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Judicious Transfusion of Fresh Frozen Plasma

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Abstract

Background: Fresh Frozen plasma is prepared by centrifugation of whole blood or apheresis donation. It contains clotting factors, fibrinogen, anticoagulants, and certain electrolytes. FFPs are used worldwide for various indications, but their usage is mainly governed by clinical discernment rather than scientifically proven indications. Injudicious use of FFPs is not only a burden on resources but can also lead to adverse effects such as immune and non-immune mediated reactions, infections, and cardiopulmonary complications.

Objective: The objective of this study was to assess the judicious transfusion of fresh frozen plasma.

Methodology: After approval from the Aga Khan University Ethics Review Committee, medical record numbers for patients transfused with FFP's between the period October 2021 and December 2021 were extracted. Details including demography, reason for transfusion, admitting department and coagulation profile were acquired for every patient. Transfusion indications were decided as appropriate or inappropriate in view of British Committee for the Standards in Haematology (BCSH) guidelines. Data was then analyzed in SPSS v26.

Results: A total number of 310 patients were transfused FFPs between the study period, which accounted for a total of 1201 units. Age was distributed between 0 days to 81 years. Majority of the transfusions were performed by the department of Gastroenterology (14.2%), whereas adults and pediatric critical care contributed 11.6% and 8.1% respectively. Major diagnosis included sepsis (27.7%), malignancy (17.7%) and liver disease (17.4%). Most common indication revealed was deranged INR with active bleeding (28.4%). Out of the total transfusions, 68.4% of the transfusions were appropriate, leaving out 31.6% to be without a strong indication.

Conclusion: This analysis revealed a lack in judicious transfusion of fresh frozen plasma. These results can urge clinicians to make decision wisely for transfusion on the basis of research-based guidelines and evidence.

Keywords: Fresh Frozen Plasma , liver disease.

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Introduction

Plasma is the aqueous component of blood that contains proteins and salts in a suspension of red blood cells, white blood cells and platelets. It constitutes 55 % of total blood volume and contains important elements like albumin, coagulation factors, fibrinogen, physiological anticoagulants (Protein C, Protein S, Anti thrombin, tissue factor pathway inhibitor) immunoglobulins and other proteins.[1]

FFP is usually obtained by centrifuging whole blood or by apheresis donation. At a temperature of -18c, it has a shelf life of 12 months, which can be prolonged to 18 months at -25c. When needed, it can be thawed for transfusion. Once thawed, it can be used for up to 24 hours if kept at 4c.[2]

There are multiple uses of plasma, some of them include coagulation factors replacement, for the management of bleeding that is due to warfarin anticoagulation and/or vitamin K deficiency; for the treatment of deficiency of multiple coagulation factors (e.g., liver disease, disseminated intravascular coagulation); as part of massive transfusion protocols, in pre and post-operative optimization of coagulation for invasive procedures when the international normalized ratio (INR) is substantially elevated and in the management of thrombotic thrombocytopenic purpura (TTP), including plasma infusion for hereditary TTP and therapeutic plasma exchange for acquired TTP.[3] It is recommended that transfusion of plasma to correct excessive anticoagulation with vitamin K antagonists, as a volume replacement or for resuscitation, or for other causes of a prolonged international normalized ratio (INR) in the absence of bleeding should be

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avoided as it doesn't provide any mortality or morbidity benefit.[4]

There is a general increase in transfusion of fresh frozen plasma products. Many studies shows that a significant number of FFP transfusions are not justifiable, resulting in their non-judicious use.

The aim of our study was to analyze the judicious use of transfusion of fresh frozen plasma in our hospital setting.

Methodology

After getting approval from the Ethics Review Committee (ERC # 2020-1750-8746) of Aga Khan University Hospital, this prospective cross-sectional study was conducted from October 2021 to December 2021. We conducted this study at Section of Hematology and Transfusion medicine, Aga Khan University Hospital, Karachi. All inpatients regardless of age and gender were recruited who received FFP transfusion during study period. Intraoperative transfusions were excluded from the study.

The hospital-based software for blood bank was used to determine the number of FFP units transfused to inpatients. Data was collected including demographic details, number of FFP units transfused, admitting department, underlying disease while transfusion trigger and indication was determined after thoroughly going through history and progress sheets of medical record files. Pre and post transfusion laboratory coagulation parameters were also noted.

SPSS version 26 was used for data analysis. Demographic details including age and gender distribution was assessed. Number of FFPs transfused in each department was analyzed. Correlation between appropriateness of transfusion by each department and condition was also assessed.

Results

A total of 310 patients were transfused FFPs due to various indications between October 2021 till December 2021. Total units of FFPS issued by the blood bank were 1201. Age variation showed that the youngest patient was one day old neonate while the oldest patient was 81 years old. Maximum units of FFPs dispensed and transfused at a given time were 10. Majority of the fresh frozen plasma requests were received from the department of Gastroenterology which was 14.2%, whereas adult and pediatric critical care contributed 11.6 % and 8.1% of transfusions, respectively (Table I).

