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ORIGINAL ARTICLE • KNEE - ARTHROPLASTY

Intra-articular injection of tranexamic acid reduce blood loss in cemented total knee arthroplasty

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Abstract The purpose of this study was to compare the efficacy of intravenous and topical tranexamic acid (TXA) versus control group for reduction in blood loss following primary total knee arthroplasty (TKA). A total of 90 patients were prospectively allocated to each of three groups (control, intravenous IV and intra-articular) and underwent unilateral total knee arthroplasty. In the IV group, patients received one dose of TXA of 15 mg/kg before deflation of the tourniquet, while in the intra-articular group patients received 2 g TXA via the drain retrogradely after closure of the wound. The mean drained blood loss in control, IV and intra-articular groups was 415 ± 24, 192 ± 21 and 121 ± 17 ml, respectively. About 43 % (control), 23 % (IV) and 17 % (intra-articular) of each group required transfusion, and the mean transfusion was 338, 168 and 79 ml, respectively. Preoperative hemoglobin values decreased at 24 h by 2.80 ± 0.14, 2.24 ± 0.17 and 2.26 ± 0.18 mg/dl, respectively. TXA reduced blood loss and transfusion requirement. Compared with one-dose intravenous administration, intra-articular administration of TXA seems to be more effective in terms of reducing drained blood loss and transfusion frequency. We recommend administration of topical TXA in primary TKA in healthy patients to decrease perioperative blood loss.

Keywords Total knee arthroplasty · Tranexamic acid · Blood loss · Transfusion

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Introduction

Total knee replacement is a frequently done procedure of any orthopedic unit.

The major causes of postoperative blood loss following total knee arthroplasty can be attributed to surgical trauma that induces a considerable activation of both the coagulation cascade and the local fibrinolysis [1]. As this procedure is usually performed under tourniquet control, there is an associated increase in localized fibrinolysis, which contributes postoperative hemorrhage [2–4].

In some cases, allogenic blood transfusion is required which might carry the risks of immunological reactions, volume overload, infection, intravascular hemolysis, renal failure and even death [5, 6]. Therefore, how to reduce bleeding and transfusions of TKA has become an important and urgent problem to be resolved for orthopedist.

So far, a large number of methods for controlling bleeding transfusions were successfully used following TKA, which included autologous blood transfusion, intraoperative blood saving and hypotensive anesthesia [5, 7, 8].

Several meta-analyses have shown that intravenous administration of the antifibrinolytic agent tranexamic acid reduced postoperative bleeding and the need for transfusion [9–11]. However, the theoretical concerns about the safety of systemic administration of tranexamic acid and the risk of thromboembolic events such as deep-vein thrombosis or pulmonary embolism in this high-risk patient population have hindered the wide adoption of this medication in the setting of total knee arthroplasty [12].

Tranexamic acid (TXA) is an inhibitor of fibrinolysis which acts by blocking the lysine-binding site of plasminogen to fibrin and prevents the degradation of fibrin. As TXA enters the extravascular space and accumulates in tissues for up to 17 h, the basis for its mechanism of action

is thought to be inhibition of tissue fibrinolysis and consequent stabilization of clots [13].

It is generally accepted, however, that only a small percentage of intravenously injected TXA reaches the target location. Thus, a more efficient method (i.e., intra-articular injection) to deliver TXA is desirable.

Compared with IV TXA, the topical application leads to 70 % lower systemic absorption and therefore may be a safer alternative to giving it systemically [14]. Besides, the topical application has the advantages of being easy to administer, providing a maximum concentration of TXA at the bleeding site and inducing partial microvascular hemostasis by stopping fibrin clot dissolution in the affected area.

The goal of this study is to identify whether TXA has decreased the transfusion rate at our institution. Additionally, we also sought to determine whether there is a difference in the effect when it is utilized as an intravenous infusion versus intra-operative topical administration.

Patients and methods

Between February 2012 and May 2013, we enrolled 85 patients, 90 knees, with primary osteoarthritis who were to have a unilateral cemented TKA, in a prospective, randomized study. We considered for inclusion all patients younger than 85 years with primary osteoarthritis who were awaiting TKA. We excluded five patients with secondary osteoarthritis (e.g., rheumatoid arthritis, posttraumatic arthritis, psoriatic arthritis) and fourteen patients with history of thromboembolic disease, bleeding disorder, a history of hepatic or renal dysfunction and severe cardiac respiratory disease. This study was approved by the local ethical committee, and all the patients signed the informed consent.

