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Effect of fibrinogen concentrate on the initial fibrinogen level in trauma and postpartum hemorrhage

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Abstract. – OBJECTIVE: Massive hemorrhage is a serious event that threatens the lives of patients. Fibrinogen concentrate (FC) can control bleeding without causing viral complications and without volume loading, which can happen in transfusion-associated circulatory overload and transfusion-associated acute lung injury. FC application is easy and does not require dissolution or extra devices. It is a cost-effective agent when considering the blood and products used in large quantities.

PATIENTS AND METHODS: A total of 67 postpartum hemorrhage (PPH) and trauma patients' medical records, who had ASA I-III classification (The American Society of Anesthesiologists classification of physical status), were obtained. Patients were divided into two groups (fibrinogen level ≤ 100 mg/dl and ≥ 101 mg/dl). The following information was obtained from patient files: demographic parameters, history of operations, and laboratory findings (i.e., complete blood counts, coagulation tests, and fibrinogen levels). Also, the duration of intensive care unit stays and mechanical ventilation application days, the administration of fresh frozen plasma (FFP), erythrocytes, platelets, and FC numbers, and tranexamic acid infusion were recorded.

RESULTS: There was no mortality in PPH patients in either group (fibrinogen level ≤ 100 mg/dl and ≥ 101 mg/dl). The mortality rate in trauma patients was significantly higher in the group with fibrinogen levels ≤ 100. A total of 170 g of FC were given to PPH patients and 92 g to trauma patients. There were statistically significant differences between the preoperative PT (prothrombin time), postoperative APTT (activated partial thromboplastin time), postoperative PT, and postoperative INR (international normalized ratio) levels of the patients in the group with fibrinogen levels ≤ 100. Mortality rates were also significantly higher, and hospital stays significantly longer in trauma patients in the group with fibrinogen levels ≤ 100.

CONCLUSIONS: Therapy may be considered during massive bleeding and transfusion, as it can help to increase fibrinogen levels quickly and efficiently. Compared with FFP, fibrinogen concentrate may have some advantages in reducing the risk of fluid overload. FFP contains a range of clotting factors, including fibrinogen. It also contains other proteins and fluids that can lead to fluid overload, especially when given in large volumes during massive transfusions.

Key Words:
Fibrinogen, Hemorrhage, Postpartum, Trauma.

Introduction

Surgical/traumatic or postpartum hemorrhage (PPH) is a serious event that often threatens the life of the patient. Coagulopathy, which is the impaired ability of blood to clot, is often observed during PPH and is linked to a higher likelihood of morbidity and the need for massive blood transfusions, and hysterectomies[1]. As blood loss increases, fibrinogen levels tend to decrease, which can be indicative of compromised hemostasis[2,3]. Hypofibrinogenemia, or a low fibrinogen level, increases morbidity and mortality. Fibrinogen concentrate (FC) is increasingly used in acquired hypofibrinogenemia occurring in hemorrhages in many countries[4].

In massive hemorrhages, large quantities of blood and products can be used. However, undesirable allergic reactions may be encountered. The use of fresh frozen plasma (FFP), red blood cells (RBC), and platelet concentrate (PC) is associated with several transfusion-related complications and increases the cost of care[5]. Using agents with lower volume is more beneficial in terms of perioperative and postoperative outcomes. Coagulopathy risk assessment during postpartum hemorrhage (PPH) should consider not only the estimated blood loss but also any obstetric complications and underlying causes. These can include placental abruption, preeclampsia with hemorrhage, or amniotic fluid embolism with disseminated

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intravascular coagulation (DIC). These conditions can lead to abnormal clotting and fibrinogen consumption, resulting in coagulopathy[6-8]. Fibrinogen is an essential component of blood clotting, and its measurement can provide valuable information about a patient's coagulation status. In cases of PPH, where significant bleeding occurs, fibrinogen levels can drop rapidly, leading to clotting abnormalities and an increased risk of severe bleeding. Therefore, it is important to include fibrinogen measurements in coagulopathy risk assessments during PPH to identify and manage any underlying coagulation disorders effectively. This can help reduce the risk of severe bleeding and improve patient outcomes[5].

