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Clinical Use of Fresh Frozen Plasma in a Tertiary Care Hospital from India

Zastosowanie kliniczne świeżo mrożonego osocza w szpitalu referencyjnym w Indiach

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Abstract

Background. *Increased utilization of fresh frozen plasma (FFP) over the last decade has caused a rising trend in its unjustified usage exposing recipients to both infectious and non-infectious hazards. The aim of the study was to observe the pattern of clinical use of plasma at a tertiary care hospital from India.*

Material and methods. *Prospective analysis of all the requests raised for plasma was carried out. Indicators namely homogeneity of the requisition forms, patient demographics, indications for transfusion, dosage, pre-transfusion coagulation parameters and adverse events were noted. Appropriateness was defined based on compliance to both national and international standards. Data was analyzed using SPSS version 20 (IBM, USA).*

Results. *Total nine hundred ninety eight patients (Males: 66%) received 4991 units of plasma at an average of two episodes per patient. Majority were adults 83.6% (n = 835). Primary users were internal medicine (32%) and plastic surgery (17%) respectively. Most common indication was bleeding with coagulopathy seen in 41% (411/998) patients. Average plasma volume administered was 456.2 ± 287.4 (17 to 2800) mL per episode. Pre-transfusions INR value was available in only 63.2% (n = 1317) episodes. Overall, 56% (n = 1169) episodes were deemed appropriate. Total 0.28% plasma related adverse reactions were seen and reported to the national hemovigilance database. Mortality in the study group was 7.2%.*

Conclusion. *Existing transfusion practices for plasma use were moderately compliant with the standards. Commonest indications for inappropriate FFP use were for low protein states and prophylaxis without any evidence of bleeding.*

Key words: fresh frozen plasma, appropriateness, clinical usage, guidelines

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Streszczenie

Wstęp. *W ciągu ostatniej dekady znacznie zwiększyło się zużycie świeżo mrożonego osocza (fresh frozen plasma, FFP), co spowodowało rosnącą tendencję do nieuzasadnionego stosowania FFP, a tym samym narażenie pacjentów na ryzyko związane z zakażeniami i niezakaźnymi*

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powikłaniami. Badanie przeprowadzono w celu zaobserwowania, w jaki sposób stosuje się FFP w referencyjnym szpitalu w Indiach.

Materiał i metody. *Przeanalizowano w sposób prospektywny wszystkie przypadki zamówień osocza. Stosowano jednorodne formularze zamówienia i odnotowano dane demograficzne chorych, wskazania do transfuzji, dawkę, parametry krzepliwości krwi przed transfuzją oraz zdarzenia niepożądane. Prawidłowe stosowanie definiowano jako zgodność z krajowymi i międzynarodowymi standardami. Do analizy danych użyto oprogramowania SPSS, wersja 20 (IBM, Stany Zjednoczone).*

Wyniki. *Ogółem 998 chorym (66% mężczyzn) podano 4991 jednostek osocza, a średnia liczba transfuzji na pacjenta wynosiła 2. Większość stanowiły osoby dorosłe (83.6%; n = 835). Największą grupę stanowili pacjenci internistyczni (32%) i osoby poddające się zabiegom z zakresu chirurgii plastycznej (17%). Najczęstszym wskazaniem było krwawienie z koagulopatią obserwowane u 41% (411/998) chorych. Średnia objętość podanego osocza wynosiła 456,2 ± 287,4 (17 do 2800) ml na transfuzję. Wartość INR przed transfuzją była dostępna tylko w 63,2% (n = 1317) epizodów. Ogółem, 56% (n = 1169) epizodów uznano za prawidłowe. W 0,28% przypadków zaobserwowano działania niepożądane i zgłoszono je do krajowej bazy nadzoru hematologicznego. Odnotowano 72 przypadki zgonów (7,2% chorych).*

Wnioski. *Stosowana praktyka dotycząca transfuzji osocza była umiarkowanie zgodna ze standardami. Najczęściej stwierdzanymi nieprawidłowościami było stosowanie FFP w przypadku niedoborów białkowych i w ramach profilaktyki przy braku jakichkolwiek oznak krwawienia.*

