Joints

Use of tranexamic acid in total knee arthroplasty

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Abstract

Purpose: different strategies have been developed to reduce blood loss in total knee arthroplasty (TKA). The efficacy of both systemic and local tranexamic acid (TXA) administration is demonstrated in the literature. The aim of the present study was to compare the efficacy of systemic, local and combined (systemic + local) administration of TXA in reducing blood loss after TKA.
Methods: we enrolled all patients submitted to a primary TKA in our department between November 2014 and August 2015. They were divided into three groups corresponding to the method of TXA administration used: intravenous (IV), intra-articular (IA), and a combination of the two. Demographic data, as well as preoperative hemoglobin and platelet levels, were collected. The primary outcome was the maximum hemoglobin loss, while the secondary outcomes were the amount of blood in the drain (cc/hour) and the rate of transfusions; postoperative pain was also assessed. Student's t-test or a χ^2 test was used to evaluate between-group differences, using $p<0.05$ as the cut-off for statistically significant differences.
Results: the sample comprised 34 patients: IV, 10 cases; IA, 15 cases, and combined (IV + IA), 9 cases. The average age of the patients was 71.1±6.4 years. No significant differences in the outcome measures were found between the groups, with the exception of a significantly lower maximum hemoglobin loss in the combined *versus* the IV group ($p=0.02$). There were no differences between the groups in the amount of blood in the *drain* or the rate of transfusions.
Conclusions: the data from this preliminary study, as well as data from the literature, confirm that TXA administration is safe and effective in reducing total blood loss in TKA, and no administration protocol seems to be superior to the others.
Level of evidence: Level II, prospective comparative study.

Keywords: tranexamic acid, knee, arthroplasty, bleeding, blood loss.

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Introduction

Perioperative bleeding remains one of the main concerns in elective total knee arthroplasty (TKA), with blood loss ranging between 800 ml and 1800 ml (1-3). Fibrinolysis induced by surgical trauma, which may be increased by using a tourniquet, reduces the risk of venous thromboembolism, but at the same time favors postoperative blood loss (4, 5). Different methods to reduce perioperative blood loss have been studied, such as perioperative blood donation, perioperative red cell salvage, deliberate hypotension, and use of recombinant human erythropoietin. Furthermore, perioperative transfusions add to the costs of the treatment and the risks (of infection, allergic reaction and disease transmission, for example) to the patient (6, 7).
In recent years, pharmacological approaches have become more popular. As hyperfibrinolysis is consid-

ered the major cause of postoperative bleeding after TKA surgery, antifibrinolytic drugs have been proposed, including aprotin, aminocaproic acid, and tranexamic acid (TXA).

TXA is a fibrinolysis inhibitor, which prevents clot lysis by blocking the proteolytic activity of plasminogen activators (8). Since the first report by Benoni et al. (9), different studies have been published on the efficacy of TXA in reducing perioperative blood loss in total joint arthroplasty.

Theoretically, intravenous (IV) administration of TXA increases the risk of thrombotic events. Furthermore, some cases of allergic reaction to TXA have also been reported. For these reasons, some Authors consider TXA contraindicated in patients with a history of allergy, arterial or venous thrombosis, an intrinsic risk of thrombosis or thromboembolism, acute renal failure, subarachnoid hemorrhage, or a history of epilepsy (10). Other studies have demonstrated that the supposed increased risk of thrombotic events can be avoided by the usual postoperative prophylactic regimens against deep vein thrombosis (DVT), such as aspirin, warfarin, low-molecular-weight heparin (LMWH) (11-14), and even factor Xa inhibitor (15).

Different Authors have proposed topical IA administration of TXA before wound closure in order to reduce the possible complications related to the risk of thrombotic events (3, 16, 17). Another route for local administration is through the drain, with or without drain clamping (18). Some studies also showed the efficacy of orally administered TXA in patients undergoing primary TKA compared with controls (19, 20).

In the literature, there is considerable variability in the timing of administration (which may be preoperative, intraoperative or postoperative, or a combination of these), as well as in the amount of TXA administered. Reported IV TXA doses range from 10 to 20 mg/kg although, in several studies, a 1 g dose (ranging from 500 mg to 3 g) was used as standard. In continuous infusion, doses range from 2 mg/kg/h for 20 hours to 10 mg/kg/h for 3 hours. IV TXA has been used as single dose bolus or as continuous infusion (for 2-3 hours) (21-23).

