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Evaluation of the Appropriateness of Fresh Frozen Plasma Indications and Cost Analysis: A Comprehensive Study

Taze Dondurulmuş Plazma Endikasyonlarının Uygunluğunun Değerlendirilmesi ve Maliyet Analizi: Kapsamlı Bir Çalışma

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Abstract

Objective: Fresh frozen plasma (FFP) has limited indications despite its frequent use. This study aimed to investigate the clinical and laboratory findings of patients who received FFP transfusion. The suitability and effectiveness of transfusion were also examined.

Methods: We retrospectively reviewed the files of patients who underwent FFP transfusion for any reason below the age of 18 years. Transfusion suitability was determined based on the transfusion guidelines.

Results: Two hundred eight FFP transfusions to 134 patients were included in the study. In total, 429 units of FFP were transfused. Of the 208 transfusions, 156 (75%) were appropriate based on indication and 52 (25%) were considered inappropriate. In total, 87 out of the 429 units of the product (20.2%) were transfused inappropriately. None of the patients who received inappropriate transfusions exhibited signs of bleeding. Significant improvements in prothrombin time and activated partial thromboplastin time were observed in patients who received transfusions with appropriate indications.

Conclusion: In this study, the incidence of inappropriate FFP transfusion was lower compared to other centers. However, 3 out of 4 patients received prophylactic FFP for bleeding prevention. The cost of inappropriate transfusions in this study was estimated at $1640 annually. Since transfusion practices are mostly based on adult studies, our study will increase awareness regarding transfusion practices among children. Consequently, there is a need for educational programs that can reduce the rate of FFP transfusions.

Keywords: Fresh frozen plasma, transfusion, suitability, effectiveness, children

Öz

Amaç: Taze donmuş plazma (TDP) sık kullanılmasına rağmen sınırlı endikasyona sahiptir. Bu çalışmanın amacı TDP transfüzyonu yapılan hastaların klinik ve laboratuvar bulgularını araştırmaktır. Ayrıca transfüzyonun uygunluğu ve etkinliği de incelenmiştir.

Yöntem: Herhangi bir nedenle TDP transfüzyonu yapılan 18 yaş altı hastaların dosyaları retrospektif olarak incelendi. Transfüzyon uygunluğu transfüzyon kılavuzuna göre belirlendi.

Bulgular: Çalışmaya 134 hastaya yapılan iki yüz sekiz TDP transfüzyonu dahil edildi. Toplam 429 ünite TDP transfüzyonu yapıldı. Yapılan 208 transfüzyonun 156'sı (%75) endikasyonlara göre uygunken, 52'si (%25) uygunsuz olarak değerlendirildi. Toplam 429 ünite ürünün 87'si (%20,2) uygunsuz olarak transfüze

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Öz

edilmiştir. Uygunsuz transfüzyon yapılan hastaların hiçbirinde kanama belirtisi görülmemiştir. Uygun endikasyonlarla transfüzyon yapılan hastaların protrombin zamanı ve aktive parsiyel tromboplastin zamanı değerlerinde anlamlı iyileşmeler gözlendi.

Sonuç: Bu çalışmada, diğer merkezlere kıyasla uygunsuz TDP transfüzyonu insidansı daha düşüktü. Bununla birlikte, her dört hastadan üçü kanamayı önlemek için profilaktik TFP almıştır. Bu çalışmada uygunsuz transfüzyonların maliyeti yıllık 1640$ olarak hesaplanmıştır. Transfüzyon uygulamaları çoğunlukla yetişkin çalışmalarına dayandığından, çalışmamız farkındalığı artıracaktır.

