Journal of
Cardio - Thoracic Medicine

http://jctm.mums.ac.ir

Exogenous Fibrinogen Pertains Beneficial Effects in Managing Post-Cardiac Surgery Bleeding: A Randomized Clinical Trial

Mohammad Esmaeelzadeh[1], Shahram Amini[2]*, Ghasem Soltani[1], Mohammad Abbasi Tashnizi[3], Mathias Hossein Azami[4]

[1] *Anesthesiologist, Department of Anesthesiology and Critical Care, Mashhad University of Medical Sciences, Mashhad, Iran*
[2] *Anesthesiologist, Cardiac Anesthesia Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[3] *Cardiac Surgeon, Cardio-Thoracic Surgery & Transplant Research Center, Emam Reza hospital, Faculty of medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*
[4] *Cardiac Surgeon, Department of Cardiac Surgery, Kurdestan University of Medical Sciences, Kordestan, Iran*

ARTICLE INFO

Article type:
Original Article

Article history:
Received: 22 Feb 2016
Revised: 26 Jun 2016
Accepted: 15 Aug 2016

Keywords:
Cardiac Surgery
Fibrinogen
Postoperative Bleeding

ABSTRACT

Introduction: Post cardiac surgery hemorrhagic syndromes, potentialized by implementing cardiopulmonary bypass, leads to increased hazards of blood products transfusion and pertains serious impacts on immediate patients outcome.
The objective of this clinical trial was to investigate the efficiency of exogenous fibrinogen to control hemorrhagic syndromes following cardiac surgery in the intensive care unit.
Materials and Methods: Eighty patients undergoing open heart surgery at Imam Reza Hospital, Mashhad, Iran with blood drainage more than 200 ml per hour were randomly divided to receive either fibrinogen 2 grams or placebo. The patients were investigated for amount of blood drainage, units of required blood product, length of stay in intensive care unit (ICU), and mortality.
Results: The first early 3-hours drainage (443.97±169.98 vs 606.66±235.93ml; p value =0.001) and total first 24 hours drainage (1025.30 ml and 1377.60 ml; p value: 0.041) showed significant difference in favor of fibrinogen receiving group. The fibrinogen group required significantly lesser units of red blood cells, and fresh frozen plasma (FFP) (1.62 and 2.55) compared to placebo group (2.74 and 3.21) (p values: 0.010 and 0.032). Platelets units requirement did not reach significant difference between the groups. ICU length of stay was shorter in fibrinogen group (2.82 days versus 4.02 days; p value 0.045), while mechanical ventilation time did not significantly differ among the two groups. In addition, there was a trend towards decreased early mortality in fibrinogen receiving group (7.5% versus 17.5 % ; *p* value = 0.02).
Conclusion: Administration of low dose of fibrinogen in patients with postoperative bleeding can reduce ongoing and total blood drainage, transfusion of blood products, ICU length and early mortality.

▶ *Please cite this paper as:*
Esmaeelzadeh M, Amini Sh, Soltani Gh, Abbasi Tashnizi M, Azami MH. Exogenous Fibrinogen Pertains Beneficial Effects in Managing Post-Cardiac Surgery Bleeding: A Randomized Clinical Trial. J Cardiothorac Med. 2016; 4(3): 474-479.

Introduction

Postoperative bleeding is a common problem after cardiac surgery sustaining increased mortality and morbidity. Severe bleeding occurs in 3 to 5 percent in patients undergoing cardiac surgery using cardiopulmonary bypass (1). The implicated factors involved in occurrence of postoperative bleeding include incomplete surgical hemostasis, residual heparin effect, clotting factors depletion, hypothermia, depletion / dilution thrombocytopenia, platelet dysfunction, or iatrogenic fibrinolysis states.

Postoperative bleeding usually needs

*Corresponding author: Shahram Amini, Cardiac Anesthesia Research Center, Department of Anesthesiology and Critical Care, Imam Reza Hospital, Ebne Sina Street, Mashhad, Iran. Tel: 0098915 1417235; Email: aminish@mums.ac.ir

transfusions of blood products (BPs) such as red blood cells, FFP, and platelets that is associated with multiple adverse effects including immunologic reactions, volume overload, hypothermia, coagulopathy, citrate toxicity, neuro-cognitive dysfunctions, stroke, or acute lung injury; putting in parallel with increased risks of organ infection, sepsis, and viral transmissions. Increased length of stay (LOS) in intensive care units is well established to be independently correlated with increased requirements for BPs (2). Uncontrolled postoperative bleeding reaching surgical reexploration is known to adversely affect hospital mortality and morbidity (1, 3).