For topical administration, doses of TXA range from 250 mg to 3 g, diluted in 75 to 250 ml of saline solution. TXA has also been shown to be effective administered with other topical medications, like povidone-iodine solution (3 g of topical TXA in povidone-iodine solution) (24).

The aim of the present study was to compare the efficacy of systemic, local and combined administration of TXA in reducing blood loss after TKA. The hypothesis of the study was that there is no significant difference between the three treatment protocols.

Methods

All the patients who underwent a primary TKA in our department between November 2014 and August 2015 were enrolled in this study. They were divided into three groups, corresponding to the TXA administration protocol used: group 1, IV: 10 mg/kg of TXA in 50 ml of saline solution administered over a time of 10 minutes during induction and 3 hours later; group 2, IA: washing with 2 g of TXA in 20 ml of sterile saline for 2 minutes after placement of the final components; and group 3, a combination of the two methods (IV+IA). Patients with contraindications to IV administration (a medical history of DVT or pulmonary thromboembolism, acute myocardial infarction, heart failure, heart valve stenosis, ischemic stroke, coagulopathy, allergy to TXA, severe liver or kidney disease) were included in the IA protocol. All the patients received a dose of LMWH 12 hours before surgery, and LMWH treatment was continued postoperatively for 30 days.

All the surgeries were performed using a standard medial parapatellar approach, with cemented components and using a tourniquet during the cementation phase. In all the patients an IA drain (without suction) was subsequently positioned and kept in place for 24 hours. Postoperatively the knee was positioned in 50° to 70° of flexion for 6 hours (25, 26). Knee mobilization and weight bearing were allowed between day one and day two postoperatively. Continuous passive motion was started on postoperative day one.

Demographic data, as well as preoperative hemoglobin and platelet levels, were collected. Patients were interviewed about their pain preoperatively, the day after surgery, and on the fifth postoperative day. The numeric pain rating scale (NRS) was used for this purpose. Maximum hemoglobin loss (calculated as the difference between the preoperative and lowest postoperative hemoglobin level) was taken as the primary

outcome measure for evaluating the efficacy of TXA. The secondary outcomes were the amount of blood in the drain (cc/hour) and the rate of transfusions. The hemoglobin cut-off value for transfusion was 8 g/dl in symptomatic patients. However, patients with cardiac disease could also undergo transfusion also even in the presence of high hemoglobin levels.
Complications, such as postoperative fever (>38.5°), bruising, wound dehiscence, hematoma, DVT, thrombotic events and infections were recorded.
Student's t-test or a χ^2 test was used to evaluate the differences between the groups, using $p<0.05$ as the cut-off for statistically significant differences.

Results

The study population comprised 34 patients with a mean age of 71.1 years (SD 6.45; range 59-83), and a mean BMI of 29.17 kg/m^2 (SD 4.82, range 16.8 to 38.9); 58.8% (20 cases) were women and 41.2% (14 cases) were men.
In accordance with the abovementioned inclusion and exclusion criteria, the patients were divided into three groups corresponding to the method of TXA administration used: IV, 10 cases; IA, 15 cases; combined, 9 cases. The three groups were not homogenous. In particular, the IV group patients were significantly younger than those in the IA group (p=0.04), and the combined group had a significantly lower preoperative hemoglobin level compared with the IV group (p=0.04). There were no differences in gender distribution or platelet levels between the groups. The maximum hemoglobin loss (preoperative Hb – lowest postoperative Hb level) was 4.3 g/dl (SD 1.5; range 2.1 to 7 g/dl) in the IV group, 3.6 g/dl (SD 1.2; range 1.6 to 5.4 g/dl) for the IA group, and 2.8 g/dl (SD 0.9; range 1.4 to 4.3 g/dl) in the combined group. In this regard, the analysis of the data revealed no statistically significant difference between the IV and IA groups (p=0.25) or between the IA group and the combined group (p=0.13). However, the combined group showed a significantly lower maximum hemoglobin loss compared with the IV group (p=0.02) (**Tab. 1**).
The amount of blood found in the drain was 4.9 cc/h (SD 5.3; range 0.4 to 15.2) in the IV group, 10.7 cc/h (SD 12.2, range from 0.4 to 38.9) in the IA group, and 11.4 cc/h (SD 8.1, range 0.4 to 26.1) in the combined group. The rate of blood transfusions was: 10% (1 case) in the IV group, 40% (6 cases) in the IA group and 22.2% (2 cases) in the combined group. There were no statistically significant differences in these secondary outcomes (blood in drain and transfusion rate) between the three groups (**Tab. 1**). The average preoperative NRS score was statistically higher in the combined group (p=0.03) compared to the IV group, but it was similar to the score recorded in the IA group. However, there were no differences in NRS score on the first or fifth postoperative day between the IV and the combined group. The only significant difference in NRS values was found on the fifth postoperative day, when comparing the IA *vs* combined groups (p=0.006) (**Tab. 1**).
No complications occurred in any of the included patients. In particular, no DVT or other thrombotic events were detected.