The percentage of fresh frozen plasma usage by each department is given in table I, which shows the highest utilization by the department of Gastroenterology. This can be due to the fact that coagulopathy is common in liver diseases and these patients either presents with active GI bleed or massive ascites requiring ascitic tap. 18.7% patients in our study had coagulopathy associated with liver disease. FFP's transfusion was appropriate in 7.4%, however, remaining 11.3% transfusions were unjustified as they were merely done to correct coagulation profile in the absence of bleeding. BCSH doesn't supports the usage of prophylactic FFP for correction of abnormal coagulation profile in low bleeding risk procedures such as paracentesis or even elective variceal banding. However, a usual practice in our setup is to transfuse fresh frozen plasma in case INR is more than 1.5 for paracentesis.

Table I: Usage of fresh frozen plasma by each department .

	N	%
Internal medicine	37	11.9
Pediatric medicine	36	11.6
Adult surgery	19	6.1
Pediatric surgery	6	1.9
Adult critical care	36	11.6
Pediatric critical care	25	8.1
Emergency medicine	31	10.0
Hematology/oncology	33	10.6
Obstetric & gynaecology	16	5.2
CTS	14	4.5
Gastroenterology	44	14.2
Others	13	4.2
Total	310	100.0

27.7% of the patients were admitted with the diagnosis of sepsis, whereas liver disease and malignancy had 17.4% and 17.7% of the transfusions respectively (Figure 2). Various indications for the FFP transfusion revealed the most common reason to be active bleeding with deranged INR (28.4%), while other indications are mentioned in table II. Approximately 68% transfusions had an appropriate trigger, however, 31.6% of the transfusions deemed inappropriate (Figure 1). The most common inappropriate indication was abnormal coagulation profile in absence of bleeding (22.6%) followed by volume replacement (7.7%).

Table II. Indications for transfusion of FFP		
	N	%
DIC	26	8.4
Warfarin OD	7	2.3
Liver disease with active bleeding	33	10.6
Pre/Intra/Post op risk of bleeding with deranged INR	32	10.3
Massive transfusion/haemorrhage	7	2.3
Volume replacement	24	7.7
Abnormal coagulation profile in absence of bleeding	70	22.6
Active bleeding with deranged INR	88	28.4
Plasmapharesis	20	6.5
Others	3	1.0
Total	310	100.0

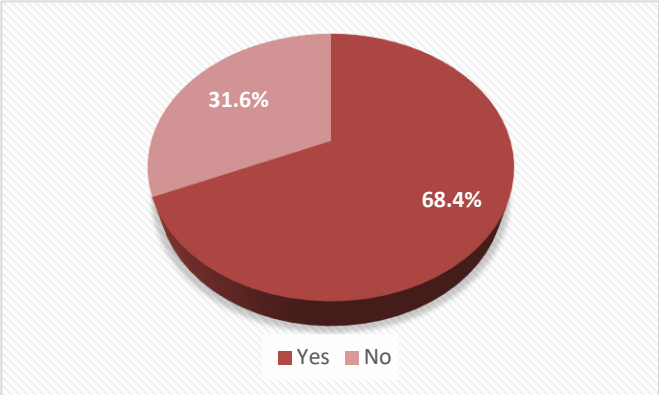

Figure 1. Appropriate Transfusion

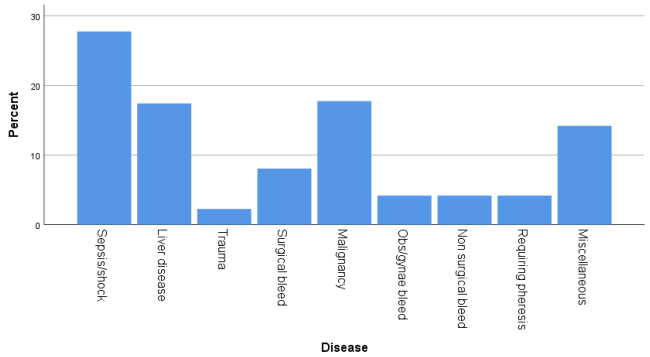

Figure 2. Distribution of Diagnoses Among Admitted Patients.

Discussion

In the light of BCSH guidelines, the designated appropriate indications in our study included: liver disease with active bleeding or undergoing major surgery, operative or procedural risk of bleeding with deranged INR, massive blood loss or transfusion, acute DIC, active bleeding with deranged INR and conditions requiring plasmapheresis such as Thrombotic thrombocytopenic purpura. As prothrombin complex concentrates (PCC) are not available in our medical facility hence, use of FFP in management of warfarin toxicity was also considered appropriate in this study. Single factor deficiency in case of unavailable concentrates was also deemed appropriate however only one such case was found in this study period i.e., factor IX deficiency. The inappropriate indications included correction of abnormal coagulation profile in absence of bleeding and volume replacement.

