

Repeated doses of intravenous tranexamic acid are effective and safe at reducing perioperative blood loss in total knee arthroplasty

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Summary

Fibrin sealant (FS) and tranexamic acid (TXA) have been used in total knee arthroplasty (TKA) to minimize perioperative blood loss. The efficacy of FS has been debated, and few studies have looked into the effects of FS and TXA on perioperative coagulability. The current study retrospectively reviewed 100 cases of unilateral primary TKA. Twenty-five cases served as blank controls, FS was used without TXA in 23, TXA was used without FS in 20, and both FS and TXA (FS + TXA) were used in 32. FS was sprayed before wound closure whereas 1 g of TXA was intravenously administered before incision and 1 g was administered 15 min before tourniquet release. Hematocrit and hemoglobin levels and thromboelastography (TEG) parameters were assessed pre-operatively and on day 1, 4, and 9 post-operatively. Blood transfusions were noted and the incidence of symptomatic DVT/PE was determined. Hematocrit and hemoglobin levels were significantly higher in the TXA and FS + TXA groups compared to the control and FS groups on day 1, 4, and 9 post-operatively. Hematocrit and hemoglobin levels in the control group were similar to those in the FS group and hematocrit and hemoglobin levels in the TXA group were similar to those in the FS + TXA group. TEG parameters (R, K, α , MA, and CI) remained within normal ranges. Mean CI was less than +3 in all four groups, suggesting that hypercoagulation was not promoted. One patient in the FS group received an allogeneic transfusion. Incidence of symptomatic DVT/PE was not noted. Intravenous TXA significantly reduced perioperative blood loss in patients undergoing a TKA but FS did not. Administration of FS in addition to TXA was not superior to TXA alone. FS and/or TXA did not increase the risk of hypercoagulation according to TEG parameters. Intravenous administration of 1 g of TXA pre-operatively and administration of 1 g before tourniquet release is an effective and safe method of reducing blood loss in TKA.

Keywords: Tranexamic acid, total knee arthroplasty, thromboelastography, fibrin sealant, blood loss

1. Introduction

Total knee arthroplasty (TKA) is considered one of the most successful orthopedic procedures as indicated by a high level of patient satisfaction. However, management of perioperative blood loss continues to be a significant concern and challenge.

In addition to intraoperative loss and drain output, up to 50% of total blood loss in TKA consists of hidden blood loss such as residual hemarthrosis, extravasation of blood into surrounding tissues, and hemolysis (1). The total blood loss associated with TKA can be up to 1,700 mL (1), leading to a substantial risk of allogeneic blood transfusions, which in turn have the potential to lead to transfusion reactions, graft-versus-host disease, hyperkalemia, fluid overload, and infections (2,3).

Numerous alternatives have been used to avoid allogeneic blood transfusions, including preoperative autologous blood donation, epoetin alpha, iron supplements, normovolemic hemodilution, intraoperative blood cell salvaging, hypotensive

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anesthesia, and hemostatic agents (4-7), although these alternatives also have significant risks. For instance, retransfused blood from blood salvage systems can be hemolyzed and contain inflammatory mediators (8) and hypotensive anesthesia and normovolemic dilution can increase the risk of myocardial infarction, cerebral ischemic events, and even death (7).

Fibrin sealants (FS) and tranexamic acid (TXA) are two hemostatic agents widely used to reduce perioperative blood loss in TKA. FS achieves hemostasis by mimicking the final phase of the coagulation cascade in which thrombin converts fibrinogen into fibrin threads (9). TXA is an antifibrinolytic that binds to specific sites of both plasminogen and plasmin, competitively inhibiting the activation of plasminogen to plasmin and thus inhibiting dissolution of clots. Opinions are mixed over the true efficacy of FS in reducing perioperative blood loss and reducing the need for blood transfusion (10-16). In contrast, multiple trials have clearly demonstrated that TXA is highly reliable (17-20). However, few studies have compared the efficacy of FS and TXA or whether combined use of FS and TXA would be more effective than use of either alone since their mechanisms of action affect different stages of the coagulation pathway.

One of the major concerns for hemostatic agents, especially when they are systematically administered, is the increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE). Although most trials have not found FS and/or TXA to promote hypercoagulation after TKA, that possibility cannot be ruled out.