Aiming at lessening to resort to transfuse BPs, non-blood products such as fibrinogen were introduced to reduce the amount of postoperative bleeding leading to favorable outcomes on morbidity in cardiac surgery (2, 4, 5). In line with the latter, recent reports indicated efficient prophylactic actions of exogenous fibrinogen to reduce hazards of postoperative bleeding after cardiac surgery and less BPs transfusions postoperatively (6, 7). The beneficial effects of fibrinogen administration has also been investigated and reported in the setting of major aortic surgery for ongoing bleeding (8-9).

The objective of this prospective randomized clinical trial was to investigate the advocated effects of fibrinogen in the setting of early postoperative bleeding after cardiac. The primary outcome was attempted to determine the effects of exogenous fibrinogen administration on the amount of postoperative bleeding. The secondary outcomes pointed at investigating possible quantitative differences in mean required BPs units, rate of surgical reexploration, mechanical ventilation time, ICU LOS, and hospital mortality.

Materials and Methods

After obtaining informed written consent, eighty adult patients undergoing cardiac surgery with postoperative bleeding more than 200 ml per hour after admission to post-cardiac ICU, Imam Reza Hospital, Mashhad, Iran from October 2013 to February 2014 were included in this clinical trial. Exclusion criteria included massive intraoperative bleeding and transfusions (more than 2 units of red blood cells or any FFP and platelets), use of clopidogrel, Omega 3, and other drugs affecting coagulation preoperatively, known history of coagulopathy, abnormal preoperative coagulation studies, moderate to severe preoperative anemia (Hb less than 10 g/dL), low ejection fraction (less than 40%), use of intraaortic balloon pump (IABP), congenital adult cardiac surgeries, and history of previous cardiac surgeries.

All patients received a standard intravenous anesthesia using a propofol based protocol. Perioperative heparinasation was carried out using 1mg/kg and 0.5mg / kg for patients undergoing on and Off-pump surgery, respectively. Heparin was re-administrated by 0.5mg/ kg if perioperative regular ACT checks were below 400/s. By the end of procedure, heparin reversal was performed by intravenous prothamine according to ¾ of total administrated heparin. Perioperative BPs transfusion was left on the discretion of in charge anesthetist to achieve optimal hemostasis guided by ACT sampling. Patients were transferred to the ICU while intubated, and upon arrival in ICU they were put under analgesia using intravenous paracetamol and fentanyl; being monitored in regards to pulse rates, respiratory rates, 12-leads electrocardiography, pulse oximetry, central venous pressures, and invasive arterial blood pressure.

In the case of ongoing bleeding, all patients were treated by intravenous prothamine sulfate 20 mg and tranexamic acid 15 mg/kg (max 1 gram). Thereafter, the patients received either 2 grams of fibrinogen (n=40) or placebo (normal saline) (n=40) according to a computer based system elaborating randomization. The patients were evaluated by checkpoints of fifteen minutes for amount of bleeding. If the bleeding continued, 2 units of FFP and 1 unit of red blood cells were administered until bleeding stopped. The patients were taken back to the theater for explorative re-sternotomy if the blood drainage would reach 400, 800 or 1000 ml in the first, second, the third postoperative hours after ICU admission, respectively, or in the case of hemo-dynamic deterioration regardless of bleeding output.

Four platelets units were used primarily for patients underwent on pump procedures in the case of ongoing bleeding, and further at each checkpoint if required. Concerning off-pump patients, platelets were rather transfused only after re-sternotomy and/or in the case of continuing uncontrolled blood drainage; a policy derived on presumed preservation platelets function when avoiding cardio-pulmonary bypass.

Further red blood cells were transfused according to the following algorithm: hemoglobin less than 8, hemoglobin less than 10 with signs of hypoperfusion including $ScVO_2$ less than 70%, lactate more than 4 mmol, or requiring vasopressor or inotropes to maintain mean arterial blood pressure more than 70 mmHg.

The patients were extubated according to the local weaning protocol using pressure support ventilation within 6 hours if awake, hemo-dynamically stable, not requiring high dose inotrope or vasopressor, absence of perioperative MI, with acceptable biologic indicators, adequate

respiratory function mechanics including blood gas sampling, and no more than 50 ml hourly drainage for the last 2 hours.