The patients were randomly allocated to one of three groups as follows: group 1 patients were included in the control group. Group 2 patients received one dose of TXA (10 % Transamin, 5 ml, 500 mg, Daiichi Sankyo, Tokyo, Japan) of 15 mg/kg intravenously before deflation of the tourniquet, and group 3 patients received 2 g TXA intra-articular after skin closure. Randomization were obtained by closed envelops. Ninety envelops were kept by a research pharmacist who was not involved in the care of the patients. On the day of surgery, one envelope was opened randomly and the patient was included in one of the three groups. Five patients were operated bilaterally 6 months between the two procedures. In three patients one knee was included in group 1 and the other in group 3, in one patient one knee was included in group 1 and the other in group 2, and in one patient both knees were included in group 1, which means that 29 patients were included in group 1 and 30 patients in each of the remaining 2 groups.

All patients were given spinal anesthesia with levobupivacaine 5 mg/ml 3 ml. Postoperative analgesia was obtained with femoral block with catheter levobupivacaine 2.5 mg/ml 20 ml bolus and continuous infusion 1.25 mg/ml 4 ml per hour for 48 h postoperatively.

The same surgical team with the same technique performed all procedures, and the same implant (Columbus, Aesculap, Tuttlingen, Germany) was used in all patients.

Ischemia was performed with pneumatic tourniquet at 100 mmHg above systolic arterial pressure. After a midline skin incision was made, a medial parapatellar approach was used. An intra-medullary alignment rod was used for femoral and for tibia cutting. The femoral canal for intramedullary guidance was routinely plugged with bone. The patella was not replaced, the posterior cruciate ligament was retained, and all components were fixed with cement in all patients. Cement in use was Palacos R + G (Heraeus Medical, Hanau, Germany). We did not use red cell salvaging device. At the end of the procedure, the tourniquet was deflated and major bleeding was controlled by diathermy before closure. Fifteen minutes before tourniquet release, intravenous TXA was given to patients included in group 2.

Lateral retinacular releases were performed for seven TKAs in the control group, eight in the intravenous TXA group and six in intra-articular TXA group.

Intra-articular blood loss was calculated from blood-soaked gauzes and suction bottles.

We used an intra-articular drain connected to a vacuum bag (Redax, 500 ml, Poggio Rusco, MN, Italy) in all patients. In the intra-articular study group, administration of TXA was injected via the drain retrogradely after closure of the wound. The drain was then clamped for 3 h in all patients. The drain was removed 24 h postoperatively.

The total blood loss was calculated according to the Gross formula [15, 16]

$$\text{Total blood loss} = \text{PBV} \times \left(\text{Hct}_{\text{pre}} - \text{Hct}_{\text{post}}\right)/\text{Hct}_{\text{ave}}$$

where Hct_{pre} represents the initial preoperative Hct level; Hct_{post}, the Hct on the morning of the third postoperative day; Hct_{ave}, the average of the Hct_{pre} and Hct_{post} and PBV, the patient's blood volume (PBV, l). It was assessed according to the formula of Nadler et al. [17].

$$\begin{aligned}\text{Blood volume (l)} &= \text{height (m)}^3 \times 0.356 + \text{body weight (kg)} \\ &\quad \times 0.033 + 0.183 \text{ (woman)} \\ &= \text{height (m)}^3 \times 0.367 + \text{body weight (kg)} \\ &\quad \times 0.032 + 0.604 \text{ (men)}\end{aligned}$$

If allogenic transfusion was performed, the total blood loss is equal to the loss calculated from the change in Hct plus the volume transfused [16].

The established practice of transfusion in our unit is that patients are transfused if:

1. Postoperative Hb is <8.5 mg/dl in patients with no coronary heart disease, or <9.5 mg/dl in patients who have coronary heart disease.
2. Physiological signs of inadequate oxygenation such as hemodynamic instability or symptoms of myocardial ischemia occur.
3. Drainage of more than 1 l of blood in the first 24 h. If transfusion was necessary, one unit of packed red blood cells (350 ml) was transfused at a time to increase the hemoglobin to accepted level.

Thromboembolic complications, such as clinical deep-vein thrombosis and pulmonary emboli, and other complications (e.g., wound complications) were noted during the hospital stay. All patients were discharged from the hospital on the fifth day after surgery.

