RESEARCH ARTICLE

Prophylactic Fibrinogen Reduces Excessive Bleeding in Total Hip Arthroplasty Surgery: A Randomized Double-blinded Placebo-controlled Trial

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Abstract

Objectives: Excessive blood loss is a critical complication of total hip arthroplasty. We intended to determine whether preoperative fibrinogen administration reduces perioperative bleeding and the need for blood transfusion in total hip arthroplasty surgery.

Methods: In 4 months, 178 patients who underwent total hip arthroplasty were randomly assigned equally to intervention and placebo-control groups in a double-blinded, parallel two-arm randomized controlled trial. Both intravenously, 30 min before the start of the surgery, the intervention group received two grams of fibrinogen concentrate dissolved in 100 ml of distilled water. In contrast, the control group received 100 ml of normal saline solution. The amount of postoperative blood loss served as the main result, and the requirement for blood transfusions served as the secondary outcome.

Results: In comparison to the placebo, administering fibrinogen concentrate considerably reduced the amount of blood loss (P=0.001) and the requirement for blood transfusions (P=0.004). Patients who got fibrinogen concentrate experienced no side effects. In addition, patients in the fibrinogen group had significantly lower hemoglobin and higher fibrinogen levels in the recovery room and received lesser blood transfusions (P<0.005) than the placebo group.

Conclusion: In total hip arthroplasty, fibrinogen concentrate lessens postoperative bleeding and the requirement for blood transfusions.

Level of evidence: II

Keywords: Bleeding, Fibrinogen, Prophylaxis, Total hip arthroplasty

Introduction

Arthroplasty surgery is known to cause severe bleeding and a significant need for blood transfusions.[1,2] The expenses and potential risks of blood transfusion have been described previously in total hip arthroplasty (THA).[3,4] The prevalence of allogeneic red blood cell (RBC) transfusions has been estimated to be more than 20%.[4-6] Although allogeneic RBC transfusions can potentially save lives, they are also accompanied by a variety of hazards, such as pathogen transmission, immunomodulation, and transfusion-related lung injury (TRALI).[7,8] Additionally, studies have shown that blood product transfusions may raise the risk of immediate and long-term morbidity and mortality.[9-11] Transfusion needs are also influenced by patient-related and surgery-related parameters, such as gender, operating and anesthesia techniques, and preoperative hemoglobin levels.[12-14] The majority of THA patients are older, and the subsequent anemia may affect postoperative functional recovery and restrict mobility.[6]

The primary plasma protein responsible for maintaining homeostasis, fibrinogen, is the first coagulation factor to be severely depleted with substantial surgical bleeding.[15-17] Therefore, the clotting function is maintained in severe bleeding by replenishing the plasma fibrinogen.[15,18] A low preoperative plasma fibrinogen concentration has been linked to an increased risk of excessive bleeding, according

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to studies in different surgical settings.[19-22] It has been revealed that the quantity of intraoperative bleeding is correlated with the fibrinogen level before hip arthroplasty surgery.[23]

The amount of fibrinogen in fresh-frozen plasma is insufficient to compensate for the severe hypofibrinogenemia.[24] However, some research suggested that using fibrinogen concentrate can help lessen surgical bleeding.[25,26] Nevertheless, some research claimed there was no association between preoperative fibrinogen levels and surgical blood loss.[27,28]

In the current study, we hypothesized that using fibrinogen as a pretreatment might reduce bleeding during and after hip replacement surgery. Furthermore, as secondary hypotheses, we assumed that using fibrinogen might have no significant side effects and might reduce the need for blood transfusion in this type of surgery.

Materials and Methods

This randomized, double-blind, placebo-controlled trial with a ratio to cases 1:1 was registered with the Iranian Registry of Clinical Trials (IRCT20120910010800N3, https://fa.irct.ir/user/trial/62685/view) and the Iran National Committee for Ethics in Biomedical Research (IR.SBMU.RETECH.REC.1400.1221) and designed based on the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement.[29] Before enrollment, all patients provided written informed consent. Patients who were scheduled for primary total hip arthroplasty surgery and aged over 18 were included. Between May 22 and September 23, 2022, the study was carried out in the Orthopedic Surgery Department of a University Hospital. Patients were excluded if they were pregnant or had an uncontrolled underlying condition, sickle cell anemia, contraindication to receive anticoagulation prophylaxis, an infected wound bed, a history of drug abuse, a history of previous surgery in the area of the current procedure, a recent history of coagulation disorders, a history of taking food or drugs that alter coagulation, or if they refused to receive homologous blood products.

