Fibrinogen Versus Fresh Frozen Plasma on the Patients’ Outcome with Hemorrhagic Shock Induce Chronic Diseases Caused by Multiple Trauma: A Randomized, Double-blinded, Clinical Trial Study

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Abstract

Objectives: The current study aimed to investigate the effect of fibrinogen compared to fresh frozen plasma (FFP) on outcomes of patients with traumatic hemorrhagic shock (THS).

Methods: In this double-blind RCT study, traumatic hemorrhagic shock patients with chronic diseases referred to the emergency department (ED) were evaluated. Patients were randomly divided into three equal groups; The first group received fibrinogen concentrate (70 mg/kg), the second group was treated with FFP, and the third group received crystalloid. Transfusion of FFP and packed red blood cells (PRBC) was in a 1:1 ratio. The need for admission in intensive care units, PRBC transfusion units, multiple organ failure, hospitalization days, and mortality rate were compared in both groups.

Results: In total, 45 patients were studied. The number of red blood cells (RBCs) transfused in patients treated with crystalloid, FFP, and Fibrinogen was 2.93, 2.37, and 2, respectively, which was statistically significant (P = 0.03). Two patients (13.3%) in the Fibrinogen-treated group, 4 (26%) in the FFP group, and 2 in the control group had multiple organ failure (P = 0.5). The incidence of sepsis was significantly higher in the FFP-treated group. In addition, mortality was significantly higher in patients who received crystalloid (46.7%) (P = 0.13).

Conclusions: This study demonstrated that treating patients with fibrinogen concentrate was associated with a decreased number of PRBC transfusion units and mortality. Therefore, management of traumatic patients with fibrinogen concentrate not only can improve the outcomes but also declines patients’ exposure to allogeneic blood products.

Keywords: Chronic Diseases, Fresh Frozen Plasma, Fibrinogen, Trauma, Hemorrhagic Shock

1. Background

Trauma is the first cause of mortality and the main cause of disability in active populations in developing countries (1-3). However, less attention has been paid to this issue in these countries (4). According to the forecasts of the World Health Organization (WHO), by 2024, the accidents will become the second leading cause of lost years of life all around the world (5).

On the other hand, trauma is associated with a high economic and social burden, both direct and indirect. Nowadays, the policies of WHO are based on the preventive measures and care needs of trauma patients (6, 7). Trauma-hemorrhagic shock (THS) is the main cause of traumatic death (8). THS causes activation of myocardial Nuclear factor-kappa B (NF-κB) and Tumor Necrosis Factor Alpha (TNFα) (9). Myocardial damage, known as a chronic disease, requires ongoing medical attention. So, THS can induce secondary cardiac injuries (10, 11). These policies not only have resulted in reduced mortality rates attributable to the trauma and socioeconomic burden of the disease but also have improved the outcomes of patients (12, 13).

Quick and appropriate diagnosis and treatment can be effective in improving the outcomes of these patients. The main treatment involves fixation and the patient’s hemodynamic rehabilitation using isotonic fluids and blood products to provide the necessary conditions for surgery or angiography. According to the recent literature, fibrinogen plays a vital role in the acquisition and maintenance of homeostasis, especially in patients with severe blood loss. It seems that plasma fibrinogen concentration, which is
a glycoglycoprotein in coagulation falls, is independently associated with hypertension and prophylaxis fibrinogen concentrate infusion (14, 15).

Fibrinogen level has been introduced as a determining factor in the 28-day death prediction of patients with intense and more severe bleeding (16). The injection of fibrinogen concentrate compared with fresh-frozen plasma (FFP) can bring better results concerning improving the outcome and reducing the need for other blood components as well as the enhanced likelihood of survival without increasing the risk of hypobo embolism (17-19).

It seems that factors such as the severity of the trauma, breeding characteristics, underlying diseases, severity of the fracture, and type of fractures contribute to plasma fibrinogen and its reduction in the pursuit of hematological diseases. In any case, the final comment on the effects of fibrinogen injection, instead of products such as FFP, requires more and more accurate studies with regard to other effective variables in the outcome of these patients. However, it seems that fibrinogen has a valuable role in improving the outcomes of patients with severe trauma.

2. Objectives

The current study aimed to investigate the effect of fibrinogen compared to FFP on outcomes of patients with traumatic hemorrhagic shock.

3. Methods

In this double-blind, randomized clinical trial study, hemorrhagic shock patients (caused by multiple traumas) with chronic diseases referred to the emergency department (ED) of Golestan Hospital, Ahvaz (Iran) are investigated. First, patients were examined by a physician for both clinical assessment and physical examination.