Physiotherapy was started on the first day after surgery. As part of the postoperative care for the three groups, continuous passive motion began after removal of the drains, and standing and full-weight-bearing walking were allowed on postoperative day (POD) 2.

Following surgery, all patients underwent intravenous prophylactic antibiotic therapy consisting of Teicoplanin 800 mg before surgery and one dose 12 h postoperative. All patients received 3.500 IU of tinzaparin sodium (Innohep injection; Merrell Pharmaceuticals Inc., USA; Gruppo Lepetit S.p.A., Italy) for venous thromboembolism prophylaxis given subcutaneously for 30 days beginning on postoperative day.

Preoperative investigations included hemoglobin (Hb) level, hematocrit, platelet count, prothrombin index (PI), international normalized ratio (INR) and activated partial thromboplastin time (aPTT).

Preoperative hemoglobin was obtained within 30 days of surgery. Postoperative hemoglobin and hematocrit levels were obtained each day until the day of discharge.

Variables under comparison included hemoglobin determinations at 12 and 24 h after surgery and the day of discharge 5 days postoperatively, visible blood loss (the total volume of drained blood 24 h postoperatively), total blood loss, transfusion requirements (as the number of units of packed erythrocytes) and additional costs generated by transfusion.

Our follow-up routine was 2 weeks, 6 weeks, 3 months, 6 months and 12 months postoperatively, and then annually. At follow-ups, we examined the patients for clinical deep-vein thrombosis and wound complications; no DVT screening test was performed.

Nonparametric Mann–Whitney *U* test and Kruskal–Wallis test were used to compare variable between the patient groups. SPSS v. 16.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses. A p value <0.05 was considered statistically significant.

Result

Among the three groups, there were no significant differences in patient characteristics of gender, age, body weight, height and ASA score. Neither did preoperative laboratory values and surgical characteristics (surgical duration and tourniquet time) differ between the groups (Table 1).

The mean (±SE) intra-operative blood loss was 277 ± 22 ml in group 1, 285 ± 26 ml in group 2 and 235 ± 23 ml in group 3. No significant difference was observed in comparison between the groups (p value >0.23).

The mean (±SE) drained blood loss for the control group, intravenous and intra-articular injection of tranexamic acid groups was 415 ± 24, 192 ± 24 and 121 ± 17 ml, respectively. Both the intravenous and intra-articular groups differed significantly from the control group ($p = 0.0001$), and significant difference were also observed between the two study groups ($p = 0.006$) (Table 2; Fig. 1).

The mean calculated total blood loss was higher (1455 ± 116 ml) in the control group comparing with the two study groups (1086 ± 102 ml in IV TXA group and 943 ± 87 ml in intra-articular TXA group $p \leq 0.02$). There were no significant difference between the two study groups ($p = 0.82$) (Table 2; Fig. 2).

Given that every PRC unit includes 350 ml of blood, the mean (±SE) transfusion volume was lower (p value $= 0.009$) in patients receiving tranexamic acid intra-articular (79 ± 35 ml) than in the control group (338 ± 79 ml). The transfusion volume in patients receiving tranexamic acid intravenously (168 ± 56) did not differ significantly with either of the groups (p value ≥ 0.11).

The proportion of patients requiring transfusion was 43 % (13/30) in group 1, 23 % (7/30) in group 2 and 17 % (5/30) in group 3; significant difference was reached in comparison between intra-articular injection and control group (p value 0.02, Table 2). The number of PRC units in group 1, 2 and 3 were 29, 14 and 7, respectively, with significant difference in comparison between group 1 and 3 (p value 0.009).

The hemoglobin values at 12 and 24 h postoperative were higher ($p \leq 0.03$) in patients receiving intra-articular injection of tranexamic acid than in the control group. The comparison between the intravenously receiving tranexamic acid group and the two other groups did not reach significance ($p \geq 0.09$) (Table 3).