Fibrinogen is the primary coagulation factor in coagulopathy, and when its concentration decreases <150 mg/dl, severe surgical blood loss may happen, and hemorrhage increases excessively[9-11]. Fibrinogen is a natural blood protein that plays a crucial role in the coagulation process. Low levels of fibrinogen can result in prolonged bleeding and increased morbidity and mortality rates. FC is widely used instead of traditional sources of fibrinogen, such as the blood products FFP and cryoprecipitate (a pooled concentrated plasma product)[4]. It is also worth noting that traditional sources of fibrinogen, such as fresh frozen plasma and cryoprecipitate, are still used in many parts of the world. These blood products are derived from donated blood and contain a variety of clotting factors, including fibrinogen. However, they carry certain risks, such as the potential for transmission of infectious diseases and adverse reactions. Hypofibrinogenemia is a condition characterized by low levels of fibrinogen in the blood, which can lead to abnormal bleeding for all ages. The European Journal of Anaesthesiology (EJA) guideline suggests administering fibrinogen concentrate as an alternative to cryoprecipitate for the treatment of hypofibrinogenemia in children suffering from perioperative bleeding[12].

The main preventable cause of death in severe trauma patients is uncontrolled bleeding. Fibrinogen is the first clotting factor to decrease during trauma-induced coagulopathy (TIC), suggesting that pharmacological replacement may help control early bleeding. Mechanisms of coagulopathy in trauma include loss of clotting factors due to bleeding and consumption, dilution due to intravenous fluid and RBC administration without sufficient clotting factors (FFP and platelets), and coagulation protease dysfunction. Tissue hypoperfusion and direct tissue trauma initiate acute coagulopathy in trauma patients, with an increase in fibrinolysis. Fibrinogen is the first clotting factor to reach critically low levels during trauma, and hepatic synthesis is not enough to compensate for rapid intensive consumption[13].

In this study, our aim is to examine the relationship between fibrinogen levels and the amount of FC used, and mortality and morbidity in hemorrhagic patients who underwent emergency surgery (PPH or trauma).

Patients and Methods

This study was performed in the Anesthesiology and Reanimation Clinic of a tertiary training hospital in Istanbul, Turkey. Patients who had bleeding and had emergency surgery (PPH/trauma) were admitted to the Intensive Care Unit (ICU). We retrospectively identified 67 patients, ASA I–III, with PPH and trauma who were admitted to the ICU between January 2015 and December 2018. Patients were divided into two groups: fibrinogen levels ≤100 mg/dl group (n: 35) (PPH: 26, trauma: 9 patients) and fibrinogen levels >101 mg/dl group (n: 32) (PPH: 11, trauma: 21 patients). The study flow diagram is shown in Figure 1. Medical records were reviewed, and the data recorded included demographic (age, gender) parameters, operations, and laboratory findings (i.e., complete blood count, coagulation tests, and fibrinogen levels). We recorded the duration of ICU stays and specific interventions performed during the stays, including mechanical ventilation, administration of fresh frozen plasma, units administered of RBC, platelets, fibrinogen concentrate, and tranexamic acid infusion. The exclusion criteria of the study were patients under the age of 18 and patients who were not administered fibrinogen concentrate. This study was approved by the University of Health Sciences Istanbul Kanuni Sultan Suleyman Education and Training Hospital Ethics Committee (No. 2019.01.18).

Statistical Analysis

All statistical analyses were performed using the SPSS statistical package, version 22.0 (IBM Corp., Armonk, NY, USA) for Windows. Data are presented as mean SD or median (range). Data were checked for normal distribution using the SPSS statistical package. Nonparametric tests (Mann-Whitney U-test and χ^2= Chi-Square test) were used because the data were not normally distributed. Fisher's exact test value was reported when the number of

