, indicating that FFP can effectively correct coagulopathy in patients based on correct indications, appropriate doses, and management measures. Bleeding and coagulopathy in patients, and regular auditing of FFP use to ensure appropriate and effective use.

Despite the valuable benefits of FFP and the therapeutic advantages it offers and the ability to adjust patients' INR values, it is a process that requires a number of units that may reach 10 units per patient. Based on this, some alternative therapies were introduced, such as the prothrombin complex (PCC), which discussed the effects of using Kim et al. [7] and Franchini and Libby [8] and found that PCC can reduce INR levels effectively, quickly, and less demanding, and was able to reduce risk of bleeding complications compared to FFP. However, they found an association between PCC and an increased risk of thromboembolic events, and that PCC should be used with caution in patients with cirrhosis.

Conclusions

Based on the analyzed data, it can be concluded that the administration of fresh frozen plasma (FFP) shows promise in reducing international normalized ratio (INR) levels in patients experiencing bleeding, undergoing surgical procedures, or presenting with high INR values. There appears to be a positive correlation between the use of FFP units and a reduction in post-INR values.

One significant finding is that the correlation between FFP and INR reduction is strongest when the pre-INR values are higher. This suggests that FFP may be particularly effective in cases where the INR levels are elevated, indicating a greater degree of coagulopathy or impaired blood clotting function. By providing essential clotting factors and other components necessary for hemostasis, FFP can potentially restore balance and improve coagulation.

In conclusion, FFP administration appears to be an effective intervention for reducing INR levels in bleeding, surgical, and high INR patients. The positive correlation observed between the use of FFP units and INR reduction suggests that FFP can be particularly beneficial in cases with higher pre-INR values. However, it is crucial to evaluate each patient on an individual basis and consider the broader clinical context when determining the appropriateness of FFP administration.

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