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A Study of Usage of Fresh Frozen Plasma in Liver Diseases and its Effect on PT and INR in Post Transfusional State

Dr. Vijay Kapse[1], Dr. Vishal Kulkarni[2], Dr. Renuka Gahine[3], Dr. Jyoti Chaudhary[4]

[1]Associate Professor, Department of Pathology and State of art Model Blood Bank, Pt.J.N.M. Medical College Raipur (C.G.)

[2]Assistant Professor, Department of Pathology, Pt.J.N.M. Medical College Raipur (C.G.)

[3]Director,Professor& Head of Department of Pathology, Pt.J.N.M. Medical College Raipur (C.G.)

[4]Post Graduate Student Department of Pathology, Pt.J.N.M. Medical College Raipur (C.G.) (Corresponding Author)

Abstract: ***A variety of abnormalities of coagulation is seen in patients with liver diseases. The magnitude of haemostatic abnormalities correlates with the degree of parenchymal damage. Reduced clotting factor synthesis may predispose to bleeding, which may be exacerbated by dysfibrinogenaemia, thrombocytopenia and increased fibrinolysis, reflected by prolonged Prothrombin Time (PT) and International Normalized Ratio (INR). Fresh Frozen Plasma (FFP) for transfusion is most often used when a patient has abnormal results on coagulation screening tests, as a treatment or for prophylaxis which is presumed to improve the clinical outcome and laboratory results.***

Keywords: Prothrombin Time, International Normalized Ratio, Fresh Frozen Plasma

1. Introduction

Fresh Frozen Plasma (FFP) is a good source of coagulation factors, including labile factors V and VIII. The use of FFP has significantly increased in the past 10 years.[1] Absolute indications include replacement of single-factor deficiencies when factor concentrate is not available, immediate reversal of warfarin effect, vitamin K deficiency associated bleeding, Disseminated Intravascular Coagulation (DIC), Thrombotic Thrombocytopenic Purpura (TTP) and liver diseases.

The scientific rationale for administering FFP rests on the assumptions that patients are at risk of adverse effects from inadequate coagulation factors, and that FFP transfusions can decrease those risks. Laboratory abnormalities of coagulation areconsidered by many clinicians to help predict bleeding. This is supported by data from non-randomised studies in patients with mild to moderate abnormalities in coagulation tests. Although complete normalization of the haemostatic defect may not always occur.[2]

New trials are needed to evaluate the efficacy and adverse effects of plasma, both in bleeding and non-bleeding patients, and to determine whether presumed benefits outweigh the real risks.[3, 4, 5] In addition, new haemostatic tests that better define the risk of bleeding and monitor the effectiveness of FFP use should be validated.

2. Aims and Objectives

a) To determine pre and post FFP transfusion values of PT/INR in patients with liver diseases with bleeding diathesis.
b) To assess appropriateFFP usage in the patients with liver disease.

3. Material and Methods

The present study was carried out in the Department of Pathology, Pt. Jawaharlal Nehru Medical College, Raipur, Chhattisgarh in association with Model Blood Bank Raipur, Dr. Bhim RaoAmbedkar Memorial Hospital Raipur Chhattisgarh over a period of 1 year. A total of 96 patients were included in the study which comprised admitted patients with liver disease presenting with bleeding diathesis. Patients in the age groups between 18 to 80 years were selected and detailed clinical, laboratory and imaging data were recorded according to a set proforma. Diagnosis of liver disease and bleeding was documented by clinical, laboratory and imaging studies. An informed consent was taken of patients who were willing to participate in the present study.

Exclusion criteria

Patients presenting in emergency, pediatric patients, patients in whom some other surgical intervention was not planned after FFP transfusion, patients with concomitant use of anticoagulant drugs, e.g.heparin, warfarinetc. and patients associated with other bleeding diathesis. Also excluded patients were not willing to participate in the study.

Prothrombin Time Estimation

The PT test measures the clotting time of recalcified plasma in the presence of an optimal concentration of tissue extract (thromboplastin) and indicates the overall efficiency of the extrinsic clotting system. Although originally thought to measure prothrombin, the test is now known to depend also on reactions with factors V, VII and X and on the fibrinogen concentration of the plasma.

