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Original Article

Pathology Section

The Effect of Fresh Frozen Plasma Transfusion on International Normalized Ratio in Critically Ill Patients

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ABSTRACT

Introduction: Patients with mild prolongation of coagulation values are often transfused with Fresh Frozen Plasma (FFP) on the assumption that FFP will correct coagulopathy.

Aim: To assess the effect of FFP transfusion on International Normalized Ratio (INR) in critically ill patients.

Materials and Methods: All adult patients with a pre-transfusion INR of more than 1.2 and whose post transfusion INR available within one hour of completing the transfusion were included in this analysis. Those patients receiving blood products or supplements other than Vitamin K and FFP were excluded from the analysis. Patients receiving vitamin K were included in the study since it requires four to eight hours to exert its effect. Pre-transfusion INR was categorized into three groups, mild (INR <2), moderate (INR 2-3) and severe elevation (INR >3). Post-transfusion INR results were collected from the case records and the improvement in INR per unit of FFP was calculated. The magnitude of improvement in INR per unit of FFP was also calculated and the significant improvement was measured using the formula derived by Holland and Brooks. This study was done in all critically ill patients admitted at a tertiary care centre in South India for a period of one year.

Results: Percentage of patients showing significant improvement in INR was maximum (72.7%) in those patients having severe elevations in INR (INR>3) and is minimum (28.6%) in those patients with mild elevations in INR (INR<2)(p=0.031). A linear relationship was found between pre-transfusion INR and improvement in INR per unit of FFP (Pearson correlation value r=0.929, p<0.05) showing that the improvement in INR per FFP increases with patient's pre-transfusion INR. Also found that of the total 38 patients showing significant improvement in INR, 63% were receiving therapeutic transfusions whereas only 26% were receiving prophylactic transfusions and 10.5% were receiving inappropriate transfusions for mild elevations in INR (p=0.027). A significant association was found between bleeding and improvement in INR. Those patients with bleeding showed more improvement in INR (66.6%) than those who do not (41.6%, p<0.05)

Conclusion: It is concluded that prophylactic transfusion of FFP in mild and moderate prolongation of INR is of no use and this practice should be discouraged.

Keywords: Coagulopathy, Fresh plasma, Prophylactic plasma transfusion

INTRODUCTION

Blood component transfusion plays a significant role in the management of various diseases and is many a times considered as a life-saving treatment. There has been a significant increase in demand for this product over the past two decades, mainly as a result of the advances in haemato oncological therapies, increase in major surgeries and trauma [1]. Fresh frozen plasma (FFP) is a blood product produced from whole blood after centrifugation and separation of packed red cells and platelets. The plasma thus separated is frozen at -18°C within six hours after collection. It is a good source of coagulation factors both stable and labile. FFP also contains antibodies including ABO antibodies which in turn can cause antibody mediated complications like haemolytic transfusion reactions and transfusion related acute lung injury [2].

It is also capable of transmitting viruses like human immunodeficiency virus, hepatitis B virus, hepatitis C virus and parvovirus, although transmission of agents transmitted by cellular products like herpes virus, malaria and cytomegalovirus have not been reported [3-5]. Other complications like allergic reactions and fluid overload associated with blood transfusion can also occur with plasma infusion [6]. Hence, FFP should be used cautiously to avoid danger associated with it.

Understanding the properties of FFP as well as appreciation of its complications is very important in ensuring appropriate use of FFP. International Normalized Ratio (INR) is a calculation made to standardize prothrombin time and is used to monitor oral anticoagulants like warfarin. This test has only been validated for use in such clinical settings. But, it is used as the main reporting measure in many hospitals.

Intensive Care Study of Coagulopathy (ISOC) had found that around half of the recruiting centres reported coagulation results in critical care as INRs. [7].

Also, INR is used as a measure of clotting in other settings such as liver disease but again, there are doubts whether the INR correlates with bleeding risk in this setting [8].

Though the evidence for effectiveness of FFP transfusion to correct abnormal coagulation test results are weak, its use before invasive procedures for mildly prolonged PT/INR values is a common practice [9-15].It is also understood that modest elevations in INR and/or PT does not predict bleeding and correct with FFP transfusion [9]. In addition, liver disease can be associated with coagulopathy and increased risk of bleeding, but, there is little evidence that FFP transfusion has got some benefits in such patients[16].