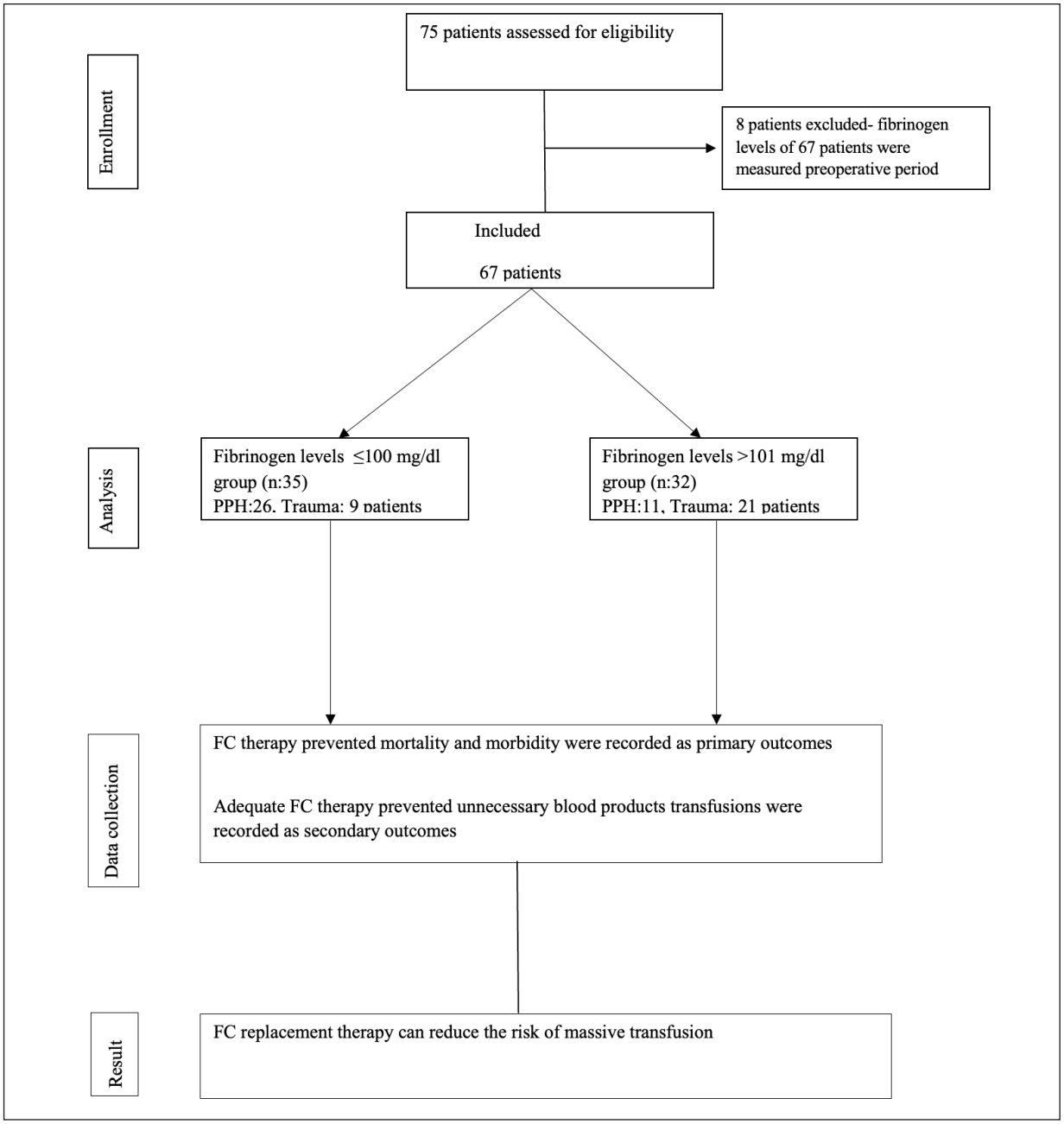

Figure 1. Study flow diagram.

observed variables was less than five. A p-value < 0.05 was considered statistically significant.

Results

Table I presents data on the demographic and clinical characteristics of the patients who were included in the study sample.

According to the findings in the study, 37 (55.2%) out of the 67 patients included in the sample were diagnosed with postpartum hemorrhage, and 30 (44.8%) were diagnosed with massive bleeding due to trauma. The patients in the PPH group consisted of individuals who experienced atonia (51.4%), abruptio (21.6%), or previa (27.0%). Patients in the trauma group were individuals who experienced abdominal

Table I. Patients' characteristics (n: 67).

