«Original Articles »

Role of Fresh Frozen Plasma Transfusion in Prevention of Brain Contusion Enlargement in Patients Following Head Trauma

Salehe Rasras[1], Fardin Ranjbar[1]*

1-Neurosurgery Department Group, Ahvaz Jundishapur University of Medical science, Ahvaz, Iran.

Abstract

Background: Hemorrhagic progression of a contusion (HPC) is one of the main problems in neurosurgery, which is associated with several adverse effects and increasing the risk of mortality. The present study investigated the effect of transfusion of fresh frozen plasma (FFP) in the prevention of HPC.

Material and methods: In this randomized clinical trial, 100 patients with cerebral contusion were divided into two control and FFP groups. The patients received placebo or FFP after one week admitting to ICU. Contusion level of Glascow Coma Scale (GCS) was determined both on arrivals at the hospital, and after a month. Moreover, the duration of stay in ICU and hospital, mortality and other complications were recorded and the data were compared between the two groups.

Results: Contusion level was significantly increased in both groups, but there was no significant difference between the two groups ($P>0.05$). GCS also improved in both groups after one month, but no significant difference was found between the two groups. The duration of stay in the ICU (13±2.5 days vs. 9.8±2.4 days) and hospital (18.1±2.6 days vs. 13.5±3.3 days) was significantly higher in the control group ($P<0.0001$). Mortality (6% in the FFP group and 10% in control group) and complication rates were similar in both groups ($P>0.05$).

Conclusion: It seems that FFP transfusion has no effect in preventing HPC and mortality, but may lead to a reduction of ICU and hospital staying duration.

Keywords: Cerebral contusion, fresh frozen plasma, hemorrhagic progression of a contusion (HPC)

***Corresponding Author:**
Fardin Ranjbar; Neurosurgery Department Group, Ahvaz Jundishapur University of Medical science, Ahvaz, Iran.
Tel: 0917-315-2275
Email: Ranjbar_Fardin@yahoo.com

►*Please cite this paper as:*
Role of Fresh Frozen Plasma Transfusion in Prevention of Brain Contusion Enlargement in Patients Following Head Trauma. Jentashapir J Health Res 2014; 5(2):37-44

Received: 02.04.2013 **Accepted: 29.05.2013**

Introduction

Traumatic brain injury (TBI) as a severe head trauma with GCS (Glasgow Coma Scale) is defined between 3 to 8 (1) and is considered as one of the most debilitating and challenging problems in emergency centers (2,3). TBI often leads to severe physical, cognitive, behavioral and emotional damages, which may affect a patient throughout the life (4-6). In the United States of America around 2.5 million people suffer from traumatic brain injuries, 350,000 of which need hospitalization due to the severity of the brain damage (7). Almost half of those who survive suffer from disability caused by the injury throughout the life (5,6,8). In the United States the costs of TBI impact throughout life (including health care costs and costs arising from not being able to work and produce), is estimated at $60 billion annually, which alone imposes one of the biggest financial pressure on healthcare system (6-4). Although there is no measured information on the incidence of such injuries in Iran, there are reports indicating that the prevalence and severity of traumatic brain injury is growing in the country (7).

TBI includes a variety of severe brain injuries of which hemorrhagic contusion of the brain is one of the most important and most fundamental ones (3). In fact, the TBI with cerebral contusion is one of the major causes of mortality and disability in trauma victims who reach to the hospital alive (9). Unfortunately contusion is along with hemorrhagic outgrowing as a secondary damage and due to subsequent bleeding, causes progressive brain damage. This situation severely worsens the patient's condition in a few hours to several days after the initial event, and when at hospital (3). Regarding the risks and consequences resulted from outgrowing of hemorrhagic contusion, great efforts are made to prevent the incidence of this phenomenon in patients with severe TBI (7); however available statistics show that these efforts and approaches had not desirable and successful outcomes.

Recently, Acute Traumatic Coagulopathy (ATC) has been identified as a key factor in stimulating continuous bleeding after trauma (10). Current rehabilitation protocols using crystalloid and RBC transfusion may not be effective in control of bleeding along with ATC (11). For this reason, many researchers have stated that in early stages after trauma, fresh frozen plasma (FFP) should be used immediately to inhibit ATC (12).