Sample collection and preparation

Citrated plasma was prepared by adding1 part (0.2ml) of 3.2% trisodium citrate solution to 9 parts(1.8 ml) of blood. Collected samples were centrifuged immediately for 15 minutes at 3000 rpm to obtain a platelet poor plasma. The supernatant plasma was transferred to a siliconized glass tube immediately without disturbing the buffy coat. The test was performed within 2 hours, of blood collection.[6, 7, 8, 9, 10]

Procedure

- The reagent vials were gently swirled before use.
- Enough pre warm PT reagent was dispensed for immediate use, into a thoroughly clean dry test tube.
- Hundred (100) microliter of plasma was pipetted into test cuvette at 37°C and incubated for 3 minutes. Two hundred (200) microliters pre warmed PT reagent was added to it.
- Timer is started simultaneously which recorded the clotting time in seconds.
- Reference interval for PT of 10 -15 seconds and INR of 0.8-1.5 were considered.

Calculation

$$Prothrombin\ Ratio = \frac{\text{Mean PT of patients plasma in second}}{\text{Mean Normal PT for the reagent}}$$

Mean Normal PT: is calculated by plasma from at least 20 normal healthy individuals.
The resultswere expressed as the mean of the duplicate readings (in seconds) or as the ratio of the mean patient's plasma time to the mean normal control plasma time and themean normal PT was calculated.

FFP Preparation

From the whole blood collected in bags, packed cells, FFP and platelets or packed cells, FVIII deficient plasma and cryoprecipitate are separated. When the plasma frozen at 80^0C is thawed at 4^0C, a cryoglobulin remains as a precipitate which is called cryoprecipitate. It contains mainly F-VIII and fibrinogen.

FFP must be thawed between 30 °C and 37 °C in a water bath. The plasma must be transfused as soon as possible after thawing, but in any case within 24 hours, if stored at4 ± 2°C. Infusion of 10-15 ml/kg body weight of the patient was considered as adequate dose of FFP.

Measurements

Patient age, sex, date and the number of FFP transfusion and the indication we recorded.The patients were categorized on the basis of Pre transfusion INR values as follows:

Mild - INR < 2
Moderate - INR 2-3
Severe - INR >3

Statistical Analysis

The recoeded data was expressed in percentage and mean ± S.D.Kolmogorove-Smirnove analysis was performed for checking linearity of the data.Student's paired t test was used to check the significance of difference between two parameters in parametric data. Pearsoncorrelation analysis was performed to check the correlation between two categorical variables.Fischer's exact test was used to analyze the significance of difference between frequency distribution of the data.P value <0.05 was considered as statistically significant.SPSS© for windows™ Vs 17, IBM™ Corp NY and Microsoft excel™ 2007, Microsoft® Inc USA was used perform the statistical analysis.

Observations

In the present study, age of the patient ranged from 18to 80 years. Of the total 96 cases, most patients were in their 4^{th} decade of life, with a maximum in the age-group 38-48 years (29 out of 96 cases) about (30%).Mean age of study subjects was 43.7 yrs.

Out of 96 cases, 75 cases were males and 21 were females.Gender ratio was 1:3.57.

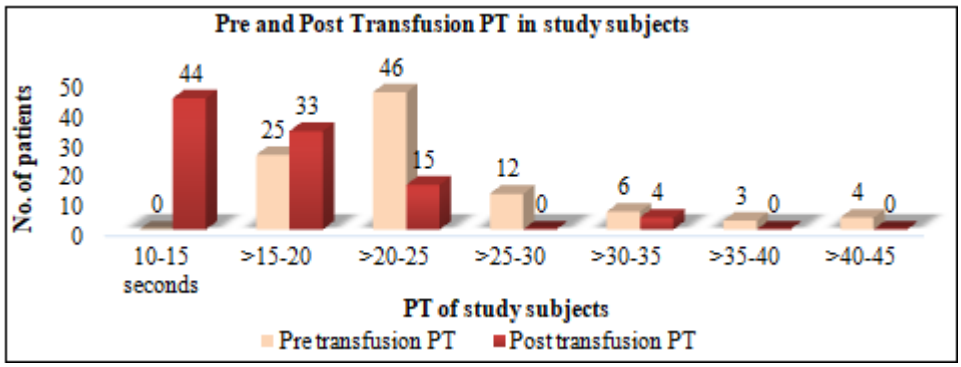
In the present study, a total of 330 units FFP were transfused to 96 patients, ranging from 02 to a maximum of 04 units transfusion of FFP per patient. A maximum number of patients (57) required a total of 04 units of FFP transfusion in part of their treatment which is 59.4% of total cases. Fifteen patients received 02 units of FFP as depicted in Table No. 1

