International Journal of Anesthesia and Clinical Medicine
2022; 10(1): 16-23
http://www.sciencepublishinggroup.com/j/ijacm
doi: 10.11648/j.ijacm.20221001.13

A Comparative Study Between Tranexamic Acid (TXA) and Fibrinongen Concentrate in Bleeding Control of Total Hip Arthroplasty (THA)

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To cite this article:
Jehan Mohammad Ezzat Hamed, Rabab Mohamed Mohamed. A Comparative Study Between Tranexamic Acid (TXA) and Fibrinongen Concentrate in Bleeding Control of Total Hip Arthroplasty (THA). *International Journal of Anesthesia and Clinical Medicine.* Vol. 10, No. 1, 2022, pp. 16-23. doi: 10.11648/j.ijacm.20221001.13

Received: March 23, 2022; **Accepted**: April 9, 2022; **Published**: April 14, 2022

Abstract: Total hip arthroplasty (THA) faces the hazard of surgical blood loss and significant invisible blood loss due to bleeding into tissue and hemolysis. Tranexamic acid (TXA) and fibrinogen are important agents among a diversity of intraoperative blood management protocols. During the coagulation cascade, thrombin enhances fibrinogen and hastens fibrin polymerization forming an intense network important in clot formation. Our study included sixty male patients that were randomized into two groups; patients receiving 15 mg/kg TXA given as a single slow intravenous bolus injection 15 minutes before incision were placed in (group 1). Patients receiving 30 mg/kg fibrinogen concentrate administered post induction of general anesthesia were placed in (group 2). Intraoperative (IO) mean heart rate (HR) and mean arterial pressure (MAP) showed no significant differences. There was a significant decrease in IO blood loss in fibrinogen (723.03. ± 117.69) group compared to TXA (879.30 ± 168.54) (p=0.001), with significant (P=0.010) differences in the amount of transfused packed RBCs (IQR:1-2). Field visibility also improved significantly (p=0. 017) in fibrinogen group. The amounts of Lactated Ringer's (LR) solution infused during surgery were not significantly different while a significant (p=0.037) decrease in the additional amount of hydroxyethyl starch (HES) solution infused in patients with fibrinogen (211.87 ±32.30) over TXA (250.63 ± 43.65) was noted. In conclusion, administration of fibrinogen concentrate before procedure in patients undergoing THA reduces blood loss. Consequently, this therapeutic process has the potential to change the treatment model for perioperative hemorrhage in patients with potentially life-threatening coagulopathy.

Keywords: Tranexamic Acid, Fibrinogen Concentrate, Total Hip Arthroplasty, General Anesthesia

1. Introduction

THA risks high surgical blood loss as well as significant hidden blood loss caused by bleeding into tissue and hemolysis [1, 2]. Park et al. have reported that approximately 1500 mL of blood is required during surgery [9]. Despite increasing knowledge and technology, the incidence of allogeneic blood transfusions in the orthopedic field has not decreased. Studies on the needs and methods of patient blood management are guaranteed considering the side effects and social costs of transfusions (e.g., immune deactivation, acute and delayed hemolytic reaction, anaphylaxis, transfusion-linked acute lung injury, host response and postoperative infection). Pharmacological modalities of peri-operative bleeding control are being intensely researched. TXA (Cyklokapron) is one such pharmacologic field of inquiry as an important agent among several blood management protocols [10, 11]. When activation of the fibrinolytic pathway occurs, plasminogen is converted to fibrinolytic plasmin through tissue plasminogen activator (t-Pa). TXA is a synthetic lysine amino acid derivative moving through competitive suppression of lysine binding sites on plasminogen, thus preserving and stabilizing fibrin matrix structure [3, 4]. Consequently, TXA is an elementary candidate for minimizing the number of patients presenting with postoperative anemia therefore decreasing transfusion

rates. Nevertheless, TXA optimal dose, perfect time and route of administration still have conflicting literature findings [5]. Fibrinogen is a crucial protein in the management of bleeding. During the coagulation cascade, thrombin activates fibrinogen and facilitates polymerization of fibrin, forming a network essential for clot formation [6].

