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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

KORONER ARTER BAYPAS GERFT OPERASYONLARINDA KARDİYOPULMONER BAYPASTAN SONRA UYGULANAN FİBRİNOJEN İNFÜZYONUNUN KANAMA ÜZERİNE ETKİSİ: RETROSPEKTİF KARŞILAŞTIRMALI ÇALIŞMA

THE EFFECT OF FIBRINOGEN INFUSION APPLIED AFTER CARDIOPULMONARY BYPASS ON BLEEDING IN CORONARY ARTERY BYPASS GRAFT SURGERY: RETROSPECTIVE COMPARATIVE STUDY

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ÖZET

AMAÇ: Açık kalp cerrahisinde ciddi bir sorun olmaya devam eden postoperatif kanamanın riskini azaltmak için uygulanan fibrinojen konsantrelerinin etkisi tartışmalıdır. Koroner arter baypas greftleme operasyonlarında (KABG) kardiyopulmoner baypas (KPB) sonrası uygulanan fibrinojen infüzyonunun postoperatif kanama üzerine etkisini sunmayı amaçladık.

GEREÇ VE YÖNTEM: Çalışmaya, KABG yapılan ve fibrinojen düzeyleri KPB sonrası 2.5 g/L altında ölçülen 67 hasta dahil edildi. Fibrinojen konsantresi verilen 32 hastanın (Grup F; n=32 hasta) verileri, fibrinojen konsantresi verilmeyen 35 hastanın verileri ile (Grup NF; n=35 hasta) karşılaştırıldı.

BULGULAR: KPB sonrası fibrinojen düzeylerini 2,5 g/L ve üzerine çıkarmak için hastalara fibrinojen konsantresi uygulandı. KPB sonrası fibrinojen seviyeleri, her iki grup için preoperatif seviyelere göre anlamlı olarak azaldı (p<0.01), ancak azalma oranı açısından gruplar arasında fark yoktu (p=0.321). Grup F'deki hastalara 2,94±0,91 g fibrinojen uygulandı. Gruplar arası postoperatif drenaj hem 0-12 saat (p=0,142) hem de 12-24 saat (p=0,309) arasında anlamlı değildi.

SONUÇ: Fibrinojen konsantresi, düşük plazma fibrinojen düzeylerini artıran ikincil etkilerle postoperatif drenaj miktarını azaltabilir ve pıhtılaşma fizyolojisinin düzelmesine katkıda bulunabilir. Ancak bu azalma istatistiksel olarak anlamlı olmadığı için fibrinojen konsantrelerinin sadece kanama riski yüksek hastalarda ve KPB sonrası fibrinojen düzeyi <1.5 g/L'nin altında olan hastalarda kullanılması gerektiğini düşünüyoruz.

ANAHTAR KELİMELER: Fibrinojen, Koroner arter baypas cerrahisi, Postoperatif kanama

ABSTRACT

OBJECTIVE: The effect of administered fibrinogen concentrates in reducing the risk of postoperative bleeding that remains a serious problem in open heart surgery is controversial. We aimed to present the effect of fibrinogen concentrates on postoperative bleeding applied after cardiopulmonary bypass (CPB) in coronary artery bypass grafting (CABG).

MATERIAL AND METHODS: 67 patients who underwent CABG and measured below 2.5 g / L fibrinogen after CPB were included in the study. Data of 32 patients (Group F; n=32 patients) who were given fibrinogen concentrate were compared with 35 patients (Group NF; n=35 patients) who were not given fibrinogen concentrate.

RESULTS: After CPB, fibrinogen concentrate was applied to patients in order to increase fibrinogen levels to 2.5 g/L and above. For both groups, fibrinogen levels decreased significantly after CPB compared to preoperative levels (p<0.01), however, there was no difference between the groups in terms of reduction rate (p = 0.321). 2.94±0.91 g fibrinogen was administered to the patients in Group F. Postoperative drainage between the groups was not significant in both the 0-12 hour period (p=0.142) and 12-24 hour period(p = 0.309).