All steps of the study were performed following the Helsinki ethical principles after receiving the code of ethics, clinical trial code (code: IRCT20150704023046N4, https://www.irct.ir), and informed consent to participate in the study.

3.1. Inclusion Criteria

Patients with hemorrhagic shock (caused by multiple trauma), older than 18 years, systolic blood pressure < 90 mmHg, the possibility of significant bleeding, intra-abdominal bleeding evidence, and patients who need blood products according to the clinical conditions.

3.2. Exclusion Criteria

Being pregnant, having known coagulopathy, history of receiving anticoagulant and antiplatelet drugs, other causes of shock such as neurogenic shock, having a history of receiving blood products during the last 6 months, and dissatisfaction to participate in the study.

3.3. Intervention

The first group was treated with fibrinogen extract, the second group received FFP, and the third group underwent a routine treatment (i.e. crystalloid and packed red blood cells (PRBC)). Seventy mg/kg of fibrinogen (Avin Darou Company, Tehran, Iran) was injected, and FFP in proportion (FFP: PRBC ratio 1:1) was performed.

3.4. Outcome

3.4.1. Primary

The vital signs of patients were recorded in their records, and the patient’s blood pressure was recorded at a distance of 3 to 5 minutes. In assessing the effectiveness of each of these therapies in controlling coagulation disorders and outcomes of patients, blood pressure, pH with arterial blood gas (ABG) test, base excess level, and oxygenation index with pulse oximetry were recorded 4 and 12 hours after admission.

3.4.2. Secondary

Information such as brain injuries and organs in the short- (24 hours), medium- (7 days), and long-term (28 days), or discharge from hospital (with the level of consciousness and discharge time) were recorded. Also, the need for admission in special departments, the number of infused blood units, the occurrence of multiple cases of failure, and duration of hospitalization, and death were recorded.

3.5. Randomization

Boxes that contained the name of medications were labeled and classified based on a table of random numbers using computer software. Only the pharmacist and statistician of the research team were aware of the boxes. Finally, all coded medicine boxes were turned over. Based on the method of blocks, four subjects were randomly divided into three equal groups.

3.6. Blinding

In this study, the physician and patients were not aware of the intervention, and injections were performed by a third person.
3.7. Sample Size

In this study, the sample size was calculated using a literature review (20), and the minimum size of the statistical populations was calculated as 32.

3.8. Statistical Analysis

After collecting the data, SPSS (V 20) was used to analyze the data. The findings are described using the mean (standard deviation), frequency, and percentage. To analyze the quantitative variables, ANOVA or Kruskal-Wallis tests were used. The chi-Square test was used to compare the data. Statistical significance was considered when P-value < 0.05.

4. Results

In this study, 45 patients were studied (Figure 1). The mean age of patients was 42 ± 13.8, ranging from 20 to 60 years. Most of the participants were male (33 or 73.3%) (Table 1). The mean Glasgow Coma scale (GCS) of the three groups was similar. There was no significant difference in systolic and diastolic blood pressure, heart rate, respiratory rate, pH level, and O2 Sats of patients in all three groups. However, hemoglobin level was significantly higher in patients who received crystallization (Table 2) (Figures 2 and 3).

The number of RBCs in patients treated with crystalloid, FFP, and fibrinogen was 2.93, 2.37, and 2, respectively, which the difference was statistically significant (P = 0.03). The mean days of hospitalization in FFP, fibrinogen, and crystalloid groups was 15, 13, and 16.3 days, respectively (P = 0.3). The proportion of individuals requiring hospitalization in each of the three groups did not show any difference (P = 0.3). Also, the need for ventilation was similar in all three groups. Two patients (13.3%) in the fibrinogen group, 4 (26%) in the FFP group, and 2 in the control group (P = 0.5). The incidence rate of sepsis was significantly higher in the FFP group. In contrast, the mortality rate in the crystallization group (46.7%) was significantly higher than the rest of the groups. The lowest mortality rate was observed in the fibrinogen group (P = 0.13) (Table 3).

5. Discussion

According to the findings, the number of RBC injection in patients treated with fibrinogen was significantly lower than patients who received FFP and those in the control group. Given that the primary Hb level in patients treated with fibrinogen was lower, probably some products were injected to improvement for the initial level of Hb, and no modification of the product had been injected.

The findings also showed that the incidence of mortality and multiple limb defects in FFP and the control group were more than the fibrinogen group. However, the differences were not statistically significant. These findings were also related to other studies in this regard.