Acute blood loss and volume revival can lead to dilutional coagulopathy and lowering of fibrinogen levels, normal fibrinogen levels are between 150 and 350 mg/dL [12] and studies have shown that hypofibrinogenemia enhances the risk of perioperative bleeding in different types of surgery. In recent literature, fibrinogen is highlighted as an initiator for managing bleeding in surgical patients [7, 8, 18].

1.1. Aim

The aim of this study is to compare the effect of TXA with fibrinogen concentrate in control of bleeding with THA surgery as first complication.

1.2. Design

This study was a prospective comparative clinical trial.

2. Patients & Methods

This prospective study was conducted in anesthesia and orthopedic department at Tanta University Hospital from July 2021 to January 2022. After Approval of the study protocol by ethnical committee number (35230), all patients signed fully informed written consents.

Randomization was conducted using sealed envelopes, containing cards carrying the group label either T for TXA or F for fibrinogen group and prepared by an assistant who was blinded about the target of the study. Envelopes were chosen by patients. Sixty male patients patients were randomized into 2 groups, including: TXA (group 1): For patients receiving TXA, 15 mg/kg tranexamic acid (TXA group) given as a single slow intravenous bolus injection 15 minutes before incision. Fibrinogen concentrate (group 2):

30 mg/kg fibrinogen concentrate was administered in the fibrinogen group post induction of general anesthesia.

2.1. Inclusion Criteria

The study included sixty male patients above 21 years of age undergoing either a primary or revision, unilateral THA operation with preoperative hemoglobin (Hb) values ≥11 g/dL and ordinary international normalized ratios (INR), prothrombin times (PT), and partial thromboplastin time (PTT) values.

2.2. Exclusion Criteria

The following conditions were excluded: allergy to TXA, presenting with renal or hepatic dysfunction, history of ischemic heart disease, chronic heart failure bilateral THA, history of seizures, cerebral infarction, bleeding tendencies, hemodialysis under anticoagulant medication, or the use of long-acting nonsteroidal anti-inflammatory drugs (NSAIDs).

2.3. Anesthetic Procedure

All patients were pre-medicated with midazolam at a dose of 0.05mg/kg. Anesthesia was conducted using propofol (2mg/kg), fentanyl (1-2 ug/kg), and cis-atracurium (0.15mg/kg) to smooth endotracheal intubation. Equiponderant anesthesia was continued using sevoflurane in oxygen air, fentanyl and cis-atracurium. Ventilation was adjusted to maintain $paCO_2$ levels of 32-35 mmHg using 100% O_2 in air in semi-closed circuit with a tidal volume of 6-8ml/kg. Intraoperative analgesia was provided by persistent infusion of fentanyl 0.2-0.4ug/kg according to the need of patients to help maintain hemodynamics. At the end of surgery, residual neuromuscular blockade was reversed by neostigmine 0.05mg/kg with atropine 0.02mg/kg i.v., patients were extubated and shifted to post anesthesia care until (pACU).

2.4. Intraoperative Fluid Management

6% hydroxyethyl starch in saline (6% HES 130/0.4; Voluven) in a dose of 3 mL/kg over 10-15 min was received initially and LR solution in a dose of 5mL/kg/h throughout surgery time. Additional boluses of HES were given to maintain hemodynamics and urine output >0.5mL/kg/h.

2.5. Measurements

Patients' demographics (age, body mass index—BMI, American Society of Anesthesiologists (ASA) score), as well as operative time, preoperative platelet count, Hb values at baseline and following surgery, intraoperative blood loss, units of blood transfused, postoperative blood loss, post operative platelet count, field visibility score, HES solution loading dose (mL), additional dose, frequency and LR solution (mL) were screened for all patients. Hemodynamic data of patients of both groups, complication as vaso-occlusive events (VOEs) and other adverse events were also recorded.

2.6. Field Visibility Score

Slight bleeding needs no suction.
Slight bleeding sometimes needs suction.
Low bleeding often needs suction.
Average bleeding, field is only visible after suction.
Constant bleeding with continued suction [20].