Table 1: Distribution according to no. of FFP transfusions in study subjects:

Units of FFP transfused	No. of Patients	Percent (%)
2 units	15	15.6
3 units	24	25
4 units	57	59.4
Total	96	100

The Pre transfusion PT ranged from16.4 to 40.5 seconds. Maximum number of patients (46) had a pre transfusion PT ranging between 20.1-25 seconds.

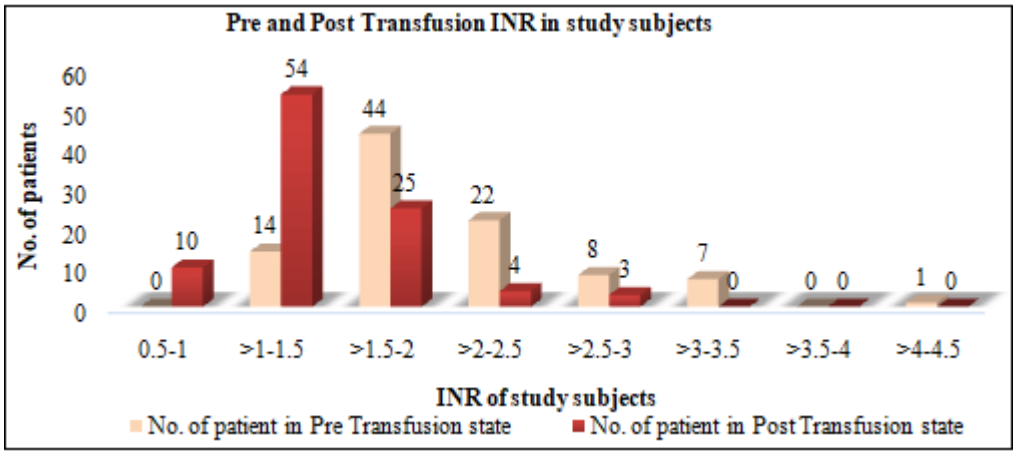
The Post transfusion PT ranged from10.2 - 32.1seconds. A maximum number of patients (44) had a post transfusion PT ranging between 10-15 seconds. The reversal of PT to normal was seen in 44 patients as depicted in Graph no 1.



Graph 1

The Pre transfusion INR ranged between1.32 - 4.46. with a Mean of 2.06. Maximum number of patients(44) had a pre transfusion INR in the range of 1.6-2.

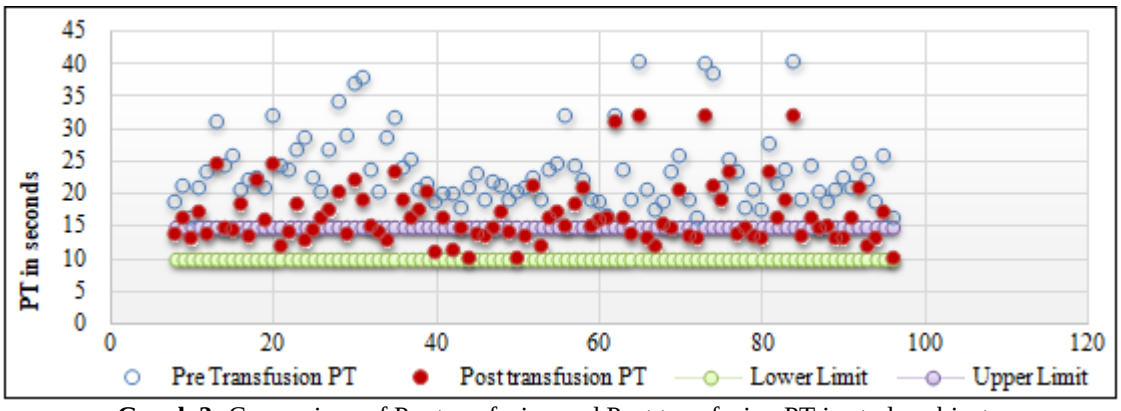
The Post transfusion INR ranged between 0.8 - 2.83.with a Mean of 1.42, A maximum number of patients (54) had a post transfusion INR in the range of 1.1 - 1.5 as depicted in Graph no. 2. Normal INR in the present study ranged from 0.8-1.5. Reversal to normal INR was seen in 64 patients.The significant improvement in INR in present study was 66.67%.