CONCLUSIONS: Fibrinogen concentrate may reduce the amount of postoperative drainage with secondary effects which increased low plasma fibrinogen levels and contributes to recovery of coagulation physiology. However, because this decrease was not statistically significant, we think that fibrinogen concentrates should be used only in patients with a high risk of bleeding and in patients with fibrinogen levels below <1.5 g/L after CPB.

KEYWORDS: Fibrinogen, Coronary artery bypass graft, Postoperative bleeding

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INTRODUCTION

Fibrinogen, which is synthesized in the liver and is an acute phase reactant, plays an important role in coagulation due to its effect on platelet activation and insoluble clot form (1). Many factors such as the foreign surface effect of cardiopulmonary bypass (CPB) circuits used in cardiac surgery, CBP-related reactions, hypothermia and hemodilution lead to a decrease in fibrinogen levels (2). The relationship between fibrinogen levels and the amount of postoperative bleeding has been described in the literature (3). However, the determinants of bleeding in open heart surgery are multifactorial and especially CPB causes abnormalities in the hemostasis system, making hemostasis management difficult (3,4). On the other hand, bleeding-related reoperation and massive blood transfusion increase both mortality and morbidity rates, and prolonged hospital stay (5). Today, specific coagulation factor concentrates are widely used to facilitate hemostatic strategies and reduce allogeneic blood use. Especially fibrinogen concentrate is preferred more frequently because of the low risk of contamination (6). In fact, the use of fibrinogen concentrates has become popular after the first pilot study proving that postoperative bleeding rates can be reduced (7). In the literature, the results of studies on the effect of fibrinogen concentrate on postoperative bleeding are controversial (7-9). However, fibrinogen concentrate was used in different doses in these studies.

In this study, we aimed to investigate whether the amount of postoperative bleeding is statistically significant compared to patients with or without fibrinogen concentrate, based on the fibrinogen levels measured immediately after CPB.

MATERIAL AND METHODS

The patients were informed about the use of fibrinogen in the preoperative period. Between June 2014 and June 2016, 67 patients who underwent CPB with CPB and had fibrinogen levels below 2.5 g/L just after CPB were included in the study. These patients were divided into two groups as 32 patients who were given fibrinogen concentrate (Group F; n=32 patients) and 35 patients who were not given fibrinogen concentrate (Group NF; n=35 patients). Patients under 18 years of age, bleeding diathesis, history of anticoagulant medication in the last 7 days, patients with chronic kidney failure, percutaneous coronary intervention (PCI) in the last month, patients with mechanical support device applied preoperatively or postoperatively, patients which died early or without CPB and emergency surgical procedures were excluded from the study.

As the demographic findings and laboratory tests of the patients, HbA1c (%), blood urea nitrogen (BUN, mg/dL), creatinine (Cr; mg/dL), hemoglobin (Hb; g/L), hematocrit (Htc;%), platelet number (PLT, cell/µL), partial thromboplastin time (aPTT, seconds), prothrombin time (PT, seconds), international normalized rate (INR,%), aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L) and fibrinogen (g/L) values were recorded.

Fibrinogen (g/L) levels were measured in the preoperative period, immediately after CPB and at the 12th and 24th hours of postoperative follow-up with the Clauss method, and the results of the fibrinogen value studied in an average of 10 minutes with this method were obtained within 15 minutes via the electronic patient file system of our hospital. Fibrinogen threshold value after CPB was accepted as 2.5 g/L (10). In order to increase the fibrinogen levels below the threshold value defined as the target level to 2.5 g/L and above, patients were administered fibrinogen concentrate (Haemocomplettan©P CSLBehring, Marburg, Germany) by weight. The fibrinogen concentrate dose was calculated with the formula below based on the fibrinogen value measured immediately after (11) CPB:

$$\text{Fibrinogen dose } \left(\frac{\text{mg}}{\text{kg}}\right) = \frac{[\text{Target level(g/l)} - \text{Measured level(g/l)}]}{0.017}$$

The dose of fibrinogen concentrate determined by weight was given as an intravenous infusion within 15 minutes by dissolving with 50 ml of saline before the sternum was closed.