Government Medical College, Trivandrum is the largest multi-specialty hospital in South Kerala which caters not only to the inhabitants of Trivandrum and nearby districts but also to southernmost parts of Tamil Nadu. This 3000-bedded hospital admits 80,000 patients a year and provides over 75,00,000 OP consultations. Clinical significance of this study lies in the fact that, like many other centres, the clinicians in our centre also transfuse FFP frequently to patients with mildly prolonged INR under the assumption that it will correct coagulopathy and prevent bleeding. This practice not only causes wastage of valuable resources but also increases the treatment cost and exposes the patients to unnecessary risks associated with plasma transfusion. A lot of published guidelines encourage appropriate use of FFP but poor adherence was noted. Therefore, we have decided to measure the laboratory effect of FFP transfusion on International Normalised Ratio in critically ill patients admitted in various Intensive Care Units in our centre. This study was planned as part of improving quality assurance activity in the hospital and thereby establish guidelines for Fresh Frozen Plasma transfusion.

MATERIALS AND METHODS

This is a prospective study done in critically ill patients admitted in Intensive care units of Government Medical College, Thiruvananthapuram, for a period of one year from 1 April 2011 to 31 March 2012. For studying the effect of FFP transfusion on INR, the complete details of those patients receiving FFP in various intensive care units were retrieved from the blood transfusion request forms and analysed. Before enrolment, all patients were counselled regarding the nature of the study and a written informed consent was given by the recipients. The study protocol was approved by the Human Ethical Committee of Government Medical College, Thiruvananthapuram. Study was conducted in accordance with the principles of good clinical practice.

Methodology

Complete details of those patients receiving FFP in various Intensive Care Units (ICUs) which includes age, sex, weight of the patient, number of units of FFP requested, department, diagnosis, indication, presence and type of bleeding and pre-transfusion INR report were retrieved from the transfusion request forms and verified with respective consultants and lab reports. Also, some of the details which were not available from the requests forms including post transfusion INR were collected prospectively from the patient records and were entered in the data sheet during the data collection.

Inclusion Criteria

1. Adult patients with a pre-transfusion INR of more than 1.2 and whose post transfusion INR available within one hour of completing the transfusion were included in this analysis.
2. Since vitamin K takes four to eight hours to exert its effect, those patients receiving Vitamin K were included. The total variation was considered to be equal to the actual FFP induced variation because of the short time gap between measurements of coagulation Tests.

Exclusion Criteria

1. Those patients receiving blood products or supplements other than Vitamin K and FFP were excluded from the analysis.
2. Paediatric cases were also excluded to make the results comparable.

Of the total 978 adult patients receiving FFP in the study period, 284 were critically ill patients admitted in various intensive care units. Of that total 284, some patients were receiving other blood products like packed red cells or platelets (n=88) and some patients' post transfusion INR was not recorded within 1 hour of completing the transfusion (n=162). So, these patients were excluded and the rest 66 cases were included in the analysis. Four patients receiving vitamin K for warfarin reversal were also included in this analysis. Few patients had received more than one transfusion and, in such cases, we have included data from the first transfusion episode to ensure that each patient was represented only once in the data sheet.

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Sample size was calculated using the following equation

Where n= sample size

Z= 1.96 for 95% Confidence Interval (1.96)

P= prevalence of improvement in INR

d= precision (20% of p)

Prevalence was found to be 60% from a pilot study done in our Department of Transfusion Medicine. Similar results were seen in other studies, 64.9% by Shingare SA et al., [17] and 50 % by Holland LL et al., [18].

So, prevalence of 60% was taken and sample size was calculated

The pre-transfusion INR was categorized into three groups, mild (INR <2), moderate (2-3) and severe elevation (>3) [19,20].

$$n = \frac{1.96^2 \times 60 \times 10 - 61}{(60 \times 20\%)^2}$$

Number of patients showing bleeding manifestations like hematemesis, melena, haematuria and bleeding from wound site due to underlying pathologies like cirrhosis liver, severe gastritis, cancer stomach, severe urinary infections etc with elevated INR was calculated and the type of FFP transfusion received by the patients was analysed, either therapeutic or prophylactic in the ICU. The dosage of FFP received by the patients was calculated based on the body weight and an infusion of 10-15mL/kg was considered as adequate dose [21]. We have calculated the improvement in INR per unit of FFP as well as the magnitude of improvement to the pre-transfusion INR per unit of FFP. Significant improvement in the INR was determined by using the following formula derived by Holland and Brooks [19].