Discussion

This study demonstrated that TXA is effective in reducing total blood loss, transfusion rate and blood in the drain, without increasing the rate of complications.
As different Authors have demonstrated, IV administration of TXA in TKA is safe and effective, both when given as a single dose and when adding a second or third dose intraoperatively or postoperatively (27-29). In particular, Levine et al., in a randomized controlled trial, demonstrated that a standard dose of 1 g IV can be used with the same efficacy as weighted doses (20 mg/kg) (30). Iwai et al. demonstrated that a double IV dose of TXA produced a further reduction of postoperative blood loss in TKA compared to a single administration (31), especially if the doses were given preoperatively and intraoperatively. Similarly, Maniar et al., also in a randomized controlled trial, demonstrated that a three-dose regimen (adding a postoperative dose) may be even more effective (32). Most of the studies confirmed the efficacy of different doses of IV TXA in reducing transfusion rates and total blood loss (27, 33-38) (**Tabs. 2, 3**).
However, some Authors reported a potential increased risk of thrombotic events and some cases of allergic reaction (10). For these reasons, the IA route of TXA administration was proposed. Different Authors have

Table 1. Results of the study.

	Maximum Hb loss (g/dl)	Lowest Hb (g/dl)	Blood in drain (cc/hour)	Transfusion rate (%)	NRS		
					Preoperative	1st postop. day	5th postop. day
IV GROUP	4.3 ± 1.55	10.1±1.54	4.94±5.33	10%	8.7 ±0.67	5.1 ±2.68	3.4 ±2.59
IA GROUP	3.64 ± 1.24	9.3±0.94	10.67±12.25	40%	9 ±0.76	3.8 ±1.97	1.73 ±1.83
p-value	0.25	0.14	0.18	0.10	0.32	0.18	0.07
IV GROUP	4.3 ± 1.55	10.1±1.54	4.94±5.33	10%	8.7 ±0.67	5.1 ±2.68	3.4 ±2.59
IV+IA GROUP	2.8 ± 0.92	9.54±1.53	11.43±8.17	22.2%	9.4 ±0.73	4.4 ±1.42	3.55 ±2.79
p-value	*0.02	0.48	0.06	0.47	*0.03	0.52	0.89
IA GROUP	3.64 ± 1.24	9.3±0.94	10.67±12.25	40%	9 ±0.76	3.8 ±1.97	1.73 ±1.83
IV+IA GROUP	2.8 ± 0.92	9.54±1.53	11.43±8.17	22.2%	9.4 ±0.73	4.4 ±1.42	3.55 ±2.79
p-value	0.13	0.63	0.88	0.37	0.17	0.4	*0.006

* p statistically significant (<0.05)
Abbreviations: TXA = tranexamic acid; IV = intravenous; IA = intra-articular; Hb = hemoglobin; NRS = Numerical Rating Scale score.

confirmed the efficacy of IA administration, albeit proposing different doses and different methods of topical administration (washing or through the drain) (24, 38-42). In particular, Georgiadis et al. randomized patients to two groups receiving either 2 g of TXA in 75 ml of saline or a placebo solution intraoperatively. The Authors demonstrated a significant reduction of total blood loss in the TXA group, without the potential complications related to IV administration (39). Patel et al., in a study of 89 patients who underwent a primary TKA, demonstrated that IV administration of 10 mg/kg of TXA and IA administration of 2 g TXA were equally effective in reducing blood loss (16). Similarly, various recent studies have demonstrated the efficacy of IA TXA administration in reducing blood loss after TKA (**Tabs. 2, 3**) (24, 29, 40-47).

Furthermore, recent meta-analyses showed no difference between topical and IV TXA administration (44, 48-55), even though some Authors reported conflicting results (43, 46, 47, 56).