Surgical procedures were performed with CPB. CPB perfomed with a membrane oxygenator and non-pulsatile roller pump was maintained under moderate hypothermia (rectal tempera-

ture 32-340C) with an average arterial pressure of 60-80 mmHg and activated clotting time (ACT)>480 seconds. When the CPB was terminated, the effect of heparin was neutralized with protamine sulfate with 1: 1 ratio.

In the postoperative period, laboratory values and the amount of drainage from the chest tubes were recorded. The first 12-hour drainage amount postoperatively, according to Universal Definition of Perioperative Bleeding criteria (12); defined as mild (600-800 ml), moderate (801-1000 ml) and heavy (≥1000 ml) bleeding. The count of erythrocyte suspensions, fresh frozen plasma and platelet suspensions administered to the patients during their hospitalization were recorded.

Ethical Committee

This retrospective comparative study was approved by the ethics committee of our hospital (decision 20.05.2014/10-49), in accordance with the Helsinki Declaration Principles and patient information was obtained from the patient files of our clinic.

Statistical Analysis

Data analyzes were performed with the IBM® SPSS (Statistical Package for the Social Sciences) 21.0 program. Suitability of variables to normal distribution was determined by Shapiro-Wilk test. Variables that are suitable for normal distribution are given as mean ± standard deviation, and variables that are not suitable are given as median. Categorical variables were given in frequency (percent). Student t test was used for continuous numerical data and chi-square test was used for categorical data. In the evaluation of repeated measurements, two-way analysis of variance (Repeated Measures two-way ANOVA) and Bonferroni correction were used for repeated measurements for variables suitable for normal distribution. The quantities of changes that do not fit the normal distribution were compared with the Mann Whitney U test and Paired-samples t test. The relationship between postoperative bleeding amount and applied fibrinogen concentrate was evaluated by Post-hoc analysis. Situations where P values were below 0.05 were considered statistically significant.

RESULTS

The demographic and clinical features of the patients are given in **Table 1**. The average age of 32 patients (Male/Female; 23/9) in Group F was 63.5 ± 7.3 years and the average age of 35 patients (Male/Female; 25/10) in Group NF was 64.2±9.8 years. There was no difference between the groups in terms of age (p = 0.736), gender distribution (p = 0.968), weight (p = 0.576), ejection fraction (EF; p = 0.646) and Euroscore II values (p = 0.121). 25 of 33 diabetic patients were on insulin therapy. None of the patients had bleeding diathesis, kidney failure, acute myocardial infarction and a history of PCI in the past month.

Table 1: Demographic and clinical features of patients

	Group F (n=32)	Group NF (n=35)	p value
Age, years	63.5±7.3	64.2±9.8	0.736
Male , n, %	23(71.9%)	25 (71.4%)	0.592
Patient weight, kg	76.0±8.7	77.1±8.2	0.576
Smoker	14 (43.8%)	15 (42.9%)	0.941
DM	14 (43.8%)	19 (54.3%)	0.389
HT	16 (50%)	17 (48.6%)	0.907
COPD	8 (25%)	10 (28.6)	0.742
EF, %	52.7±8.7	51.8±8.5	0.646
Hb, g/dL	15.1±1.0	14.9±0.7	0.328
Htc, %	45.6±4.3	44.3±3.0	0.135
PLT, hücre/µL	250.9±56.6	251.1±63.3	0.994
BUN, mg/dL	16.5±5.8	17.1±3.9	0.821
Cr, mg/dL	0.91±0.1	0.95±0.3	0.386
ALT, U/L	23.5±8.7	22.6±8.9	0.977
AST, U/L	20.1±8.5	19.6±8.1	0.950
aPTT, second	28.4±4.1	28.5±5.3	0.970
PT, second	14.8±2.8	14.5±3.4	0.666
INR, %	1.02±0.08	1.03±0.09	0.596
HbA1c, %	6.5±1.7	6.7±1.5	0.425
Fibrinogen, g/L	3.42±0.38	3.37±0.35	0.585
Euroscore II	1.87±0.85	1.58±0.97	0.121
CPB duration, minutes	83.6±14.0	80.2±12.9	0.310
Distal anastomosis number	3.4±0.8	3.3±0.7	0.393