Significant Change ≥ 8.9% [pre-transfusion INR] with this formula, a decrease of 8.9% or more in a pre-transfusion INR per unit of FFP was considered as a significant improvement. This significant improvement in INR was then compared with categories of pre-transfusion INR, types of FFP transfusion, bleeding and dosage of FFP to find out any significant association between these variables.

STATISTICAL ANALYSIS

All statistical data were analysed using SPSS software version 16.0 Continuous variables were expressed as mean ± standard deviation and qualitative data was expressed as percentage. Categorical variables were compared using Chi Square tests. Paired t test was used to compare quantitative variables which were continuous. All p values were two tailed and values of p<0.05 was considered statistically significant. Correlations between variables were done using Pearson correlation test.

RESULTS

Of the total 978 adult patients receiving FFP in the study period, 284 were critically ill patients admitted in various ICU. Of that total 284, some patients were receiving other blood products like packed red cells or platelets (n=88) and some patients' post transfusion INR was not recorded within one hour of completing the transfusion (n=162). So, these patients were excluded and the rest 66 cases were included in the analysis. Four patients receiving vitamin K for warfarin reversal were included in this analysis as vitamin K requires four to eight hours to exert its effect and we analyzed only those post transfusion INRs available within 1 hour of completing the transfusion.

Majority of the study subjects were in the age group 46 -60, accounted for about 36.3% (24) cases out of 66. Mean age of the study subjects was 47.5 with a SD of 17.48.Out of 66 cases 44(66.7%) patients were males and 22 (33.3%) were females. Most of the study subjects had a body weight between 56-65Kg with a mean weight of 60.23+ 5.6. A Maximum of 63.6% patients were receiving adequate dose of FFP in the range of 10-15 mL/Kg. The minimum dose of FFP was 7.3 mL/Kg and a maximum was of 19.6mL/Kg. The mean dose of FFP was 12.5 mL/Kg with a SD of 3.07. Bleeding in the form of hematemesis, melena, haematuria, bleeding from wound site etc was seen in 42 (63.6%) cases whereas 24(36.3%) patients had no bleeding manifestations. Out of total 66 cases, 46% (30) cases had moderate elevation of INR (2- 3), followed by 33% with severe elevation (INR >3) and 21% of mild elevation of INR (<2). This shows that a maximum of 67% of patients were receiving FFP for mild to moderate prolongation of INR.

Distribution of pretransfusion INR in study subjects and improvement after FFP transfusion are shown in [Table/Fig-1]. Of the total 66, 38(58%) patients showed significant improvement in pretransfusion INR (i.e., Improvement/FFP was >8.9% of pre-transfusion INR) but 28(42%) showed no significant improvement in INR [Table/Fig-2].Comparison of significant improvement in INR based on 3 categories of pre-transfusion INR [Table/Fig-3]. The percentage of patients showing significant improvement in INR is maximum (72.7%) in those patients having severe elevations in INR and is minimum (28.6%) in those patients with mild elevations in INR and these differences were statistically significant. Linear relationship between pre-transfusion INR and improvement in INR per unit of FFP (Pearson linear correlation, r =0.929, p <0.001).

	N	Mean	SD	Range
Pre INR	66	3.36	2.397	1.3 - 12
Post INR	66	1.85	0.70	1.2 - 4.5
Improvement/FFP	66	0.388	0.478	0.02 -2.5

[Table/Fig-1]: Distribution of INR values of the study subjects.

Pre-Transfusion INR	N	Improvement per unit of FFP		
		Range	Mean	SD
1-1.9	14	0.02-0.3	0.12	0.08
2-2.9	28	0.03-0.5	0.23	0.13
4-4.9	5	0.42-0.6	0.56	0.08
>5	8	0.38-2.5	1.37	0.80
3-3.9	11	0.25-0.53	0.33	0.09

[Table/Fig-2]: Improvement in INR per unit of FFP according to pre-transfusion INR.