At the day of discharge, the hemoglobin values were higher in the intravenous and intra-articular tranexamic acid groups than in the control group ($p \leq 0.02$). No

Table 1 Baseline Characteristics of the three groups

Group	Group 1	Group 2	Group 3	Significance
Demographic characteristics				
Knees	30	30	30	
Sex (male/female)	2/28	2/28	7/23	NS
Left/right	15–15	12/18	16/14	NS
Age	68 ± (5.5)	70 ± (6.5)	71 ± (7.0)	NS
Weight (kg)	84 ± (10.9)	81 ± (9.1)	82 ± (12.1)	NS
Height (cm)	160.8 ± (4.36)	161.4 ± (5.75)	163.5 ± (7.52)	NS
ASA score	2	2	2	
Preoperative laboratory values				
Hemoglobin (g/dl)	13.2 ± 1.02	13.3 ± 1.25	13.5 ± 1.15	NS
Platelet count	250 ± 62.0	265 ± 61.8	244 ± 63.4	NS
INR	0.99 ± 0.11	1.05 ± 0.09	1.04 ± 0.08	NS
aPTT	31 ± 3.2	30 ± 8.5	29 ± 3.5	NS
Surgical characteristics				
Surgical duration (min)	84.3 ± 9.1	84.6 ± 11.7	85.6 ± 11.3	NS
Tourniquet time (min)	69.5 ± 9.2	69.0 ± 10.7	71.5 ± 10.9	NS

Values expressed as mean ± SD

NS not significant, *ASA* American Society of Anesthesiologists

Table 2 Blood loss and transfusion requirement compared among groups

Group	Group 1	Group 2	*p* value Group 1 versus 2	Group 3	*p* value Group 1 versus 3	*p* value group 2 versus 3
Knees	30	30		30		
Intra-operative blood loss (ml)	277 ± 22	285 ± 26	0.93	235 ± 23	0.26	0.23
Drained blood loss (ml)	415 ± 24	192 ± 21	0.0001	121 ± 17	0.0001	0.006
Total blood loss (ml)	1455 ± 116	1086 ± 102	0.02	943 ± 87	0.004	0.82
Transfusion (ml)	338 ± 79	168 ± 56	0.11	79 ± 35	0.009	0.32
No. patients transfused	13 (43.3 %)	7 (23.3 %)	0.12	5 (16.6 %)	0.021	0.44
No. of PRC units	29	14	0.11	7	0.009	0.32

Values expressed as mean ± SE

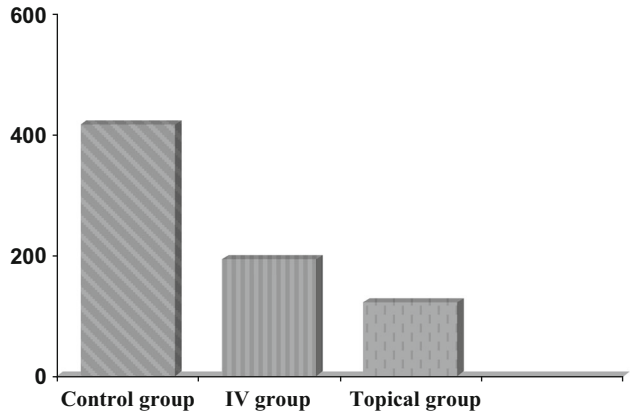

Fig. 1 Drain blood loss. The histogram showed that drain blood loss in the IV and topical TXA groups was significantly less than that in the control group (Mann–Whitney *U* test)

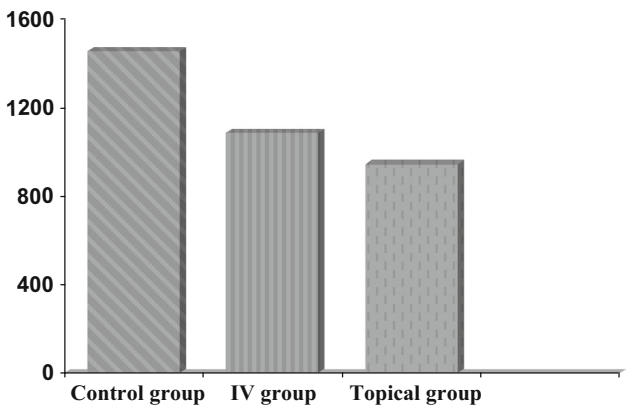

Fig. 2 Total blood loss. The histogram showed that total blood loss in the IV and topical TXA groups were significantly less than that in the control group (Mann–Whitney *U* test)