DM, diabetes mellitus; HT, hypertantion; COPD, chronic obstructive pulmonary disease; EF, ejection fraction of lef ventricle; Hb, hemoglobin; Htc, hematocrit; PLT, platelet; BUN, blood urine nitrogen; Cr, creatinin; ALT, alanin aminotransferase; AST, aspartate aminotransferase; aPTT, activated partial thromboplastin time; PT, prothrombi time; INR, international normalized rate

Patients were operated by the same team. Between groups, the duration of CPB (83.6±14.0 vs 80.2 ± 12.9 minutes, p=0.310, respectively) and the number of distal anastomoses (3.4 ± 0.8 vs 3.3 ± 0.7, p=0.393, respectively) were similar. After CPB, fibrinogen values were significantly decreased in both groups compared to preoperative values (p <0.01). The reduction rate of fibrinogen was similar in comparison between groups (Mann-Whitney test corrected value; p = 0.321) **(Table 2)**.

Table 2: Fibrinogen values by time

Time	Group F, n=32	p*	Group NF, n=35	P*	Difference between two groups	p≠ value
Preoperative value	3.42±0.38		3.37±0.35		0.58±0.1	0.585
Post-CPB value		<0.01		<0.01		
(Min-max.)	1.90±0.24		1.95±0.25		0.05±0.3	0.321
	(1.45-2.41)		(1.22-2.35)			
Postoperative value						
12. hour	3.29±0.29		2.77±0.28		0.53±0.3	<0.01
		<0.01		<0.01		
24. hour	4.18±0.38		3.64±0.34		0.54±0.5	<0.01

CPB, cardiopulmonary bypass; p*, value compared within groups; p≠, comparison value between two groups

It was observed that fibrinogen values decreased more as the duration of CPB increased (p <0.01). According to the fibrinogen values measured after CPB, 2.94 ± 0.91 g fibrinogen concentrate was administered to Group F patients according to the formula (mg/kg). Fibrinogen levels measured after CPB were compared with values measured at 12th and 24th hours postoperatively. According to the values measured after CPB, the increase in fibrinogen values at the 12th and 24th hours was significant for both groups (p<0.01), however, in the comparison between groups, the increase in fibrinogen value was greater for Group F Table 2.

In the postoperative period, drainage amounts from the mediastinum and thorax tubes were evaluated for the first 12 hours (0-12) and 12-24 hours in milliliters. Although the amount of drainage was lower in both follow-ups in Group F, there was no significant difference. Drainage amounts were 476.5 ± 219.5 ml in Group F and 554.2 ±241.4 ml in Group NF (p=0.142) in the first 12 hours and 228.1 ± 82.2 ml in Group F and 248.5±80.8 ml in Group NF between 12 - 24 hours (p=0.309). In addition, in the regression analysis; no correlation was found between the increase in fibrinogen level and the amount of drainage in the first 12 hours (p = 0.433) and at 12-24 hours (p = 0.531). In post-hoc regression analysis, prolonged aPTT values were associated with postoperative drainage rate (Odds Ratio 0.53; p <0.01). It was noted that platelet count (p =0.028) and aPTT time (p =0.033) improved faster than Group NF in the fibrinogen group. In addition, there was no difference in erythrocyte suspension (p=0.169), fresh frozen plasma (p=0.370) and platelet suspension (p=0.314) used in both groups. Two patients in Group F and five patients in Group NF were revised within 12 hours postoperatively due to heavy bleeding (≥1000 ml) (p=0.253) **(Table 3)**. Although there is no statistical difference, this may point to the role of fibrinonegen in the coagulation cascade and that bleeding may be multifactorial.

Allergic reaction, thrombotic event and myocardial infarction did not occur in any patient.