Nienaber et al. (21), in a comparative study of the comparison of FFP and the concentration of coagulation factor on the mortality and morbidity of trauma and bleeding, reported a difference in the general mortality level between the two groups. However, there was a significant difference concerning the morbidity and the need for allogeneic injection. In fact, the findings of this study showed that management of traumatic patients was better with coagulation factors than by FFP injection (21).

Wafaisade et al. (22) evaluated the effect of the administration of fibrinogen concentrate for improving patients with severe trauma and showed that the early use of fibrinogen concentrate was associated with significant improvement in reducing six-hour mortality and also increasing the time until the occurrence of death. However, patients who received fibrinogen showed a higher rate of multiple limb defects (22).

Akbari et al. also evaluated the effect of fibrinogen in comparison with FFP for the outcome of traumatic patients and showed that the use of fibrinogen caused a significant reduction in mortality, sepsis, and the need for RBC product injection (23). Minimizing or refusing to deal with the blood products is highly favorable. FFP injection always increases the risk for health problems such as pulmonary injury following blood transfusion, blood circulation, acute respiratory distress syndrome, immune modulation, and pathogen transmission (24, 25). A few amounts of FFP is not effective in correcting the condition of the patient’s coagulation. Therefore reducing the injection of FFP units is not reversible (26, 27).

Therefore, FFP injection should be prescribed at a high rate, which also increases the influence over hematocrit, and therefore the need for RBC injection. On the other hand, through increasing plasma fibrinogen levels, fibrinogen infusion increases the level of clots, even in people with low platelet levels. Besides, it may reduce the platelets (28, 29).

Moreover, the concentrate of coagulation factors may cause faster blood cessation and decreased hemodialysis compared to the blood allogeneic products. In addition to the reduction of injection volume, a decrease in coagula-
Figure 1. CONSORT 2010 flow diagram

Table 1. Basic Characteristic of Patients

| Characteristics            | Control (N = 15) | Fibrinogen (N = 15) | Fresh Frozen Plasma (N = 15) | P-Value |
|----------------------------|------------------|--------------------|-------------------------------|---------|
| Age, Mean ± SD             | 41.13 ± 14.34    | 42.33 ± 13.88      | 42.73 ± 14.30                 | 0.95    |
| Gender, No. (%)            |                  |                    |                               | 0.25    |
| Male                       | 13 (86.7)        | 11 (73.3)          | 9 (60)                        |         |
| Female                     | 2 (13.3)         | 4 (26.7)           | 6 (40)                        |         |
| Traumas site, No. (%)      |                  |                    |                               |         |
| Head                       | 8 (42.1)         | 11 (37.9)          | 10 (34.5)                     | 0.7     |
| Abdomen                    | 14 (50)          | 8 (28.6)           | 6 (21.4)                      | 0.9     |
| Limb                       | 9 (40.9)         | 10 (45.45)         | 3 (13.63)                     | 0.32    |
| Chest                      | 5 (25)           | 13 (65)            | 2 (10)                        | 0.04    |
| GCS, Mean ± SD             | 10.20 ± 2.48     | 10 ± 2.53          | 10 ± 3.31                     | 0.97    |

tion factors will probably have less effect on the amount of hematopoietic, and it can be improved in the formation of clots (30).

Moreover, the concentration of coagulation factors in the production process, which is placed under the virus infection and the risk of transmission of viral infections in these products is nearly zero. On the other hand, the risk of transmission of blood-borne infections in plasma products should always be considered as a serious risk. Therefore, fibrinogen concentrate, in addition to improving the outcomes of patients, decreases the risk of infection transmission, and therefore it can be suggested as a beneficial
Figure 2. The box plot of systolic BP, diastolic BP, HR, RR, PH, and BE in 3 groups.

substitute for FFP in multiple trauma.

5.1. Limitations

The current research was a pilot study, and few samples were investigated. The study was carried out in only one center. Symptoms of blood transfusion were not considered. Hence, Randomized Clinical trials are recommended to confirm the findings of the present study.
5.2. Conclusions

This study demonstrated that treating patients with fibrinogen concentrate was associated with reduced mortality and the need for RBC products. Therefore, it seems that management of traumatic patients with fibrinogen, while reducing patient exposure to blood allogenic products, can improve treatment outcomes of patients with multiple trauma.

Footnotes

Authors’ Contribution: MM and JM conceived the original idea, designed the scenarios, and collected the data. HB carried out the analysis of data, drafted the manuscript. EK revised it, drafted the manuscript, approved the final version that was submitted.