The patients were investigated for amount of bleeding hourly and totally in the first 24 hours, the number of units of transfused BPs (including red blood cells, FFP, and platelets), rate of mandated re-sternotomy, duration of mechanical intubation, LOS in ICU, and mortality.

The patient and the one who analyzed the data were blinded to the study.

We considered a difference in total amount of bleeding of 20% to be clinically significant. A sample size of 34 was required to detect such a difference between the groups for a power of 80% at a significance level of 5%. Assuming a 20% missing, we increased the sample size to 40 in each group.

Statistical Analysis

Data were prospectively collected and entered in a SPSS software for Windows, version 11 (SPSS Inc, Chicago, IL, USA) computing descriptive and analytic statistics. Independent student t-tests was used to compare continuous variables exhibiting normal distribution, and chi-squared or Fisher's exact test for non-continuous variables. A p value < 0.05 was considered significant.

Results

All eighty patients (40 in each group) completed the study. The patients were similar with regard to demographic parameters, preoperative ejection fraction, comorbidities including hypertension and diabetes mellitus, hemoglobin level, and coagulation status (Table 1).

There was also no significant difference between the both groups when it comes to the frequency of the type of procedures, as well as on-pump surgery (Table 2).

The first three-hours (443.97±169.98 vs 606.66±235.93ml; *P* value=0.001) and total drainage volumes in the first 24 hours (955.52±364.30 and 1426.62±742.26 ml; *P* value=0.001) were significantly different between fibrinogen receiving and placebo groups, respectively. The patients in the fibrinogen group required less red blood cells and FFP units in the first 24 hour hours. However, the amount of transfused platelets units did not differ among the both groups (Table 3).

Sixteen patients (40%) in the fibrinogen and 17 patients (42.5%) in the control group met aforementioned criteria for re-sternotomy (*P* value= 0.74), displaying surgical failure in 1(2.5%) and 2(5%) patients belonging to the off-pump CABG wing of fibrinogen and placebo groups, respectively. Although the patients in the placebo group required longer mechanical ventilation, there was no significant difference with respect to its duration between the two groups. LOS in ICU was significantly reduced in fibrinogen group, furthermore, hospital mortality displayed a trend in favor of fibrinogen receiving patients compared to placebo group and reached statistical significance (7.5% and 17.5% in the fibrinogen and placebo group, respectively; *P* value = 0.02) (Table 3).

Table 1. Patients' characteristics

Characteristic	Fibrinogen	Placebo	*P value*
Age (years)	60.35±8.09	58±10.68	0.27
Gender (male: female)	33:7	30:10	0.41
Diabetes	8(21.1%)	12(30%)	0.38
Hypertension	12(30%)	15(37.5%)	0.38
Preoperative EF(%)	48.15±11.07	48.46±10.07	0.89
PT(second)	14.82±2.82	14.59±5.26	0.66
PTT(second)	36.22±13.61	38.73±28.26	0.65
INR	1.49±1.79	1.20±0.80	0.35
Hb (g/dL)	13.21±1.61	13.87±1.73	0.08
Platelet counts(x1000)	212.97±79.47	246.63±78.24	0.07
Euro II score	2.04± 1.63	1.58 ±0.94	0.12

Data are presented as mean± SD, numbers, or percentage
Prothrombin time (PT)
Partial thromboplastin time (PTT)
international normalized ratio (INR)

Table 2. Surgical data of patients undergoing cardiac surgery in fibrinogen and control group.

	Fibrinogen	Placebo	*P value*
CABG	33(82.5%)	33(82.5%)	0.91
Off-pump CABG	27(67.5%)	26(65%)	0.81
On-pump CABG	6(15%)	7(17.5%)	0.81
Valvular heart surgery	7 (17.5%)	7 (17.5%)	0.91
Pump time (minute)	106.23±78.01	99.17±60.76	0.78
Heparin dose (unit x 1000)	16.62±8.25	18.14±9.56	0.45
Prothamin dose (mg)	168.00±85.40	193.28±97.84	0.22

Data are presented as mean± SD, numbers, or percentage
Coronary Artery Bypass Grafting (CABG)

Table 3. Postoperative data of patients undergoing cardiac surgery in fibrinogen and control group