2.7. Blood Loss Calculation

Intraoperative blood loss was weighted using an electric weighing scale with a fineness of 0.1 mg (Alexandra Scale Pvt. Ltd., Gujarat, India). All blood-stained mops and the blood in the suction cylinders were included in the blood loss. The postoperative blood loss was studied using two methods: First, the blood loss was specified based on the blood collected from the suction drainage (hemovac attached to the surgical wound) 12, 24, and 48 h after surgery. Second, the blood loss was estimated based on hematocrit equilibrium using Gross' formula [21], which included the blood loss of extravasation in the tissues. Gross' formula are as follows:

Estimated blood loss=Estimated blood volume× (initial hematocrit−final hematocrit)/mean hematocrit.

Estimated blood volume = body weight (kg) ×70ml/kg

The total blood loss (clinical) was decided by adding intraoperative and postoperative blood loss. To prevent thrombosis, graduated compression stockings were used for the whole hospital stay as a non-pharmacological measure together with the use of prophylactic anticoagulant medications.

Blood transfusions were administered post-operatively at a drop of Hb values beneath 7g/dl. Patients with cardiovascular disease and patients who did not tolerate low Hb values were transfused at Hb levels of <8g/dl and <10g/dl respectively as recommended by patient blood management chart reviews.

2.8. Study Outcome

Primary outcome was the ability of the study medications to reduce the amount of transfusion related to blood loss to maintain no significant differences in HGC pre and postoperatively.

Secondary outcome was to maintain hemodynamics and decrease length of hospital stay.

2.9. Sample Size Calculation

A purposeful convenience sample was employed to recruit a total of 60 (n=30 in each group) patients after reviewing many randomized controlled studies and using Epi-info software statistical package created by World Health Organization and center for disease control and prevention Atlanta, Georgia, USA version 2002 with:

1. 95% confidence limit.
2. 80% power of study.
3. 1:1 for each study group.

The sample size was found at n = 30 patients in each groups with total 60 patients.

2.10. Statistical Analysis

Statistical analysis was conducted using: SPSS 24, IBM, Armonk, NY, United States of America.

Quantitative data were expressed as mean± standard deviation (SD). Independent-samples t-test of significance was used when comparing between two means.

Qualitative data were expressed as frequency and percentage. Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters.

Abnormally data expressed as a median (IQR). Mann Whitney test to compare between two studied group.

All tests were two-sided, $p<0.05$ was considered significant.

3. Results

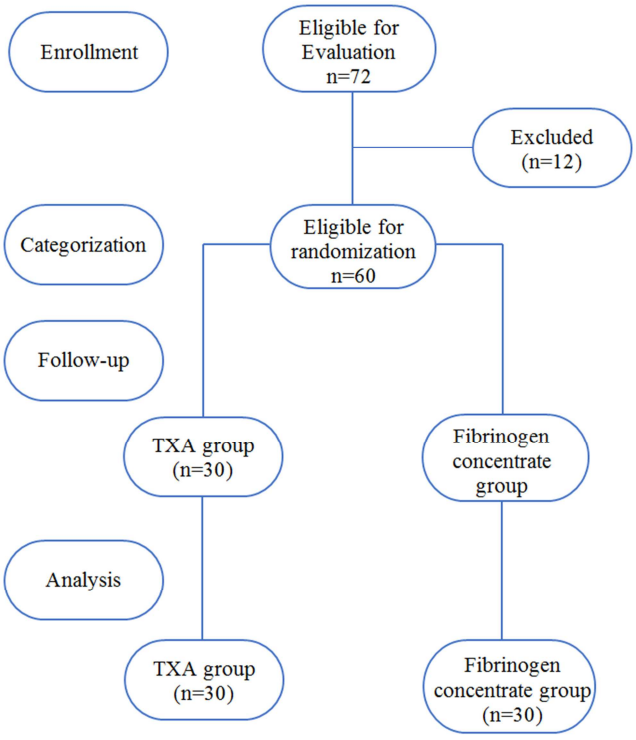


Figure 1. *Consort flow chart of patients.*

Table 1. *Enrollment data of patients of both groups.*

		TXA			Fibrinogen			t. test	p. value
Age (years)	Range	31	–	60	30	–	58	1.256	0.214
	Mean ± S.D	45.63	±	8.57	42.83	±	8.69		
BMI (Kg/m^2)	Range	24.5	–	35.7	23.9	–	37.2	0.244	0.808
	Mean ± S.D	29.70	±	3.27	29.48	±	3.80		
ASA	I (%)	12 (40%)			14 (46.7%)			X^2: 0.269	0.602
	II (%)	18 (60%)			16 (53.3%)				
Preoperative PLT (X10^3)	Range	135	–	430	129	–	398	0.077	0.939
	Mean ± S.D	285.30	±	86.96	283.67	±	76.49		
Operative time (h)	Range	1.8	–	4	1.5	–	4.2	1.159	0.251
	Mean S.D	2.91	±	0.68	2.68	±	0.81		