This study primarily aimed to determine the quantity of bleeding from surgery commencement through the next 24 h. The number of administered blood products and complications from blood transfusions (hemolytic reactions, allergic reactions, and TRALI were secondary outcomes. All data was gathered before, during, and after the surgery by the anesthesiologist in charge of the patient.

The sample size was calculated via a pilot study due to a limited number of comparable studies. The sample volume was calculated using G*Power software (version 3.1.9.3)[30] as 59 patients in each group based on an effect size of 0.67, a two-sided Type I error (α) of 0.05, and a power (1-β) of 0.95. This was done based on our pilot study, which included 60 patients (30 in each group) and average intraoperative bleeding of 845 ml in the control group and 598 ml in the fibrinogen group. In light of a 30% withdrawal rate, 154 patients were decided upon for enrollment. Finally, 178 patients—the total number of research participants—were evaluated. The final study contained all of the data from the pilot study.

The attending anesthesiologist invited subjects to participate, all potential side effects and aims of the study were explained to the participants, and their informed consent during the examination before surgery was obtained. The blocks-of-four randomization and computer-generated allocation, which were performed by a third party before the study began, were written in opaque envelopes (numbered consecutively). A nurse anesthetist who was not involved in the later stages of the study opened an envelope when a new subject was enrolled and read the contents before designating the person to the intervention or control group. The allocation was a secret to all participants, healthcare experts, outcome assessors, and statisticians. At first, a nurse anesthetist administered two grams of fibrinogen concentrate (Haemocomplettan® P; CSL Behring GmbH, Marburg, Germany) for 30 min after diluting it in 100 mL of sterile water or an equivalent volume of 0.9% saline solution as a placebo. Using paper-wrapped syringes, the research infusion's contents were kept secret. Injections were administered without knowledge of preoperative serum fibrinogen level.

Blood samples were taken from all patients to measure hemoglobin, platelets, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT), and the international normalized ratio at the time of their entry into the operating room and before administration of any medications (INR). The patients were monitored using electrocardiography, non-invasive blood pressure, pulse oximetry, body temperature, and bispectral index (BIS VISTA equipment, Aspect Medical Systems, Newton, MA, USA). Each patient underwent five minutes of preoxygenation with an inspired oxygen fraction of one before general anesthesia establishment. In terms of drug prescription and determining the depth of anesthesia, general anesthesia was carried out on all patients using the same technique. The dosage of propofol was adjusted to keep the bispectral index between 40 and 60. After the anesthesia, an arterial catheter was inserted into the radial artery. All THAs were performed in the lateral position, and only the same surgical team performed all the procedures. If tranexamic was required, the patient was excluded from the study. The patient's mean arterial blood pressure was kept within a range of 60 and 80 mmHg during the procedure.

Arterial blood gas samples were taken to monitor and maintain the correct acid-base balance throughout the surgery. According to the national guidelines for the provision of anesthetic services, if it was needed, patients received blood products. Body temperature was kept steady during operation using a forced air warming device. Before the end of the surgery, 0.15 mg/kg of intramuscular morphine and one gram of intravenous acetaminophen were administered to each patient. The expected blood loss was determined by counting the gauze, measuring the amount of blood in the suction container, and evaluating the surgical field.

Blood samples were taken 24 h following the surgery to assess the hemoglobin, fibrinogen concentrations, and other coagulation tests. At this point, blood loss and other potential problems were also evaluated. Early surgical complications such as deep vein thrombosis, cardio-pulmonary events, and cerebrovascular accidents were evaluated by clinical and para-clinical examinations, both throughout the hospital stay and in the two weeks after discharge. Depending on the patient's condition, any further evaluations were decided.

