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Evaluation of efficacy and safety of systemic and topical intra-articular administration of tranexamic acid in primary unilateral total hip arthroplasty

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Abstract

Background: Tranexamic acid (TXA) is an antifibrinolytic agent used to reduce bleeding in major surgical procedures. This study evaluates the efficacy and safety of the systemic and topical intra-articular administration of TXA in total hip arthroplasty (THA).

Methods: Patients (N = 123) scheduled for primary unilateral THA were divided into 3 treatment groups: control group; TXA, systemic, repeated 1 g bolus; TXA, topically intra-articularly, 2 g in 50 mL saline. Primary readouts used were intra- and postoperative bleeding, transfusion requirement, postoperative hemoglobin levels and complications.

Results: Both systemic and topical intra-articular TXA administrations decreased bleeding and transfusion requirements. Topical intra-articular use of TXA led to the reduction in intraoperative and postoperative bleeding and affected hemoglobin levels compared with control. Systemic administration of TXA led to a significant reduction of postoperative bleeding and transfusion rate compared with control and was not different in efficacy and complication incidence when compared to topical administration of TXA.

Conclusions: The use of TXA to reduce blood loss and transfusion requirements in THA is an effective and safe concept in practice. The dose of 2 g TXA topically intra-articularly and a repeated bolus of 1 g TXA systematic led to lower intra- and postoperative bleeding and a significantly lower transfusion rate than the control group. Topical intra-articular TXA administration could be a reasonable alternative in high-risk patients.

Abbreviations: aTXA = topical intra-articular administrationTXA, DVT = deep venous thrombosis, Hb = hemoglobin, MI = myocardial infarction, PE = pulmonary embolism, RCT = randomized controlled trials, sTXA = systemic administration TXA, THA = total hip arthroplasty, TXA = tranexamic acid.

Keywords: antifibrinolytic agent, blood loss, systemic administration, topical intra-articular administration, total hip arthroplasty, tranexamic acid

1. Introduction

Hip replacement surgery is among the most common procedures in orthopedic and trauma surgery. The procedure is typically accompanied by relatively small intraoperative but dramatic postoperative blood loss exceeding 1000 mL. Before the implementation of hemostatic drugs, 57% of patients undergoing total hip arthroplasty (THA) received at least 1 perioperative blood transfusion.[1]

Numerous approaches have been used to minimize transfusion requirements in THA, including blood salvage, improved surgical hemostasis techniques, minimally invasive surgery, and the stimulation of erythropoiesis with erythropoietin alfa. These methods were shown to be successful; however, each introduced additional costs. The amount of perioperative blood loss depends on blood coagulation and fibrinolytic activity of the individual patient. Recently, the use of pharmacologic agents, namely antifibrinolytics has been investigated to minimize perioperative blood loss associated with total joint arthroplasty. In particular, tranexamic acid (TXA) was 7 to 10 times more potent in inhibiting fibrinolysis than ε-amino-caproic acid.[2]

TXA (4-aminomethyl cyclohexanecarboxylic acid) is a synthetic amino acid derivative of lysine, known to inhibit fibrinolysis via interaction with lysine in the binding site of plasminogen to fibrin. As a result, fibrin is not degraded in a

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thrombus.[3,4] These agents effectively reduce postoperative bleeding by inhibiting fibrinolysis and thrombus degradation.[5]

The history of TXA dates back to the 1960s when Shosuke Okamoto and Utako Okamoto introduced it, and it was first prescribed to females with heavy blood loss during menstruation and to patients with hereditary bleeding disease.[6] The application of TXA has been associated with significantly lower intra- and postoperative bleeding, in reduced numbers of transfusion in patients undergoing total joint arthroplasty, and consequently has become a well-established choice in orthopedic surgery.[7] TXA can be administered intravenously, locally or topically to the area designated for surgery, but combined administration and[8] enteral route[9,10] were also used. Since the 60s,[2] the efficacy of TXA has been studied in various orthopedic surgical procedures and evaluated in a range of dosing regimens and formulations.[11] More than 2100 publications have shown that TXA applied intravenously or topically can decrease operative bleeding and the number of transfusions, without increasing the risk of complications.[5]

There is a growing interest in using TXA for minimizing blood loss and the requirement of transfusion in patients undergoing THA. Because TXA does not have clear guidelines as to the indications in the field of orthopedic surgery, its use in complete joint arthroplasty is typically off-label in the Slovak Republic. Our study aimed to evaluate the efficacy (bleeding, transfusion rate, hemoglobin [Hb] levels, total drainage) and risks (any possible complications) of TXA in THA and compare 2 administration routes of this drug, that is, systemic and local intra-articular.

