Prophylactic Administration of Fibrinogen Concentrate in Perioperative Period of Total Hip Arthroplasty: a Randomized Clinical Trial Study

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Abstract- According to limitations in blood product resources and to prevent unnecessary transfusions and afterwards complications in perioperative period of total hip arthroplasty, authors administered fibrinogen concentrate in a pilot randomized clinical trial to evaluate bleeding and need to blood transfusion in preoperative period. Thirty patients (3-75 years old) with ASA physical status class I or II and candidate for total hip arthroplasty consequently enrolled in this study and randomly assigned into two groups: taking fibrinogen concentrate and control. Two groups were similar in serum concentration of fibrinogen, hemoglobin, and platelet preoperatively. After induction of general anesthesia 30mg/kg fibrinogen concentrate was administered in the fibrinogen group. Blood loss, need to blood transfusion and probable complications were compared between two groups. The mean operation time was 3.3 ± 0.8 hours in the fibrinogen group and 2.8 ± 0.6 hours in the placebo group, and this difference was statistically significant (P=0.04). There was a significant correlation between operation time and blood loss during surgery (P=0.002). The mean transfused blood products in the fibrinogen and control group was 0.8 ± 1.01 units and 1.06 ± 1.2 units respectively (P=0.53). The mean of perioperative blood loss was 976 ± 553 ml in the fibrinogen group and 1100 ± 350 ml in the control group, but this difference was not significant between two groups. By adjusting time factor for two groups, we identified that the patients in fibrinogen group had lower perioperative bleeding after adjusting time factor for two groups (P=0.046). None of the patients had complications related to fibrinogen concentrate administration. The prophylactic administration of fibrinogen concentrate was safe and effective in reducing bleeding in the perioperative period of total hip arthroplasty.

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Keywords: Fibrinogen; Bleeding; Coagulation; Total hip arthroplasty

Introduction

Haemostasis is a complex process consisting of a constellation of cells, haemostatic factors, cofactors, and modulators which is activated in response to endothelial injury and results in ceasing bleeding. Coagulation factors deficiencies might be inherited or acquired. Most often acquired fibrinogen deficiency occurs in synthesis processes, increasing loss or excessive consumption such as disseminated intravascular coagulation (DIC), hepatic failure, dilutional coagulopathy following administration of colloids and crystalloids, severe trauma or long-term treatment with corticosteroids (1-3). Excessive blood loss, usually, accompanies orthopedic surgeries on hip and spine. Fibrinogen is made in the liver and turns into fibrin during the coagulation. During acute blood loss, some fibrinogen is lost due to bleeding and some amounts turn into clots and liver does not have enough time to reproduce a new fibrinogen. No alternative source is available; this may lead to more blood loss and reach serious concentrations of fibrinogen that would increase the need for transfusion of blood products containing fibrinogen such as fresh frozen plasma and cryoprecipitate. This process exposes the patient to probable deleterious effects of blood transfusion. The current study evaluated the safety and efficacy of prophylactic administration of fibrinogen concentrate in reducing blood loss and transfusion

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requirement in the perioperative period of total hip arthroplasty.

Materials and Methods

In this study, 30 total hip arthroplasty surgery candidates were consequently enrolled between Aug. 2011and Feb. 2013. The study approved by the local committee of the department of anesthesia and critical care of Tehran University of Medical Sciences; thereafter the ethical approval was obtained from the committee of ethics of Tehran university of medical sciences (90/D/130/662/28-July/2011). This study was registered by Iranian Registry of Clinical Trials as IRCT201012264784N2 (www.irct.ir).