Data are presented as mean± SD, BMI=Body mass index, ASA: American Society of Anesthesia, PLT; platelet count; p>0.05 indicates non-significant differences.

Table 2. *Hemodynamic data of patients of both groups.*

	TXA group (n=30)	Fibrinogen group (n=30)	T test	P value
HR (beats/min)				
Baseline	76.77 ± 4.31	76.33 ± 5.78	0.329	0.743
During intubation	80.97 ± 5.66	81.03 ± 6.56	0.042	0.967
15 min.	79.40 ± 5.68	78.57 ± 5.66	0.569	0.572
30 min.	77.30 ± 4.36	77.00 ± 6.07	0.220	0.827
45 min.	76.80 ± 6.33	75.63 ± 6.63	0.698	0.488
60 min.	74.60 ± 4.16	74.47 ± 6.78	0.092	0.927
75 min.	75.00 ± 7.87	76.97 ± 6.59	1.050	0.298
90 min.	74.67 ± 6.09	76.20 ± 6.26	0.962	0.340
120 min.	76.10 ± 4.83	77.37 ± 6.35	0.869	0.388
End of surgery	78.37 ± 6.27	77.93 ± 4.88	0.299	0.766
After extubation	77.53 ± 6.22	78.73 ± 4.53	0.854	0.397
MAP (mmHg)				
Baseline	86.07 ± 4.98	85.47 ± 9.70	0.301	0.764
During intubation	88.80 ± 4.36	88.07 ± 4.18	0.665	0.508
15 min.	88.27 ± 3.97	87.67 ± 4.26	0.564	0.575
30 min.	87.23 ± 4.07	87.60 ± 2.97	0.398	0.692
45 min.	86.97 ± 3.91	86.00 ± 4.18	0.926	0.359
60 min.	85.80 ± 4.01	85.23 ± 3.41	0.589	0.558
75 min.	85.70 ± 2.68	86.63 ± 2.92	1.290	0.202
90 min.	86.97 ± 5.22	86.23 ± 9.89	0.359	0.721
120 min.	85.33 ± 3.08	86.10 ± 9.96	0.403	0.689
End of surgery	86.47 ± 2.62	86.70 ± 9.80	0.126	0.900
After extubation	86.17 ± 3.61	85.87 ± 5.57	0.248	0.805