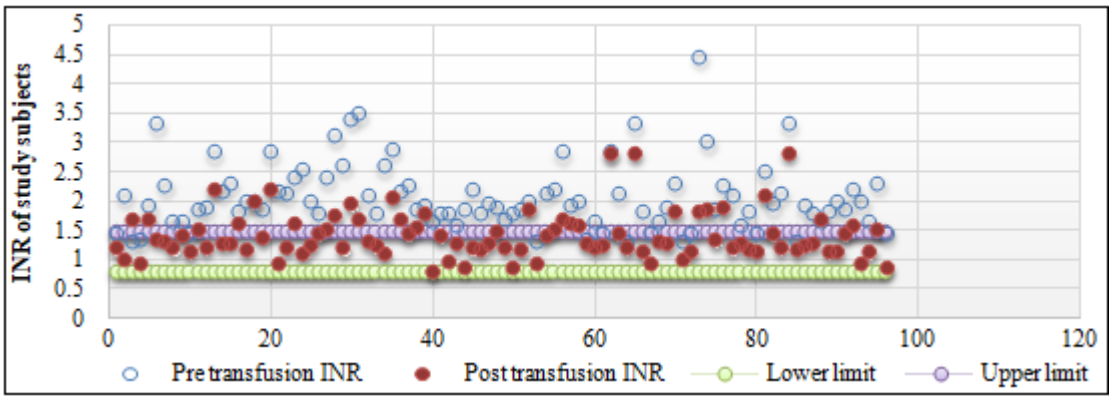
Graph 2

Normal INR in the present study ranged from 0.8-1.5.

The Pre and Post Transfusion PT and INRvalues of the study subjects is depicted in Graph No3 and 4 respectively. The normal range is depicted with lower and upper limits. Forty four patients had PT values, and sixty four patients had their INR values reverting to the normal range post transfusion.



Graph 3: Comparison of Pre transfusion and Post transfusion PT in study subjects



Graph 4: Comparison of Pre and Post Transfusion INR in study subjects

4. Discussion

A total of 96 patients were included in the present study which comprised admitted patients with liver disease presenting with bleeding diathesis.Similar studies of Holland LL et al,[11]Lekshmy N. et al,[12]S.Pybus et al,[13] Youssef et al,[14] N. Jayanthi et al,[2]Shinagare SA et al,[15] Baruah S. et al,[16] with a total of 37, 66, 88, 100, 100, 100 and 576 patients respectively.

The study included patients with their age varying from 18 to 80 yrs. The youngest patient receiving FFP was of 18 years and the eldest of 76 years, with a mean age of 43.7yrs. Similar studies of S. Pybus et al,[13]LekshmyN. et al,[12] Youssef et al,[14]included patient's age ranging from 23 to 87 yrs, 15 to 74 and 30 to 71 yrs respectively. Maximum number of patients in the present study were in the age group of 38 to 48yrs(30%). Similar study of LekshmyN. et al,[12] had a majority of patients in the age group 46-60 yrs(36.3%), with a mean age of 47.5.

Out ofatotal 96 patients, in the present study,75(78%) were males and 21(22%) were females. Gender ratio was found to be 1:3.5. Similar studies of S. Pybus et al,[13]Lekshmy N. et al,[12] Baruah S. et al,[16] observed a gender ratio of 1:1.3, 1:20, 1:6.14 respectively.

Number of Units transfused:
The present study, a total of 330 units of FFP were transfused to 96 patients, while 1935 units of FFP transfused to 576 patients in similar study of Baruah S. et al,[16] 324 units transfused to 121 patients in study of Omar I et al[17] and 573 units transfuse to 88 patients in study of S. Pybus.[13]In a few studies, there was a trend toward higher volumes of FFP infusions being more successful in correcting coagulopathy, although the results in those studies were not statistically significant.