Although there is conflicting information about the efficacy of FFP in the control of ATC due to using improper methods to conduct proper studies, there are several retrospective studies supporting the effect of FFP transfusion along with RBC with determined ratios in first 24 hours after admission to a hospital (11-14). However, several other studies have shown that the effect of RBC transfusion along with FFP had no effect on the outcome of treatment in patients with trauma or patients admitted to the ICU (15-19). However, to our best knowledge, there are still fundamental disagreements about the effectiveness and efficiency of FFP transfusion in patients with trauma specifically head trauma. On the other hand, patients with head trauma are highly susceptible to severe coagulation disorders and it is reported that the occurrence of these disorders was greater than 22.7% when transferring a patient to the emergency room (20). That's why finding an approach to control these clotting disorders seems vital. In patients with TBI thromboplastin is locally released in tissue and the number of platelets is reduced (12). Considering the necessity of contusion progression preventing in patients with TBI and lack of efficacy in the current approaches and also regarding the information gap on the impact of FFP injection, the present study was conducted to investigate the issue and acquire more information in this regard.

Material and methods

In this randomized clinical trial, 100 patients with head trauma resulting in brain contusion admitted to and under treatment plans in Golestan Hospital in Ahvaz, Iran, participated after completing a consent form by patient or their parents. This study is from the project U-91095 approved by Research Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences with the following reference: ETH-555.

The exclusion criteria in this study included: the complications resulted from this study, dying within first 48 hours after admission, the need for emergency craniotomy within the first 48 hours after admission due to severe contusion enlargement, the existence of life-threatening injuries such as severe trauma to the chest or abdomen, chronic diseases of pulmonary, cardiovascular, hepatic or renal, and a history of allergy to FFP and pregnancy. In this study non-randomized sampling and simple method was used. In a randomization method, the first subject was devoted to FFP group and the second one to the control group and this procedure continued until the number of samples was completed.

First, patients with head trauma and cerebral contusion transported to the hospital emergency unit, were examined clinically. After recovery and stabilization of the patient's condition, CT scan was performed and based on the lesion size observed in CT, the patients either were transferred or admitted to the ICU, or were placed under a craniotomy, and were admitted to the ICU. If the contusion level was greater than 20 cc based on CT and intraventricular pressure (ICP) was increased, patients were subjected to surgery. Before transferring the patients into the ICU, their GCS levels were determined and the contusion level was recorded based on CT. Patients were randomly assigned to two groups. In one group, patients admitted in the ICU, were daily given 4 units of FFP regardless of the PT and PTT. In the other group, patients received normal saline with the same amount. Patients received FFP and saline for one week, and then after seven days of hospitalization in the ICU, they were reevaluated using CT. The number of days staying in the ICU and hospital were recorded for all the patients. The incidence of any complication resulted from transfusion including symptomatic DVT, gastrointestinal bleeding, fever and mortality rate were recorded in each group. Patients were reexamined one month later. In this visit, GCS levels were determined again and patients were reevaluated using CT to determine the final levels of contusion. Finally, after collecting the required data, all were statistically analyzed.

In this study, quantitative data were presented as mean ±SD and qualitative data as numbers and percentages. To compare quantitative data between the two groups, independent *t*-test and Mann-Whitney U test were used. To compare quantitative data before and after the study, paired *t*-test and the Wilcoxon test were used. Qualitative data were compared between the two groups using the Pearson's chi-squared test and Fisher's exact test. All statistical analyses were performed using statistical software SPSS ver.16. In this study, $P<0.05$ was considered as significant.

Results

Mean age of patients in both FFP and control groups were respectively 33.1±9.4 (20-55 years) and 36.4±10.2 years (21-58 years), which were statistically similar (P=0.09). In FFP group, there were 37 men and 13 women, this was respectively 32 and 18 in the control group, with no significant difference between the two groups (P=0.028).

In this study, the cerebral contusion level was measured using CT and it was found that the contusion level pre and post treatment and also the contusion changes rate between the two groups were similar,

but the contusion level was significantly increased in both groups (Table 1).

Moreover, the GCS level of patients was measured at admission to the hospital and before and after one month of transfusion and compared between the two groups. It was revealed that there was no difference between the two groups. However, the GCS level was significantly increased within both groups (Table 1). It was also found that the duration of staying in the ICU and at hospital was significantly lower in FFP group than the control group (Table 1).

In FFP group, 3 patients (6%) and in the control group 5 patients (10%) died with no significant difference between the two groups (P=0.715). The studied complications in this study involved DVT, fever and gastrointestinal bleeding which showed no significant difference between the two groups (Table 2).