Conventional coagulation assays are performed only on plasma rather than on whole blood. Therefore, the role of platelets in clot strength and formation is often not considered. Thromboelastography (TEG) is a method of testing the efficiency of blood coagulation, including parameters that conventional assays cannot measure, *e.g.*, platelet function, clot strength, and fibrinolysis. The current study attempted to compare combined and individual use of FS and TXA in order to provide additional evidence of their efficacy in reducing perioperative blood loss during TKA. This study also sought to use TEG to determine whether these agents would promote hypercoagulation in patients undergoing TKA.

2. Materials and Methods

2.1. Patient characteristics

Cases of patients who suffered from osteoarthritis or rheumatoid arthritis and who underwent selective unilateral TKA at this Hospital from January 2012 to April 2014 were retrospectively reviewed. Patients with a physical status of I-III according to the American Society of Anesthesiologists (ASA) were enrolled in the study. Patients with history of thromboembolic

disease, recent anti-coagulation therapy, chronic renal failure, or anemia (preoperative Hb < 110 g/L) and those who were allergic to FS or TXA were excluded. This study was approved by the ethics committee of this Hospital.

2.2. Surgical and perioperative treatment

A medial parapatellar approach and pneumatic tourniquet were used for all surgeries. Cemented prostheses (Genesis II, Smith & Nephew, Memphis, Tennessee, USA and Palacos R+G, Heraeus Medical, Wehrheim, Germany) were implanted in all patients. Before cementing, an autologous bone plug was used to fill the hole in the femoral canal left by the intramedullary guide. Local infiltration anesthesia was given after successful prosthesis implantation. Bleeding was precisely controlled with electrocautery. For topical application of FS, 5 mL of fibrin sealant (human thrombin and fibrinogen, Shanghai RAAS, Shanghai, China) was sprayed over the surgical site before wound closure. For intravenous administration of TXA (Jinhua Conba, Jinhua, Zhejiang Province, China) (IV-TXA), 1 g was administered before incision and 1 g was administered 15 min before tourniquet release. A single vacuum drain was used in the first 24 h after TKA and retrieved on the morning of day 2 post-operatively. Low molecular weight heparin (LMWH, Fraxiparine, GlaxoSmithKline, Notre-Dame-de-Bondeville, France) was administered immediately for thromboembolic prophylaxis and was subsequently administered daily until day 14 post-operatively. All surgeries were performed after general anesthesia with a femoral nerve block. An allogeneic blood transfusion was deemed necessary if Hb < 80 g/L during surgery.

2.3. Data collection

Hematocrit (Hct) and hemoglobin (Hb) levels and TEG parameters (R, K, α , MA, and CI) were assessed pre-operatively and on day 1, 4, and 9 post-operatively. The incidence of symptomatic DVT/PE was determined and diagnosed with ultrasound and CTA during hospitalization. Transfusion details were also recorded. TEG was performed with kaolin as a coagulation activator and was measured with a TEG5000 hemostasis analyzer (Haemoscope, Niles, Illinois, USA). Numerous parameters indicating clot formation are determined by TEG. R is the time elapsed until the first evidence of a clot. K is the time from the end of R until the clot reaches 20 mm and represents the speed of clot formation. α is the angle of the curve made as K is reached and offers information like that from K. The maximum amplitude (MA) is an indication of the maximum strength of the clot. A mathematical formula can be used to determine a coagulation index (CI) (or overall assessment of coagulability) that

takes of these parameters into account (21). In TEG, hypercoagulability can be defined as CI > +3 (22).

2.4. Statistical analysis

Statistical data were presented as means \pm standard deviation (S.D.) for continuous variables with a normal distribution and n (%) for categorical variables. One-way ANOVA was used to compare the means of continuous variables with a normal distribution and Pearson's Chi-square test was used to compare the proportion of categorical variables for the control, FS, TXA, and FS + TXA groups. All statistical analyses were performed using SPSS19.0 (IBM, Armonk, New York, USA). A $p < 0.05$ was regarded as statistically significant.

3. Results

3.1. Patient selection

A total of 100 patients met the aforementioned criteria. No hemostatic agents had been used in 25 of these patients (control, group 1, $n1 = 25$), topical FS spray but not TXA had been used in 23 patients (FS, group 2, $n2 = 23$), intravenous TXA but not FS had been used in 20 patients (TXA, group 3, $n3 = 20$), and both FS and TXA had been used in 32 patients (FS + TXA, group 4, $n4 = 32$). There were no significant differences in

patient demographics, including gender, age, and body weight (Table 1).