Table 2

Authors	No. of Units transfused	No. of Patients
Holland LL et al[11]	62	37
Omar I et al[17]	324	121
S. Pybus et al[13]	573	88
Baruah S. et al[16]	1935	576
Present study	330	96

Range of PT and INR
Out of total 96 cases, 56% (54 cases) had mild elevation,(INR<2), followed by 35% (34 cases) with moderate elevation (INR between 2-3) and 9 % (8 cases) of severe elevation of INR (INR>3). A maximum of 56% of patients received FFP for mild prolongation of INR, which is not concordant with studyof author Lekshmy N. et al,[12] which observed maximum of 46% of patients received FFP for moderate prolongation of INR as depicted in table no. 3

Table 3

Authors	Degree of elevation of INR		
	Mild	Moderate	Severe
Lekshmy N. et al[12]	21%	46%	33%
Present study	56%	35%	9%

Comparison of Pre transfusion and Post transfusion PT and INR was performed using paired t test. Post transfusion PT and INR was found to be significantly lower compared to the prior ($p<0.0001$). Similar studies were performed with the Means of Pre and Post transfusion PT and INR as depicted in table no. 4.

Table 4

Authors	Year	No. of Patients	Pre Transfusion				Post Transfusion			
			Mean PT	SD PT	Mean INR	SD INR	Mean PT	SD PT	Mean INR	SD INR
Youssef et al[14] Retrospective	2003	80	17.5	4	-	-	15.9	2	-	-
Youssef et al[14] Prospective	2003	20	20	4.9	-	-	17.3	2.6	-	-
Lekshmy N. Et al[12]	2018	66	3.36	-	3.36	2.397	-	-	1.85	0.70
Present study	2018	96	23.70	5.83	2.06	0.566	16.63	4.63	1.42	0.42

Improvement in the PT and INR values:
In present study Significant improvement in INR was 66.67%, this could be attributed to deterioration of underlying disease condition. A high linear correlation has been found between pre transfusion INR and change in INR which is concordant to study of Baruah S. et al.[16]The present study also determined the magnitude of change in INR through linear regression analysis and found that mean change in INR per unit of FFP was 0.64 which is concordant to 0.27 in similar study of Baruah S. et al.[16]

Table 5

Authors	Year	Improvement in INR	Total No. of Patients
Holland LL et al[11]	2006	50%	37
Shinagare SA et al[15]	2010	64.9%	100
Kulkarni et al[18]	2012	33%	--
Lekshmy et al[12]	2018	58%	66
Present study	2018	66.67%	96

The present study analyzed the effect of FFP transfusion on INR in patients with various liver diseases.Holland and Brooke observed retrospective study 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.[11]Improvement in post transfusion values was seen in study of Youssef et al.[14]In patients with chronic liver disease with prolonged PT found that PT improved minimally by the infusion of 2–6 units of FFP.

A few studies however observed that the response to FFP is often unpredictable in liver disease patients and does not completely normalise PT or INR valuesHshieh et al,[19] Observed on chronic liver disease patients with oesophagealvarices who were given FFP transfusions based on raised INR and concluded that INR is a poor predictor of bleeding and it more likely reflected 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.[20]

There are also limitations to the volume of FFP infusion tolerated by patients. It was noted that many of the patients who failed to normalize their prolonged PT, actually received sufficient FFP to correct their coagulopathy based on a published formula.[21,22,23]

Appropriateness of the use of FFP

Many studies haveshown a high incidence of inappropriate use of FFP.[3,24] Inappropriate use not only leads to a wastage of limited resources depriving more needy patients, but also leads to an increased healthcare cost and increased risk of transfusion related complications.

FFP transfusion is appropriate in bleeding patients; patients undergoing invasive procedures with coagulopathy resulting from DIC, massive blood transfusion or liver failure and plasma exchange for thrombotic thrombocytopenic purpura.[25,26,27] Using British Committee for standards in Haematology(BCSH) guidelines, 60.3% FFP prescriptions were found inappropriate by Kakkar et al,[28] in 2004 which however reduced to 26.6% after educational campaigns of clinicians.

5. Conclusions

FFP transfusion significantly improves the PT and INR values and subsequently the clinical outcome in the patients suffering from liver disease. The results of the present study are expected to benefit patients with liver diseases and contribute to improve FFP transfusion practice

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