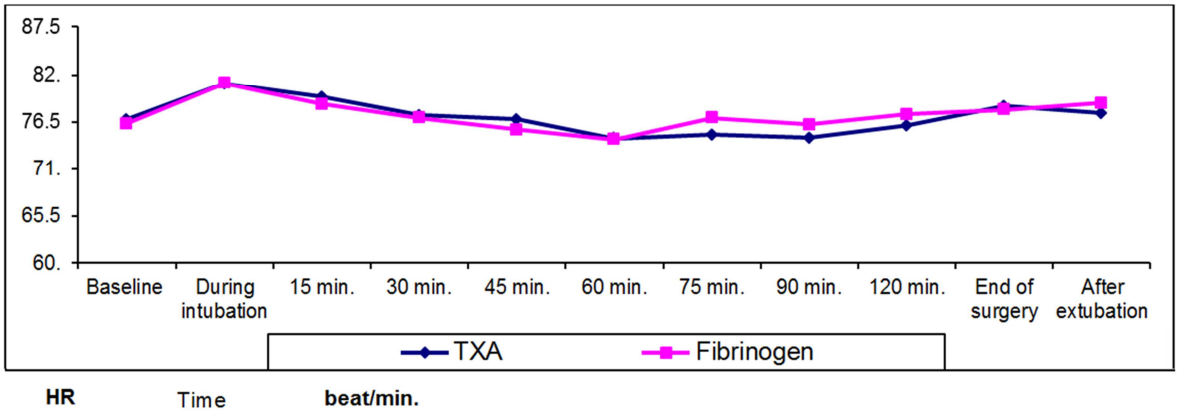
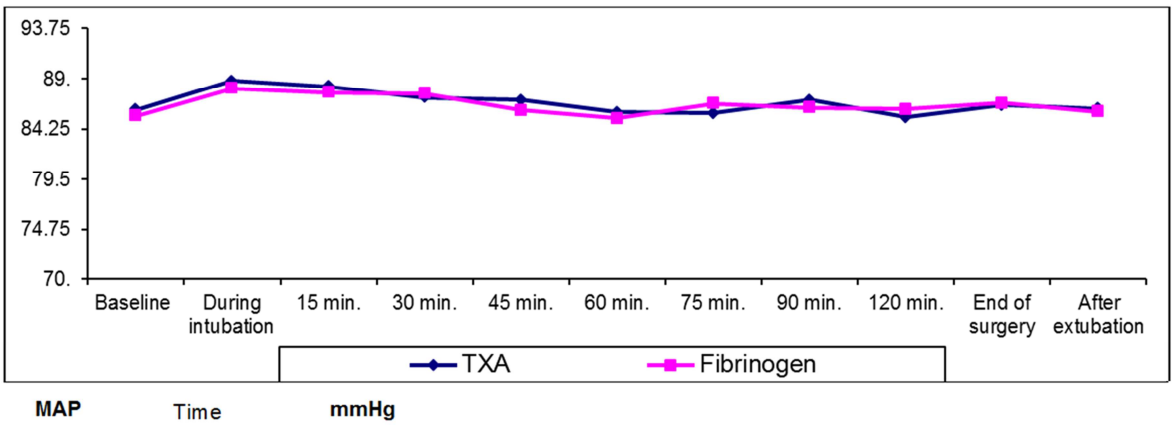


Figure 2. *Heart rate changes in both groups.*



Data are presented as mean± SD, P>0.05 indicates non significant difference between both groups. HR=Heart rate; MAP=Mean arterial pressure

Figure 3. *Mean arterial pressure changes in both groups.*

Table 3. *Operative data of patients of both groups.*

		TXA			Fibrinogen			t. test	p. value
Pre operative HGC	Range	11.1	–	13.2	11.1	–	13.1	0.938	0.352
	Mean ± S.D	11.77	±	0.55	11.90	±	0.58		
Post operative HGC	Range	10.5	–	12.2	10.5	–	12.7	0.152	0.880
	Mean ± S.D	11.29	±	0.54	11.32	±	0.64		
Intraoperative Blood loss (mL)	Range	658	–	1325	548	–	958	4.164	0.001*
	Mean ± S.D	879.30	±	168.54	723.03	±	117.69		
Amount of transfused units	IQR	1	–	2	1	–	2	Z: 2.583	0.010*
	Median	2			1				
Post operative Blood loss (mL)	Range	152	–	400	125	–	371	1.170	0.247
	Mean ± S.D	286.00	±	61.52	264.57	±	79.25		
PLT post ($X10^3$)	Range	160	–	420	150	–	425	0.271	0.787
	Mean ± S.D	271.03	±	69.14	276.23	±	79.24		
Field visibility score	0 (%)	0 (0%)			0 (0%)			X^2: 8.143	0.017*
	1 (%)	3 (10%)			8 (26.7%)				
	2 (%)	15 (50%)			19 (63.3%)				
	3 (%)	12 (40%)			3 (10%)				
HES Loading dose (mL)	Range	285	–	400	295	–	396	1.257	0.214
	Mean ± S.D	342.10	±	33.28	352.67	±	31.81		
Additional dose Frequency	Yes (%)	17 (56.7%)			9 (30%)			X^2: 4.339	0.037*
	No (%)	13 (43.3%)			21 (70%)				
Amount (mL)	Range	195	–	352	165	–	287	3.910	0.001*
	Mean ± S.D	250.63	±	43.65	211.87	±	32.30		
LR (mL)	Range	845	–	952	851	–	955	1.829	0.073
	Mean ± S.D	887.97	±	33.46	902.20	±	26.40		

Data are presented as mean± SD, P>0.05 indicates non significant difference between both groups; p<0.05 indicates significant difference between both groups; IQR=interquartile range; HGC=HB concentration; HB=Hemoglobin; HES= Hydroxyethyl starch; LR= Lactated Ringer's; PLT; platelet count.