Anahtar Kelimeler: Taze donmuş plazma, transfüzyon, uygunluk, etkinlik, çocuklar

Introduction

Fresh frozen plasma (FFP) is a component of blood that contains coagulation factors, antibodies, electrolytes, and plasma proteins. FFP transfusion is commonly used for the treatment of bleeding disorders or hemostasis in patients at high bleeding risk. It is important to note that FFP transfusion should be performed based on careful consideration of each patient's clinical condition, laboratory values, and specific needs. The decision to administer FFP should be made by healthcare professionals following appropriate guidelines and protocols[1,2]. The number of regular, voluntary blood donors in our country is below the national level. Therefore, the acquisition of blood products is difficult and costly. The unnecessary use of blood products not only poses risks of side effects but also contributes to the early depletion of high-cost products that are difficult to obtain. The indications for FFP transfusion are notably limited. Similar to other blood components, FFP has the potential for transfusion reactions and infection risks.

Materials and Methods

The medical records of patients aged 18 years and younger who received TFP transfusion at the University of Health Sciences Turkey, Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital were retrospectively evaluated. The suitability of transfusion indications was determined according to the transfusion guidelines[3,4]. The FFP dose was adjusted according to the patient's weight[1,3].

Clinical and demographic characteristics of the patient (gender, age, blood type, diagnosis), clinical department where the patient was hospitalized, indication for hospitalization, and coagulation parameters were recorded.

The indication for FFP administration, acute reactions, and post-transfusion laboratory values specific to the patient were documented. According to the Turkish Healthcare Practice Directive, the total cost of FFP transfusions performed with inappropriate indications was calculated, with each unit of FFP priced at 18.85 USD.

This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital. Ethics committee approval number and date: 2017/08-05, 08/06/2017. Informed consent was not obtained as this was a retrospective study.

Statistical Analysis

Data were analyzed using SPSS software. Normality was checked via the Shapiro-Wilk test. For normally distributed data, mean ± standard deviation was presented; for non-normal data, median (IQR) was used. Categorical variables were compared with the chi-square or Fisher's exact test, while continuous variables were analyzed using independent t-tests or Mann-Whitney U tests. ANOVA or Kruskal-Wallis tests were used for comparisons across multiple groups, with post-hoc tests as needed. Statistical significance was set at $p<0.05$.

Results

A total of 208 FFP transfusions were included in our study, including 134 patients. Among the 134 patients, 55 (41%) were female, and 79 (59%) were male, with a median age of 1 years (minimum: 1 month-maximum: 18 years). Of the patients, 52 (38.8%) were from surgical departments (30 from cardiovascular surgery and 22 from pediatric surgery), whereas 82 (61.2%) were from pediatric services (neonatal intensive care 31). In total, 429 units of FFP were administered, with 165 units (38.5%) administered in surgical clinics and 264 units (61.5%) administered in pediatric clinics.

Of the 208 transfusions administered, 156 (75%) were classified as appropriate based on the defined criteria, whereas 52 (25%) were categorized as inappropriate (Table 1). Regarding the total product units, 20.2% (87/429 units)

was transfused inappropriately (Table 2). It was observed that there was a significantly higher rate of inappropriate transfusions in surgical departments compared with internal medicine clinics (p=0.001).

Among the eight inappropriate transfusions in internal medicine clinics, four showed disseminated intravascular coagulation without bleeding, and two exhibited prolonged coagulation parameters. None of the patients who received inappropriately transfused FFP at internal medicine clinics presented with bleeding symptoms. In surgical departments, out of the 44 inappropriate transfusions, 34 (77.2%) were performed during surgeries, nine (20.5%) were due to coagulation disorders, and one (2.7%) was classified as "other". None of the patients who received inappropriate transfusions at the surgical branches showed signs of bleeding.

In terms of appropriate transfusions, pre- and post-transfusion values of prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer were evaluated, revealing no significant differences in D-dimer and fibrinogen, whereas pre-transfusion PT and aPTT values were found to be longer. No significant differences were found in all evaluated coagulation parameters before and after inappropriate transfusions (Table 3, 4).

