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The Trends of Use of Fresh Frozen Plasma at a Tertiary Care Hospital

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Background: The term fresh frozen plasma (FFP) refers to the liquid portion of human blood which has been frozen and preserved quickly after a blood donation and later used for transfusion. The capitalized term Fresh Frozen Plasma is the proper name in the United States for the fluid portion of one unit of human blood that has been centrifuged, separated, and frozen solid at −18 °C (−0.4 °F) (or colder) within 6 hours of collection. Fresh frozen plasma is used in situation when oxygen carrying capacity of blood is not in question. The use of FFPs is now reserved for conditions requiring therapy in which replacement of multiple plasma constituents are needed or for which the specific constituent is not commercially available in purified injection or transfusion form. Plasma however contains numerous protein and chemicals which can be potentially harmful. Therefore judicious use of plasma is extremely important where its benefits must outweigh its potential risks. Although concrete guidelines are available for its optimum use, these guidelines are not strictly adhered to at some institutions. Mere knowledge is not sufficient and we often require auditing and periodic reinforcement to mould the clinical practice in line with guidelines for appropriate and safe transfusion.

Material and Methods: The prospective review of FFPs transfusion request forms from different units of PIMS hospital at blood bank of PIMS during the months of September and October 2009 was done. We evaluated all FFP transfusions, classified them as appropriate or inappropriate according to the recent FFP transfusion guideline (College of American Pathologist 1994).

Results: During the study period, 100 cases were selected randomly. 64% of cases were considered inappropriate according to the guidelines. The most ***inappropriate*** requests were made by Burn Unit while the most **appropriate** requests were made by Thalasemia Center.

Conclusion: This study highlights the pitfalls in use of fresh frozen plasma among clinicians. The high rates of inappropriate transfusion reflect the lack of knowledge as well as non-adherence to the guidelines among clinicians, about the appropriate laboratory criteria as the basis for **`FFP`** usage for clotting support.

Keywords: Fresh Frozen Plasma (FFP), Coagulation Profile, Component therapy, Transfusion

Introduction

Component therapy has had a profound impact on the practice of transfusion medicine. The extraction of various constituents, including plasma, from whole blood has led to increased efficacy and economic utilization of the blood supply[1].

John Elliott, laboratory chief at Rowan Hospital in North Carolina, had been experimenting with methods of separating plasma from blood, when a patient who had been stabbed in the heart presented at the emergency room. As there was no time to obtain a blood sample for type and crossmatching, so Elliott decided to try transfusing the patient with the plasma he had in the laboratory. He found that the patient was improving with it. Elliott found that, in addition to having many of the beneficial properties of whole blood transfusion, plasma retained its usefulness for months. This was first use of plasma, as an adjunct to therapy. In August 1940, Americans launched Plasma for Britain program, headed by Charles Drew .Under Drew's directorship, this program was a tremendous success, collecting blood from nearly 15,000 people, which produced 5500 vials of plasma[1].

Major component of plasma is water, which constitutes approximately 85% to 90% of the plasma volume. solute component constitutes 0.3 mol/L, of which about 30% is made up of proteins; with colloids, crystalloids, clotting factors, hormones, vitamins, and trace elements making up rest. The term fresh frozen plasma (FFP) refers to the liquid portion of human blood which has been frozen[2]. Fresh frozen plasma (FFP) is a blood product produced from plasma which is separated from packed red cells and platelets after

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centrifugation of donated whole blood, single-donor plasmapheresis, or as a by-product of cytapheresis [e.g., platelet or red blood cell (RBC); concurrent plasma].and frozen to -30°C or below within six hours after collection[1]. It is a good source of coagulation factors, including labile factors V and VIII. Plasma may be transfused up to 24 hours after thawing and contains slightly decreased levels of Factor V (66±9%) and decreased Factor VIII levels (41±8%). The fresh frozen plasma has been available since 1941 and was initially used as volume replacement[3].Today there is no justification for the use of FFPS as volume expanders as much safer alternative (colloid and crystalloids) are available. The use of FFPs is now reserved for conditions requiring therapy in which replacement of multiple plasma constituents is needed or for which the specific constituent is not commercially available in purified injection or transfusion form and also for Plasma exchange in TTP and Reversal of warfarin effect if immediate hemostasis is required. The appropriate use of FFP requires an understanding of the properties of FFP and its inadequacies, as well as an appreciation of the complications of FFP usage[4]. The College of American Pathologists[5] and the British Committee for Standards in Haematology[3] have published guidelines to highlight these issues and minimize misuse.