3.2. Comparisons of peri-operative blood loss

Preoperative Hct and Hb levels were comparable in the four groups. Blood loss was significantly reduced on day 1, 4, and 9 post-operatively as Hct and Hb levels were considerably higher in the TXA and FS + TXA groups (Table 2, Figure 1). There were no differences between the control group and FS group and between the TXA group and FS + TXA group. Hct and Hb levels were significantly higher in the TXA group than in the FS group (Hct: day 4, Hb: day 1 and 4).

3.3. Comparison of the change in coagulation

TEG parameters (R, K, α , MA, and CI) were comparable preoperatively. There were no significant differences in R, K, α , MA, or CI on day 1, 4, and 9 post-operatively, with the exception of K that differed slightly in the four groups on day 1 (control vs. FS, $p = 0.023$; TXA vs. FS + TXA, $p = 0.046$). Despite these differences, the means of TEG parameters remained within their normal ranges during the assessed perioperative period (Table 3 and Figure 2).

3.4. Transfusions and DVT/PE

Table 1. Patient characteristics preoperatively

Items	Group 1 (Control) $n1 = 25$	Group 2 (FS) $n2 = 23$	Group 3 (TXA) $n3 = 20$	Group 4 (FS+TXA) $n4 = 32$	Total $n = 100$	p
Gender, n(%)						0.181
Male	7 (28.0)	2 (8.7)	5 (25.0)	11 (34.4)	25 (25.0)	
Female	18 (72.0)	21 (91.3)	15 (75.0)	21 (65.6)	75 (75.0)	
Age (years)						0.420
Mean \pm S.D.	71.52 \pm 8.18	68.30 \pm 7.49	70.80 \pm 6.24	69.78 \pm 5.83	70.08 \pm 6.94	
Min, Max	56, 87	54, 83	61, 83	56, 80	54, 87	
Weight (kg)						0.316
Mean \pm S.D.	67.48 \pm 8.81	65.96 \pm 13.15	70.85 \pm 10.86	70.25 \pm 8.54	68.69 \pm 10.32	
Min, Max	46, 88	43, 95	55, 90	53, 91	43, 95	

Table 2. RBC and Hb on day 1, 4, and 9 post-operatively

Items	Group 1 (Control) $n1 = 25$	Group 2 (FS) $n2 = 23$	Group 3 (TXA) $n3 = 20$	Group 4 (FS+TXA) $n4 = 32$	p
Preoperatively					
Hct (%)	38.69 \pm 2.49	39.13 \pm 3.45	38.80 \pm 2.30	39.20 \pm 3.49	0.912
Hb (g/l)	126.8 \pm 10.9	128.1 \pm 12.2	129.0 \pm 8.0	131.2 \pm 12.2	0.507
Day 1					
Hct (%)	30.02 \pm 6.71	31.88 \pm 3.55	33.59 \pm 2.40	34.58 \pm 2.94	0.001
Hb (g/l)	102.8 \pm 11.4	105.3 \pm 13.0	112.5 \pm 7.8	116.7 \pm 10.2	0.000
Day 4					
Hct (%)	28.63 \pm 3.83	28.65 \pm 3.42	31.13 \pm 2.84	31.44 \pm 3.89	0.004
Hb (g/l)	93.9 \pm 14.6	95.4 \pm 12.9	104.2 \pm 8.7	106.3 \pm 13.4	0.001
Day 9					
Hct (%)	29.96 \pm 3.19	30.93 \pm 3.64	32.43 \pm 2.28	32.11 \pm 3.08	0.025
Hb (g/l)	97.6 \pm 11.6	101.1 \pm 13.3	106.8 \pm 7.4	103.3 \pm 11.8	0.006

One patient in the FS group received 2 units of RBC and 200 mL of plasma. No incidence of symptomatic DVT/PE was observed in any of the 100 patients.

4. Discussion

As shown in this study, groups given TXA (TXA and FS + TXA) had higher Hct and Hb levels during the postoperative period while FS alone did not conspicuously reduce postoperative blood loss. Prior to this study, Aguilera *et al.* arrived at a similar conclusion, favoring IV-TXA over FS (15). The efficacy of FS has been debated as some surgeons have found FS to be ineffective (14-16). Their finding could be true or it could also be due to insufficient dosage (23) or improper topical application (24). In addition, certain FS formulations contain TXA, e.g. Quixil (Ethicon, Johnson & Johnson) (25). The current study used 5 mL of FS based on the contention by Notarnicola *et al.* that the efficacy of 5 mL of FS was comparable to a larger dose (26). However, the current findings suggest that FS was ineffective, regardless of whether it was administered in combination or individually.