Słowa kluczowe: świeżo mrożone osocze, prawidłowe stosowanie, zastosowanie kliniczne, wytyczne

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Introduction

Blood components therapy has profoundly impacted the bank inventory as well as patient safety over the last two decades. Globally a rising trend in the clinical usage of fresh frozen plasma (FFP) has been witnessed. However, multiple loop-holes exist in its ordering and optimal utilization in compliance to the existing national and international standards. Furthermore, FFP carries a potential of causing both infectious and non-infectious harm to the recipient. Hence the use of FFP is not only without potential danger it should be rather administered only when clearly indicated [1]. In addition, inappropriate usage continues to grow invariably from one institution to another ranging anywhere from 21.3% to 83% [2]. Surplus interest has therefore been shown worldwide, to streamline the transfusion practices by means of ensuring scientific as well as cost-effective use of plasma. Being a 2032 bedded multi-specialty tertiary care center and considering the increased demand of this selective blood component, we decided to do a prospective analysis on the pattern of its ordering, dose requested and the compliance of its clinical use based on both national [Directorate General of Health Services (DGHS)] and international guidelines such as British Committee for Standards in Hematology (BCSH) [3, 4]. The primary aim of this study was to observe the pattern of clinical use of plasma and optimize the existing transfusion practices at our center.

Material and methods

It was designed as a prospective study from December 2012 to November 2013, where clinicians requested for plasma for various reasons. A written informed consent was obtained from the recipients prior to any transfusion in accordance with the hospital transfusion policy. As per the institutional policy an approval by the ethical committee was obtained prior to the commencement of the study. It was conducted in accordance with the principles of good clinical practices.

Study methodology

The study timeline included the following phases:

Phase I: It included ten month period (from December 2012 to September 2013) for prospective monitoring of all the transfusion requests of FFP. The study was further divided into steps such as defining indicators to design a study criteria-based *Proforma*, patient demographics (age, gender, service and body weight), monitoring of the transfusion requisition forms and identifying appropriateness of indication and dosage pattern to the established guidelines. The complete details regarding FFP requisitions were collected and entered in the *Proforma*. Data was captured simultaneously during every transfusion episode (An episode was defined as each time we issued one or more therapeutic doses of FFP to a patient).
Phase II: It included two month period (from October to November 2013) for final analysis and interpretation of the data.

Defining Study Criteria

Completeness of compilation of requisition forms

It was evaluated as the percentage of entry in ten areas [patients' name, age & gender, blood group, location, pre-transfusion coagulation parameters, provisional diagnosis, history of previous transfusion and or any adverse reaction, type of request (urgent or planned), type and number of blood component as well as requesting doctor's signature] on the requisition forms. This was captured in the study *Proforma.* The requests were defined as "excellent" (if greater than 70%); "good" (50% and 70%) and "poor"(less than 50%) based on the percentage of the areas filled.

Indications for transfusion and dosage

Appropriateness was defined based on compliance to both national and international standards. The indications and dosage of FFP (10–15 mL per kg bodyweight) as ordered on the requisition forms were noted.

Pre & Post-transfusion coagulation parameters

Pre-transfusion coagulation parameters like *prothrombin time* (PT), *International normalized ratio* (INR), *partial thromboplastin time* (PTT) and platelet count within 12 hours preceding the request and similar parameters performed within 24 hours after transfusion were considered for defining appropriateness.

Adverse reactions

Any adverse transfusion reactions due to FFP administration were noted.

Morbidity and mortality

Midterm morbidity and mortality in the treated population was obtained from the medical and/or nurses clinical records of the patients.

Inclusion & exclusion Criteria

All the hospitalized patients who received FFP transfusions were included in the study. However, the requests which came to the department for plasma exchange procedures were excluded from the study because of the lack of supportive guidelines to judge the appropriateness of same in such situations.