Patients who received the highest number of FFP transfusions were those diagnosed with sepsis and those undergoing preoperative preparation. When examining the coagulation parameters of patients with sepsis, a significant decrease in the pre-transfusion PT median value from 18.0 to 15.9 s was observed after transfusion (p=0.001). Likewise, pre-transfusion aPTT decreased from 36.1 to 34.3 after transfusion (p=0.001). No complications related to transfusion were

Table 1. The number of appropriate transfusions and the amount of product used

	Number of transfusions	Amount of product used (units)
Preoperative preparation	37 (23.9%)	98 (28.9%)
Coagulation disorder + bleeding	14 (9.0%)	33 (9.8%)
DIC + bleeding	94 (59.9%)	197 (57.9%)
Massive transfusion and blood exchange	9 (5.8%)	9 (2.8%)
Liver failure	1 (0.7%)	1 (0.3%)
TTP	1 (0.7%)	1 (0.3%)
Total	156 (100%)	342 (100%)

DIC: Disseminated intravascular coagulation, TTP: Thrombotic thrombocytopenic purpura

Table 2. Inappropriate fresh frozen plasma transfusions and the amount of product used

	Number of transfusions	Amount of product used (units)
Preoperative preparation	34 (65.4%)	48 (55.1%)
Burn diagnosis	11 (21.2%)	25 (28.8%)
Sepsis	7 (13.4%)	14 (13.1%)
Total	52 (100%)	87 (100%)

Table 3. Pre and post-transfusion coagulation parameters in transfusions with appropriate transfusion indications

	BT	AT	p
PT Median (min-max)	19.0 (11.2-60)	16.6 (8-54.6)	**0.001**
aPTT Median (min-max)	39.5 (20.3-109.8)	34.3 (20.6-80)	**0.001**
D-dimer Median (min-max)	1784 (72-43433)	1752 (72-42213)	0.860
Fibrinogen Median (min-max)	188 (42-751)	185 (36-835)	0.362

BT: Before transfusion, AT: After transfusion, PT: Prothrombin time, aPTT: Activated prothrombin time

Table 4. Pre and post-transfusion coagulation parameters in transfusions with inappropriate transfusion indications

	BT	AT	p
PT Median (min-max)	12.7 (10.5-20.4)	13.8 (10.7-17.9)	0.777
aPTT Median (min-max)	32.5 (24-41.4)	32.0 (26.9-41)	0.469
D-dimer median (min-max)	931 (122-6787)	762.5 (303-4915)	0.674
Fibrinogen Median (min-max)	210 (98-523)	261 (132-336)	0.735

BT: Before transfusion, AT: After transfusion, PT: Prothrombin time, aPTT: Activated prothrombin time

observed. A significant decrease in PT and aPTT values was detected in the majority of patients who received FFP transfusion with appropriate indications compared with pre-transfusion values, indicating effective improvement of laboratory findings with appropriate FFP transfusion.

Discussion

FFP is used for both prophylactic (prevention of bleeding) and therapeutic (stopping bleeding) purposes. Despite the specified indications for FFP in national guidelines, clinical practice can vary significantly[5]. Inappropriate usage rates can reach 50%[6]. Non-evidence-based uses were reported approximately 30 years ago[7-9]. In this study, we evaluated the rates and distributions of transfusions performed outside the indications of FFP transfusion according to the national transfusion guidelines at our center.

FFP transfusion is most commonly used in surgical, intensive care, and hematology services[10]. In our study, transfusions were predominantly performed in pediatric and neonatal intensive care units (n=89), surgical services (n=44), and hematology services (n=27).

In this study, the rate of inappropriate FFP transfusion was 25%. This rate was found to be similar to our study (21%) in the study conducted by Moiz et al.[11], whereas Kakkar et al.[12] reported a rate of 60.3%.

In certain centers, a significant variation in this rate is observed, encompassing a wide range from 37% to 73%. [13,14]. In a study conducted by Camkurt et al.[15]. In our country in 2011, the rate was found to be 67% among 204 patients. Another study emphasized that this rate could be reduced through educational programs[16]. Kakkar et al.[12] demonstrated that this rate decreased to 26.6% with educational campaigns targeting clinicians.