Table 3: Postoperative features of patients

	Group F, n=32	Group NF, n=35	p value
Drainage, ml			
0-12 hour	476.5±219.5	554.2±241.4	0.142
12-24. hour	228.1±82.2	248.5±80.8	0.309
Hb, g/dL			
0-12. hour	9.7±1.0	9.4±1.1	0.160
12-24. hour	10.3±0.5	10.0±0.6	0.322
Htc, %			
0-12. hour	28.3±2.7	27.4±2.5	0.149
12-24. hour	31.2±3.4	30.5±3.1	0.216
PLT, cell/µL			
0-12. hour	148.7±55.3	139.8±49.5	0.028
12-24. hour	163.6±72.4	151.3±52.8	0.041
aPTT, second			
0-12. hour	39.4±10.8	46.2±16.7	0.033
12-24. hour	29.1±8.3	37.5±12.1	0.039
PT, second			
0-12. hour	19.9±3.7	23.6±4.2	0.090
12-24. hour	15.6±2.4	18.2±3.1	0.106
ES	1.56±0.7	1.71±0.5	0.169
FFP	2.4±1	2.6±0.7	0.370
PS	0.16±0.3	0.2±0.4	0.314
Revision, n, %	2 (6.2%)	5 (14.2%)	0.253

Hb, hemoglobin; Htc, hematocrit; PLT, platelet, aPTT, activated partial thromboplastin time; PT, prothrombin time; ES, erythrocyte suspension; FFP, fresh frozen plasma; PS, platelet suspension

DISCUSSION

This study showed that plasma fibrinogen levels were significantly reduced after CPB, and a faster increase in fibrinogen levels was achieved with the administered fibrinogen concentrate (p<0,01), but had no statistically significant effect on bleeding in the postoperative period (p = 0.142 for the first 12 hours).

Postoperative bleeding continues to be an important condition since it increases morbidity rates, the number of uses of allogeneic blood products and hospital costs in open heart surgery, as well as causing more than half of re-operations (13, 14). Therefore, preventive measures such as autologous blood transfusion, antifibrinolytic agents and coagulation factor concentrates have been developed to prevent complications of bleeding (6, 15,16).

It is critical in fibrinogen coagulation and it is recommended to maintain plasma levels above 1.5 g / L (17). Causes such as foreign surface effect of CPB, hemodilution and consumption coagulopathy cause a decrease in fibrinogen levels (3, 9, 16). In addition, the first coagulation factor affected by major bleeding is fibrinogen (18). This has made the use of fibrinogen, a coagulation factor concentrate, popular in patients undergoing cardiac surgery (6, 7, 19).Ternström et al. (20) stated that fibrinogen operations before the next two hours, but after 24 hours

were reduced to about 50% of said increased expression. in coronary artery bypass surgery with CPB, Momeni et al.,(21). Emphasized that fibrinogen levels decreased significantly after CPB and when the patient came to the intensive care unit compared to off-pump CABG. We obtained similar results in our study. It was found that the fibrinogen levels of all patients decreased after the CPB compared to the preoperative values ($p < 0.01$) and in the correlation analysis, this decrease was associated with the duration of the CPB ($p < 0.01$). In the 12th and 24th hour measurements, it was observed that the fibrinogen level increased and this increase was higher in the group given the fibrinogen concentrate (Group F) ($p < 0.01$).

Although it has been shown in many studies that the decrease in fibrinogen levels is associated with postoperative bleeding, in the meta-analysis published by Gielen et al., (2), it was stated that there was weak-moderate correlation (22). Alagha et al., (23) emphasized that fibrinogen levels below 3.1 g/L were associated with bleeding in their measurements in 550 patients undergoing CABG. Ranucci et al. (10) reported the fibrinogen threshold value as 2.5 g/L. Kindo et al. (5), published that fibrinogen values measured in the postoperative early period were more important in determining the risk of bleeding. In our study, we accepted the fibrinogen threshold value of 2.5 g/L. In group NF, although the average fibrinogen levels after KPB decreased below 2 g/L (1.95 ± 0.25), we did not detect correlation with the amount of drainage ($p=0.448$ for the first 12 hours; $p=0.509$ for 12-24 hours). This may possibly be due to the corrective effect of fibrinogen in coagulation physiology, such as the fibrinogen's significant increase in the first 12 hours in the postoperative period, the reduction of aPTT times ($p < 0.05$) and the increase in the number of PLT ($p < 0.05$) (24).