Statistical analysis

SPSS software version 20 (IBM Inc., Armonk, NY, USA) was used for data analysis. Simple descriptive statistics were expressed as mean ± standard deviation and quantitative data was expressed as percentage. The χ^2 test was used to compare the completeness and appropriateness of requests arriving from different specialties; p value less than 0.05 was considered as statistically significant. The two-tailed t-test was used to compare paired data such as pre and post transfusion coagulation test values.

Results

Patient demographics

Total nine hundred ninety eight patients (Males: 66%) received 4991 units of plasma (200 ± 20) mL at an average of two episodes per patient. On age-wise distribution majority were adults (82%). Median weight (inter-quartile range) amongst the infants was 2.78 (2.1–3.1), in adolescent 16 (10–29) and adults 57 (51.5–61) kg respectively. Blood group-wise majority patients were of O group. Major users of plasma were internal medicine (32%) against plastic surgery (17%). Highest use was made in operation theatres (42%) followed by intensive care units [ICU] (30%). The commonest diagnosis of patients who were administered plasma was liver disease (25.1%) followed by 14.5% disseminated intravascular coagulation [DIC] (Table 1).

Completeness of the compilation of requisition forms

Total two thousand eighty two (2082) requisition forms were received. They were analyzed for homogeneity of completeness. Among them 50% [n = 1040/2082] forms were defined as good against 3% [n = 62/2082] poorly filled. Pre-coagulation

Table 1. Diagnosis-wise distribution of Fresh Frozen Plasma usage in patients

Tabela 1. Rozkład częstości stosowania świeżo mrożonego osocza w zależności od rozpoznania

Diagnosis	No. of patients [%]	No. of requisition forms
Liver disease	251 (25.1%)	541
*DIC with sepsis	145 (14.5%)	259
Cardiac Surgery	119 (11.9%])	159
Malignancies	113 (11.3%)	187
Trauma	100 (10.0%)	174
Hypovolemia in Burns	71 (7.1%)	356
Infectious diseases	64 (6.4%)	135
Peri-operatively [surgical cases]	46 (4.6%)	74
Poisoning & others	27 (2.7%)	56
Obstetric complications	20 (2.0%)	29
Renal disease	20 (2.0%)	44
#TTP/HUS	11 (1.1%)	36
Factor deficiency	11 (1.1%)	32
Total	998 (100%)	2082

*DIC — disseminated intravascular coagulation; #TTP — thrombotic thrombocytopenic purpura; HUS — hemolytic uremic syndrome

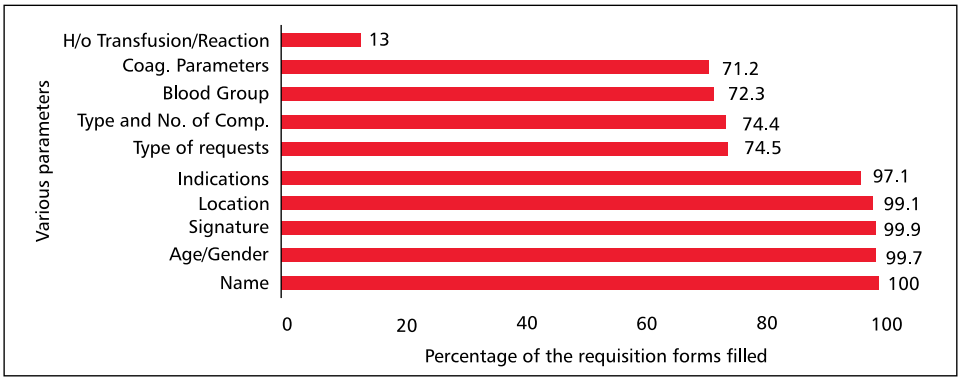

Figure 1. Degree of homogeneity of information on the blood requisition forms

parameters were entered in 71% forms against previous transfusion and adverse reactions filled in only 13% forms (Fig. 1).

Bleeding sites & invasive procedures

Commonest bleeding sites were upper gastrointestinal (32%) followed by mucocutaneous (17%). Bleeding of knee joint was present in 60% of hemophilia patients. Total 37% (n = 372/998) underwent various surgical and/or invasive procedures. Cardiac & other vascular surgeries were performed in 27% (n = 100/372) patients. Prophylactic transfusions were given prior to wound debridement, central venous catheterizations and liver biopsies in 16% (61/372), 14% (53/372) and 7% (27/3720 respectively.