There are only few studies in the literature that have examined the association of an IV protocol with a local one in patients undergoing TKA. Jain et al. showed better results in terms of mean total blood loss, transfusion rate and hemoglobin drop, using a combined protocol compared to only IV administration (57). Similarly, Lin et al., in a study of 120 patients, demonstrated greater reductions in blood loss, hemoglobin drop, total drain amount and transfusion rate using a combined protocol compared to IA administration alone (28). Karaaslan et al. evaluated the efficacy of an association of three different methods of TXA administration in bilateral TKA: a bolus dose of 15 mg/kg 10 min before the inflation of the tourniquet, followed by IA administration of 3 g 10 min before the deflation of the tourniquet, associated with an IV infusion of 10 mg/kg/h for 3h following the surgery. The Authors concluded that this method of TXA administration was effective in reducing total blood loss in bilateral TKA (34). Huang et al. compared the results of IV TXA administration (3 g) with those of a combined approach (1.5 g IA and 1.5 g IV). The Authors concluded that the two approaches were similarly effective in reducing transfusion rate and total blood loss, but the combined protocol gave better results in terms of maximum decline of hemoglobin, drainage volume, postoperative knee pain, knee swelling, length of hospital stays and short-term satisfaction (29).

In view of the established efficacy of TXA in TKA irrespective of the method of administration, we conducted a preliminary prospective cohort study in 34 patients, divided into IV administration, IA administration, and a combination of the two. The aim of this study was to evaluate whether one method of administration was more effective than the others. The results of the study showed no differences in hemoglobin loss, amount of blood in the drain, and rate of

Table 2. Summary of meta-analyses on the efficacy of tranexamic acid in total knee arthroplasty.

AUTHOR	YEAR	PROTOCOL	STUDIES	OUTCOMES EVALUATED	RESULTS
Alshryda S. et al. (44)	2011	IV or topical or oral	19 RCTs (18 involving IV administration, 1 IA administration, and 1 oral administration)	Blood loss, transfusion rate	Reduction in blood loss (MD 591 ml; 95% CI 536 to 647, p<0.001; heterogeneity I^2 = 78%), reduction in transfusion rate (RR 2.56, 95% CI 2.1 to 3.1, p<0.001; heterogeneity I^2 = 75%)
Zhang H. et al. (48)	2012	IV	15 RCTs	Blood loss, transfusion rate	Reduction in blood loss (MD 487ml, 95% CI -629 to -344), reduction in transfusion rate (risk difference - 0.4, p<0.00001)
Panteli M. et al. (49)	2013	Topical	7 (4 RCTs, 1 PCS, 2 quasi-RCTs)	Blood loss, hemoglobin drop, transfusion rate	Reduction in total blood loss (MD = - 220.08 ml, p<0.00001, 95% CI = -279.54 ml to -160.63 ml), maximum hemoglobin drop (MD = -0.94 gr/dl, 95% CI = -1.24 gr/dl to -0.65 gr/dl, p< 0.00001); lower risk of transfusions (RR = 0.47, p=0.01, 95% CI = 0.26 to 0.84)
Wang H. et al. (50)	2014	IV or topical	6 (5 RCTs, 1 PCS)	Total blood loss, Hemoglobin drop, drain output, transfusion rate	No differences as regards total blood loss (MD –14.36, 95% CI – 92.02 to 63.30), hemoglobin loss (MD 0.43, 95% CI – 0.25 to 1,11), total drain output (MD 21.91, 95% CI – 85.01 to 128.82), transfusion rate (RR 1.02, 95% CI 0.70 to 1.9)
Alshryda S. et al. (51)	2014	Topical	14 RCTs (11 knee replacement, 1 hip replacement, 1 both)	Transfusion rate	Reduction in transfusion rate (RR 4.51; 95% CI: 3.02 to 6.72; p<0.001; heterogeneity I^2= 0%)
Kim TK. et al. (52)	2014	IV or topical	28 RCTs (22 involving IV administration; 6 IA administration)	Blood loss, drain output, transfusion rate	Reduction in blood loss (range = 191 ml to 942 ml, 14 % to 64 % reduction), drain output (range = 65 ml, 8% reduction to 785 ml, 66% reduction), hemoglobin drop (range = 0.4 g/dl, to 2.8 g/dl, 12% to 70% reduction). Variability in transfusion rate and conflicting results in comparison between IV and topical
Wu Q. et al. (53)	2015	IV or topical	34 RCTs	Blood loss (intra operative and postoperative), hemoglobin drop, safety	Reduction in total blood loss [IA (SMD -0.86, 95%CI -1.14 to -0.59, p=0.000) IV (SMD = -1.01, 95%CI -1.43 to -0.60; p=0.00)], in postoperative blood loss [IA (SMD = -1.32, 95 % CI -2.08 to -0.55; p=0.001) IV (SMD = -1.11, 95%CI -1.61 to -0.61; p=0.000)]. No reduction in intraoperative blood loss. Reduction in hemoglobin drop [IA (SMD = -0.65, 95%CI -0.96 to -0.35; p=0.000) IV (SMD = -0.85, 95 CI -1.26 to -0.44; p=0.000)]. No complications