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Table 2. Comparison of Outcomes Between the Three Groups

| Characteristics | Control (N = 15) | Fibrinogen (N = 15) | Fresh Frozen Plasma (N = 15) | P-Value |
|-----------------|-----------------|---------------------|-------------------------------|---------|
| Systolic BP     | 85.86 ± 5.75    | 86.06 ± 3.39        | 86.2 ± 4.0                   | 0.97    |
| Diastolic BP    | 60.26 ± 1.57    | 59.46 ± 3.44        | 61.2 ± 4.27                  | 0.46    |
| HR              | 19.26 ± 7.85    | 121.6±6.47          | 126.3 ± 5.63                 | 0.01    |
| RR              | 19.95 ± 4.57    | 21.73 ± 3.20        | 21.47 ± 3.25                 | 0.37    |
| PH              | 7.3 ± 0.034     | 7.28 ± 0.05         | 7.29 ± 0.05                  | 0.66    |
| BE              | 6.0 ± 2.13      | 6.08 ± 2.29         | 7.13 ± 2.33                  | 0.3     |
| O₂Sat           | 90.40 ± 5.7     | 89.46 ± 5.39        | 90.27 ± 5.90                 | 0.8     |
| HB              | 10.6 ± 1.08     | 9.48 ± 0.73         | 9.38 ± 1.02                  | 0.002   |
| PC              | 2.91 ± 1.09     | 2 ± 0.8             | 2.7 ± 1.03                   | 0.035   |
| Fluid           | 3.2 ± 0.9       | 3.26 ± 0.79         | 4 ± 1.14                     | 0.04    |
| Hospitalization | 16.3 ± 7.8      | 11 ± 4.6            | 15.2 ± 5.49                  | 0.3     |
| ICU             | 13 (86.7)       | 11 (73.3)           | 14 (93.3)                    | 0.3     |
| Ventilation     | 8 (46.7)        | 7 (46.7)            | 9 (60)                       | 0.7     |
| Multiple organs | 2 (13.3)        | 2 (13.3)            | 4 (26.7)                     | 0.54    |

Values are expressed as No. (%) or mean ± SD.

Table 3. Frequency of ICU, Ventilation, Multiple Organ, Sepsis, and Mortality Rate for Patients

| Characteristics | Control (N = 15) | Fibrinogen (N = 15) | Fresh Frozen Plasma (N = 15) | P-Value |
|-----------------|-----------------|---------------------|-------------------------------|---------|
| ICU             | 13 (86.7)       | 11 (73.3)           | 14 (93.3)                    | 0.3     |
| Ventilation     | 8 (46.7)        | 7 (46.7)            | 9 (60)                       | 0.7     |
| Multiple organ  | 2 (13.3)        | 2 (13.3)            | 4 (26.7)                     | 0.54    |
| Adverse effect  |                |                     |                              |         |
| Sepsis          | 3 (20)          | 3 (20)              | 8 (53.3)                     | 0.07    |
| Mortality       | 7 (46.7)        | 2 (13.3)            | 5 (33.3)                     | 0.139   |