After the first pilot study (7) investigating the effect of exogenous fibrinogen on postoperative bleeding in coronary bypass graft operation fibrinogen concentrates have started to be used in many areas of open heart surgery (9, 19, 25).

In terms of the homogeneity of the study, we included only patients who underwent CABG. There is no exact information or guideline in the literature about the dose of fibrinogen to be administered (26). In the guide published by the European Society of Anesthesiology in 2017, the starting dose of fibrinogen concentrate was defined as 25-50 mg/kg as the level of evidence '2C'. (27). Karlsson et al. (7), used 2 g of fibrinogen concentrate preoperatively in twenty disease pilot studies, while Sadeghi et al. (28) applied 1 g of fibrinogen 30 minutes before anesthesia induction. Solomon et al [9] and Rahe-Meyer et al. (29) suggested using high-dose (average 5-8 g) fibrinogen to reduce the risk of bleeding in open heart surgery, but their studies do not include isolated CABG. We used the fibrinogen dosage formula stated in the manufacturer's package and FDA (Food and Drug Administration) based on the fibrinogen levels after CPB. Accordingly, we administered an average of 2.94 ± 0.91 g fibrinogen concentrate in Group F. This dose we administered increased the fibrinogen level faster for Group F, and this increased value was found to be more significant than Group NF (the difference between groups for the 12th hour measurement was 0.53 ± 0.3 g; $p < 0.01$).

Although there was a significant increase in fibrinogen levels and less drainage in group F, no statistical difference was found between the two groups (Table 3). Our results are compatible with the results of some studies mentioned in the literature (30 - 32).

Lupu et al. (33), stated that 1 gr fibrinogen concentrates administered in their retrospective studies did not affect bleeding. The long duration of CPB in patients who administered fibrinogen suggests that it could not provide sufficient increase in fibrinogen levels. Bilecen et al. (28) attributed the 2 gr dose of fibrinogen not to be effective for postoperative bleeding, the application of the fibrinogen dose at low doses, and the low doses of fibrinogen not showing enough hemostatic effects. Rahe-Meyer et al. (34), in the REPLACE studies, described the high dose fibrinogen applied after CPB as an unexpected finding that unlike previous studies, the amount of bleeding and the use of allogeneic blood was ineffective. In our study, we administered a fibrinogen concentrate to exceed the target value by weight. In Group F, although not statistically significant, less drainage than the group without fibrinogen suggests that fib-

rinogen acts as a major factor in the coagulation pathway. Because fibrinogen concentrate causes rapid rise of plasma fibrinogen levels and increases both clot formation rate and clot strength (24, 34).

In our post-hoc regression analysis, we found that prolonged aPTT values increased postoperative drainage risk (Odds Ratio 0.53; $p<0.01$). The shorter aPTT duration ($p<0.05$) and higher platelet count ($p<0.05$) in the fibrinogen-treated group support that fibrinogen may contribute with secondary effects on the amount of drainage (9, 30). The fact that Ranucci et al. (35) stated that the amount of bleeding was lower in thrombocytopenic patients with high fibrinogen levels supports this situation. Fibrinogen plays an important role in binding FXIII to clot stabilization and has a central role in platelet activation and aggregation by binding to the platelet glycoprotein receptor GPIIb/IIIa (36). Although there was no difference in the amount of drainage, the drainage rate in Group F was lower than in group NF. (476.5±219.5 and 554.2±241.4 for the first 12 hours; 228.1±82.2 and 248.5±80.8 for the 12-24 hours, respectively).

There are some important factors that limit this study. These are the study's retrospective and low number of patients, the application of fibrinogen dose by calculating the target fibrinogen level with the help of a formula without using fibroelostometry (ROTEM, FIBTEM MCF; EXTEM CT vb.) (37). Due to the expensive fibrinogen concentrates, we determined the target fibrinogen value to be 2.5 g/L and therefore having to use less dose of fibrinogen may have affected the results of the study. We believe that prospective studies with different threshold values will be more beneficial.