Frequencies, means, and standard deviation (SD) were used to characterize the variables. In the case of a non-normal distribution, the median and interquartile ranges (IQR) were utilized. The normality of the outcome variables was examined with the Shapiro–Wilk test. Kruskal–Wallis and Spearman's correlation tests were used for further nonparametric testing. A *P*-value of less than 0.05 was considered statistically significant. The SPSS (Version 17.0 for Windows; SPSS Inc., Chicago, IL) was used for all analyses.

Results

One-hundred seventy-eight participants (93.7% of the 230 total) were examined. The majority (n=22) of the 52 patients who were not assessed had not fulfilled the criteria for inclusion, 14 cases had declined to participate, six cases' data were insufficient, six cases had received tranexamic acid, and four cases' surgeries had been postponed [Figure 1].

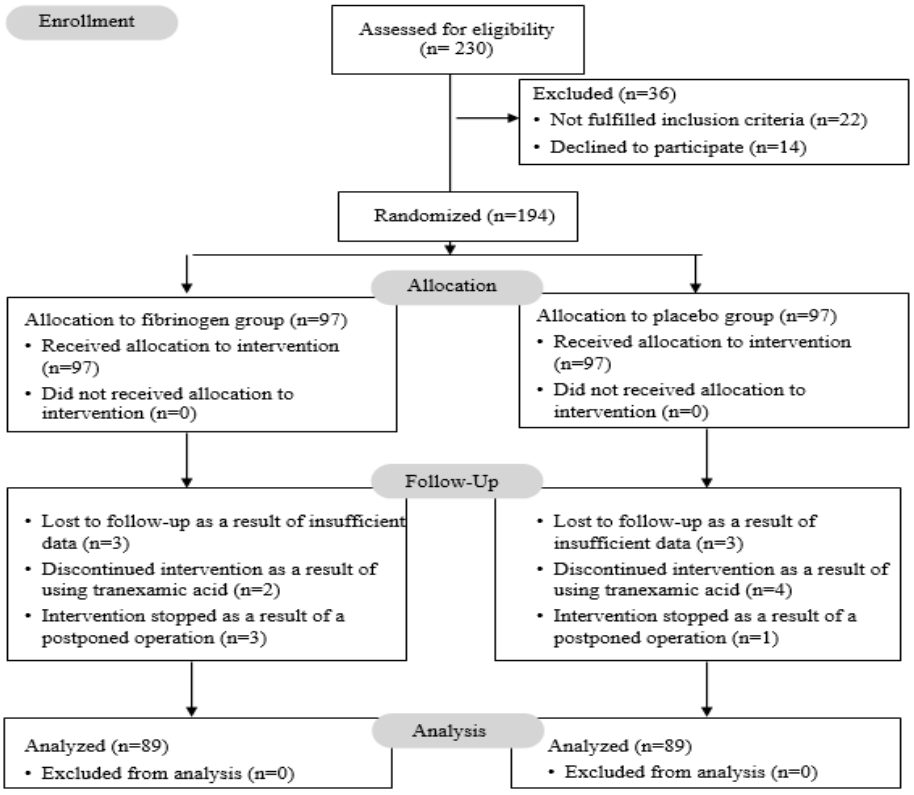

Figure 1. Flow diagram of the number of patients assessed and included at each stage of the randomized controlled trial

The age of the participants was 18 to 73 years, the mean (SD) age of them was 31.78 (8.73) years, and most participants were female (57.9%). The groups of individuals had similar baseline characteristics [Table 1]. Preoperatively, no noticeable differences were observed between the two groups in PT, PTT, INR, Hb, platelets, and fibrinogen levels in samples before surgery. The surgical time was comparable between the two groups.

Table 1. Baseline characteristics of the population

Variables	Fibrinogen	Placebo	*P*-value (Kruskal-Wallis Test)
Age, median (IQR), year	32 (10)	31 (11)	0.929
BMI, median (IQR), kg/m2	76.13 (5.4)	26.61 (5.3)	0.641
Sex (Females), Number (%)	52 (58.4%)	51 (57.3)	0.880
Surgery duration, median (IQR), min	130 (47.50)	120 (70)	0.417

IQR: interquartile range; BMI: body mass index

The primary and secondary results were shown in [Table 2]. With a P value of 0.003, bleeding in the intervention group was considerably lower than in the control group (median=700.00 ml, IQR=700.00 versus median=900.00 ml, IQR=450.00). The amount of bleeding in the recovery room was practically the same as in the intervention and control groups (median=40.00, IQR=30.00 versus median=40.00, IQR=10.00), and the results were not statistically significant (P=0.094). The same findings were observed in terms of the amount of bleeding 24 h following surgery (median=320,000, IQR=112,000 versus median=320,000, IQR=157,500), and once more, the difference was not statistically significant (P=0.145). Finally, a substantial difference was seen between the two groups in the total amount of bleeding from the time of surgery to 24 h after the procedure (P=0.001).