Inclusion criteria consisted of all patients candidate for total hip replacement arthroplasty, with ASA physical status class I or II, metabolic equivalent of the task (MET) ≥4, hemoglobin level ≥10 g/dl. Participants signed an informed consent form. Exclusion criteria was consisted of having no consent to stay in project at any time, ASA class>II, MET<4, pregnancy, any history of sensitivity to blood products, history of myocardial infarction, deep veins thrombosis, pulmonary emboli, cerebrovascular accident and any known hematologic disorder such as thrombocytopenia and coagulopathy. According to the table of random numbers, the patients were randomly assigned into the two groups: fibrinogen and placebo. All of the patients were anesthetized with a single protocol of general anesthesia. After primary monitoring consisting of ECG, non-invasive blood pressure (NIBP), pulse oximetry, 0.2 mg/kg midazolam and 3μg/kg fentanyl were administered intravenously and after two minutes 5mg/kg sodium thiopental and 0.5 mg/kg atracurium were injected intravenously, after three minutes endotracheal intubation was performed. The adequacy of ventilation was measured by capnography simultaneously to keep end-tidal CO2 around 35 mmHg. After the induction of anesthesia intra-arterial catheter was inserted in non dominant hand's radial artery and blood sample was obtained and sent to laboratory for checking the serum concentration of fibrinogen, thereafter the arterial line was connected to transducer and invasive blood pressure monitoring were performed. A central venous catheter inserted in right internal jugular vein to monitor the preload and guide the fluid therapy to keep the central vein pressure (CVP) between 5- 8 mmHg during surgery. After induction of general anesthesia, 30 mg/kg fibrinogen concentrate (Haemocomplettan-P; CSL Behring, Germany) dissolved in distilled water and reached 100 ml then was infused within 10 minutes in fibrinogen group. In the placebo group, normal saline was administered in the equivalent volume. Maintenance of anesthesia was provided by isoflurane 1.2–2%, oxygen 3 lit/min, fentanyl 50-100 μg/h and atracurium 30 mg/h. Depth of anesthesia was monitored by cerebral state monitoring (CSM) and maintained between 40- 60. After primary preparations according to surgeon's opinion, positioning was done in lateral or supine position, and the surgical procedure was started. At first blood pressure was controlled by adjusting anesthetics and depth of anesthesia and then by using vasoactive drugs such as ephedrine, nitroglycerin and labetalol to maintain the mean arterial pressure (MAP) between 60-90 mmHg if necessary.

According to the amount of blood in the suction bottle, enumeration of gauze, longazes and assessing the surgical field, the blood loss was estimated. Each blood-full gauze and longaze was estimated to contain 20 and 50ml blood, respectively. Blood pressure recording was performed every five minutes by NIBP. Arterial blood gas samples were obtained to monitor and keep the normal acid-base balance during surgery. Transfusion of blood products was performed, if necessary. After one hour from start of operation blood sample for checking, hemoglobin was obtained. Forced warm air provided normothermia during surgery. By incremental doses of IV injection of morphine sulfate, pain was controlled if necessary. Twenty-four hours after the surgery, blood samples were obtained for checking hemoglobin and fibrinogen concentration and blood loss during this period was estimated by measuring blood volume in the drainage bottle (hemovac drain) and the number of blood-full gauzes, as mentioned earlier.

Early postoperative complications such as deep vein thrombosis, pulmonary emboli, myocardial infarction, and cerebrovascular accidents were checked during the hospitalization period and three weeks after discharge. The data were entered and analyzed in SPSS software version 18.0. Data were presented as mean ± SD. Parametric data were analyzed by using analysis of variance, followed by post hoc tests. Nominal data were analyzed by using the Chi-square test. Adjustment blood loss with time was performed with linear regression test. P values < 0.05 were considered statistically significant.

Results

A total of 20 participants were female. The demographic data of patients were compared between two groups (Table1).

Table 1. Comparison of parameters between the fibrinogen group Moreover, placebo the group

	Fibrinogen group	Placebo group	*P*.value
Number of cases	15	15	-
Number of male patients (%)	7 (46%)	3(20%)	0.12
Number of ASA class II (%)	6 (40%)	7 (46%)	-
Mean age(years)	52.8± 14.9	51.3± 14.1	0.78
Preoperative serum concentration of fibrinogen(mg/dl)mean ±SD (range)	322.4 ±86 (147-476)	298.8 ± 70.8 (189-413)	0.42
Total serum levels of preoperative and postoperative fibrinogen (mg/dl)mean ±SD	537.4± 149	478.4± 99	0.19
Preoperative hemoglobin concentration (g/dl) mean(range)	13.3 (9.7-16)	12.6 (10-16)	0.25
Preoperative platelet count mean (range)	318000 (132000-421000)	227200 (120000-400000)	0.27

ASA: American Society of Anesthesiologist; SD: Standard Deviation
Nominal data were analyzed by using the chi^2 test statistic. Adjustment blood loss with time was performed with linear regression test. P values < 0.05 were considered statistically significant

Two groups were similar in plasma concentration of fibrinogen and hemoglobin preoperatively. Fibrinogen group had a little more platelet count than a placebo group, but no association was between platelet count and bleeding during surgery (*P*=0.89). The mean operation time was 3.3 ± 0.8 hours in the fibrinogen group and 2.8 ± 0.6 hours in the placebo group, and this difference was statistically significant (*P*=0.04). Significant correlation was between operation time and blood loss during surgery (*P*=0.002).