Our data analysis revealed that 31.6% of FFP transfusion were inappropriate. Audit conducted in our center in 1997 reported unjustified intraoperative FFP transfusions in about 45.1%. Another observational study conducted at a tertiary care center in Karachi revealed as high as 21.3% of the FFP transfusions to be inappropriate.[5]

Our results demonstrated that 22.6% of the patients were transfused FFPs with deranged INR without evidence of bleeding or any planned procedure, which is a huge proportion. As per an audit performed in UK in 2009, it was observed that about 50% of the patients received FFPs in the absence of any bleed.[6] Moreover, it was observed that transfusion was performed before invasive procedures at an INR of <1.5. Transfusion of FFPs without any evidence of surgical bleed has also been reported in certain systematic reviews. Two separate systematic reviews suggested that a deranged PT/INR does not govern the extent of bleeding during a surgery.[7,8] Patel et al. suggested that a detailed history including past episodes of bleeding, drugs being used, and knowing the extent of surgery were more important factors in determining whether a patient is likely to bleed.[9] At many centers, it is a practice to transfuse FFPs prophylactically with the aim to reduce a bleeding event or in the presence of abnormalities in coagulation profile, but there are studies that negate this practice.[10]

A study being conducted by Muller and colleagues in 2015 was a non-inferiority randomized controlled trial to assess the effectiveness of transfusion of FFP to patients admitted in the critical care area with INR between 1.5-3.0 showed that the regime was not supported by an increased risk of bleeding, and therefore this study was aborted before completion.[11] Large doses tend to normalize lab figures for coagulopathy but are often associated with deleterious

effects such as volume overload.[12] Similarly, Durila et al conducted a study on 119 patients undergoing tracheostomy.[13] Patients were divided into two groups, one with INR < 1.2 and the other with INR > 1.2 up to 1.84, and the groups had no difference in surgical bleeding.

There is a class 2C recommendation by the British Society of Hematology that plasma should not be used to replace volume or to resuscitate patients. A meta-analysis performed on various regimes for fluid resuscitation showed that there was no mortality benefit over crystalloids, or decrease in the incidence of the use of renal replacement therapy.[14] Besides literature suggesting that FFPs should not be used as volume expanders, various studies report the side effects associated with administration of FFPs. These include risk of transmissions of virus, non-immunological and immunological reactions, transfusion associated cardiac overload (TACO), transfusion associated acute lung injury (TRALI) and pulmonary edema.[15] In our study, 7.7% of the patients were given FFPs as volume expanders with majority of the transfusions done for neonates. A study done on neonates shows that there has been a trend of transfusing FFPs to neonates even without evidence of bleeding.[16]

Disseminated Intravascular Coagulopathy (DIC) is another condition in which clotting factors are being consumed and there is an overall decrease in the procoagulating substances in the blood, which can lead to life threatening bleeding. Patients in DIC without active bleeding might not be suitable candidates for transfusion of FFPs ([17]). In our study, 8.4% of the transfusions were performed due to acute DIC.

Warfarin toxicity is a life-threatening condition which can result in the development of hemorrhagic shock. Treatment of warfarin toxicity involves administration of vitamin K intravenously and prothrombin complex.[18] At our center, PCC is not available. Therefore, the treatment involved transfusion of FFP and giving intravenous vitamin K, even though literature suggests FFP to be inferior to PCC for warfarin toxicity[19] 2.3% of the patients were transfused FFP due to warfarin toxicity. Use of warfarin has been reduced significantly after the advent of newer generation anti coagulants, and absolute indications are only a few.

Approximately 28% of our patients were transfused FFPS in the presence of sepsis or septic shock. Patients in sepsis often have deranged coagulopathy, with hypo or hyper coagulopathy and presence of DIC. A study conducted on outcomes associated with liberal use of FFPs for patients with sepsis suggested a significantly increased mortality.[20] On the other hand, a sub trial involving transfusion a fixed dose of FFP (12ml/kg) to critically ill patients showed a statistically significant reduction in cytokines and inflammatory markers.[21] Another study shows that a high ratio of FFP to RBC transfused to patients with trauma and normal INR results in reduced mortality.[22] Further studies are needed to form a basis of the use of FFPs as an anti-inflammatory agent rather than to correct bleeding due to coagulopathy.

In our study, fresh frozen plasma was used as an exchange fluid for apheresis procedures in 6.5% of patients. The conditions included thrombotic microangiopathies (Thrombotic thrombocytopenic purpura) and neuromuscular disorders (Myasthenia Gravis).

Using fresh frozen plasma in conditions for which it is not indicated, not only uses up hospital resources but also adds up to the medical expenses of the patient since a thawed unit cannot be preserved indefinitely. Many studies have suggested that inappropriate utilization of fresh frozen plasma results in adverse outcomes including a higher incidence of mortality. Limitations of our study is a short observation period of three months only. First transfusion during the hospitalization was investigated, subsequent transfusions were not considered. Intraoperative transfusions were also not a part of this study.

Conclusion

The most common indication of FFP transfusion in our study was deranged INR with active bleeding. Although this is an accepted indication, our study also highlighted that in 32% of patients, transfusion of fresh frozen plasma which was not indicated. There is room for improvement in judicious transfusion of fresh frozen plasma which will not only help in saving valuable resources but will also curb the adverse effects associated with injudicious use of FFPs.

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