When the patient entered the recovery room, a substantial difference in the serum level of fibrinogen was seen between the two groups (P<0.001). Within 24 h of the operation, this disparity vanished. Although the serum fibrinogen levels were lower in the recovery room, the intervention group experienced this difference at a far lower rate than the control group [Table 2]. The intervention group experienced a decrease in serum fibrinogen levels that were nearly 4 times lower than that of the control group (median=3.70, IQR=3.69 versus median=15.19, IQR=9.76).

Table 2. Primary and secondary outcomes

Variables	Fibrinogen	Placebo	*P*-value (Kruskal- Wallis Test)
Total bleeding, median (IQR), mL	1100 (605.00)	1300 (405.00)	0.001
Hb baseline, median (IQR), g/dL	11.70 (1.65)	11.60 (2.00)	0.635
Hb recovery, median (IQ)R, g/dL	10.40 (1.55)	9.90 (1.75)	0.008
Hb 24 h, median (IQR), g/dL	10.90 (1.25)	10.90 (1.50)	0.611
PLT baseline, median (IQR), /microliter	186.00 (55.00)	202.00 (70.50)	0.359
PT baseline, median (IQR), s	12.00 (1.50)	12.00 (1.80)	0.388
PTT baseline, median (IQR), s	27.00 (7.45)	24.30 (6.35)	0.720
INR baseline, median (IQR)	1.00 (0.10)	1.00 (0.10)	0.486
Fibrinogen baseline, median (IQR), mg/dL	241.00 (127.00)	234.00 (107.00)	0.941
Fibrinogen recovery, median (IQR), mg/dL	237.00 (116.00)	200.98 (104.00)	0.012
Fibrinogen 24 h, median (IQR). mg/dL	222.00 (84.50)	216.00 (94.00)	0.599
Changes in fibrinogen levels, median (IQR), ng/dL	9.00 (10.00)	38.00 (18.50)	<0.001
Cases of blood transfusions, median (IQR), numbers	0.00 (1.00)	1.00 (1.00)	0.004
Packed cell used for transfusion, median (IQR), numbers	0.00 (1.00)	1.00 (1.00)	0.007

IQR: interquartile range; HB: hemoglobin, PLT: platelet count; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio

The intervention group required significantly fewer blood transfusions and total packs of RBCs than the control group [Tables 2, 3]. Transfusion was performed on 52.8% of the patients in the control group and 31.5% of the patients in the intervention group (P=0.004). Furthermore, patients in the fibrinogen group received significantly fewer blood units (28 units) than the control group (47 units) (P=0.007). Patients in neither group received fresh frozen plasma (FFP).

As noted, the postoperative hemoglobin levels in the recovery room were significantly lower in the control group (P=0.008). However, postoperative hemoglobin values at 24h after surgery were the same as the two groups.

Table 3. Number of transfused red blood cell units

Number of transfused RBC units	Fibrinogen	Placebo
0	61 (68.5%)	42 (47.2%)
1	17 (19.1%)	30 (33.7%)
2	8 (9.0%)	12 (13.5%)
3	3 (3.4%)	5 (5.6%)
Total number of transfused RBC units per group	28 (31.5%)	47 (52.8%)

RBC: red blood cell

Using Spearman's correlations test, total perioperative bleeding was correlated with fibrinogen administration (P=0.001), duration of surgery (P=0.014), hemoglobin concentration before surgery (P<0.001), fibrinogen before surgery (P=0.018), and the number of changes in fibrinogen levels during surgery (P<001). However, no correlations were found between age (P=0.936), gender (P=0.298), body mass index (P=0.329), preoperative PT (P=0.742), preoperative PTT (P=0.985), preoperative INR (P=0.522), and preoperative platelet count (P=0.507) and the amount of bleeding.