Fibrinogen level decreases significantly in patients undergoing CPB compared to preoperative values. We believe that the fibrinogen concentrate can reduce the amount of drainage by secondary effect, contributing to increased plasma fibrinogen levels and rapid recovery of coagulation physiology. According to the results of this study, although we do not encounter side effects with the use of fibrinogen, we think that it should be used only in patients with a high risk of bleeding and with a fibrinogen level <1.5 g/L after CPB, since the cost of the drug will increase hospital costs.

REFERENCES

1. Kannel WB. Overview of hemostatic factors involved in atherosclerotic cardiovascular disease. Lipids. 2005;40(12):1215-20.

2. Gielen C, Dekkers O, Stijnen T, et al. The effects of pre- and postoperative fibrinogen levels on blood loss after cardiac surgery: a systematic review and meta-analysis. Interactive CardioVascular and Thoracic Surgery. 2014;18:292–9.

3. Ucar HI, Oc M, Tok M, et al. Preoperative Fibrinogen Levels as a Predictor of Postoperative Bleeding after Open Heart Surgery. The Heart Surgery Forum. 2007;10(5):392-6.

4. Paparella D, Brister SJ, Buchanan MR. Coagulation disorders of cardiopulmonary bypass: a review. Intensive Care Med. 2004;30:1873–81.

5. Kindo M, Minh TM, Gerelli S, et al. Plasma fibrinogen level on admission to the intensive care unit is a powerful predictor of postoperative bleeding after cardiac surgery with cardiopulmonary bypass. Thrombosis Research. 2014;134(2):360-8.

6. Cardoso TAAM, Neto CN, Silva CGS, et al. Use of lyophilized fibrinogen concentrate in cardiac surgery: a systematic review. Heart, Lung and Vessels. 2015;7(1):47-53.

7. Karlsson M, Ternström L, Hyllner M, et al. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. Thromb. Haemost. 2009;102:137–44.

8. Jeppsson A, Waldén K, Roman-Emanuel C, et al. Preoperative supplementation with fibrinogen concentrate in cardiac surgery: A randomized controlled study. British Journal of Anaesthesia. 2016;116(2):208-14.

9. Solomon C, Pichlmaier U, Schoechl H, et al. Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. Br J Anaesth. 2010;104(5):555–62.

10. Ranucci M, Jeppsson A, Baryshnikova E. Pre-operative fibrinogen supplementation in cardiac surgery patients: an evaluation of different trigger values. Acta Anaesthesiol Scand. 2015;59(4):427-33.

11. https://www.fda.gov/downloads/Biolog...inonatedPlasmaProducts/ucm094006.pdf Erişim Tarihi: 13.12.2016.

12. Dyke C, Aronson S, Dietrich W, et al. Universal definition of perioperative bleeding in adult cardiac surgery. J Thorac Cardiovasc Surg. 2014;147:1458–63.

13. Ateş M, Kayacıoğlu İ, Şaşkın H ve ark. Açık Kalp Cerrahisi Sonrası Kanama Nedeniyle Yapılan Revizyon Ameliyatları (2 Yıllık İzlem). Türk Göğüs Kalp Damar Cer Derg. 2003;11:207-10.

14. Pavie A, Szefner J, Leger P, Gandjbakhch I. Preventing, minimizing, and managing postoperative bleeding. Ann Thorac Surg. 1999;68:705-10.

15. Kurnaz F, Ulaş T. Antifibrinolitik Ajanlar. Turkiye Klinikleri J Hematol-Special Topics. 2016;9(4):63-7.

16. Blome M, Isgro F, Kiessling AH, et al. Relationship between factor XIII activity, fibrinogen, haemostasis screening tests and postopera-tive bleeding in cardiopulmonary bypass surgery. Thromb Haemost. 2005;93:1101-7.

17. Levy HJ, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. Transfusion. 2014;54(5):1389-405.

18. Hiippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg. 1995;81(2):360-5.

19. Esmaeelzadeh M, Amini Sh, Soltani Gh, et al. Exogenous Fibrinogen Pertains Beneficial Effects in Managing Post-Cardiac Surgery Bleeding: A Randomized Clinical Trial. J Cardiothorac Med. 2016;4(3):474-9.