	Fibrinogen	Placebo	*P value*
Bleeding first 3 hours (ml)	443.97±169.98	606.66±235.93	0.001
Bleeding first 24 hours (ml)	955.52±364.30	1426.62±742.26	0.001
Weaning duration (hours)	10.36±7.7	13.30±4.57	0.28
ICU length of stay (days)	2.85±84	3.62±1.56	0.01
Ward length of stay (days)	4.26±1.33	4.84±3.01	0.33
PT (seconds)	16.02±3.36	15.29±2.64	0.28
PTT (seconds)	68.72±37.22	79.88±64.82	0.24
INR	1.37±52	1.57±0.47	0.09
Hb (mg/dL)	11.29±3.72	13.15±5.38	0.32
Platelets (x 1000)	158.86±62.24	155.57±71.10	0.82
Packed cells (units)	1.46±1.16	2.54±1.26	0.0001
Platelets (units)	0.35±1.16	0.37±1.10	0.92
FFP (units)	1.34±1.54	3.05±1.39	0.0001
Re exploration	16(40%)	17(43.6%)	0.74

Data are presented as mean± SD, numbers, or percentage.
Prothrombin Time (PT)
Partial Thromboplastin Time (PTT)
International Normalized Ratio (INR)
Fresh Frozen Plasma (FFP)

Discussion

Significant bleeding is a common and deleterious clinical issue after cardiac surgery mandating massive BPs transfusions. In the United States, cardiac operations consume as much as 10% to 15% of the nation's blood supply (10). BPs transfusion is seldom effective solely in managing ongoing postoperative bleeding and often leads to surgical re-exploration. Kristensen et al demonstrated an incidence of re-sternotomy due to post-cardiac surgery bleeding approximating 7% (11). In a systematic review BPs transfusions were found to be associated with increased mortality and morbidity including sternal wound infection, acute renal failure, stroke, and prolonged mechanical ventilation (3).

Considering the proven complications issued by BPs transfusions, continuous efforts have been deployed to enhance thrombotic and coagulation pathways in an attempt at less resorting BPs transfusions.

Fibrinogen is an essential component of the clotting system. The normal plasma concentration is between 1.5 and 4.0 g/L. Fibrinogen levels can decrease following cardiac surgery due to, fibrinolysis, hemodilution, depletion, and consumption; its low levels sustains peri- and postoperative bleeding, and are associated with increased requirement in BPs transfusions .

Exogenous fibrinogen has been introduced and used for prevention of bleeding in both adult (6,12) and pediatric cardiac surgery (13, 14). A negative correlation between preoperative fibrinogen and post cardiac surgery bleeding has been pointed out in both adults (15) and children (14); although, a meta-analysis (16) has drawn a significant but weak-to-moderate correlation between pre- and postoperative fibrinogen levels and blood loss after cardiac surgery. Aside former uncertainties, the optimal perioperative protecting levels of fibrinogen in cardiac surgery remain a matter of controversy (17, 18).

Concerns have been raised regarding safer use of exogenous fibrinogen for management of bleeding after cardiac surgery, and uncertainty feeds the appropriate dose of efficiently therapeutic fibrinogen avoiding devastating possible reported thrombotic events. Fassl et al suggested that the administration of low dose fibrinogen concentrates was not associated with thromboembolic complications or adverse outcomes after cardiac surgery (19). However, thrombosis of a patient's brachial artery and the cardiopulmonary bypass circuit has been reported with prophylactic administration of fibrinogen during a complex congenital cardiac surgery (20). In the current study as to operate in safer margins, fibrinogen (2 grams) and tranexamic acid (1gram) were implemented at low doses to prevent thromboembolic complications including graft thrombosis.

The efficiency of exogenous fibrinogen in enhancing postoperative coagulation systems, thereby reducing postoperative blood drainage remains a matter of debates. In two studies reported by Tanaka et al (4) and Gorlinger et al (2, 5) beneficial effects of fibrinogen facing post-cardiac surgery bleeding were deduced. In contrast, Bilecen et al. showed that administration of fibrinogen did not decrease postoperative blood drainage and BPs transfusion during complex cardiac surgery procedures, possibly due to a low dose fibrinogen protocol implemented and its late administration (21). Karlson et al reported that prophylactic infusion of 2 g fibrinogen to patients without hereditary, acquired hypofibrinogenemia, or ongoing bleeding did not improve coagulation and platelet function during cardiac surgery (7).