AUTHOR	YEAR	PROTOCOL	STUDIES	OUTCOMES EVALUATED	RESULTS
Shemshaki H. et al. (54)	2015	IV or topical	31 RCTs	Blood loss, transfusion rate, comparison between IA and IV	Reduction in blood loss [IV (MD = 392.72 ml, 95% CI 528.12 to -257.33; p<0.001) IA (MD = 282.44 ml, 95%CI 574.73 to 9.85; p<0.001)], reduction in transfusion rate [IV (RR 0.44; 95% CI 0.33 to 0.59; p<0.001) IA (RR 0.27; 95% CI 0.16–0.45; p<0.001)]. No differences between IV or IA administration (blood loss p=0.50; transfusion rate p=0.30)
Yue C. et al. (55)	2015	Topical	12 RCTs	Blood loss, transfusion rate, comparison of dosages	Reduction in blood loss (MD -280.65 ml, 95% CI, -376.43 to -184.88; p<0.00001); reduction in transfusion rate (risk ratio=0.26; 95% CI,. 0.19 to 0.37; p<0.00001; heterogeneity I^2=34%); reduction in drainage output (MD -194.59 ml, 95% CI, -315.86 to -73.32; p<0.002; heterogeneity I^2=63%). High concentration is better than low concentration (total blood loss: mean reduction of 335.79 ml in high concentration group *versus* 213.47 ml in low concentration group; transfusion rate: risk ratio=0.23 in high concentration group *versus* 0,37 in low concentration group)

Abbreviations: TXA = tranexamic acid; IV = intravenous; IA = intra-articular; CI = confidence interval; MD = mean difference; SMD = standardized mean difference; RR = risk ratio; RCT = randomized controlled trial; Quasi-RCT = quasi-randomized controlled trial; PCS = prospective cohort study.

transfusions between the combined protocol and topical administration alone. On the contrary, less hemoglobin loss was found in the combined group compared with the IV only administration group (p=0.02). However, it must be emphasized that patients in the IV group had significantly higher preoperative hemoglobin values than those of the combined (IV + IA group), and this can be considered a bias. With regard to the secondary outcomes (blood in drain and transfusion rate), no differences were detected between the three groups. In conclusion, although the combined protocol was found to be superior to the IV protocol, both are comparable to the IA protocol in terms of efficacy.

This study has some limitations. First, it is not a randomized controlled trial and the groups are not homogeneous, so there are potential biases. In particular, there is an indication bias, since all the patients with a potential contraindication to IV TXA administration (i.e. previous thrombotic events, anti-coagulation therapy) were allocated to the IA group. For this reason, the IA group presented a higher risk of bleeding, compared with the others. However the IA protocol, even though it was applied in patients with more comorbidities and a higher risk of bleeding, nevertheless showed equivalent efficacy to the other protocols. Therefore, these preliminary results confirm the efficacy of IA TXA administration, and represent a stimulus, for the Authors, to plan a randomized control trial. A further limitation is the absence of a control group. That said, the efficacy of TXA, whether administered topically or systemically, has previously been extensively described and is widely accepted. Finally, the power of the study was certainly reduced by the small size of the sample. However, these are preliminary data, and the study will be continued, introducing a randomization procedure, to confirm the significance of the results obtained.

The above-described preliminary experience with TXA in TKA is in line with what is reported in the literature. No significant differences in maximum loss of hemoglobin were observed between the different treatment

Table 3. Summary of randomized controlled trials on the efficacy of tranexamic acid in total knee arthroplasty.