Table 1. Comparison of contusion and GCS levels between the two groups and within groups' pre and post treatment and the duration of staying in the ICU and hospital

		Control group (n=50)	FFP group (n=50)	P value
Contusion level (cc)	Baseline			
	Post one month			
	Within group comparison			
GCS	Contusion change rate			
	Baseline			
	Post one month			
	Within group comparison			
Duration of staying in the ICU				
Duration of staying in the hospital				

Table 2. Comparison of the mortality rate and other complication between the two groups

Group			
Mortality			
Side complications (Total)			
Individual complications	DVT		
	Fever		
	Gastrointestinal bleeding		

Discussion

The most important finding of this study was that in patients with cerebral contusion FFP transfusion did not affect the prevention of progression and increased the contusion level and GCS improvement. In addition, mortality and complication rates were similar in the two groups and no significant differences were found between the two groups.

HPC is a common phenomenon leading to conditions worsening in patients with head trauma and may increase the risk of mortality rate and long disability (3). Blood is one of the most toxic fluids which can be exposed to the brain and that is why HPC can have harm and destructive severe effects on this tissue and its function. In fact, the amount of destruction and injury to brain tissue following head trauma depends on two factors. The first is the injury to head that causes the bruise of brain tissue and injury to blood vessels and a simultaneous stoke. The second factor is a secondary process developed in response to trauma and early injury, which generally worsen the patient's condition and increase the extent of the lesion. For this reason, one of the major concerns of treatment plan on patients with head trauma can be to prevent progression of hemorrhagic contusion which remains a major challenge for surgeons and neurologists despite all the efforts to prevent it such as Recombinant factor VIIa (rFVIIa).

FFP which is the liquid part of blood contains the stable and unstable components of blood coagulation, complement and fibrinolytic systems, proteins which are responsible for maintaining the oncotic pressure and regulate the immune system and other proteins which have several functions. In addition, fats, minerals and carbohydrates are found in FFP with a density similar to that in the blood. There are limited indications for the use of FFP in single or combined coagulation disorders (mainly coagulation protein defects include replacing deficient clotting factors II, V, VII, IX, X and XI, excessive blood transfusion, returning the effects of warfarin to normal condition, deficiency of antithrombin III, immune system problems and treatment of Thrombotic Thrombocytopenic Purpura.

FFP contains two important clotting factors V and factor VIII. Since patients with trauma are affected by ATC (10), it seems that FFP can be very efficient and helpful in preventing bleeding in these patients. However, the results of studies currently available on FFP transfusion in trauma patients are highly inconsistent and diverse. Gonzalez et al. (2007) investigated the records of patients with trauma admitted to ICU in a retrospective study, and indicated that the current protocols of treatment of acidosis and hypothermia would be very useful, but the main problem is to control bleeding in these individuals. They indicated that finding a proper approach to prevent bleeding may be very efficient and suitable in reduction of need to RBC and subsequently reduction of the mortality rate. Finally they suggested that the transfusion protocol before transferring the patient to the ICU should involve RBC and FFP with 1 to 1 ratio, which probably would be very efficient in preventing bleeding and improvement of the outcome of treatment (11).

Holcomb and his colleagues conducted a retrospective study to investigate whether or not the hypothesis that the increased ratio of plasma transfusion and platelet to RBC can improve the results of treatment in patients with trauma. In this regard, they studied the hospital records of 467 patients and concluded that the role of plasma and platelet are widely ignored in transfusion protocols and suggested that if this ratio increased by 1 to 1 against the RBC transfusion, the outcome of treatment would be very ideal (14).

Mitra et al. (2010) investigated the effects of FFP transfusion in patients with trauma

who received severe blood transfusion (5 units or more within early 4 hrs) at recovery, and concluded that their study showed that the early survival of patients increased due to transfusion with higher ratio of FFP: RBC. However, they indicated that the more ideal ratio of transfusion of FFP: RBC may be different from the ratio of 1:1 and suggested that further studies are needed to clarify this issue. Furthermore, they stated that there would be an urgent need for further clinical trials to determine the appropriate ratio of FFP: RBC (13).

Moreover, Peiniger and colleagues (2011) investigated the effectiveness of adjunctive RBC and FFP transfusion with the ratio of 1:2 in patients with multiple trauma and head trauma. In this retrospective study, patients with severe trauma who needed severe transfusion were divided based on TBI and the ratio of transfusion FFP: RBC and the mortality and morbidity rates were compared among patients in two groups. After collecting the data, the researchers found that the mortality rate was significantly lower in patients with higher ratio of transfusion of FFP: RBC (>1:2) than in the group with low transfusion ratio (≤1:2). Regarding the incidence of multiple organ failure and sepsis, there was no significant difference between the groups. Finally, the authors stated that despite the uncertainties, their study showed that if the ratio of transfusion FFP: RBC was higher, the mortality rate could have an important role in reducing mortality in patients with trauma and the presence or absence of TBI has no effect on the issue (12).