Although the current data have further corroborated the efficacy of IV-TXA, there is still debate over the method of delivery, optimal dosage, and timing and duration of TXA administration. Zohar *et al.* (27) evaluated a 1-g oral dose (O-TXA) preoperatively and 3 1-g doses every 6 h postoperatively and found O-TXA to have comparable efficacy to IV-TXA, although O-TXA was more convenient. Irwin *et al.* favored O-TXA because it was more cost-effective than IV-TXA (28). Wong *et al.* (29) reduced postoperative bleeding by 20%-25% with intra-articular TXA injections (IA-TXA) after wound closure. IA-TXA was proven effective for both cemented and cementless

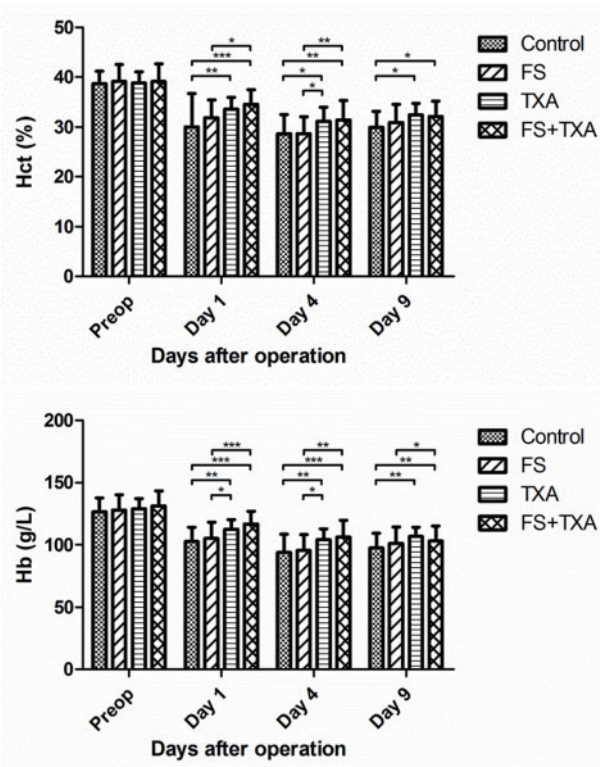


Figure 1. Perioperative blood loss in TKA. Groups that received TXA (TXA, FS + TXA) had significantly higher Hct and Hb levels postoperatively than those that did not (control/FS). (a) Hematocrit. (b) Hemoglobin. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3. Thromboelastography on day 1, 4, and 9 post-operatively

Items	Group 1 (Control) <i>n</i> 1 = 25	Group 2 (FS) <i>n</i> 2 = 23	Group 3 (TXA) <i>n</i> 3 = 20	Group 4 (FS+TXA) <i>n</i> 4 = 32	<i>p</i>
Preoperatively					
R (min)	6.00 ± 0.90	5.86 ± 0.90	5.95 ± 0.79	5.43 ± 0.95	0.062
K (min)	1.79 ± 0.38	1.60 ± 0.25	1.64 ± 0.30	1.86 ± 0.66	0.315
α (°)	69.93 ± 3.95	72.30 ± 2.40	71.76 ± 2.82	70.88 ± 5.67	0.128
MA (mm)	63.75 ± 4.67	64.47 ± 3.37	62.52 ± 4.68	62.34 ± 5.96	0.361
CI	0.74 ± 1.32	1.16 ± 0.99	0.82 ± 1.13	0.99 ± 1.65	0.712
Day 1					
R (min)	5.02 ± 1.02	4.92 ± 1.03	4.86 ± 0.83	5.10 ± 0.92	0.798
K (min)	1.59 ± 0.44	1.36 ± 0.25	1.38 ± 0.26	1.68 ± 0.52	0.315
α (°)	72.14 ± 4.65	74.64 ± 2.40	74.37 ± 2.40	72.01 ± 4.73	0.128
MA (mm)	63.63 ± 4.69	64.82 ± 4.20	64.33 ± 4.66	64.35 ± 5.07	0.852
CI	1.60 ± 1.48	2.08 ± 1.06	2.03 ± 1.21	1.59 ± 1.35	0.372
Day 4					
R (min)	5.36 ± 0.96	5.52 ± 0.92	5.12 ± 0.74	4.93 ± 1.04	0.109
K (min)	1.39 ± 0.29	1.35 ± 0.36	1.22 ± 0.29	1.30 ± 0.31	0.304
α (°)	74.04 ± 2.98	75.07 ± 3.02	76.13 ± 2.35	75.11 ± 2.98	0.125
MA (mm)	67.96 ± 4.67	65.71 ± 6.62	67.30 ± 5.53	67.37 ± 4.10	0.489
CI	2.13 ± 1.08	1.80 ± 1.10	2.42 ± 1.13	2.33 ± 1.29	0.287
Day 9					
R (min)	5.30 ± 1.24	5.55 ± 0.77	5.69 ± 1.12	5.39 ± 0.90	0.572
K (min)	1.19 ± 0.27	1.13 ± 0.17	1.18 ± 0.28	1.28 ± 0.40	0.329
α (°)	76.32 ± 2.92	76.90 ± 1.87	76.65 ± 2.87	75.58 ± 4.23	0.456
MA (mm)	70.64 ± 3.83	71.32 ± 3.15	69.94 ± 5.47	71.20 ± 4.53	0.699
CI	2.75 ± 1.31	2.71 ± 0.89	2.44 ± 1.26	2.65 ± 1.33	0.846