In our center, inappropriate FFP transfusions were most commonly observed in the following order: Preoperative preparation (n=34), burn cases (n=11), and sepsis cases (n=7). A study conducted by Camkurt et al.[15] reported that the most frequent indication for FFP transfusion was correction of elevated ınternational normalized ratio (INR).

In our study, however, none of the patients received FFP transfusion specifically to correct INR prolongation.

This finding is believed to be associated with a lower rate of warfarin use among pediatric patients.

In a study by Moiz et al.[11], the most common inappropriate transfusions occurred in patients undergoing bypass surgery without bleeding, liver disease, or coagulation disorders.

Furthermore, their study identified cases in which FFP transfusion was administered without clear indications[11].

In our study, only one patient with liver failure received an inappropriate transfusion: FFP was administered prophylactically prior to an invasive procedure. It is recommended to consider FFP transfusion in cases of liver failure with bleeding and abnormal coagulation parameters before invasive procedures[17].

To prevent unnecessary transfusions, thromboelastography is recommended. However, our retrospective study did not include thromboelastography data.

Preoperative preparation accounted for the majority of inappropriate FFP transfusions at our center. However, it has been shown that even in high-risk surgeries involving significant bleeding, such as cardiac bypass procedures, FFP transfusion does not contribute to a difference in the amount of blood lost during or after the surgery[18].

Burns were ranked second as a frequent cause of inappropriate transfusions. Transfusions were inappropriate for all 11 burn patients. Although a study conducted in the UK in 2007 suggested that toxic shock syndrome-related mortality could occur in pediatric patients even in minor burns, and FFP could be administered to support passive immunization[19], such indications are not present in the national blood transfusion guidelines[20]. Furthermore, it is emphasized that FFP should not be used as a substitute for immunoglobulin, as stated in 1992[21].

In this study, preoperative FFP administered with appropriate indications accounted for 28.7% (98/342) of the total number of FFP units. On the other hand, in a study by Moiz et al.[11], the utilization rate of FFP with appropriate indications preoperatively was 13.2%. However, the rate of invasive procedures increased to 35.6%. In our center, the rate of inappropriate FFP use preoperatively accounted for 14% of the total FFP units. Comparatively, in the study by Moiz et al.[11] even though the study focused solely on cardiac bypass surgeries, the rate of inappropriate FFP use was significantly lower compared with our center (4.6%).

In our center, the rate of inappropriate FFP use was found to be significantly low (2/55) in the pediatric intensive care unit, where the highest number of FFP transfusions was administered. Reiter et al.[22], in a study focusing solely on intensive care units published in 2013, reported that one-third of transfused FFP units were administered without appropriate indications, indicating a high rate of inappropriate use. In that study, the use of FFP was considered inappropriate unless there were abnormal coagulation parameters accompanied by bleeding or prophylactic use prior to procedures[22]. It is recommended to avoid transfusion for mild coagulation abnormalities during minimally bleeding invasive procedures in intensive care units to reduce the number of FFP transfusions[23]. Some studies have shown an association between FFP transfusion volume, mortality scoring systems, and length of stay in intensive care units. Therefore, evaluating FFP utilization in conjunction with mortality scoring systems may enhance the effectiveness of FFP use from a clinical perspective[20]. Additionally, it is known that 25% of coagulation abnormalities in intensive care units are due to vitamin K deficiency[24]. Pybus et al.[25] suggested that regular use of vitamin K in intensive care units can reduce the need for FFP transfusions. However, we did not evaluate the extent of improvement with vitamin K supplementation in patients with coagulation abnormalities or those in whom FFP transfusion was not performed in our intensive care unit.

In our study, 28% of the FFP transfusions were performed in the neonatal intensive care unit. Similarly, in a study conducted by Puetz et al.[23], neonatal patients accounted for 29% of the pediatric group. In the same study, prophylactic FFP was administered to 63% of neonatal patients without bleeding. In our study, this percentage was slightly higher at 75%. Factors such as the association between FFP transfusion and a lower incidence of retinopathy of prematurity[26] may influence the decision for higher transfusion rates. However, further studies are needed to explore this association.