Although these studies support the positive effects and performance of FFP transfusion in patients with trauma, there are other studies that do not support the FFP transfusion and suggest that it has no effect on the treatment outcome. For example, Dara et al. in a retrospective cohort study investigated the effect of FFP transfusion in critically ill patients with coagulopathy. All patients were suffering from blood coagulation disorders which were defined as INR 1.5 or greater than 1.5 of normal amount and these patients were not actively bleeding. Overall, 44 patients (38.8 %), received FFP. The INR were improved in 16 of these patients (36%). Median dose of FFP in patients with improvement of INR was 17 mL/kg and in patients with no improvement of INR was 10 mL/kg and the difference was statistically significant in both groups (P=0.018). No significant differences were found regarding the age, sex, criteria of APACHE III, hepatic disorder, treatment of Coumadin and INR levels in patients who received FFP compared with the other patients. However, invasive procedures (68.2% vs.40.8%; P=0.004) and a history of recent gastrointestinal bleeding (41% vs. 40.8% 7; P=0.004) were significantly greater in the group who had received FFP. Although in this study there was no difference between the two groups in respect to the new bleeding episodes, but new starting of acute lung injury were significantly higher in patients in FFP group (18% vs. 4% ; P= 0.021). Moreover, the duration of staying in ICU and hospital and mortality rates was similar in both groups. Dara and her colleagues concluded that the risk-benefit ration of FFP transfusion in critically ill patients with coagulopathy may not be desirable; however, there is a need to conduct randomized clinical trials which would compare the use of restrictive and liberal transfusion FFP (15).

Furthermore, Gajic and colleagues, in a review article investigated the impact of FFP and platelet transfusion in the treatment of patients without bleeding admitted to the ICU and concluded that although the beneficial results and positive effects of transfusion of FFP were suggested in some studies, the liberal use of FFP transfusion in ill patients was not optimal due to the risk-benefit ratio, and needed to do further clinical trials to evaluate the benefits and harms of FFP transfusion with liberal and limited use in

such patients (17). Mitra and colleagues in another retrospective study (2012), stated that FFP transfusion in patients with trauma had no significant impact on improving the results of treatment. They also indicated that FFP transfusion has its own risks and hazards and imposes significant costs on an individual and system. In addition, further studies to determine the suitable ratio of FFP: RBC transfusions are required (19).

Kashuk et al. (2008) in a retrospective study investigated the efficacy of FFP and RBC transfusion with the ratio of 1:1 within the first 6 hours after the accident in preventing or improvement of coagulopathy resulting to the patient's death. After data collection, the researchers concluded that although transfusion of FFP to RBC ratio of 1:1 can reduce coagulopathy, it cannot improve survival and reduce mortality rate in patients. They indicated that their findings show that the relationship between coagulopathy and mortality is complicated and further investigation is needed to recommend the routine use of this recovery regime (16). Zehtabchi and Nishijima (2009) reviewed the existing literature on the efficacy of FFP and RBC transfusion ratio of 1:1 on mortality rate in patients with trauma, and stated that although three retrospective studies and one cohort prospective study support the positive effects of FFP transfusion, in addition to methodological problems in these studies, such limited studies cannot provide enough evidence to confirm or deny the use of FFP in patients with trauma (21).

As it is seen, in general, there are significant disagreements regarding the use of FFP in recovery protocols for patients with trauma. Yet, the use of FFP may not be a suitable approach as there is no proper medical and alternative treatments to it, and as patients with severe bleeding and clotting defects undergo critical conditions.

In this randomized clinical trial study we investigated the effects of FFP transfusion in preventing contusion level in patients with cerebral trauma. Although there are some studies on FFP transfusion in these patients, to our best knowledge, the present study is the first randomized clinical trial investigating the effect of FFP transfusion in preventing contusion level. Generally, in this study, it was found that FFP cannot prevent HPC at all or even reduce its rate. In fact, in this study, the contusion level and its changes were similar in two groups, pre and post treatment. Moreover, there was no significant difference between FFP and placebo group regarding the GCS level, mortality rate and other complications. However, the notable finding of this study was that both the duration of staying in the ICU and the total number of days staying in the hospital were significantly lower in the FFP group than in the placebo group. This may be due to the positive effects of FFP transfusion in patients with cerebral contusion in some extent, the mechanism of which is not clear, though. In this study, we investigated two age, sex, initial contusion level and GCS level- matched groups and compared them, consequently, it is suggested that the observed effects on reducing the duration of staying in the ICU and hospital may be strongly due to FFP transfusion.

The present study had some limitations as in the other studies. The most important limitation of this study was that the ratio of FFP: RBC transfusion was not considered, while some retrospective studies indicated that increasing the FFP ratio can have desirable outcomes.