None of the patients in either group had complications related to fibrinogen transfusion, including deep vein thrombosis, myocardial infarction, or cerebrovascular accidents throughout the hospital stay and in the two weeks after discharge.

Discussion

The THA is typically performed in Iran as a last option for severe hip osteoarthritis. Due to some habits in the Iranian lifestyle, such as using a squat toilet and sitting on the floor instead of chairs, they may experience more hip and knee joint issues compared to other nationalities.[31] Total hip and knee arthroplasty accounts for about 10% of all transfused red blood cell units, making it the most common reason for allogeneic blood transfusion in elective surgeries.[32-36] It is important to understand that a blood transfusion is not a simple surgical procedure. Jans et al. investigated the increased mortality in THA patients who received blood transfusion.[6] Increased venous thromboembolism following total joint arthroplasty and also in pregnancy had been reported.[37,38]

This study was a double-blind randomized controlled trial designed to determine the effect of prophylactic fibrinogen administration on reducing hemorrhage in THA surgery. The results showed that the administration of prophylactic fibrinogen significantly reduces bleeding and the need for blood transfusion. Most studies in the past, similar to the present study, confirmed the effect of intraoperative fibrinogen use on reducing hemorrhage in various surgeries[15,16,18,19,28,39] and several studies have shown that low plasma fibrinogen during surgery increases the volume of the hemorrhage and the need for blood transfusion[17,20,23,40,41] Current scientific data supports fibrinogen repletion in patients with ongoing bleeding and confirmed fibrinogen deficiency[25] because it is relatively safe, and all the randomized controlled trials have not reported an increase in the rate of perioperative thrombosis in fibrinogen replacement cases.[22,42]

Nadia et al. had shown that the rate of blood transfusion in knee and hip replacement surgeries was 69%.[1] Their outcomes are comparable to those of the control group in the current study. Browne et al. investigated the significant risk factors for blood transfusion and found that they were female gender, age > 85, and preoperative anemia. Moreover, they demonstrated that patients experiencing blood transfusions had a higher rate of in-hospital mortality, longer length of hospital stay, and higher total charges compared to non-transfused patients.[4] Contrary to the findings of this research, no association between gender or age and hemorrhage was found; however, preoperative anemia was identified as a risk factor, similar to the previous study.

In a study conducted by Ucar et al., the level of fibrinogen significantly correlated with the amount of postoperative hemorrhage in patients who were candidates for coronary artery bypass graft surgery.[41] Pournajafian et al. showed that the amount of hemorrhage and the need for blood transfusion were significantly more than the control group during spinal surgery, which was consistent with the results of this study.[43] The results of the present study concerning the need for blood transfusions were consistent with the findings of the reearch conducted by Thorarinsdottir et al. on 37 patients, which showed that the administration of fibrinogen for severe hemorrhage was associated with an increased fibrinogen concentration and a significant decrease in PTT, PT, and requirement for blood transfusions.[44] Carling et al. studied patients in scoliosis surgery and found that the hemorrhage in these patients had a significant correlation with plasma fibrinogen concentration but showed no significant correlation with platelet count, PT, and PTT.[45] In a pilot study by Najafi et al., perioperative blood loss was lesser in the control group. In addition, they addressed preoperative anemia as a risk factor for bleeding. However, contrary to the present study, they failed to demonstrate the correlation between fibrinogen administration and the need for blood transfusion.[22] The results of a study by Lupu et al., in contrast to the current investigation, demonstrated that the administration of low doses of fibrinogen does not cease bleeding or the requirement for allogeneic blood product transfusion in cardiac surgery.[27]

The small sample size and the lack of follow-up were among the limitations of the current study. Additionally, we did not investigate the cost-effectiveness of fibrinogen concentrate. Further investigation is required into the early use of fibrinogen concentrate, as well as its potential advantages over fresh frozen plasma or cryoprecipitate, and whether or not its administration at high doses leads to a greater risk of adverse events.

Conclusion

Our study showed that the infusion of 2g fibrinogen concentrate reduces perioperative bleeding and significantly decreases the required number of RBC units. Prophylactic fibrinogen might improve the outcomes of THA patients by decreasing perioperative hemorrhage and blood transfusion.