Important limitations need to be borne in mind when prescribing FFP. Half-lives of some coagulation factors is short; therefore FFP should be given close to the time of invasive procedure if correction of markedly prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT) is required before surgery[4]. For specific factor or fibrinogen deficiency, the volume of FFP required for adequate replacement far exceeds that of specific factor concentrates or cryoprecipitate respectively, and should not be the preferred choice in these situations.

Over the years, the significant role of blood components in treating certain diseases or conditions has been recognized. Many studies from around the world still report a high frequency of inappropriate usage. The indications for transfusing fresh-frozen plasma (FFP), cryoprecipitate and cryosupernatant plasma are very limited. When transfused they can have unpredictable adverse effects. The risk of transmitting infection is similar to other blood components unless pathogen-reduced plasma (PRP) is used. It is 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 has not been reported[6]. FFP contains antibodies including those against ABO antigens and is capable of causing antibody-induced complications like hemolytic reactions and transfusion related acute lung injury[7]. Other complications like allergic reactions[6]and fluid overload associated with blood transfusion can also occur with plasma infusion. Hence the use of FFP is not without potential danger.

In order to avoid inappropriate use of FFPs, we need to develop behavioral modification plans for clinicians which would include changes in curriculum at undergraduate level, periodic stress on optimal and appropriate usage of FFPs in clinicopathological meetings and in transfusion committee meetings.

Our institution is a large 1000-bed general hospital in Islamabad with a broad range of medical and surgical specialties and our blood bank caters Islamabad hospital, Children hospital, MCH and Burn Unit. Our transfusion service noted that FFP usage in the hospital is very high (about half the number of units of red cells transfused each month), so we decided to conduct a prospective audit on the hospitals FFP usage with the specific aims of assessing our pattern of usage and rate of misuse. This will subsequently help us to recognize and solve problems concerning inappropriate use of FFPs.

Objective

1. To *evaluate the trends* in the use of FFPs.
2. To carry out an *audit of appropriateness* of FFP transfusion with reference to international guidelines.
3. To *educate and bring about the behavioral changes* in clinical practice according to the guidelines.

Material and Methods

During the months of September and October 2009, the prospective review of FFPs of blood transfusion request forms from different units of PIMS hospital (Islamabad, Children Hospital and burn unit) at blood bank of PIMS was done. Total 100 FFPs transfusion request forms of different patients from Islamabad Hospital, Children Hospital and Burn Unit were selected randomly. Data recorded include department requesting for FFP, patient's presenting complaints, reason for FFP request, date of transfusion, number of units transfused, coagulation profile of patient and causes of coagulopathy if investigated. Also recorded were blood group required, age and sex of the patient and any history of

previous transfusion. The coagulation profile was traced by computer record (Islamabad Hospital), through telephonic conversation with concerned doctors (Children Hospital) and by the patient's record file. We evaluated all FFP transfusions, classifying them as appropriate or inappropriate according to the recent FFP transfusion guideline.

The College of American Pathologists (CAP) has determined following practical parameters for FFPs transfusion (1994)[5].

1) If there is a history or clinical course suggestive of a coagulopathy due to a congenital or acquired deficiency of coagulation factors, with active bleeding or other invasive procedure. This must be documented by at least one of the following:

a) Prothrombin time (PT) greater than 1.5 times the mid point of the normal range. (Usually greater than 18 seconds).

b) Activated partial Thromboplastin time (aPTT) greater than 1.5 times the top of the normal range (usually > 55-60 seconds) (fibrinogen must be functionally normal with a level generally > 1.0 g/l, and the specimen must be free of heparin for the PT and PTT to be accurate).

c) Coagulation factor assay of less than 25% activity.

2) Massive blood transfusion: Replacement of more than 1 blood volume (approximately 5000 m1 in a 70 kg adult) within several hours with evidence of a coagulation deficiency (as in 1) with continued bleeding.

3) Reversal of Warfarin effect: If immediate hemostasis is required to stop active bleeding or prior to emergency surgery or an invasive procedure (PT > 18 seconds; international normalized ratio > 1.6)

4) If there is a documented congenital or acquired coagulation factor deficiency or prophylactically for surgery or invasive procedure.