References

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet. 1997;349(9061):1269–76. doi:10.1016/S0140-6736(96)07493-4. [PubMed: 9142060].
2. Naghavi M, Shahraz S, Sapanlou SG, Dicker D, Naghavi P, Pourmalek F, et al. Health transition in Iran toward chronic diseases based on results of Global Burden of Disease 2010. Arch Iran Med. 2014;17(5):321–35. [PubMed: 24784861].
3. Rowell SE, Barbosa RR, Diggs BS, Schreiber MA, Trauma Outcomes G, Holcomb JB, et al. Specific abbreviated injury scale values are responsible for the underestimation of mortality in penetrating trauma patients by the injury severity score. J Trauma. 2011;71(2 Suppl 3):S384–8. doi:10.1097/TA.0b013e31822873ed. [PubMed: 21814109].
4. London JA, Mock CN, Quansah RE, Abantanga FA, Jurkovich GJ. Priorities for improving hospital-based trauma care in an African city. J Trauma. 2001;51(4):747–53. doi:10.1097/00005373-200104000-00021. [PubMed: 11566707].
5. Crowe CS, Massenburg BB, Morrison SD, Chang I, Friedrich JB, Abady GG, et al. Global trends of hand and wrist trauma: a systematic analysis of fracture and digit amputation using the Global Burden of Disease 2017 Study. Inj Prev. 2020;26(Suppl 1):i15–24. doi:10.1136/injuryprev-2019-043495. [PubMed: 32169973]. [PubMed Central: PMC7571361].
6. Smith GS, Barss P. Unintentional injuries in developing countries: the epidemiology of a neglected problem. Epidemiol Rev. 1991;13:228–66. doi:10.1093/oxfordjournals.epirev.a018670. [PubMed: 176518].
7. Mackersie RC. Field triage, and the fragile supply of "optimal resources" for the care of the injured patient. Prehosp Emerg Care. 2006;20(3):347–50. doi:10.1080/10903120600728920. [PubMed: 16801277].
8. El Sayad M, Noureddine H. Recent advances of hemorrhage management in severe trauma. Emerg Med Int. 2014;2014:638956. doi:10.1155/2014/638956. [PubMed: 24627809]. [PubMed Central: PMC3929886].
9. Chou TC. New mechanisms of antiplatelet activity of nifedipine, an L-type calcium channel blocker. Biomedicine (Taipei). 2014;4:24. doi:10.7603/s40681-014-0024-z. [PubMed: 25520937]. [PubMed Central: PMC4265014].
10. Chapel JM, Ritchey MD, Zhang D, Wang G. Prevalence and Medical Costs of Chronic Diseases Among Adult Medicaid Beneficiaries. Am J Prev Med. 2017;53(5):543–54. doi:10.1016/j.amepre.2017.07.019. [PubMed: 2915315]. [PubMed Central: PMC5798200].
11. Lin KH, Liu CL, Kuo WW, Paul CR, Chen WK, Wen SY, et al. Early Fluid Resuscitation by Lactated Ringer’s Solution Alleviates the Cardiac Apoptosis in Rats with Trauma-Hemorrhagic Shock. PloS One. 2016;11:10.
20. Lucas CE, Ledgerwood AM. Fresh frozen plasma/red blood cell transfusion targeting a high-normal plasma fibrinogen level: a pilot study. *Thromb Haemost*. 2009;102(1):137–44. doi: 10.1600/JTH08-09-0587. [PubMed: 19572078].

21. Nienaber U, Innerhofer P, Westermann I, Schochl H, Attal R, Breitschopf R, et al. The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. *Injury*. 2011;42(7):697-701. doi: 10.1016/j.injury.2010.12.015. [PubMed: 21927260].

22. Wafaisade A, Lefering R, Maegele M, Brockamp T, Mutschler M, Lendemans S, et al. Administration of fibrinogen concentrate in exsanguinating trauma patients is associated with improved survival at 6 hours but not at discharge. *J Trauma Acute Care Surg*. 2013;74(2):387-3. discussion 393-5. doi: 10.1097/TA.0b013e3182e2410. [PubMed: 23354229].

23. Akhavan Akbari G, Mohammadian A. Comparison of the RTS and ISS scores on prediction of survival chances in multiple trauma patients. *Acta Chir Orthop Traumatol Cech*. 2012;79(6):535–9. [PubMed: 23286867].

24. 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(1):2667-71. doi: 10.1097/01.ccm.0000186745.53059.f0. [PubMed: 16278595].

25. Sarani B, Dunkman WJ, Dean L, Sonnad S, Rohrbach JL, Gracias VH. Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. *Crit Care Med*. 2008;36(4):114-8. doi: 10.1097/CCM.0b013e3181618b9d. [PubMed: 18379235].

26. Armand R, Hess JR. Treating coagulopathy in trauma patients. *Transfus Med Rev*. 2003;17(3):223–31. doi: 10.1016/s0887-7963(03)00224-1. [PubMed: 12881781].

27. Chowdary P, Saayman AG, Paulus U, Findlay GP, Collins PW. Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory hemostatic parameters in the presence of thrombocytopenia. *Anesth Analg*. 2009;108(3):751–8. doi: 10.1213/ane.0b013e3181966675. [PubMed: 19224779].

28. Velik-Salchner C, Haas T, Innerhofer P, Streif W, Nussbaumer W, Klingler A, et al. The effect of fibrinogen levels on thromboelastometric variables in the presence of thrombocytopenia. *Anesthesia*. 2009;108(3):731–8. doi: 10.1344/anesthesia.2008-0647. [PubMed: 19224779].

29. Walton BL, Lehmann M, Skorczewski T, Holle LA, Beckman JD, Cribb JA, et al. Elevated hematocrit enhances platelet accumulation following vascular injury. *Blood*. 2017;129(8):2537–46. doi: 10.1182/blood-2016-10-746479. [PubMed: 28259193]. [PubMed Central: PMC5418635].