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Conflict of interest: None

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References

1. Rosencher N, Kerkkamp HEM, Macheras G, et al. Orthopedic surgery transfusion hemoglobin european overview (OSTHEO) study: Blood management in elective knee and hip arthroplasty in Europe. Transfusion (Paris). 2003; 43(4):459-469. doi:10.1046/j.1537-2995.2003.00348.x.
2. Vuille-Lessard É, Boudreault D, Girard F, Ruel M, Chagnon M, Hardy JF. Red blood cell transfusion practice in elective orthopedic surgery: A multicenter cohort study. Transfusion (Paris). 2010; 50(10):2117-2124. doi:10.1111/j.1537-2995.2010.02697.x.
3. Bierbaum BE, Hill C, Callaghan JJ, et al. An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am. 1999; 81(1):2-10. doi: 10.2106/00004623-199901000-00002.
4. Browne JA, Adib F, Brown TE, Novicoff WM. Transfusion rates are increasing following total hip arthroplasty: Risk factors and outcomes. J Arthroplasty. 2013; 28(8 SUPPL):34-37. doi:10.1016/j.arth.2013.03.035.
5. Stanworth SJ, Cockburn HAC, Boralessa H, Contreras M. Which groups of patients are transfused? A study of red cell usage in London and southeast England. Vox Sang. 2002; 83(4):352-357. doi:10.1046/j.1423-0410.2002.00237.x.
6. Jans O, Kehlet H, Hussain Z, Johansson PI. Transfusion practice in hip arthroplasty - a nationwide study. Vox Sang. 2011; 100(4):374-380. doi:10.1111/j.1423-0410.2010.01428.x.
7. Cholette JM, Henrichs KF, Alfieris GM, et al. Washing red blood cells and platelets transfused in cardiac surgery reduces post-operative inflammation and number of transfusions: Results of a prospective, randomized, controlled clinical trial. Pediatr Crit Care Med. 2012;13(3):290-299. doi:10.1097/PCC.0B013E31822F173C.
8. Kim JL, Park JH, Han SB, Cho IY, Jang KM. Allogeneic Blood Transfusion Is a Significant Risk Factor for Surgical-Site Infection Following Total Hip and Knee Arthroplasty: A Meta-Analysis. J Arthroplasty. 2017; 32(1):320-325. doi:10.1016/j.arth.2016.08.026.2007;89 (11):1470–7.
9. Delaney M, Stark PC, Suh M, et al. Massive transfusion in cardiac surgery: The impact of blood component ratios on clinical outcomes and survival. Anesth Analg. 2017; 124(6):1777-1782. doi:10.1213/ANE.0000000000001926.
10. Santos AA dos, Sousa AG, Piotto RF, Pedroso JCM. Risco de mortalidade é dose-dependente do número de unidades de concentrado de hemácias transfundidas após cirurgia de revascularização miocárdica. Braz J Cardiovasc Surg. 2013; 28(4):509-517. doi:10.5935/1678-9741.20130083.
11. Hardiman SC, Villan Villan YF, Conway JM, Sheehan KJ, Sobolev B. Factor's affecting mortality after coronary bypass surgery: a scoping review. J Cardiothorac Surg. 2022; 17(1):1-14. doi: 10.1186/s13019-022-01784-z.
12. Fink B, Mittelstaedt A, Schulz MS, Sebena P, Singer J. Comparison of a minimally invasive posterior approach and the standard posterior approach for total hip arthroplasty A prospective and comparative study. J Orthop Surg Res. 2010;5(1):46. doi:10.1186/1749-799X-5-46.
13. Martin R, Clayson PE, Troussel S, Fraser BP, Docquier PL. Anterolateral Minimally Invasive Total Hip Arthroplasty. A Prospective Randomized Controlled Study With a Follow-Up of 1 Year. J Arthroplasty. 2011; 26(8):1362-1372. doi:10.1016/j.arth.2010.11.016.
14. Park JH, Rasouli MR, Mortazavi SMJ, Tokarski AT, Maltenfort MG, Parvizi J. Predictors of perioperative blood loss in total joint arthroplasty. J Bone Joint Surg Am. 2013; 95(19):1777-1783. doi:10.2106/JBJS.L.01335.
15. 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):555-562. doi:10.1093/bja/aeq058.
16. Kikuchi M, Itakura A, Miki A, Nishibayashi M, Ikebuchi K, Ishihara O. Fibrinogen concentrate substitution therapy for obstetric hemorrhage complicated by coagulopathy. J Obstet Gynaecol Res. 2013; 39(4):770-776. doi:10.1111/j.1447-0756.2012.02058.x.
17. Kikura M, Nishino J, Uraoka M. Clinical Simulation Model of Fibrinogen Decline during Hemorrhage in Major Noncardiac Surgery. J Surg Res. 2021; 261:43-50. doi:10.1016/j.jss.2020.12.008.
18. Heinen A, Welke V, Behmenburg F, et al. Haemotherapy with fibrinogen for perioperative bleeding prevention—a view on arterial thrombogenesis and myocardial infarction in the rat in vivo. J Clin Med. 2019; 8(6):880. doi: 10.3390/jcm8060880.
19. Innerhofer N, Treichl B, Rugg C, et al. First-Line Administration of Fibrinogen Concentrate in the Bleeding Trauma Patient: Searching for Effective Dosages and Optimal Post-Treatment Levels Limiting Massive Transfusion-Further Results of the RETIC Study. J Clin Med. 2021; 10(17). doi: 10.3390/jcm10173930.
20. Essa Y, Zeynalov N, Sandhaus T, Hofmann M, Lehmann T, Doenst T. Low Fibrinogen is Associated with Increased Bleeding-Related Re-exploration after Cardiac Surgery. Thorac Cardiovasc Surg. 2017; 66(8):622-628. doi: 10.1055/s-0037-1603205.
21. Ekelund K, Hanke G, Stensballe J, Wikkelsøe A, Albrechtsen CK, Afshari A. Hemostatic resuscitation in postpartum hemorrhage - A supplement to surgery. Acta Obstet Gynecol Scand. 2015; 94(7):680-692. doi:10.1111/aogs.12607.