Indications and dosage of plasma administration

The patients enrolled in the study were diagnosed with multiple disorders (Table 1). Most common indication was bleeding with coagulopathy 41% (n = 411) against 17.5% (n = 175) patients having hypoalbuminemia/hypovolemia. The median dose (Q1-Q3) of FFP administered was 10.1 (5.8 to 13.4) mL/kg ranging from 0.11 to 48.5 mL per episode. Higher dose of plasma was administered for the reversal of anticoagulant (11.8 mL) against

Table 2. Mean dose & changes in INR per episode of transfusion indications along-with appropriateness

Tabela 2. Średnie dawki, średnie zmiany wartości wskaźnika INR na transfuzję osocza i prawidłowość stosowania w poszczególnych wskazaniach

Indications	No. of patients (Mean no. of episodes ± S.D)	Mean dose mL/kg (± S.D)	Mean change in INR per episode of plasma (± S.D)	*Appropriateness
Coagulopathy with				
• bleeding	411 (1.98 ± 1.81)	10.9 (± 6.26)	0.41 (± 0.99)	Yes
• no bleeding	150 (2.17 ± 1.94)	10.5 (± 4.95)	0.35 (± 0.67)	No
• invasive procedure	126 (1.62 ± 1.94)	10.6 (± 4.78)	0.22 (± 0.68)	Yes
Prophylactic (Without bleeding and/or coagulopathy)	127 (1.46 ± 1.95)	8.17 (± 7.75)	–0.01 (± 0.13)	No
Low protein state and/or Hypovolemia	175 (3.05 ± 1.94)	10.3 (± 7.74)	#N.A.	No
Reversal of anticoagulants				
• With bleeding	4 (1.50 ± 1.77)	11.8 (± 4.60)	–0.26 (± 0.68)	Yes
• Without bleeding	5 (2.33 ± 1.99)	11.1 (± 3.30)	–0.15 (± 0.73)	No

*Based on Director General of Health Services [DGHS] and British Committee for Standards in Hematology [BCSH] guidelines; #N.A. Not Available

coagulopathy with bleeding (10.9 mL) ($p < 0.001$) (Table 2). Further the given dose was higher (10.93 mL in patients with INR > 3) against patients having INR < 1.5 (9.95 mL). There was statistically significant correlation between the pre-transfusion INR and the dose of plasma used ($p = 0.027$). In six percent (n = 122) of the episodes the exact weight of the patients could not be assessed, we therefore, did not include such cases for the assessment of the appropriateness of the dosage. Total 51% (n = 1002/1960) episodes were given an appropriate dose ranging from 10 to 20 $mLkg^{-1}$ against 45% (n = 888) and 4% (n = 70) episodes of under (< 10 ml kg^{-1}) and over dosages (> 20 ml kg^{-1}) respectively (Fig. 2).

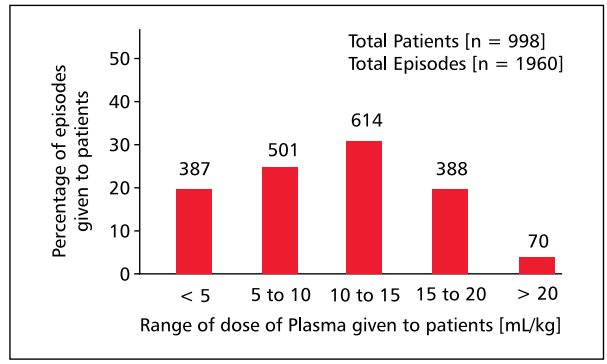

Figure 2. Dosage of Plasma administered to patients according to body weight

Pre and post-coagulation screening tests

PT/INR value within 12 hours preceding FFP transfusions was available in 63% of episodes. The average values were available (Mean value = 36.4/2.64) and varied widely. Post-transfusion PT/INR was available in only 56% of episodes (Mean value = 27.8/2.08). There was statistically significant change in PT/INR after transfusions ($p < 0.001$). Paired-t test was applied to compare means of both pre and post coagulation parameters which showed statistical significant change ($p < 0.001$).