The findings of this study showed that in patients with cerebral contusion the FFP transfusion does not affect preventing HPC and increasing the contusion level and the mortality rate, however it can significantly reduce the duration of staying in the ICU and hospital. Furthermore, concerning the higher costs of FFP contusion, the recommendations on using

this blood product in recovery of patients with cerebral trauma depends on its cost and economical cost due to reduction of the duration of staying in the ICU and hospital. In addition, further cohort and randomized studies are required to evaluate the effects of FFP.

Acknowledgments

The researchers would like to extend their special thanks to Development Unit of Clinical Research of Golestan Hospital and Mrs. Molook Salemzadeh for all their efforts. This article is issued from assistance thesis of Dr Fardin Ranjbar, the assistant of neurosurgery.

References

1-Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974; 2(7872):81-4.
2-Haddad SH, Arabi YM. Critical care management of severe traumatic brain injury in adults. Scand J Trauma Resusc Emerg Med 2012; 20:12.
3-Kurland D, Hong C, Aarabi B, Gerzanich V, Simard JM. Hemorrhagic progression of a contusion after traumatic brain injury: a review. J Neurotrauma 2012; 29(1):19-31.
4-Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil 2006; 21(5):375-8.
5-Selassie AW, Zaloshnja E, Langlois JA, Miller T, Jones P, Steiner C. Incidence of long-term disability following traumatic brain injury hospitalization, United States, 2003. J Head Trauma Rehabil 2008; 23(2):123-31.
6-Thurman DJ, Alverson C, Dunn KA, Guerrero J, Sniezek JE. Traumatic brain injury in the United States: A public health perspective. J Head Trauma Rehabil 1999; 14(6):602-15.
7-Rao V, Lyketsos CG. Psychiatric aspects of traumatic brain injury. Psychiatr Clin North Am 2002; 25(1):43-69.
8-Zaloshnja E, Miller T, Langlois JA, Selassie AW. Prevalence of long-term disability from traumatic brain injury in the civilian population of the United States, 2005. J Head Trauma Rehabil 2008; 23(6):394-400.
9-Alahmadi H, Vachhrajani S, Cusimano MD. The natural history of brain contusion: an analysis of radiological and clinical progression. J Neurosurg 2010;112(5):1139-45.
10-Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003; 54(6):1127-30.
11-Gonzalez EA, Moore FA, Holcomb JB, Miller CC, Kozar RA, Todd SR, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. J Trauma 2007; 62(1):112-9.
12-Peiniger S, Nienaber U, Lefering R, Braun M, Wafaisade A, Wutzler S, et al. Balanced massive transfusion ratios in multiple injury patients with traumatic brain injury. Crit Care 2011; 15(1):R68.
13- Mitra B, Mori A, Cameron PA, Fitzgerald M, Paul E, Street A. Fresh frozen plasma (FFP) use during massive blood transfusion in trauma resuscitation. Injury 2010; 41(1):35-9.
14-Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008; 248(3):447-58.
15-Dara SI, Rana R, Afessa B, Moore SB, Gajic O. Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy. Crit Care Med 2005; 33(11):2667-71.
16-Kashuk JL, Moore EE, Johnson JL, Haenel J, Wilson M, Moore JB, et al. Postinjury life threatening coagulopathy: is 1:1 fresh frozen plasma:packed red blood cells the answer? J Trauma 2008; 65(2):261-70.
17-Gajic O, Dzik WH, Toy P. Fresh frozen plasma and platelet transfusion for nonbleeding patients in the intensive care unit: benefit or harm? Crit Care Med 2006; 34(5 Suppl):S170-3.
18-Sperry JL, Ochoa JB, Gunn SR, Alarcon LH, Minei JP, Cuschieri J, et al. An FFP: PRBC transfusion ratio >/=1:1.5 is associated with a lower risk of mortality after massive transfusion. J Trauma 2008; 65(5):986-93.
19-Mitra B, Cameron PA, Gruen RL. Aggressive fresh frozen plasma (FFP) with massive blood transfusion in the absence of acute traumatic coagulopathy. Injury 2012; 43(1):33-7.
20-Wafaisade A, Lefering R, Tjardes T, Wutzler S, Simanski C, Paffrath T, et al. Acute coagulopathy in isolated blunt traumatic brain injury. Neurocrit Care 2010; 12(2):211-9.
21-Zehtabchi S, Nishijima DK. Impact of transfusion of fresh-frozen plasma and packed red blood cells in a 1:1 ratio on survival of emergency department patients with severe trauma. Acad Emerg Med 2009;16(5):371-8.