The results of current study point out on significant reduction in early first 3-hours and total

24-hours blood drainage in the fibrinogen receiving patients compared to placebo group, paralleling significant sparing in the required units of transfused red cell and FFP. The latter stands with expected beneficial action of exogenous fibrinogen to counterbalance iatrogenic disturbances imposed on normally functioning coagulation pathways. Such beneficial effects can be partly imputed to synergistic actions of exogenous fibrinogen and tranxemic acid used in this study as to overwhelm multifactorial genesis of post-cardiac surgery fibrinolysis. Nevertheless, the current results failed to display any significant decrease in transfused platelets units among the both groups receiving or not exogenous fibrinogen. This proves the primordial role of needed functioning platelets, often considered as front liners in managing paradigms fixing postoperative bleeding, (even in off-pump patients). An alternative explanation would be the cultural preoperative herbal auto medication that does inhibit adequate platelets function among Middle-East populations that is difficult to rule out preoperatively.

Despite present proven effects of exogenous fibrinogen in reducing blood drainage and acquired coagulopathy as the main hazard of postoperative bleeding (three surgical failure over 33 resternotomy), this study is far from restructuring surgical paradigms in undertaking mandated resternotomy, touching a more conservative approach. Rather, the latter may highlights that perioperative steps should be taken to optimize hemostasis; especially the univocal place of thromboelastogram in decision-making process and offering precise goal-directed therapies (22-24).

Despite absence of statistical difference in mechanical ventilatory time, exogenous fibrinogen resulted in significantly shorter LOS in ICU among fibrinogen receiving patients compared to placebo group; thereby, providing a therapeutic tool to resources sparing. Furthermore, the hospital mortality was higher in the placebo group. Since, the Euro II score was similar in both groups, the higher mortality rate can be attributed to complications of bleeding, blood transfusion, and reexploration.

Limitations

Our study faced several limitations mainly because of limited resources. Fibrinogen levels were not measured before surgery or at ICU admission depicting differences at baseline and post-procedure between the both groups. This might be a limitation to our study regarding administration of fibrinogen in patients with possible appropriate levels. Other limitations of our study include lack of relying on thrombelastographic monitoring, a low and unadjusted dose of fibrinogen, blood products, and prothamin (if heparin was not completely reversed in the operating room) for all patients.

Our patients comprised different cardiac surgery procedures including both off and on-pump CABG as well as valvular heart surgeries. Although, the effects of fibrinogen should be reevaluated in specific disease sets by further studies, the aim of the current study was designed to investigate beneficial effects of fibrinogen in daily post cardiac surgery practice.

Conclusion

Administrating low dose of exogenous fibrinogen in the setting of ongoing post cardiac surgery bleeding is safe and can decrease blood drainage as well as the need for red blood cells and FFP transfusions. It can also reduce ICU length of stay and portends a trend towards lowering mortality due to reduction the amount of bleeding and its adverse effects. Platelets should be included early in the management of postoperative bleeding paradigms. Exogenous fibrinogen might be incorporated in protocols dealing with ongoing postoperative bleeding, especially when operating cardiac surgery in sub-optimal settings devoided from advanced coagulation monitoring enabling goal-directed therapy.

Acknowledgment

We would like to thank deputy research of Mashhad University of Medical Sciences for its financial support and all nursing personnel at postcardiac surgery ICU at Emam Reza hospital for their contribution to this study especially Mr. Ali Bahush for collecting some data.

This study was approved by research deputy and ethical committee under license no 910249 of Mashhad university of medical sciences and registered at Iran Registry of Clinical Trial (IRCT) under no IRCT2013082714489N1

Conflict of Interest

The authors declare no conflict of interest.

References

1. Woodman RC, Harker LA. Bleeding complications associated with cardiopulmonary bypass. Blood. 1990; 76:1680-97.
2. Görlinger K, Shore-Lesserson L, Dirkmann D, Hanke AA, Rahe-Meyer N, Tanaka KA. Management of hemorrhage in cardiothoracic surgery. J Cardiothorac Vasc Anesth. 2013; 27:S20-34.
3. Biancari F, Mikkola R, Heikkinen J, Lahtinen J, Airaksinen KE, Juvonen T. Estimating the risk of complications related to re-exploration for bleeding after adult cardiac surgery: a systematic review and meta-analysis. Eur J Cardiothorac Surg. 2012; 41: 50–5.