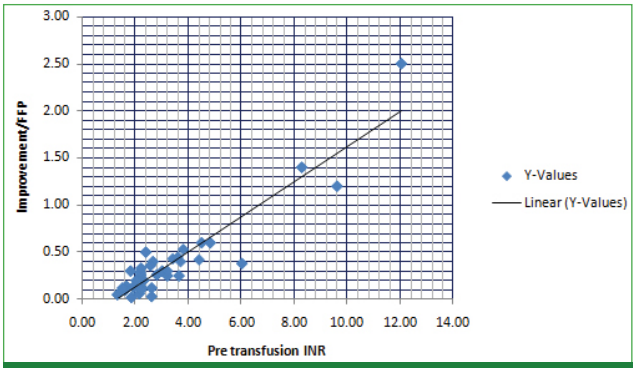
[Table/Fig-4] shows the linear relationship between pre-transfusion INR and improvement in INR per unit of FFP (Pearson linear correlation, r =0.929, p =0.000). This means significant improvement in INR is seen in patients with high pre-transfusion INR.

Out of the total 42 patients with bleeding, 66.6% showed significant improvement in INR, whereas in those patients who

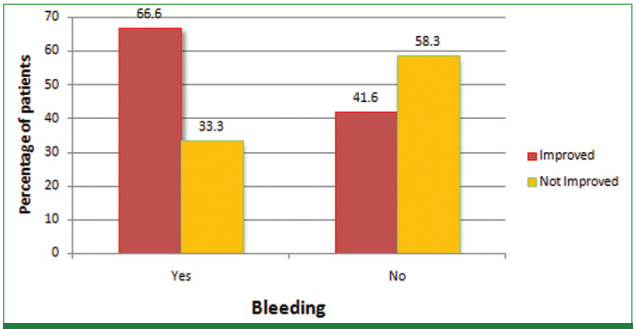
did not have bleeding, only 42% showed significant improvement and this difference was statistically significant (0.043). So those patients with bleeding will respond to FFP more effectively than those who do not have bleeding [Table/Fig-5].

Type of elevation of INR	Significant Improvement	No significant improvement	Total	x^2	p
Mild (<2)	4 (28.6%)	10 (71.4%)	14	6.962	0.031
Moderate (2-3)	18 (60%)	12 (40%)	30		
Severe (>3)	16 (72.7%)	6 (27.3%)	22		
Total	38	28	66		

[Table/Fig-3]: Comparison of significant improvement in INR based on three categories of pre-transfusion INR.
Significant at 0.05 levels



[Table/Fig-4]: Linear relationship between pre-transfusion INR and improvement in INR per unit of FFP.



[Table/Fig-5]: Comparison of significant improvement in INR based on presence of bleeding.

Factors Affecting the Outcome

1. Delay in initiation of FFP transfusion after receiving the product may affect the concentration of coagulation factors which may reduce the improvement in INR.
2. Improper Sample collection and storage can affect the INR value.
3. Sample with an elevated haematocrit can have a proportionally reduced volume of plasma which in turn can result in increased bleeding time and false elevation of INR due to increase in the ratio of anticoagulant to plasma.

DISCUSSION

The use of Fresh Frozen Plasma has increased steadily over the last twenty years. It must always be remembered that FFP transfusion is associated with serious risks to the recipient and must be used with caution. The major complication of administration of FFP, that is, transmission of viral infection, arises because asymptomatic, but infected blood donors cannot be identified by fool proof means. Recognition of complications related to the transmission of such viral infections may be delayed weeks, months or even years after the transfusion, but the prognosis from delayed sequelae may nonetheless, be ominous [22,23]. Other, more immediate complications of plasma transfusion include volume overload, allergic and anaphylactic reaction [2]. Due to the above factors, various guidelines were developed by many healthcare organizations to ensure appropriateness of transfusion practices. [21]. Furthermore, PT and aPTT are poor predictors of perioperative bleeding in patients with a negative bleeding history and the threshold of PT and aPTT prolongation of more than 1-1.5 times normal was purely based on outdated retrospective studies. Hence, the usefulness of doing such tests prior to invasive procedures has been questioned [24]. According to British Committee for Standards in Haematology guidelines bleeding history including family history, details of prior surgeries, and anticoagulant treatment should be taken prior to surgery [21]. Patients with a negative bleeding history do not require routine preoperative coagulation testing. However, some recent papers still recommend routinely performing PT, aPTT and platelet count prior to surgery and invasive procedures in adults and children. There are so many controversies regarding prophylactic FFP transfusion in mild to moderate prolongation of INR.

For this, 66 patients, with an INR >1.2 and whose post-transfusion INR available within 1 hour of transfusion were included in the study.