Overall appropriateness based upon guidelines

Total 56% (n = 1169/2082) episodes of plasma indications, 51% episodes of dosage and 63% availability of PT/INR were deemed appropriate (Table 2). Overall 56% episodes of plasma transfusions were in compliance to the guidelines.

Adverse events & mortality

Overall of 0.28% (n = 14/4991) of plasma units transfused were related with adverse reactions. Most were mild allergic (pruritus and urticarial) against one case of transfusion related acute lung injury (TRALI). Death was seen in 7.2% (n = = 72/998) patients primarily associated to massive bleed and DIC following trauma.

Discussion

Several guidelines are published and available as benchmarks for the optimal use of plasma in clinical settings. These recommendations may be

adopted or modified according to clinical needs and constraints of local institutional policies. International guidelines such as The College of American Pathologists (CAP), the British Committee for Standards in Hematology (BCSH) and national guidelines such as Directorate General of Health Services (DGHS) from the ministry of Health and Family Welfare, Government of India are among few to highlight the same. Interventions to change transfusion practices go hand in hand with monitoring of the same since both are considered as the two sides of a coin [5]. The primary motivation of doing this study was to observe the existing transfusion practices for FFP use in clinical settings. In addition examining the dose and indication for transfusion also becomes an important aspect to look at [6]. Segal and Dzik have suggested that the inappropriate plasma orders occur because of three assumptions mainly that the elevation of INR might predict the bleeding in setting of an invasive procedure, prophylactic usage of plasma will correct the prolonged clotting time results and finally with its use fewer bleeding events will occur [7]. Right at the beginning of our study we believed that a well-structured blood requisition form would facilitate us to collect data in a more systematic manner. The degree of completeness of these forms was considered as an important indicator during the data collection phase. The overall compilation was found "good" in 50% of forms. Literature supports that lack of homogeneity of the forms goes on to contribute significantly to the inappropriate transfusion practices. Hui et al. have shown that changes in blood requisition form have a considerable effect on the percentage of appropriateness itself [8].

The coagulation screening tests were not ordered in burn patients since that was considered irrelevant for their management. Other groups of patients where plasma transfusions were judged out-of-specifications (OOS) were prophylactic transfusions (during invasive procedures without any evidence of coagulopathy and/or bleeding). Studies show approximately 30 to 50% of FFP transfusions are prophylactic with or without planned surgeries [9]. This indeed constitutes a significant grey area demanding scientific evidence since there is minimal to no evidence to show benefit of any such prophylactic plasma administrations. Using the recommended dose criteria, only 51% (1002/1960) of episodes depicted an appropriate plasma request. A pilot study conducted at Umbria, Italy showed dosage appropriateness to be 62.7% [10]. Similar study calculated appropriateness based upon indications as 55.6% which is comparable to our results.

Our study showed generalized and widespread irrational usage of plasma across various specialities as a result of which several patients were inadvertently given plasma even when they did not require any. We believe that in an organized system of clinical expertise along with alert group of transfusion medicine residents and technicians, it is possible to achieve high rates of appropriateness for transfusion practices. This often requires guiding the decision of clinicians.

Allergic (urticarial) transfusion reactions are quite commonly reported to be approximately 1% to 3% of all blood transfusions [11]. In our study 0.28% (n = 14/4991) units of plasma transfusion related adverse reactions were reported. Majority were associated with cutaneous manifestations like urticarial rash, pruritus and flushing barring one patient who had symptoms suggestive of TRALI. We further observed that the transfusion reactions as reported by ward nurses were meticulous and prompt. All these adverse events were entered in the national hemovigilance software in accordance with our department protocol.

The present observational study helped us to evaluate the existing transfusion practices by taking a snapshot of 'what is happening and how it is happening'. The current plasma usage at our centre is moderately compliant with the published guidelines. Commonest indications observed for inappropriate use were low protein states and prophylactic use without any evidence of bleeding.

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