4. Tanaka KA, Egan K, Szlam F, Ogawa S, Roback JD, Sreeram G, et al. Transfusion and hematologic variables after fibrinogen or platelet transfusion in valve replacement surgery: preliminary data of purified lyophilized human fibrinogen concentrate versus conventional transfusion. Transfusion. 2014; 54:109-18.
5. Görlinger K, Dirkmann D, Hanke AA. Potential value of transfusion protocols in cardiac surgery. Curr Opin Anaesthesiol. 2013; 26:230-43.
6. Sadeghi M, Atefyekta R, Azimaraghi O, Marashi SM, Aghajani Y, Ghadimi F, et al. A randomized, double blind trial of prophylactic fibrinogen to reduce bleeding in cardiac surgery. Braz J Anesthesiol. 2014 ; 64:253-7.
7. Karlsson M, Ternström L, Hyllner M, Baghaei F, Skrtic S, Jeppsson A. Prophylactic fibrinogen infusion in cardiac surgery patients: effects on biomarkers of coagulation, fibrinolysis, and platelet function. Clin Appl Thromb Hemost. 2011; 17:396-404.
8. Rahe-Meyer N, Solomon C, Hanke A, Schmidt DS, Knoerzer D, Hochleitner G, 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.
9. Rahe-Meyer N. Fibrinogen concentrate in the treatment of severe bleeding after aortic aneurysm graft surgery. Thromb Res. 2011; 128:S17-9.
10. Ferraris VA, Brown JR, George J, Despotis GJ, Hammon JW, Reece B, et al. 2011 Update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines. Ann Thorac Surg. 2011; 91:944–82
11. Kristensen KL, Rauer LJ, Mortensen PE, Kjeldsen BJ. Reoperation for bleeding in cardiac surgery. Interact Cardiovasc Thorac Surg. 2012; 14:709–13.
12. Karkouti K, Callum J, Crowther MA, McCluskey SA, Pendergrast J, Tait G, et al. The relationship between fibrinogen levels after cardiopulmonary bypass and large volume red cell transfusion in cardiac surgery: an observational study. Anesth Analg. 2013; 117:14-22.
13. Galas FR, de Almeida JP, Fukushima JT, Vincent JL, Osawa EA, Zeferino S, et al. Hemostatic effects of fibrinogen concentrate compared with cryoprecipitate in children after cardiac surgery: a randomized pilot trial. J Thorac Cardiovasc Surg. 2014; 148:1647-55.
14. Faraoni D, Willems A, Savan V, Demanet H, De Ville A, Van der Linden P. Plasma fibrinogen concentration is correlated with postoperative blood loss in children undergoing cardiac surgery. A retrospective review. Eur J Anaesthesiol. 2014; 31:317-26.
15. Pillai RC, Fraser JF, Ziegenfuss M, Bhaskar B. Influence of circulating levels of fibrinogen and perioperative coagulation parameters on predicting postoperative blood loss in cardiac surgery: a prospective observational study. J Card Surg. 2014; 29:189-95.
16. Gielen C, Dekkers O, Stijnen T, Schoones J, Brand A, Klautz R, et al. The effects of pre- and postoperative fibrinogen levels on blood loss after cardiac surgery: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2014; 18:292-8.
17. Ranucci M, Jeppsson A, Baryshnikova E. Pre-operative fibrinogen supplementation in cardiac surgery patients: an evaluation of different trigger values. Acta Anaesthesiol Scand. 2015; 59:427-33.
18. Kindo M, Hoang Minh T, Gerelli S, Perrier S, Meyer N, Schaeffer M, 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. Thromb Res. 2014; 134:360-8.
19. Fassl J, Lurati Buse G, Filipovic M, Reuthebuch O, Hampl K, Seeberger MD, et al. Perioperative administration of fibrinogen does not increase adverse cardiac and thromboembolic events after cardiac surgery. Br J Anaesth. 2015; 114:225-34.
20. Stanzel R, Henderson M, O'Blenes S. Prophylactic fibrinogen administration during complex congenital cardiac surgery leading to thrombosis of a patient's brachial artery and the cardiopulmonary bypass circuit: a case report. Perfusion. 2013; 29:369-72.
21. Bilecen S, Peelen LM, Kalkman CJ, Spanjersberg AJ, Moons KG, Nierich AP. Fibrinogen concentrate therapy in complex cardiac surgery. J Cardiothorac Vasc Anesth. 2013; 27:12-7.
22. Theusinger OM, Stein P, Levy JH. Point of care and factor concentrate-based coagulation algorithms. Transfus Med Hemother. 2015; 42:115-21.
23. Spahn DR. TEG®- or ROTEM®-based individualized goal-directed coagulation algorithms: don't wait - act now! Crit Care. 2014; 18:637.
24. Ghavidel AA, Toutounchi Z, Shahandashti FJ, Mirmesdagh Y. Rotational thromboelastometry in prediction of bleeding after cardiac surgery. Asian Cardiovasc Thorac Ann. 2015; 23:525-9.