22. Najafi A, Moharari RS, Orandi AA, et al. Prophylactic administration of fibrinogen concentrate in perioperative period of total hip arthroplasty: A randomized clinical trial study. Acta Med Iran. 2014; 52(11):804-810.
23. Jaime-Romo R, Vidal-Cervantes F, Rivera-Villa AH, Colín-Vázquez A. [Preoperative concentration of plasma fibrinogen as a predictor of bleeding in total hip arthroplasty]. Acta Ortop Mex. 2021; 35(6):507-514.
24. Rahe-meyer N, Sørensen B. Fibrinogen concentrate for management of bleeding. J Thromb Haemost. 2011; 9(1):1-5. doi:10.1111/J.1538-7836.2010.04099.X.
25. Grottke O, Mallaiah S, Karkouti K, Saner F, Haas T. Fibrinogen Supplementation and Its Indications. Semin Thromb Hemost. 2020; 46(1):38-49. doi: 10.1055/s-0039-1696946.
26. Leal-Noval SR, Fernández Pacheco J, Casado Méndez M, Cuenca-Apolo D, Múñoz-Gómez M. Current perspective on fibrinogen concentrate in critical bleeding. Expert Rev Clin Pharmacol. 2020; 13(7):761-778. doi:10.1080/17512433.2020.1776608.
27. Lupu IM, Rebaine Z, Lhotel L, et al. A 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. doi:10.4103/ACA.ACA_145_17.
28. Soleimani M, Masoumi N, Nooraei N, Lashay A, Safarinejad MR. The effect of fibrinogen concentrate on perioperative bleeding in transurethral resection of the prostate: a double-blind placebo-controlled and randomized study. J Thromb Haemost. 2017; 15(2):255-262. doi:10.1111/JTH.13575.
29. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010; 152(11):726-732. doi: 10.7326/0003-4819-152-11-201006010-00232.
30. Universität Düsseldorf: G*Power. Statistical Power Analyses for Mac and Windows Available at: https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower. Accessed December 16, 2022.
31. Naseri MH, Panahi F, Motififard M, Teimouri M. Quality of Life and Functional Outcome after Total Hip Arthroplasty. Journal of Isfahan Medical School. 2010; 27(102).
32. Song K, Pan P, Yao Y, Jiang T, Jiang Q. The incidence and risk factors for allogenic blood transfusion in total knee and hip arthroplasty. J Orthop Surg Res. 2019; 14(1):1-6. doi:10.1186/S13018-019-1329-0/TABLES/5.
33. Frank SM, Savage WJ, Rothschild JA, et al. Variability in Blood and Blood Component Utilization as Assessed by an Anesthesia Information Management System. Anesthesiology. 2012; 117(1):99-106. doi:10.1097/ALN.0B013E318255E550.
34. Abdulwahab T, Meshram; Prashant, Althani S, Albelooshi A. Comparison of Intraarticular Versus Combined Intravenous and Intraarticular Tranexamic Acid Administration in Patients Undergoing Primary Unilateral Total Knee Arthroplasty: A Randomized Controlled Trial in the Middle Eastern Patient Population. Arch Bone Jt Surg. 2022; 10(12):1037-1043. doi:10.22038/ABJS.2022.67705.3210.