		Total (n: 67) n (%)	PPH (n: 37; 55.2%) n (%)	Trauma (n: 30; 44.8%) n (%)
Diagnosis	Atony	19 (28.4)	19 (51.4)	-
	Decolman	8 (11.9)	8 (21.6)	-
	Previa	10 (14.9)	10 (27.0)	-
	Abdominal Trauma	18 (26.9)	-	18 (60.0)
	Extremity Trauma	5 (7.5)	-	5 (16.7)
	Chest Trauma	4 (6.0)	-	4 (13.3)
	Head Trauma	3 (4.5)	-	3 (10.0)
Age Groups	≤39 years	52 (77.6)	35 (94.6)	17 (56.7)
	40-59 years	10 (14.9)	2 (5.4)	8 (26.7)
	≥ 60 years	5 (7.5)	-	5 (16.7)
	Range	*16-64*	*16-49*	*16-64*
	M ± SD	*35.48±11.68*	*31.54±6.47*	*40.33±14.64*
Gender	Female	54 (80.6)	37 (100)	17 (56.7)
	Male	13 (19.4)	-	13 (43.3)
Glasgow Coma Score (GCS)	≤14	50 (74.6)	34 (91.9)	16 (53.3)
	8-13	8 (11.9)	1 (2.7)	7 (23.3)
	≥ 7	9 (13.4)	2 (5.4)	7 (23.3)
Hospitalization	≤10 days	42 (62.7)	28 (75.7)	14 (46.7)
	≥ 11 days	25 (37.3)	9 (24.3)	16 (53.3)
	Range	*1-90*	*1-90*	*2-31*
	M ± SD	*11.87±12.18*	*11.51±14.77*	*12.30±8.17*
Mechanical Ventilation	Yes	41 (61.2)	19 (51.4)	22 (73.3)
	No	26 (38.8)	18 (48.6)	8 (26.7)
Tranexamic acid	Yes	13 (19.4)	10 (27.0)	3 (10.0)
	No	54 (80.6)	27 (73.0)	27 (90.0)
	Range	*2-7*	*2-7*	*2-4*
	M ± SD	*3.46±1.71*	*3.70±1.83*	*2.67±1.16*
Mortality	Yes	8 (11.9)	-	8 (26.7)
	No	59 (88.1)	37 (100)	22 (73.3)

n: Number, %: Percentage; Range: Minimum-Maximum; M: Mean; SD: Standard Deviation.

(60.0%), extremity (16.7%), chest (13.3%), or head (10.0%) trauma. The ages of the patients ranged from 16 to 64, and the mean age of the PPH group was 31.54 ± 6.47, while the mean age of the trauma group was 40.33 ± 14.64. All the patients in the PPH group were female (100%), and most had a Glasgow Coma Scale (GCS) score of 14 or higher (91.9%) and a hospital stay of less than 10 days (75.7%). Mechanical ventilation support was provided to 51.4% of the patients in this group, and a total of 10 patients (27.0%) were given 2-7 doses of TXA. No mortality occurred in any of the patients in this group (0.0%).

The patients in the trauma group were mostly female (56.7%) and had a GCS score of 14 or higher (53.3%). Most of these patients had a hospital stay of 11 days or more (53.3%) and received mechanical ventilation support (73.3%). A total of 3 patients (10.0%) in this group received 2-4 doses of tranexamic acid. Mortality occurred in 8 patients (26.7%) in this group.

Table II presents the results obtained from the comparison of some patient results according to the fibrinogen levels in PPH and trauma groups.

The findings in Table II show that there was no mortality in PPH patients in either group in the analysis performed according to fibrinogen levels. However, in the comparison made in the group with fibrinogen levels of 100 mg/dl and below, the mortality rate of the patients in the trauma group was found to be statistically significantly higher ($p<0.001$). On the other hand, the duration of hospital stay of the trauma patients in the group with fibrinogen level 101 mg/dl and above was statistically higher than that of PPH patients in the same group ($p<0.05$). Moreover, the length of stay in the intensive care unit of the PPH patients in the group with fibrinogen level 100 mg/dl and below was statistically significant compared to that of patients in the trauma group, whose intensive care stays were significantly shorter ($p<0.001$). Finally, it was also found that there was no statistical difference

Table II. Patients' outcomes (n: 67).