5) Plasma exchange for thrombotic thrombocytopenic purpura or haemolytic uremic syndrome.

6) Because of all the alternatives available and the many hazards associated with FFP transfusion, the use of FFP as a volume expander or to enhance wound healing is contraindicated.

In this study, in accordance with practice parameters for the use of FFP, the transfusion was considered appropriate if the prothrombin time or activated partial thromboplastin time was 1.5 times the control values. A FFP transfusion was considered inappropriate if (a) clotting profile was not done / could not be traced and (b) the PT / PTT were < 1.5 times the normal range. Results were tabulated and where appropriate presented as bar chart.

Results

During the study period 100 request forms were selected randomly. Most of the request forms did not mention the indication for transfusion. Of these 100 forms, in 34 coagulation profile was not done pre or post transfusion, so these were considered as inappropriate. While in 30 cases indications were not according to international guidelines, so they were also categorized as inappropriate. Thus a total of **64** requests were inappropriate out of 100. Rest of **36** cases were categorized appropriate. A total of **350** units were issued for these 100 cases. Out of these 350 units, 285 (81%) were inappropriately used which is alarmingly high.

The break down of these results according to the individual departments shows that maximum request was made by Pediatrics Medicine and minimum by cardiology unit (Table1). The most *inappropriate* requests were made for burn patients. The most *appropriate* requests were made by Thallassemia center. (Table 2)

TABLE 1: *Distribution of FFP Requests According to Different Departments*

Departments	Number (Percentage) of Total Requests
Pediatric Medicine (including PICU & NICU)	37 (37 %)
Medical Unit IH (including MICU)	21 (21 %)
Surgical Unit (including SICU)	12 (12 %)
Burn Unit	09 (9 %)
Pediatric Surgery	08 (8 %)
Thalasemia Center	08 (8 %)
Cardiology Unit (including CW, Cardiac Surgery & CCU)	05 (5%)
Total	100

The comparison between surgical and non-surgical cases shows that 80% of the requests made by surgical department were inappropriate as compare to

52% for non-surgical cases. (Table 3)

TABLE 2: Inappropriate FFP request made by different specialties(according to International guidelines)

Departments	Total Requests	Appropriate Requests	Inappropriate Requests
Pediatric Medicine (including PICU & NICU)	37	18 (49 %)	19 (51 %)
Medical Unit IH (including MICU)	21	07 (32 %)	14 (68 %)
Surgical Unit (including SICU)	12	02 (17 %)	10 (83 %)
Burn Unit	09	0 (0 %)	09 (100 %)
Pediatric Surgery	08	01 (13 %)	07 (87 %)
Thalasemia Center	08	07 (87 %)	01 (13 %)
Cardiology Unit (including CW, Cardiac Surgery & CCU)	05	02 (40 %)	03 (60 %)

TABLE 3 :Comparison between Surgical and Non-Surgical Specialties

Specialties	Percentage of Inappropriate Requests
Surgical (including IH, CH and ICU)	80 %
Non-Surgical (including IH, CH and ICU)	52 %

The most common inappropriate indications for FFP use came out to be in burn patients, accidental trauma (circulatory volume replacement) and hematological malignancies in adult patients (100%).The most appropriate indications came out to be coagulation factor deficiency (congenital or acquired) followed by hematological malignancies in children according to the guidelines.(Table 4)

TABLE 4 Episodes of FFP utilization according to clinical indications

Diagnosis Criteria	Number	Appropriate	Inappropriate
Burns	09	0(0%)	09(100%)
Surgical (Preoperative)	09	02(22%)	07(78%)
Cardiac Surgery	04	02(50%)	02(50%)
Trauma	02	0(0%)	02(100%)
Liver diseases	08	02(25%)	06(75%)
DIC/ sepsis	09	02(22%)	07(78%)
Coagulopathy/ Bleeding tendencies	02	02(100%)	0(0%)
Hematological (malignancy)	03	0(0%)	03(100%)
Hematological (Pediatric malignancy)	02	02(100%)	0(0%)
Total units transfused	350	65(19%)	285 (81%)

Discussion

Fresh Frozen Plasma (FFP) is a frequently prescribed blood product; its use continues to rise, despite the fact that the supply of plasma derived from allogeneic blood donation is finite. Unfortunately, this product is commonly overused or inappropriately used. Contrary to the belief among many clinicians, FFP transfusions are not risk free. Allergic reaction, fluid overload, transfusion-related acute lung injury (TRALI), immune suppression, hemolysis, and infectious complications can be caused by FFP administration. It is prudent for FFP transfusions to be given only when clearly clinically indicated, so as to avoid exposing patients to unnecessary risks[8].Inappropriate use not only leads to wastage of limited resources and depriving more needy patients of their use, it also leads to increased healthcare cost and risk of transfusion related complications like viral transmission which could lead

to significant morbidity and mortality[4].