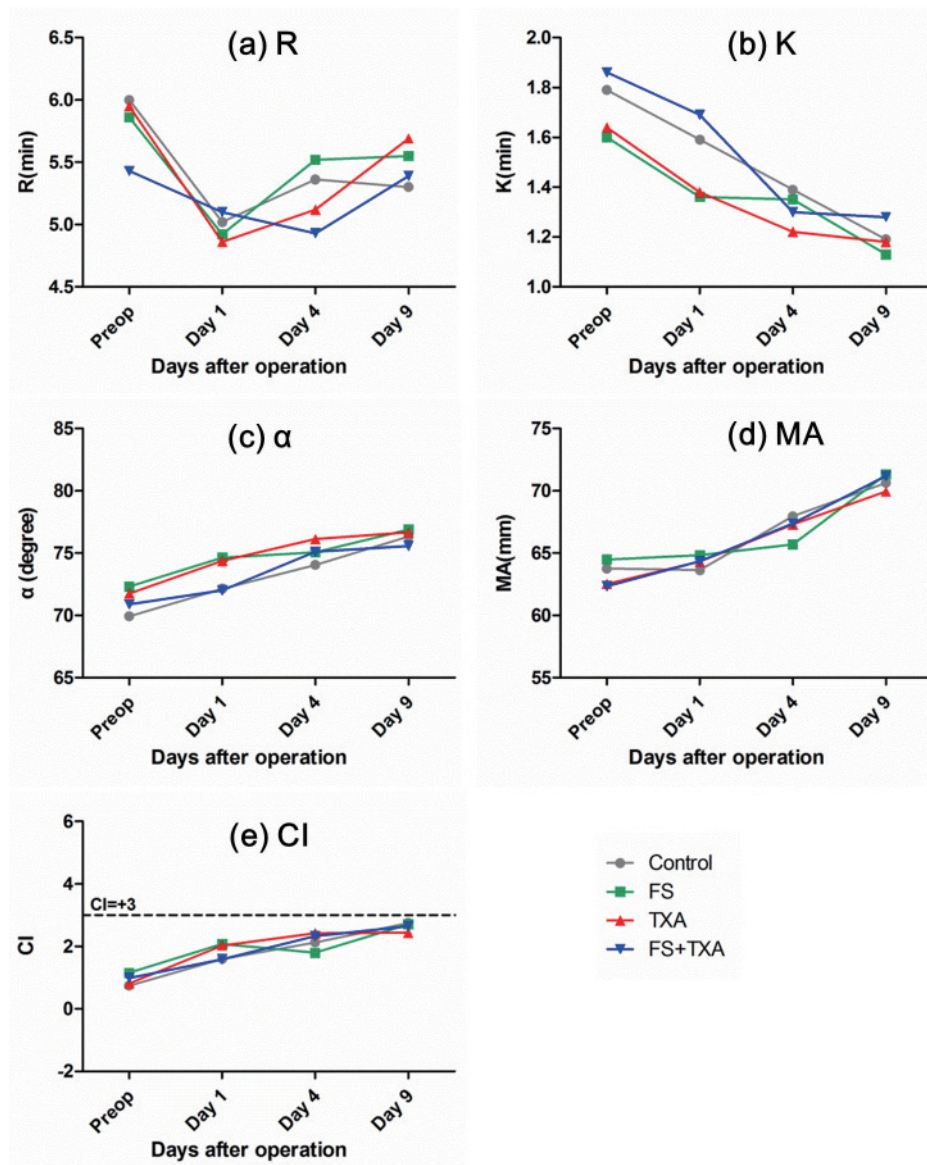


Figure 2. Thromboelastography on day 1, 4, and 9 post-operatively. There were no significant differences in R, K, α , MA, or CI on day 1, 4, and 9 post-operatively. Means of all of the parameters remained within their normal ranges during the assessed perioperative period. Mean CI was less than +3 in all groups, suggesting that neither FS nor TXA promoted hypercoagulation.

implants (30-33) and favored based on the concern that systematic administration of IV-TXA might potentially increase the risk of thrombosis (34). In contrast, the TEG data obtained in the current study suggest that IV-TXA did not promote hypercoagulation since the mean CI in the TXA and FS + TXA groups was less than +3 and this CI remained similar to that of the control group during hospitalization. Thus, one could infer that IV-TXA does not increase the risk of developing DVT.

Like this study, most trials favor IV-TXA and have not noted an increased onset of clinically significant thrombosis. A recent meta-analysis reviewed 19 randomized controlled trials (RCTs) and concluded that a multiple-dose regimen and total dose ≥ 30 mg/kg IV-TXA significantly reduced postoperative blood loss by a mean of 290 mL and total blood loss by a mean of 570 mL in comparison to a saline control (35). Most

RCTs have found no significant reduction in intraoperative blood loss between TXA and control groups (35). Tanaka *et al.* (19) posited that TXA would have its greatest hemostatic effect once before surgery and once before release of the tourniquet because suppression of fibrinolysis at the start of surgery may be more effective than suppression only when hyperfibrinolysis peaks.

Due to the scarcity of an allogeneic blood supply at this Hospital, a strict criterion for transfusion was in effect in the form of intraoperative Hb < 80 g/L. Only one patient in the FS group required such a transfusion in accordance with this protocol. None of the other patients received blood transfusions of any kind. Results were limited, so the reduction in the number of blood transfusions was not analyzed. In evidence provided by the literature (35), O-TXA, IA-TXA,