		Fibrinogen level ≤ 100 mg/dl (n: 35; 52.2%)		Fibrinogen level ≥ 101 mg/dl (n: 32; 47.8%)	
		PPH n (%)	Trauma n (%)	PPHn (%)	Trauma n (%)
Mortality	Yes	0 (0.0)	5 (100.0)	0 (0.0)	3 (100.0)
	No	26 (86.7)	4 (13.3)	11 (37.9)	18 (62.1)
	Test and significance	χ^2 =16.852, p<.001***		χ^2 = 1.734, p=.534	
Hospitalization	≤ 10 days	18 (81.8)	4 (18.2)	10 (50.0)	10 (50.0)
	≥ 11 days	8 (61.5)	5 (38.5)	1 (8.3)	11 (91.7)
	Test and significance	χ^2 =1.759, p:.243		χ^2 =5.772, p=.023*	
ICU admission	≤ 7 days	24 (88.9)	3 (11.1)	11 (44.0)	14 (56.0)
	≥ 8 days	2 (25.0)	6 (75.0)	0 (0.0)	7 (100.0)
	Test and significance	χ^2 =13.187, p=.001**		χ^2 = 4.693, p=.066	
Mechanical Ventilation	Yes	13 (61.9)	8 (38.1)	6 (30.0)	14 (70.0)
	No	13 (10.4)	1 (7.1)	5 (41.7)	7 (58.3)
	Test and significance	χ^2 = 4.213, p=.056		χ^2 =.453, p=.501	

*p<.05; **p<.01; ***p<.001; χ^2= Chi-Square. n: Number, %: Percentage. Fisher's Exact test value was reported when the number of observed variables was lower than five.

between the PPH and trauma patients receiving mechanical ventilation support in either group according to fibrinogen levels (p >.05).

Table III shows the results of blood transfusion and replacement therapy during hospitalization. The results are based on the fibrinogen levels of the patients in the PPH and trauma groups at the time of hospitalization.

According to the findings in Table III, there were various differences in terms of blood products and replacement therapy used for PPH and trauma patients in both groups (fibrinogen levels below 100 mg/dl and above 101 mg/dl). The differences between the groups were not statistically significant (p >.05). Fibrinogen concentrates were administered as follows: in the group with a fibrinogen level of 100 mg/dl and below (n: 26), a total of 141 g to PPH patients and 45 g to trauma patients (n: 9); in the group with a fibrinogen level of 101 mg/dl and above (n: 11), a total of 29 g to PPH patients and 47 g to trauma patients (n: 21).

Table IV presents the results obtained from the comparison of blood values of preoperative and postoperative patients in the PPH and trauma groups based on fibrinogen levels at the time of hospitalization.

According to the findings in Table IV, there were statistically significant differences between the pre-op PT, post-op APTT, post-op PT, and post-op INR levels of the patients in the group with fibrinogen levels of 100 mg/dl and below (p<0.05). Measurements from trauma patients were higher than measurements from PPH patients. On the other hand, in the group with fibrinogen levels

Table III. Number of used blood products and Tranexamic acid.

	Fibrinogen level ≤ 100 mg/dl					Fibrinogen level ≥ 101 mg/dl				
	PPH		Trauma		*Test*	PPH		Trauma		*Test*
	n	M (SD)	n	M (SD)	*significance*	n	M (SD)	n	M (SD)	*significance*
Red Blood Cell	25	4.24 (1.90)	5	3.80 (2.49)	z=-656 p=.552	8	4.13 (2.10)	19	3.53 (1.58)	z=-819 p=.449
Fresh Frozen Plasma	25	2.80 (1.16)	7	3.29 (1.50)	z=.801 p=.474	9	2.33 (1.41)	18	3.33 (1.85)	z=1.788 p=.131
Thrombocyte Suspension	12	3.75 (2.45)	2	4.00 (2.83)	z=.190 p=1.00	2	4.00 (0.0)	3	2.33 (1.53)	z=-1.291 p=.400
Tranexamic acid	7	3.43 (1.62)	1	4.00 (0.0)	z=.450 p=.750	3	4.33 (2.52)	2	2.00 (0.0)	z=-1.291 p=.400

n: Number, M: Mean; SD: Standard Deviation; z: Mann Whitney U test.

Table IV. Laboratory values of patients on preoperative (pre-op) and postoperative (post-op) time.