Although guidelines exist since eighties but the use of FFP in hospital practice has risen by over 20%in the past few years and concern has been raised about the appropriateness of its clinical use. Unlike red cell transfusion, where the traditional threshold of 10 g/dl has been found to be unnecessarily high in some settings like surgery and intensive care by prospective randomized studies[9] such studies do not exist for FFP usage. Even, the threshold of PT and aPTT prolongation of 1.5 times normal was based on dated retrospective studies[9,10].

Furthermore, some studies have shown that PT and aPTT were only crude predictors of surgical bleeding and their utility had been questioned[11,12].Our audit showed widespread uncertainty about the appropriate use of FFP among our doctors resulting in a high number of inappropriate requests.

In our study the most inappropriate use of Fresh Frozen Plasma (FFP) based on International Criteria was in burn unit. We discussed the issue with the In-charge of the Burns Unit in details along with their staff. They informed us that they initially use plasma expanders such as Ringers solution after dehydration effect is vanished. However in order to replace massive protein loss, FFP is used as the synthetic albumin is either unavailable or unaffordable by the patient due to its high cost[13]. However the use of FFP should be used judiciously and curtailed as much as possible as it carries many risks. The coagulation profile should be carried out before and after FFP transfusion.

The next most common misuse was FFPs use for circulatory volume replacement. The use of FFP for the purpose of volume expansion is totally unwarranted. In massive bleeding it has been shown that there is no indication for FFP unless the blood loss is in excess of 5000 ml[14].

The high rates of inappropriate transfusion may reflect poor understanding of the clinicians about the appropriate laboratory criteria as the basis for FFP usage for clotting support. It is reflected by the results as only 36% of the total request had either PT /APTT values more than 1.5 times normal.

Also in surgical services, the prophylactic transfusion of FFPs in patients with normal coagulation profile before or after procedures with the potential for haemorrhage was quiet high and was inappropriate .In the absence of consumption coagulopathy; it has been shown that FFP is unnecessary if whole blood is transfused [15].

There are other situations where products more effective and safer than FFP are available for correction of coagulopathy: recombinant or virally inactivated specific clotting factor concentrates for treatment of haemophilia, von Willebrand's disease and hypofibrinogenemic states; and prothrombin complex concentrates and vitamin K for warfarin reverse[16] but these are difficult in our setup as these factor concentrates are neither available nor affordable.

Other common indication for FFP usage is sepsis with disseminated intravascular coagulopathy (DIC), bleeding and patients undergoing invasive procedures. FFP use is clearly appropriate in DIC where there is activation of the coagulation system with consumption of coagulation factors leading to a generalized coagulopathy but according to the CAP guidelines, FFP should be given only in the setting of bleeding in these patients.

Many international studies and audit have been conducted on use of FFPs. Most of them show similar results. Three audits in London and Oxford between 1993 and 2000 identified that 34% of transfusions were for reasons outside the guidelines. A similar audit was done Venezuela General University hospital in 1999 showing (48.7%) were inappropriate transfusion[17].

Transfusion practice is now a complex therapeutic discipline, requiring all the skills of a trained pathologist. The transfusion of a blood component can never be taken lightly; it should only be given for a good reason after careful evaluation of the clinical situation. Blood Banking or Transfusion Medicine should be part of curriculum of medical college in initial years with continuous reinforcement.

Conclusion

This study highlights the pitfalls in the use of fresh frozen plasma among clinicians.

The high rates of inappropriate transfusion reflect the lack of knowledge as well as non-adherence to the guidelines among clinicians, about the appropriate laboratory criteria as the basis for FFP usage for clotting support.

So our recommendations are,

- In such state of affairs is that proper education of medical staff and regular auditing programmes about the use of blood and its components is needed.
- Periodic reinforcement about proper use of blood products in clinicopathological conferences and meetings of hospital blood transfusion committees should be done.

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