35. Bagheri N, Amini MA, Pourahmad A, Vosoughi F, Moharrami A, Mortazavi SJ. Comparison of combined intraarticular (IA) and intravenous (IV) administration of tranexamic acid with IA and IV alone in patients undergoing total knee arthroplasty without drainage catheter: a clinical trial study. Arch Bone Jt Surg. 2022; 10(12): 1037–1043. doi:10.22038/ABJS.2022.64446.3097.
36. Vrontis K, Tsinaslanidis G, Drosos GI, Tzatzairis T. Perioperative Blood Management Strategies for Patients Undergoing Total Hip Arthroplasty: Where Do We Currently Stand on This Matter? Arch Bone Jt Surg. 2020; 8(6):646-655. doi:10.22038/ABJS.2020.45651.2249.
37. Shohat N, Ludwick L, Goh GS, Sherman M, Paladino J, Parvizi J. Blood transfusions increase the risk for venous thromboembolism events following total joint arthroplasty. Scientific Reports.2021; 11(1):1-11. doi:10.1038/s41598-021-00263-0.
38. Wang C, le Ray I, Lee B, Wikman A, Reilly M. Association of blood group and red blood cell transfusion with the incidence of antepartum, peripartum and postpartum venous thromboembolism. Scientific Reports. 2019; 9(1):1-7. doi: 10.1038/s41598-019-49566-3.
39. Fathi M, Lashay A, Massoudi N, Nooraei N, Nik MA. Fibrinogen prophylaxis for reducing perioperative bleeding in patients undergoing radical cystectomy: A double-blind placebo-controlled randomized trial. J Clin Anesth. 2021; 73:110373. doi:10.1016/j.jclinane.2021.110373.
40. 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(1):137-144. doi:10.1160/TH08-09-0587/ID/JR0587-3.
41. Ucar HI, Oc M, Tok M, et al. Preoperative fibrinogen levels as a predictor of postoperative bleeding after open heart surgery. Heart Surg Forum. 2007; 10(5):E392-6. doi:10.1532/HSF98.20071065.
42. Cushing MM, Haas T. Fibrinogen concentrate for perioperative bleeding: what can we learn from the clinical trials? Transfusion (Paris). 2019; 59(11):3295-3297. doi:10.1111/trf.15437.
43. Pournajafian A, Ghodraty M, Mohseni M, Ghamari AA, Sadeghi F. Reduction of intraoperative bleeding with fibrinogen administration in posterior spinal fusion surgery. Journal of Isfahan Medical School. 2015; 33(347):1370-9.
44. Thorarinsdottir HR, Sigurbjornsson FT, Hreinsson K, Onundarson PT, Gudbjartsson T, Sigurdsson GH. Effects of fibrinogen concentrate administration during severe hemorrhage. Acta Anaesthesiol Scand. 2010; 54(9):1077-1082. doi:10.1111/J.1399-6576.2010.02289.X.
45. Carling MS, Jeppsson A, Wessberg P, Henriksson A, Baghaei F, Brisby H. Preoperative fibrinogen plasma concentration is associated with perioperative bleeding and transfusion requirements in scoliosis surgery. Spine (Phila Pa 1976). 2011; 36(7):549-555. doi:10.1097/BRS.0B013E3181D952DC.