and IV-TXA all have the ability to reduce rates and quantities of blood transfusions in TKA. Like reduction of perioperative blood loss, whether FS can reduce the need for allogeneic transfusion is a question that has yet to be answered (16,36).

The current study included a few patients with coronary stents and/or brain infarctions who depended on regular anti-platelet treatment with aspirin and/or clopidogrel hydrogen and who stopped that medication one week prior to surgery. Caution was exercised with regard to whether IV-TXA would further disturb coagulation in these patients who were at risk for thromboembolic events. In a trial of high-risk patients who were ASA III-IV conducted by Whiting *et al.* (37), TXA was not associated with an increase in symptomatic thromboembolic events (6.7% vs. 4.3%; $p = 0.270$) and was associated with a decrease in transfusion rates (17% vs. 48%; $p = 0.001$). Similarly, the current findings revealed few differences in the TEG parameters of all four groups, suggesting that both TXA and FS slightly affect coagulation in patients with severe comorbidities.

In this retrospective study, FS and TXA were used either individually or in combination depending on various findings and conjectures concerning the use of hemostatic agents in the literature at the time. This led to an uneven distribution of patients in the four groups. A well-designed RCT would serve to refine the results of this investigation.

In summary, IV-TXA significantly reduced perioperative blood loss during TKA. FS did not significantly reduce blood loss and it was less effective than TXA. FS in addition to IV-TXA was not superior to IV-TXA alone. TEG parameters (R, K, α , MA, CI) were similar for all four groups, suggesting that neither FS nor IV-TXA increased the risk of hypercoagulation, regardless of whether the agent was administered individually or in combination. At this Hospital, topical FS is no longer in use but IV-TXA has been incorporated into the care protocol. One g of IV-TXA is administered pre-operatively and 1 g is administered before tourniquet release, which appears to be an effective and safe method of reducing perioperative blood loss in TKA.

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