Table 4. *Incidence of complications of patients of both groups.*

Complication	TXA group (n=30)		Fibrinogen group (n=30)		X^2	P value
	N	%	N	%		
Number of patients developed anaphylactic reactions						
Hypotention	0	0	0	0	-	-
Rash	0	0	0	0	-	-
Number of patients developed Seizures	0	0	0	0	-	-
Thrombo embolic Incidences						
DVT	1	3.3	0	0	1.018	0.313
PE	2	6.7	2	6.7	0.0	1.0
MI	0	0	0	0	-	-
Stroke	0	0	0	0	-	-
Length of hospital stay (days)						
Up to 5days	27	90	28	93.3	0.223	0.640
More than 5days	3	10	2	2.7		
ICU (%) admission	3	10	2	6.7	0.223	0.640

Data are presented as numbers and percentages. DVT=Deep vein thrombosis; PE=Pulmonary embolization. P>0.05 indicates non significant difference.

The study included 72 patients eligible for evaluation, 60 were included in the study and were randomly categorized into two equal groups (Figure 1). The enrollment data of patients of both groups were not significantly different as well as the preoperative platelet count and the mean operative time of both groups (p>0.05) as seen in (Table 1). Intraoperatively, Mean HR and MAP recorded in both groups showed a non-significant increase in HR and a non-significant decrease in MAP at 30, 45 and 60 min IO in patients of the Fibrinogen group compared to patients of the TXA group (p>0.05)) there was no significant differences between HR and MAP at 75, 90, 120 min IO between both groups. At the end of surgery there was a non-significant (p>0.05) increase in MAP and a non significant decrease in HR in fibrinogen group compared to TXA group. There was no significant differences recorded in other scheduled time (Table 2, Figure 2, Figure 3).

Preoperative HGC and platelets showed non-significant differences (p>0.05) between both groups with a non-significant (p>0.05) decrease in post operative HGC in TXA group compared to fibrinogen group (Table 3). Intraoperative blood loss decreased significantly (p=0.001) in fibrinogen (723.03±117.69) group compared to TXA (879.3±168.54) with significant (p=0.010) differences in the amount of transfused packed RBCs (IQR: 1-2).

Another finding, is the resulting of a significant (p=0.017) improvement in the field visibility in fibrinogen group upon TXA group. No significant (p>0.05) differences was noted regarding the amount of LR solution infused during surgery. while a noted significant (p=0.037) decrease in the additional

amount of HES solution infused in patients with fibrinogen (211.87±32.30) compared toTXA (250.63±43.65) was noted. Moreover, there was a non-significant reduction in post operative blood loss in patients received fibrinogen than TXA patients (Table 3). Five patients (12%) were admitted to ICU. 3 (10%) of them among the TXA group; 1 (3.3%) patient presented with peripheral DVT and 2 (6.7%) cases of both groups were having some sort of shortness of breath and shifted quickly to ICU where they were received prompt management and follow up care (Table 4). No manifestation of anaphylactic reaction as regard hypotension or Rash was recorded in both groups of patients.

4. Discussion

THA often causes massive blood loss during surgery accompanied by fibrinolysis that continues throughout the postoperative period [13]. After THA, marked blood loss may lead to higher transfusion rates, which may negatively impact surgical outcome leading to higher complication rates [19, 34].