Table 3 Postoperative hemoglobin (Hb) level

Group	Group 1	Group 2	*p* value Group 1 versus 2	Group 3	*p* value Group 1 versus 3	*p* value Group 2 versus 3
Knees	30	30		30		
Hb at 12 h	11.3 ± 0.22	11.5 ± 0.18	0.24	11.9 ± 0.21	0.03	0.17
Hb at 24 h	10.5 ± 0.19	10.9 ± 0.21	0.09	11.3 ± 0.18	0.003	0.20
Postoperative day 5	10.2 ± 0.16	10.8 ± 0.12	0.002	10.7 ± 0.17	0.02	0.71
Changes in Hb (g/dl)						
Preoperative day 1	2.80 ± 0.14	2.24 ± 0.17	0.002	2.26 ± 0.18	0.02	0.72
Day 1–day 5	0.26 ± 0.17	0.26 ± 0.19	0.97	0.32 ± 0.12	0.28	0.37

Values expressed as mean ± SE

difference were observed between the two groups that received tranexamic acid ($p = 0.71$).

The mean hemoglobin decrease at 24 h postoperatively was lower ($p \leq 0.02$) in the patients receiving tranexamic acid (2.24 ± 0.17 in group 2 and 2.26 ± 018 in group 3) than in the control group (2.80 ± 0.14) (Table 3). No difference were observed between the two study groups ($p = 0.72$). Analysis failed to show statistical difference ($p \geq 0.28$) for hemoglobin changes between the POD (postoperative day) 1 and the day of discharge (Table 3).

Complications

One patient, from the control group and one from the intra-articular group developed a superficial wound infection, which responded to short courses of oral antibiotics. No deep infections occurred. One patient in the intra-articular group received intravenous antibiotics for a chest infection from the second day postoperatively. One patient from the intravenous group developed a femoral DVT and was given warfarin therapy 25 days after surgery. Patients who did not show clinical evidence of DVT were not systematically investigated. There were no fatalities during the study.

The cost of one ampoule of 500 mg tranexamic acid was 0.334 €. The cost per unit of allogenic blood was 296.40 € (source: Greek Blood Service. Cost is that stated on October 1, 2012). The total cost of transfused blood in control group was 8595.6 €. In the IV group, the total cost of transfused blood was 4149.6 € and the cost for tranexamic acid was estimated to be 30.06 €. The respective cost in the intra-articular group was 2074.8 and 40.08 €.

Discussion

Despite several clinical studies that proved the efficacy of tranexamic acid in reducing the blood loss during surgery, there is no consensus regarding the most effective regimen for tranexamic acid administration.

The most important finding of the present study is that TXA reduces blood loss in TKA and the need for transfusion accordingly. Comparing two TXA groups, intra-articular injection of TXA seems to be more effective than one dose of intravenous injection in terms of the amount of blood loss.

The application of IV TXA in orthopedic surgery has been well established in the literature [18–28].

We find that a single intra-operative intravenous dose decreased the drain loss and total blood loss compared with the control group. Probably multiple or higher dose of TXA could effect the transfusion requirement as well. The mean reduction in total blood loss was 369 ml and 20 % reduction in the proportion of patients requiring transfusion compared with the control group. Our results are in accordance with the findings by Yang et al. [27] that reported a mean reduction in blood loss of 504.9 ml and a 23 % reduction in the proportion of patients requiring transfusion in their meta-analysis of intravenous tranexamic acid use in total knee arthroplasty.

Similar to these findings, Alshryda et al. [18] in a systematic review and meta-analysis of trials using intravenous tranexamic acid in total knee arthroplasty surgery reported that it reduced total blood loss by a mean of 591 ml and that there was a fourfold increase in transfusion rates when it was not used. In the studies included in this meta-analysis, the regime of delivery and doses of intravenous TXA vary from a single bolus given preoperatively, to repeated boluses, and continuous infusion.

The topical use of TXA has been suggested as superior to IV administration because it could mitigate negative systemic sequelae and might maximize drug activity at the site of administration [29].

The results of several randomized controlled trials [14, 30–33] and a meta-analysis [34] involving primary total knee replacement with cemented implants confirmed significantly lower transfusion rates and blood loss [30] in patients treated with topical TXA compared with placebo. Retrospective and cohort studies containing a large number

of patients have also confirmed the efficacy of topical TXA [35–39].

We observed that the intra-articular regime of TXA reduced significantly blood loss and transfusion requirement compared with the control group. Comparing with the IV group, total drain output but not total blood loss was significantly reduced in the topical group. It may be that the intra-articular group had a better and quicker topical hemostatic effect than the IV TXA because of the higher local concentration of TXA. So, much more postoperative blood loss in IV group was calculated in the form of drainage volume. Thus, that accounted for why we observed the higher drainage volume in the IV group. Topical application of TXA reduced the transfusion requirement compared with IV group, but the difference did not reach significance.