AUTHOR	YEAR	NUMBER OF PATIENTS	PROTOCOL
Jain NP. et al. (57)	2016	119	IV *versus* combined
Aguilera X. et al. (43)	2015	150	IV (2 g) or topical (1g) versus placebo
Shen PF. et al. (33)	2015	92	IV 15 mg/kg in 100 ml saline, 10 minutes before tourniquet release
Hourlier. et al. (27)	2015	106	IV single dose 30 mg/kg intraoperative *versus* 10 mg/kg + 2 mg/kg as continuous infusion 2 h later for 20 h
Karaaslan F. et al. (34)	2015	81 undergoing bilateral TKA	IV 15 mg/kg 10 min before inflation of the tourniquet (and continued at 10 mg/kg for 3 h) + 3 g IA 10 min before deflation of the tourniquet
Carvalho LH Jr. et al. (24)	2015	125	IA 1.5 and 3.0 g in povidone-iodine solution
Lin SY. et al. (28)	2015	120	Combined *versus* IA *versus* placebo drop; total drain amount
Gomez-Barrena E. et al. (46)	2014	78	IA 3 g in 100 ml saline and two 15 mg/kg IV doses (before tourniquet release and after three hours)
Yang Y. et al. (45)	2015	80	IA 500 mg in 20 ml saline
Huang Z. et al. (29)	2014	184	IV 3 g *versus* combined IV 1.5 g + topical 1.5 g
Soni A. et al. (3)	2014	40	3 IV doses *versus* topical
Patel JN. et al. (16)	2014	89	IV 10 mg/kg versus topical 2 g
Sarzaeem MM. et al. (56)		200	IV 1500 mg *versus* IA 3 g in 100 cc saline *versus* 1.5 g injected through the drain versus placebo
Sa-Ngasoongsong P. et al. (41)	2013	135	IA 250 mg *versus* IA 500 mg (both injected through the drain with a 2 h drain clamping)

OUTCOMES EVALUATED	RESULTS
Blood loss, transfusion rate	Combined use of IV and topical TXA provided better results than IV use alone: less total blood loss (p=0.001), lower transfusion rate (p=0.001), smaller hemoglobin drop (p=0.001).
Blood loss, transfusion rate, hidden blood loss, safety	Both effective in reducing loss (p=0.001), reduction in transfusion rate; no differences between the two TXA groups (p=0.073)
Intraoperative blood loss; postoperative drainage at 12 h; total drain amount; hidden blood loss; total blood loss; transfusion volumes; number of transfusions; postoperative hemoglobin at 1, 3, and 5 days; D-dimer; number of lower limb ecchymose	Significant reduction in postoperative drainage amount at 12 h (p=0.000), total drain amount (p=0.000), hidden blood loss (p=0.001), total blood loss (p=0.004), and postoperative D-dimer value at 24 h (p=0.000).
Blood loss, safety	A single bolus of TXA 30 mg/kg is as effective as a continuous infusion (p=0.68)
Volume of drained blood 48 h postoperatively, decrease in hemoglobin levels 12 h postoperatively, amount of blood transfused	Drained blood (p=0.05), hemoglobin drop (p=0.05) and transfused units were lower in the TXA group compared with controls
Mean postoperative hemoglobin levels, blood loss, safety	Higher mean hemoglobin level (p=0.001, p=0.003) and lower blood loss (p=0.07, p=0.09) in the TXA group compared with controls
Mean total blood, transfusion rate; postoperative hemoglobin	Combining preoperative IV injection and topical administration of TXA can effectively reduce blood loss (p=0.001), total drain amount (p=0.001) and transfusion rate (p=0.009).
Drain blood loss at 24 and 48 hours, transfusion rate	Topical administration is as effective and safe as IV administration, with no differences in blood loss at 24 h (p=0.948), blood loss at 48h (p=0.837) or transfusion rate (0% in both groups)
Blood loss, transfusion rate, safety	Less total blood loss and lower transfusion rate in the TXA group compared with controls (p=0.05)
Transfusion rate, total blood loss, safety	Combined administration obtains smaller maximum decline of hemoglobin p=0.031), smaller drain volume (p=0.011), less postoperative knee pain, less knee swelling, shorter length of hospital stays. No differences in transfusion rate
Blood loss, blood in drain	No differences in hemoglobin drop (p=0.38) and blood in drain (p=0.48)
Hemoglobin level, total drain output, transfusion rate	Systemic and topical TXA administration found to be equally effective as in terms of hemoglobin drop (p=0.108), transfusion rate (p=0.342), total drain output (p=0.339) and safety
Hemoglobin drop, blood in drain, transfusion rate	All administrations showed smaller hemoglobin drop versus controls (p=0.05); IV administration is more effective in reducing hemoglobin drop p=0.05) and transfused units (p=0.031) compared with other groups. Joint irrigation is better than drug administration through the drain for obtaining hemoglobin drop (p=0.001)
Hemoglobin drop, transfusion rate, safety	The two protocols were equally effective in reducing total blood loss (p=0.001) and transfusion rate (p=0.05)