20. Ternström L, Radulovic V, Karlsson M, et al. Plasma activity of individual coagulation factors, hemodilution and blood loss after cardiac surgery: a prospective observational study. Thromb Res. 2010;126(2):128-33.

21. Momeni M, Carlier C, Baele P, et al. Fibrinogen Concentration Significantly Decreases After On-Pump Versus Off-Pump Coronary Artery Bypass Surgery: A Systematic Point-of-Care ROTEM Analysis. Journal of Cardiothoracic and Vascular Anesthesia. 2013;27(1):5-11.

22. Karlsson M, Ternström L, Hyllner M, et al. Plasma fibrinogen level, bleeding, and transfusions after on-pump coronary artery bypass grafting surgery: a prospective observational study. Transfusion. 2008;48:2152-8.

23. Alagha S, Songur M, Avcı T, et al. Association of preoperative plasma fibrinogen level with postoperative bleeding after on-pump coronary bypass surgery: does plasma fibrinogen level affect the amount of postoperative bleeding? Interactive CardioVascular and Thoracic Surgery. 2018;27:671–6.

24. Kamath S, Lıp Gyh. Fibrinogen: biochemistry, epidemiology and determinants. Q J Med. 2003;96:711–29.

25. Ranucci M, Pistuddi V, Baryshnikova E, et al. Fibrinogen Levels After Cardiac Surgical Procedures: Association With Postoperative Bleeding, Trigger Values, and Target Values. Ann Thorac Surg. 2016;102:78–85.

26. Ranucci M. Fibrinogen supplementation in cardiac surgery: where are we now and where are we going? J Cardiothorac Vasc Anesth. 2013;27(1):1-4.

27. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol. 2017;34:332–95.

28. Sadeghi M, Atefyektaa R, Azimaraghi O, et al. A randomized, double blind trial of prophylactic fibrinogen to reduce bleeding in cardiac surgery. Rev Bras Anestesiol. 2014;64(4):253-7.

29. Rahe-Meyer N, Solomon C, Hanke A, et al. Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. Anesthesiology. 2013;118:40-50.

30. Bilecen S, Peelen LM, Kalkman CJ, et al. Fibrinogen concentrate therapy in complex cardiac surgery. J Cardiothorac Vasc Anesth. 2013;27(1):12-7.

31. Jeppsson A, Waldén K, Roman-Emanuel C, et al. Preoperative supplementation with fibrinogen concentrate in cardiac surgery: A randomized controlled study. Br J Anaesth. 2016;116(2):208-14.

32. Yang L, Vuylsteke A, Gerrard C, et al. Postoperative fibrinogen level is associated with postoperative bleeding following cardiothoracic surgery and the effect of fibrinogen replacement therapy remains uncertain. J Thromb Haemost. 2013;11:1519–26.

33. Lupu LM, Rebaine Z, Lhotel L, et al. Low-dose Human Fibrinogen is not Effective in Decreasing Postoperative Bleeding and Transfusion Requirements during Cardiac Surgery in Case of Concomitant Clinical Bleeding and Low FIBTEM Values: A Retrospective Matched Study. Ann Card Anaesth. 2018;21(3):262–9.

34. Rahe-Meyer N, Levy JH, Mazer CD et al. Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy. Br J Anaesth. 2016;117(1):41-51.

35. Ranucci M, Baryshnikova E, Ranucci M, et al. Fibrinogen levels compensation of thrombocytopenia-induced bleeding following cardiac surgery. International Journal of Cardiology. 2017;219:96-100.

36. Velik-Salchner C, Haas T, Innerhofer P, et al. The effect of fibrinogen concentrate on thrombocytopenia. J Thromb Haemost. 2007 May;5(5):1019-25.

37. Ranucci M, Baryshnikova E, Crapelli GB, et al. Randomized, Double-Blinded, Placebo-Controlled Trial of Fibrinogen Concentrate Supplementation After Complex Cardiac Surgery. J Am Heart Assoc. 2015;4:e002066.