Seo et al. [29] found in accordance to our study that intra-articular route of administration is more effective than intravenous administration in terms of reducing blood loss and transfusion frequency. Maniar et al. [40] conducted an RCT that compared topical TXA with four IV TXA administration protocols. They found similar to our study that topical TXA was much effective than a single-dose regimen of IV TXA. Three doses (preoperative, intra-operative and postoperative) regimen produced maximum effective reduction in total blood loss and drain loss when compared with placebo group. However, an RCT conducted by Soni et al. [41] found a different result. They compared topical with triple intravenous dose (preoperative, intra-operative and postoperative) regimens and concluded that topical TXA was equally effective as triple intravenous dose regimen in reducing blood loss during total knee arthroplasty surgery.

Variation in methodology, applicative techniques of intra-articular regime, different doses of IV TXA and different methods to calculate blood loss account for heterogeneity among the studies, making it difficult to compare the results between them.

The tourniquet used in our study was deflated, and bleeding was controlled by diathermy before closure of the wound in order to minimize the total blood loss. However, a strong debate is found in the literature about the usefulness of the tourniquet in TKA. A recent meta-analysis showed that using a tourniquet in TKA could reduce intraoperative blood loss but did not decrease the calculated blood loss, which indicates the actual blood loss. The use of tourniquet could not reduce the possibility of blood transfusion. Moreover, the use of a tourniquet increased the risk of either thrombotic events or nonthrombotic complications [42]. The answer to the complicated dilemma "tourniquet or not?" is still difficult despite the extensive research on this subject. Further research is required to clarify these ambiguous aspects of tourniquet use and to construct definite guidelines.

Theoretically, TXA carries a risk of thrombosis. According to the meta-analyses conducted on the topic, the risk of venous thromboembolism is not increased by TXA, but great care is mandatory in patient selection and in the choice of administration route and dosage because of the antifibrinolytic effect of TXA [10, 19, 43].

In the present study, a single DVT was detected, in the group treated with IV TXA. The small numbers of patients involved prevented us from drawing an accurate conclusion in this topic.

Given that perioperative fluid replacement, crystalloid and colloid were not significantly different between the groups, the change in Hb values can also be used as a marker of blood loss. Hemoglobin levels fell in all 3 groups progressively through the study period, despite the allogenic blood transfusion. The fall in Hb level was greatest in the controls and similar in the TA groups.

A limitation to this study is the lack of power to measure differences in transfusion rates. Further study may be warranted to evaluate the effects of topical TXA on blood transfusion rate. There is no standardized method to measure blood loss. This study used the drop in hematocrit which could be affected by factors such as patient hydration. Another limitation of this study was our decision not to routinely screen all patients for postoperative DVT. Also, serum concentrations of TXA were not measured.

Despite the potential limitations, the advantages of this study include the prospective nature of the study, as well as the blinded nature of those recording drain outputs, and measuring postoperative hemoglobin levels. The same surgical team operated all patients with the same technique and same prosthesis.

The use of TXA saved 147 and 216 € per patient in IV and intra-articular group, respectively, compared with the control group based on both TXA and transfusion cost. This amount can be much higher if we calculate the cost of transfusion-related total joint complications Parvizi et al. [44] estimated a cost of 68–107$ per total joint infection depending on the organism type. Greater healthcare savings may be recognized if variables such as transfusion complication or infection rates are included in the cost analysis. The calculation of transfusion cost savings is approximate, for Greece only, and may not be the same for other countries.

Conclusion

This prospective comparative study showed that during TKA, TXA reduced blood loss and transfusion requirement demonstrating a consistent safety profile and no increase in thromboembolism. Intra-articular dose of 2 g of TXA was more efficacious than one-dose (15 mg/kg) IV injection with respect to reduce drained blood loss, and they

achieved equal control of transfusion requirement without complication.

The topical route may be attractive to surgeons caring for patients who are at increased risk of thromboembolic disease or in whom intravenous tranexamic acid is cautioned, e.g., renal impairment. As topical administration of TXA in knee arthroplasty will continue to evolve, further studies with a larger sample size are required to figure out whether topical application is better than IV regimen.

Conflict of interest None.

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