	Fibrinogen level ≤ 100 mg/dl			Fibrinogen level ≥ 101 mg/dl		
	PPH (n: 26)	Trauma (n: 9)	Test significance	PPH (n: 11)	Trauma (n: 21)	Test significance
	M (SD)	M (SD)		M (SD)	M (SD)	
Pre-op APTT (s)	59.504 (36.93)	69.33 (32.29)	*z*=1.359 *p*=.184	32.87 (7.06)	40.57 (7.06)	***z*=2.203 *p*=.027***
Pre-op PT (s)	25.00 (21.92)	26.78 (7.71)	***z*=2.058 *p*=.038***	15.52 (3.29)	17.76 (3.33)	*z*=1.772 *p*=.081
Pre-op INR	2.01 (1.38)	2.97 (2.07)	*z*=1.909 *p*=.056	1.31 (.31)	1.65 (.54)	*z*=1.950 *p*=.051
Pre-op Hb (g/dL)	7.13 (2.14)	7.74 (2.74)	*z*=.757 *p*=.449	9.21 (1.99)	6.86 (2.00)	***z*=-2.776 *p*=.005****
Pre-op Hematocrit (%)	21.45 (6.54)	23.78 (7.34)	*z*=.925 *p*=.355	27.41 (5.79)	21.10 (5.96)	***z*=-2.821 *p*=.004****
Pre-op Plt (10^3 cells/μL)	122496.15 (71816.55)	90777.78 (76039.10)	*z*=-1.378 *p*=.171	153972.73 (105938.79)	163380.95 (89291.51)	*z*=.556 *p*=.584
Post-op APTT (s)	31.24 (6.18)	57.56 (45.65)	***z*=2.247 *p*=.025***	25.36 (4.15)	31.47 (6.44)	***z*=2.972 *p*=.002****
Post-op PT (s)	13.75 (2.15)	18.72 (6.68)	***z*=3.243 *p*=.001****	12.57 (1.76)	13.71(2.19)	*z*=1.148 *p*=.271
Post-op INR	1.15 (.18)	1.51 (.36)	***z*=2.865 *p*=.004****	1.07 (.19)	1.14 (.18)	*z*=.963 *p*=.367
Post-op Fibrinogen (mg/dl)	246.73 (90.42)	182.89 (64.39)	*z*=-1.775 *p*=.076	288.46 (67.17)	255.19 (61.10)	*z*=-1.528 *p*=.133

*p<.05; **p<.01; *z*: Mann Whitney U test; n: Number, %: Percentage; M: Mean; SD: Standard Deviation. APTT: Activated Partial. Thromboplastin Clotting Time, PT: Prothrombin Time, INR: International Normalised Ratio, Hb: Hemoglobin, Plt: Platelet.

of 101 mg/dl and above, the differences between pre-op APTT, pre-op Hb, pre-op Htc, and post-op APTT values of the patients were statistically significant (p<0.05). The pre-op APTT and post-op APTT values of the trauma patients were high, whereas the PPH patients had higher pre-op APTT and post-op APTT values. In other blood value comparisons made according to the fibrinogen level groups of PPH and trauma patients, it was found that there was no statistically significant difference between the groups (p >.05).

Discussion

Massive transfusion involves the transfusion of a large volume of blood and blood products, often in the setting of significant blood loss or trauma. FFP is a commonly used blood product in massive transfusion protocols, as it contains clotting factors, including fibrinogen. However, FFP also contains a large volume of fluid, which can contribute to fluid overload and its associated complications, such as pulmonary edema and impaired oxygenation[12].

FC is a concentrated source of fibrinogen that can be administered rapidly and in smaller volumes than FFP. By reducing the volume of fluid administered, fibrinogen concentrate may potentially decrease the risk of fluid overload and its associated complications. Additionally, fibrinogen concentrate may provide a more targeted approach to restoring clotting factors. It contains only fibrinogen and no other clotting factors that may not be necessary or may even contribute to coagulopathy in certain clinical scenarios[5].

PPH is one of the major preventable causes of maternal death[14]. The present study determined that there was no mortality in PPH patients in either group (fibrinogen level ≤ 100 mg/dl and ≥ 101 mg/dl); however, in the comparison made in the group with fibrinogen levels of 100 mg/dl and below, the mortality rate of the trauma patients was found to be statistically significantly higher. There was no mortality in any of the PPH patients because the rate of FC given was higher. Several recently published studies[15,16] have examined the benefits of using fibrinogen concentrate in PPH. Wikkelso et al[15] found that women with preterm postpartum bleeding were randomly assigned to receive either a 2 g dose of fibrinogen or saline as preemptive therapy[15]. There was no difference between the two groups in the incidence of ES

transfusion or secondary outcomes. No point-of-care coagulation testing was used[16].