No significant difference was between the mean of mean arterial blood pressures (MAP) recorded during the procedure and the recovery time (*P*=0.6). The mean concentration of the intraoperative hemoglobin in fibrinogen group and placebo group were 11.9 ± 1.6 and 10.9 ± 1.6 g/L respectively (*P*=0.09). The mean of total blood loss in perioperative period was 976 ± 553 ml in the fibrinogen group and 1100 ± 350 ml in the placebo group, but this difference was not significant between two groups (*P*=0.85). By a simple linear regression model, outcome was blood loss, and time and intervention group were independent variables therefore, the effect of time is controlled for fibrinogen group and adjusted for both groups, and it was found that the patients in fibrinogen group had lower bleeding during and after surgery and this difference was statistically significant (*P*=0.046). None of the patients in both groups had complications related to fibrinogen transfusion including deep vein thrombosis, cerebrovascular accident (CVA), myocardial infarction (MI) and so on in the perioperative period (Table 2).

Table 2. The comparison of intraoperative and postoperative variables between two groups

	Fibrinogen group	Placebo group	*P*.value
Supine position (%)	9 (60%)	10 (66%)	0.7
The mean Operation time (hour)	3.3 ± 0.8	2.8 ± 0.6	0.04
Intraoperative blood loss (ml)	744.6 ± 337	870 ± 498	0.42
Sum of transfused Packed RBC (unit)	0.8 ± 1.01	1.06 ± 1.2	0.53
mean concentration of the intraoperative hemoglobin (g/dl)	11.9 ± 1.6	10.9 ± 1.6	0.09
Post operative serum concentrations of fibrinogen(mg/dl)	430 ± 140	359.3 ± 83.9	0.10
Postoperative hemoglobin concentration (g/dl)	12 (10.3-14.4)	11.1 (9.5-12.5)	0.037
Postoperative platelet count mean (range)	355100 (156000-429000)	239400 (156000-429000)	0.04
Postoperative blood loss (ml)	231.6 ± 67	236.6 ± 81	0.85

Nominal data were analyzed by using the chi–square test statistic

Discussion

The current pilot study was performed as a single blind randomized clinical trial and evaluated the safety and efficacy of prophylactic administration of fibrinogen concentrate on blood loss and blood transfusion

perioperatively. Significant association was between fibrinogen administration and bleeding during and after surgery. Although less packed cell was transfused in fibrinogen group, but no association was found between prophylactic administrations of fibrinogen and need to blood transfusion. Fibrinogen is an acute phase reactant and the normal plasma concentration ranges from 2.0 - 4.5 g/l with half-life 3–5 days (4). Fibrinogen is the first coagulation factor that reaches its dangerous concentration during severe hemorrhage even before thrombocytopenia develops (5). It is reported that plasma concentration of fibrinogen varies with physiological factors such as age and female sex and pathological events such as liver disease (6). Crystalloids and colloids in massive hemorrhage lead to the development of a dilutional coagulopathy with a drop of fibrinogen below a critical concentration (7). The critical threshold at which fibrinogen should be substituted is less than 1.0 g/L (7). However, according to the guidelines we must maintain a plasma fibrinogen concentration at least 1.5–2.0 g/l in severe bleeding (8). These guidelines recommend us a higher target of fibrinogen plasma concentration because clot firmness continues to increase with fibrinogen concentration throughout its normal range (9-11). In current study preoperative and postoperative serum concentrations of fibrinogen were more than 2.5 g/l and need for transfusion were related to factors other than fibrinogen concentration, such as age, coexisting diseases, prolonged operation time, surgical manipulation and blood loss more than allowable blood loss (ABL). Generally ABL is calculated according to desirable hemoglobin for age and sex. To maintain adequate oxygen carrying capacity, we set Hb concentration of 10 as transfusion threshold to avoid hypovolemic ischemia because of blood loss. All of the patients in this study were ≥ 50 years old, the authors considered probable coexisting coronary artery diseases and atherosclerosis. This might have decreased transfusion threshold and did not allow us to determine the net effect of fibrinogen on perioperative blood loss and transfusion. It is reported that women with a fibrinogen concentration of 2.0 g/l may be at risk of severe hemorrhage in the post-partum period (12). We have traditionally replenished fibrinogen with fresh frozen plasma (FFP) and cryoprecipitate, but we should infuse a liter of FFP or 260 ml of cryoprecipitate to increase plasma concentration of fibrinogen by 1g/L (13). Fibrinogen concentrate provides rapid replacement in low volumes. It is reported that three g of fibrinogen concentrate increases the plasma fibrinogen by 1 g/L (14). In vitro study showed that optimal clot formation occurs at fibrinogen concentrations exceeding 2 g/l (5). In a prospective study that patients underwent aortic aneurysm surgery, administration of fibrinogen reduced bleeding and transfusion requirements significantly. Mean concentration of plasma fibrinogen was 3.6 g/L in fibrinogen group compared to 2.5 g/L in the control group (6). Moreover, fibrinogen has a low administration volume with no need for blood group matching (15) therefore, administered in less time than either FFP or cryoprecipitate and reduced the time to control bleeding. The authors assessed the effect of fibrinogen on intraoperative blood loss and it was found that by controlling time factor, fibrinogen transfusion had correlation with perioperative bleeding so that in fibrinogen group perioperative bleeding was less than placebo group. It means that if two groups had same operation time it would be less intraoperative bleeding, and this is concordant with other studies performed earlier (16-28). It is reported that pre-operative plasma concentration of fibrinogen within the low normal range in patients undergoing coronary artery bypass grafting (CABG) surgery increases postoperative bleeding and pre-operative fibrinogen supplementation may reduce post-operative hemorrhage (29-30). Fibrinogen concentrate was recently shown to decrease blood transfusion and thrombotic events in patients who underwent cardiovascular surgery (31). In patients who underwent radical cystectomy, fibrinogen administered versus placebo and it was found that amount of transfusion and bleeding were similar in the two groups intraoperatively, whereas packed cell were administered significantly more to patients in the placebo group versus fibrinogen group postoperatively (23). Another study in patients who underwent coronary bypass graft surgery showed that prophylactic administration of fibrinogen concentrate decreased bleeding by 32% (P=0.010), moreover, blood products transfusion were less in the fibrinogen group compared to placebo group (6). This strategy enables comprehensive treatment of coagulopathy with fibrinogen alone and the potential for larger reductions in blood products transfusion. The common cause of intraoperative and postoperative bleeding is inadequate surgical homeostasis applied by the surgeon therefore, in present study this finding can be explained by this fact that hip joint field of surgery has a lot of muscle bulk that precludes adequate homeostasis and oozing from muscle continues slowly during surgery and the more time spent on procedure the more blood loss would be expected. In the current study, the mean operation time in fibrinogen group was more