to be continued

Continued from **Table 3**

AUTHOR	YEAR	NUMBER OF PATIENTS	PROTOCOL
Alshryda S. et al. (40)	2013	157	Topical
Georgiadis AG. et al. (39)	2013	101	IA 2 g in 75 saline versus placebo
Lee SH. et al. (15)	2013	72	IV in patients undergoing prophylaxis with factor Xa inhibitor
Seo JG. et al. (47)	2013	150	IV 1.5 g in 100cc saline versus IA 1.5 g in 100cc saline
Chareancholvanich K. et al. (35)	2012	240	IV 10 mg/kg 20 min before inflating the tourniquet, repeated 3 hours after surgery + 1500 mg /day of oral TXA for 5 days + drainage clamping
Lin PC. et al. (37)	2012	151	IV 1 dose of 10 mg/kg *versus* IV 2 doses of 10mg/kg *versus* placebo
Roy SP. et al. (38)	2012	50	IA 500 mg/5 ml saline (through the drain after wound closure)
Lin PC. et al. (36)	2011	100	IV 10 mg/kg
Ishida K. et al. (42)	2011	100	IA 2 g/20 ml saline (through the drain after wound closure)

Abbreviations: TXA = tranexamic acid; TKA= total knee arthroplasty; IV= intravenous; IA= intra-articular; Hb= hemoglobin.

groups, with the exception of the finding of a greater value in the combined than in the IV one. However, as mentioned, there are different confounding factors in this study, and it will be necessary to increase the sample size and to randomize the patients in order to increase its power. In conclusion, TXA administration in TKA is safe and efficient in reducing total blood loss, hemoglobin loss, blood in drain and transfusion rate. Intravenous TXA administration is reported to be related to an increased thrombotic risk, but this assumption is not completely confirmed by the literature. Instead, there is agreement regarding the comparable efficacy of IA TXA administration, which is not associated with a potential increased thrombotic risk.

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OUTCOMES EVALUATED	RESULTS
Blood transfusion rate, drain blood loss, hemoglobin drop, generic quality of life (EuroQol), length of stay, cost, safety	Topical TXA administration is effective in reducing transfusion rate (p=0.001), blood loss (p=0.0003) and length of stay (p=0.041)
Blood loss, transfusion rate, safety	Smaller hemoglobin loss and calculated blood loss in TXA group (p=0.001); differences were not significant for transfusion rate
Blood loss, transfusion rate, blood in drain, safety	The treatment group showed reduced transfusion rate (p=0.007) and blood in drain (p=0.001). No differences were detectable regarding hemoglobin drop. There was no interaction with factor Xa inhibitor
Blood loss, transfusion rate	Both TXA groups showed significantly reduced amount of blood loss (p=0.001) and transfusion rate (p=0.001) compared with the placebo group. IA administration seems to be more effective than systemic administration
Blood in drain at 48 hours postoperatively,hemoglobin drop, transfusion rate	TXA is effective in reducing volumes of drained blood and amount of blood transfusion compared with placebo (p=0.005) Drain clamping combined with TXA administration is more effective than using TXA or drain clamping alone as regards hemoglobin levels (p=0.001) and transfusion rate (p=0.05)
Hemoglobin drop, transfusion rate	A single dose is effective in reducing blood loss (p=0.0001) and transfusion rate (p=0.006). No differences between single and double dose administration (blood loss p=0.148; transfusion rate p=0.672)
Blood loss, blood in drain, transfusion rate	IA TXA administration is effective in reducing both hemoglobin drop (p=0.05) and total drain collection at 48 hours (p=0.001)
Blood loss, transfusion rate	Effective in reducing both total blood loss (p=0.001) and hidden blood loss (p=0.01)
Blood loss, blood in drain, transfusion rate, leg diameter	Decreased blood loss (p=0.01) and less knee joint swelling (circumference at the superior patellar border) in TXA group *versus* controls p=0.05

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