Massive transfusion in children is defined as the transfusion of blood components equal to one or more blood volumes within a 24-hour period or half of the blood volume within 12 hours[27]. Neff et al.[28] defined massive blood transfusion as a situation in which all blood products given at any time during the first 24 hours exceeded the threshold of 40 mL/kg. Exchange transfusion in neonates is one of the situations in which massive blood transfusion is seen.

In our study, nine massive transfusions were performed in the neonatal intensive care unit as exchange transfusions. The approximate ratio of FFP to red blood cell suspension used in each exchange transfusion was approximately 1:2, which is consistent with the recommended ratio for massive transfusions. Studies have not demonstrated the superiority of a 1:1 ratio of FFP to red blood cell suspension over a 1:2 ratio in massive transfusions[29].

In our center, coagulation parameters were evaluated in nearly all patients following FFP transfusion. In a study conducted by Pybus et al.[25], the evaluation of coagulation parameters after transfusion was performed in only 34.5% of cases.

Improvements in aPTT and PT were observed in patients who received FFP transfusion with appropriate indications, whereas no significant differences were found in fibrinogen and D-dimer levels pre- and post-transfusion. In patients who received FFP transfusion with inappropriate indications, no significant differences in any of the coagulation parameters were observed between pre- and post-transfusion values. In a study by Motta et al.[30] that focused on the neonatal age group, significant shortening of PT and aPTT values was interpreted as an effective dose being administered based on pre-transfusion values. In our study, significant shortening of aPTT and PT values, especially in patients diagnosed with

sepsis and those who received transfusion with appropriate indications, suggests that an adequate amount of FFP was transfused.

No transfusion reactions were observed during FFP transfusions in our study. In line with our findings, Camkurt et al.[15] also reported the absence of transfusion reactions during FFP transfusions in their study. However, enhancing awareness and reducing the rate of inappropriate transfusions. In addition to transfusion reactions, FFP transfusion has been shown to increase the systemic inflammatory response in relation to the volume of the transfused product[31] and does not correct for coagulation abnormalities in critically ill patients. Furthermore, higher FFP transfusion rates were associated with increased mortality. Despite the knowledge that FFP transfusion is not effective and not recommended in many clinical scenarios, inappropriate usage continues to persist, as highlighted in several studies[23]. Moreover, it has been suggested in multiple studies that FFP transfusion should not be performed for mild prolongation of coagulation parameters[32-34]. Specifically, when the INR value is below 1.7, FFP administration has been shown to have no laboratory correction effect[35].

Moreover, considering that 20.2% of the product volume was transfused inappropriately, the cost of inappropriate FFP transfusions was calculated to be $1640 within 1 year. Each inappropriate transfusion not only carries the risks associated with transfusion but also results in a significant loss of labor and material resources during product procurement. Therefore, it is evident that improvement efforts would also provide financial benefits.

The lack of calculation of the administered FFP dose was a limiting factor in evaluating the effectiveness of transfusion in terms of dose in our study. Additionally, not considering the prematurity status and the number of days of life in the evaluation of patients transfused in the neonatal intensive care unit suggested the need for a separate study specifically focusing on this age group.

Conclusion

Considering that existing knowledge regarding transfusion practice is mostly based on studies conducted in adults, we believe that this study, which focused on the pediatric age group, will contribute to raising awareness regarding TDP transfusion practice. This, in turn, can facilitate the implementation of targeted educational programs designed to achieve defined transfusion goals.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital. Ethics committee approval number and date: 2017/08-05, 08/06/2017.

Informed Consent: Informed consent was not obtained as this was a retrospective study

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.G., Y.O., Concept: Y.G., Y.O., Design: Y.G., Y.O., C.V., Data Collection or Processing: Y.G., Analysis or Interpretation: Y.G., Y.O., Literature Search: Y.G., Y.O., Writing: Y.G., Y.O., C.V.

Conflict of Interest: No conflict of interest was declared by the authors.

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