A total of 170 g of FC were given to PPH patients and 92 g to trauma patients in our study. In cases such as severe trauma, surgical bleeding, and postpartum, fibrinogen levels deteriorate faster than other clotting factors. Consequently, the aggressive administration of fibrinogen plays an important role in hemostasis[17].

In the present study, there were statistically significant differences between the pre-op PT, post-op APTT, post-op Pt, and post-op INR levels of the patients in the group with fibrinogen levels of 100 mg/dl and below. Measurements from trauma patients were higher than measurements from PPH patients. One advantage of using FC is that it does not require ABO blood group compatibility testing, unlike transfusion with allogenic blood products, such as fresh frozen plasma or cryoprecipitate. In emergency situations where rapid and effective treatment is critical, the use of FC may offer significant benefits over traditional transfusion strategies. However, despite many randomized controlled trials (RCTs) demonstrating the efficacy of FC in elective surgery, there is a lack of studies investigating its use in emergency settings. Recently, the number of studies on the use of FC in trauma or postpartum situations has increased[17]. Therefore, further research is needed to evaluate the effectiveness and safety of FC in emergency situations, including PPH, trauma, and other critical care settings. This research will help to determine whether the use of FC can improve patient outcomes compared to traditional transfusion strategies in these high-risk situations.

In surgical patients with severe perioperative bleeding and hypofibrinogenemia, the European Society of Anesthesiology recommends the use of fibrinogen concentrate to correct low levels of fibrinogen[12]. In the European Trauma Guidelines (2019)[18] fibrinogen replacement with fibrinogen concentrate is also recommended in patients with fibrinogen levels of <1.5 g/L. Schlimp et al[19] investigated the evolution of plasma fibrinogen levels following trauma in patients with or without FC therapy. They showed that FC therapy does not lead to higher plasma fibrinogen levels among trauma patients and stated that FC can be used safely in trauma patients[19]. The present study suggests that the administration of earlier and higher doses of FC to PPH patients compared to trauma patients had a positive effect on the patients, and no mortality was observed in PPH patients.

Preventing uncontrolled bleeding in severe trauma patients is essential to improving survival rates and reducing preventable deaths. Fibrinogen is the first factor to decline in trauma-induced coagulopathy (TIC). The critical fibrinogen value is unclear, but some suggest that 100 mg/dl is sufficient[20]. Recent studies[21] in literature have shown the role of fibrinogen availability in TIC. Hemodilution, hyperfibrinolysis, acidosis, and hypothermia all deplete the availability of fibrinogen and, as a result, disrupt the coagulation process. In the present study, in the group with fibrinogen levels of 100 mg/dl and below, the mortality rate and length of hospital stay of the trauma patients were found to be statistically significantly higher. Additionally, recent retrospective studies of trauma patients suggest that fibrinogen supplementation may be beneficial[21].

Conclusions

In summary, while fibrinogen concentrate has been increasingly used in some countries, there is still a need for more research to determine its safety and efficacy. Traditional sources of fibrinogen, such as fresh frozen plasma and cryoprecipitate, remain important options in many parts of the world. The use of any fibrinogen replacement therapy should always be based on a thorough evaluation of the individual patient's needs and risks. During massive transfusions, fibrinogen concentrate might reduce the risk of fluid overload compared with FFP[12,22,23].

Although fibrinogen concentrate has become more widely used in some countries, it is important to note that there is still a lack of adequate knowledge derived from previous research to support its widespread use. This may be due to the fact that many studies on fibrinogen concentrate have been small, and the results have been mixed. Therefore, more extensive research is needed to fully understand the benefits and risks associated with fibrinogen concentrate use.

Ethics Approval

This study was approved by the University of Health Sciences Istanbul Kanuni Sultan Suleyman Education and Training Hospital Ethics Committee (No. 2019.01.18).

Informed Consent

Written informed consent was not obtained because this study was a retrospective study.

Conflict of Interest
The authors declare that they have no conflict of interest.

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Authors' Contributions
All authors read and approved the final manuscript. Methodology, data collection, data
collection, writing, review, supervision.

Data Availability
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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