than the control group. This is related to several factors such as technical and equipment related factors that are out of reach of anesthesiologists and may affect the amount of bleeding, and show itself in places with difficult to homeostasis as seen in hip joint surgery. The safety of fibrinogen concentrate had 1) very low risk of thromboembolic complications and 2) an excellent margin of virus safety (33-34). The authors applied 30 mg /kg fibrinogen that is in a lower range of doses administered in other studies; although this dose was partially effective in this study, authors suggest that the administered dose is increased up to 70 mg/kg with respect to other studies performed in this field. None of our patients in the fibrinogen group showed adverse effects of fibrinogen such as hypersensitivity, thrombotic events and so on in a one month perioperative period that is adaptable with earlier studies performed and insists on safety of this product (35-37). Surgeons' approach to joint was lateral or anterolateral that was performed under supine and lateral decubitus positions, respectively. We had no participation in position selection, and our surgeon was blinded to randomization and allocation. We followed the position selected by him to provide the best for the patients. We chose the patients operated by the most expert surgeon in our hospital on total hip arthroplasty to minimize the effect of different skill and style and personal preferences and choose the best for the patients. Theoretically, patient positioning may be effective in blood loss volume. Blood pooling in surgical field in the lateral position leads to provide adequate cells to form clot, that may not be likely in the supine position while blood is shedding from the incision and there is no blood accumulation, on the other hand by limiting view and lowering the accuracy of joint manipulation by the surgeon in the lateral position suctioning of pooled blood is more than the supine position and the effect of the pooled cells is offset by suction and may cause more blood loss than the supine position. Our study was a pilot study with a sample as little as 15 patients in two groups, and this may have little power. On the other hand, we found significant results in a little sample size, and we have no claim in insignificance. We believe that the reduction in blood loss is more important than the low power of the study, and this may compensate the sample size.

Overall, in this study, the patients' position had no effect on blood loss volume; however, the patients were operated in the supine position had less bleeding during surgery. A limitation of this study was small sample size and use of a single center. However, the treatment effect size was determined as a 30 percent change in the mean of the amount of packed RBC administered. The performance of the study in a single center may limit applicability to other centers, but it will also have reduced variability in clinician and technique of study. We recommend that further studies of fibrinogen concentrate administration to perform in larger numbers of cases, in different surgical procedure and in subjects with different preoperative conditions to evaluate the efficacy and safety of this strategy in perioperative period.

In conclusion, administration of fibrinogen concentration before operation in patients undergoing hip arthroplasty decreases blood loss. Consequently, this therapeutic approach has the potential to change the treatment paradigm for perioperative hemorrhage in patients with potentially life-threatening coagulopathy.

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