Significant reduction of total blood loss as well as reduced amount of transfusion units were recorded with the use of fibrinogen concentrate 30 mg/kg IV after induction of general anesthesia. The study demonstrated how unscathed and effective role of fibrinogen in peri operative hemostasis in THA patients. In a prospective randomized similar clinical trial, Najafi et al. compared the use of fibrinogen concentrate versus placebo in a total of 30 patients and reported significant decrease in total blood loss together with a decrease in the transfusion units [22]. Our study goes hand in hand with a study in patients who underwent aortic aneurysm surgery that concluded that patients who received fibrinogen concentrate showed significant reduction of intraoperative bleeding and transfusion requirements with a reported serum fibrinogen of 3.6g/L compared to 2.5g/L in the control group. [30]. Bardia et al. Found that the use of 1 gm IV fibrinogen concentrate 5 minutes after induction of general anesthesia was promising and had improved hemostasis in spine surgery resulting in lower intraoperative and postoperative bleeding. [23]. In contrast to the results of our study and studies previously reported in literature, M. Soleimani et al. reported non-significant influence of fibrinogen administered preoperatively on either intra or post operative blood loss in patients undergoing TUR-P surgery [24]. Also, fibrinogen was studied against placebo in radical cystectomy surgery and it was found that values of transfusion and bleeding were comparable in the two groups intraoperatively, whereas packed cells were significantly more in the placebo group [37]. Regarding TXA in THA patients, meta analysis studies were conducted by Baskarani et al. [25] and C. E Pinz'on et al. [26] where they reported that TXA is effective in reducing total blood loss but with no significant differences considering operative time or the amount of transfusion. Yang et al. conducted a meta-analysis on the performance of TXA, the results of which indicated a drop in blood loss of 504 ml and a decrease in the number of units transfused per patient of 1.43 units after traditional total knee athroplasty [27]. Several studies were in accordance with our work concluding that in selective patients; administration of TXA reduced the necessity for blood transfusions by almost one third [28] and substantially reduced blood deprivation [29]. In the current study we demonstrated a significant reduction in HES amount and frequency of use in the fibrinogen group while no difference in LR solution given during the surgery with maintained hemodynamics comparable all over the study in both groups. A prospective study looking at 66 major orthopedic surgery patients who randomly received volume revival with modified gelatin solution, HES, or LR showed that fibrinogen concentrate supplementation can inverse the effects of intravascular volume therapy and promote hemostasis [17]. Our study found a significant improvement in the visibility of surgical field with its importance in this type of surgery. This can be explained by the fact that hip joint field of surgery has a lot of muscle bulk that prohibit adequate homeostasis and oozing from muscle continues slowly during surgery and the longer the duration of the procedure the more blood loss would be expected.

Inadequate surgical hemostasis is the common cause of intraoperative and postoperative bleeding. Although field visibility was improved, there was no significant reduction in the mean operative time and this could be supported by the previously assumed explanation. Fibrinogen concentrate played a dynamic role in hemostasis accompanied by low risk of thromboembolic complications with an outstanding margin of safety [14-16]. These findings were proven by many studies in which fibrinogen could be administered safely in a wide range from 30 mg/kg up to 70 mg/ kg. [31, 32]. One patient had peripheral type of DVT, two patients in each group developed initial manifestations of PE, as a consequence they were shifted to ICU to be fully investigated and received the prompt care and management within the perioperative period. All patients received prophylactic anticoagulation measurements commenced early after surgery, therefore it was in accordance with earlier studies that were performed and insists on the integrity of the study drugs [33, 35]. There is a theoretical increase in the possibility of the risk of VOEs in patients treated with TXA as a result of the inhibition of fibrinolysis with subsequent overriding coagulation [36]. When less aggressive methods of pharmacological anticoagulation prophylaxis with a targeted level of INR <2.5 were chosen after THA, the incidence of hyper-coagulation and risk of VOEs were of major concern with the use of TXA [37]. Contrarily to our findings, Zufferey et al and Emara et al described an increase in VOEs risk with TXA use concluding that this may be the result of TXA induced hyper coagulable state [38, 39], while several published studies have found no significant increase in the prevalence of DVT with the use of TXA in THA surgery [40, 41]. Others explained that routine pharmacological prophylaxis may mask any increased risk of VTE arising from TXA based on a review of 1035 patients who underwent THA surgery [42].

5. Conclusion

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

6. Limitations

1. Sample size was relatively small and my need further studies with increased sample size.
2. More randomized trials need to be conducted using different concentrations of both studied medications to verify and support our findings.

Conflict of Interest

The authors declare that they have no competing interests.

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