Out of total 66 study subjects, majority were in the age group 46-60 years (36.3 %). The youngest one receiving FFP was of 15 years and the elder one was of 74 years old with a mean age of 47.5 + 17.48. 67% were males and the remaining were females. Of the total 66 patients, 42 had bleeding in the form of haemetemesis, malena, bleeding from wound site or endotracheal tube. Also, when degrees of elevation in pre-transfusion INR was analyzed, 46% had moderate prolongation (INR 2-3), 33% had severe prolongation (INR>3) and 21% had mild elevation (INR<2). So, majority (67%) had mild to moderate prolongation of INR. Out of 66 transfusion episodes, 51.5% were therapeutic, 27.2% were prophylactic (significant coagulopathy and prior to invasive procedure) and 21.2% were inappropriate (INR 1.3-1.9 in liver disease with or without invasive procedure).

Out of 66 study subjects, 58% showed significant improvement in INR per unit of FFP using the formula derived by Holland and Brooks [18].In similar studies, 50% of patients showed significant improvement of INR/ unit of FFP by Holland LL et al & 64.9 % in a study by Shinagare SA et al., [17,19]. We

found that, the percentage of patients showing significant improvement in INR was maximum (72.7%) in those patients having severe elevations in INR (INR>3)and is minimum (28.6%) in those patients with mild elevations in INR (INR<2), and these differences were statistically significant. We also found a linear relationship between pre-transfusion INR and improvement in INR per unit of FFP (Pearson correlation value r=0.929,p<0.05)showing that the improvement in INR per FFP increases with patients' pre-transfusion INR. These findings are consistent with the findings of Holland LL and Brooks [17]. Another study by Shinagare SA et al., also showed similar result(Pearson correlation value r=0.890) [17].

We also found that of the total 38 patients showing significant improvement in INR, 63% were receiving therapeutic transfusions whereas only 26% were receiving prophylactic transfusions and 10.5% were receiving inappropriate transfusions for mild elevations in INR and these differences were found to be statistically significant. This result shows that FFP is less effective in correcting INR in prophylactic transfusions to prevent bleeding or in cases with mildly prolonged pre-transfusion INR. Many studies have reported the same finding [18,25]. Many of the published studies showed that, patients with minimal elevation of the INR (INR <2), were not at increased risk of bleeding in association with invasive diagnostic procedures[18,26,27].

In the present study, we observed that percentage of patients showing bleeding in all the three groups (mild, moderate and severe) was not significantly different and the mild difference noted in percentage was not statistically significant(p=0.829) This shows there is no association between bleeding and INR value. In 2005, Lin and co-workers studied 163 patients undergoing paracentesis procedures in which 142 had an INR of more than 1.5 prior to the procedure, but only two cases developed minor cutaneous bleeding. Although both had an INR between 2.6 and 2.9, they were thrombocytopenic too [28]. Recently, in 2012, Carino and colleagues, observed 287 central venous catheter insertions, 100 of which were placed in patients with an INR greater than 1.5 and of those, 77 did not receive FFP, and 23 were transfused with FFP prophylactically but only one bleeding event was observed and this occurred in a patient with an INR of 3.9 who had been treated with FFP prophylactically [29].

But, we found a significant association between bleeding and improvement in INR. Those patients with bleeding showed more improvement in INR (66.6%) than those who do not (41.6%) and this was statistically significant (<0.05).From this result, we could conclude that FFP is effective in correcting INR in the presence of bleeding.

We also compared significant improvement in INR with dose of FFP received by the patients. We found that, in all the three dose groups (10ml, 10-15 mL and >15mL), the percentage of patients showing significant improvement in INR did not differ much (60%, 57% and 57%) and this mild difference noted was not statistically significant (p=0.986). So, there was no significant association found between dose and improvement in INR in our study which may be due to the small sample size.

All these observations may help us to improve the Fresh Frozen Plasma transfusion practice in our centre by refining the institutional guidelines. Since, FFP is a precious product, we recommend to use FFP only for those patients who fulfil the criteria and have a high pre-transfusion INR.

LIMITATION

1. Data was collected from the case records

2. Time gap between issue of FFP and its transfusion was not recorded. Long-time storage in room temperature can affect the coagulation factor activity which in turn can affect the result.

4. Effect of FFP transfusion was assessed only in terms of improvement in INR. Effect of FFP on bleeding was not assessed separately.

5. Study design could have been case control because in mild coagulation abnormalities, natural correction is seen after treating the underlying pathology.

CONCLUSION

It is concluded that prophylactic transfusion of FFP in mild and moderate prolongation of INR is of no use and this practice should be discouraged

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