2. Material and methods

The present open prospective, randomized control trial was performed at the University Hospital Trencin from January 2017 to April 2019. A total of 123 adult patients with end-stage coxarthrosis scheduled for primary unilateral THA were included in the study. Before enrollment, patients signed an informed consent form. The institutional ethics review committee of the University Hospital Trencin approved the study.

Participants were excluded based on:

- hypersensitivity to TXA,
- a coronary or vascular stent placed within 6 months,
- deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI),
- or ischemic stroke within the past 12 months,
- hypercoagulable state/disorder,
- history of convulsions or epilepsy,
- renal insufficiency (creatinine clearance <30 mL/h),
- color vision impairment,
- hormonal contraceptive use.

One hundred twenty-three patients were enrolled in the study and were divided into 3 groups, each comprised of 41 patients:

1) Control group: without the use of TXA (male = 18, female = 23).
2) Tranexamic acid group, systemic administration of TXA (sTXA), repeated 1 g bolus: (male = 15, female = 26)
3) Tranexamic acid group, topical intra-articular administration of TXA (aTXA), 2 g in 50 ml saline: (male = 13, female = 28)

The main readouts in our study included intra- and postoperative blood loss, transfusion requirement, postoperative Hb levels and complications, and were compared among the 3 treatment groups.

2.1. Perioperative regime

Nadroparin (Fraxiparin, Aspen, 0.4 mL subcutaneous) was used as prophylaxis for DVT 1 day before surgery. The dose was repeated after 24 hours, as well as 3 days after surgery when the dose was adjusted to weight response as recommended by the manufacturer. Alternatively, we began DVT prophylaxis with oral rivaroxaban (Xarelto, Bayer). To prevent postoperative infection, we primarily used cefuroxime IV (1.5 g), and in case of allergy to cefuroxime, we used clindamycin IV instead (600 mg), with 2 follow-up doses administered in 8-hour intervals. The surgery was performed in a supine position using the antero-lateral hip approach. To reduce surgical bleeding, we used TXA (Exacyl 5×5 mL [0.5 g], Sanofi, France) in treatment groups sTXA and aTXA.

In the sTXA group, patients received a 1 g intravenous bolus dose of TXA diluted in 100 ml saline solution before skin incision with an additional 1 g bolus administered 3 hours later. In the aTXA group, we diluted 2 g TXA (20 mL Exacyl) in a 50 mL saline solution. We applied approximately one-fourth of the liquid solution topically intra-articularly into the acetabulum and periacetabular tissue, using a syringe with a needle for the best irrigation effect before implanting the acetabular cup. With the rest of the fluid, we irrigated all areas of the wound with the potential for bleeding after the hip prosthesis was finally reduced. The applied TXA was given at least 5 minutes to act, and the remaining fluid was removed before finishing fascial closure.

A suction drain was placed under the fascia of each participant and was left closed for 30 minutes after surgery. The drain was removed the next morning after surgery. All procedures were performed by experienced surgeons.

We recorded the amount of intraoperative blood loss during THA, postoperative bleeding volume captured by the suction drain, and the number of blood transfusions. Hb levels were examined on the day before surgery, then on the day of surgery, and additionally on the 1st and 4th postoperative days in all patients. We monitored the healing of the surgical wound, the presence of hematoma and the occurrence of any potential adverse effects of TXA. We used the Doppler ultrasound examination or computed tomography angiography to detect an arterial or venous thromboembolic event.

2.2. Statistical analysis

Data were analyzed using GraphPad Prism version 9.0. Continuous variables were expressed as mean ± standard deviation (SD) and means were compared using independent unpaired sample *t* test or analysis of variance Tukey multiple comparisons test. χ^2 test was used to compare categorical variables, and $P < .05$ was considered statistically significant.

3. Results

3.1. Patients characteristics

No significant differences between the groups were found when considering demographic data, specifically age, sex, and body weight. Baseline characteristics of all study groups are shown in Table 1, and in Figures 1 and 2.

Table 1

Baseline characteristics.

Characteristics	Control group	THA-sTXA	THA-aTXA	*P*			
				Control vs THA-sTXA	Control vs THA-aTXA	THA-sTXA vs THA-aTXA	
n = 41 (Male/female)	18/23	15/26	13/28	.6528	.3625	.8161	Fisher exact test
Age, y	67.93 ± 8.88	67.46 ± 7.124	65.88 ± 12.29	.9744	.6041	.7389	Ordinary 1-way ANOVA (Tukey multiple comparisons)
Age, y, male	66.28 ± 10.19	65.27 ± 5.378	58.62 ± 15.06	.9603	.1309	.2377	Ordinary 1-way ANOVA (Tukey multiple comparisons)
Age, y, female	69.22 ± 7.69	68.73 ± 7.77	69.25 ± 9.26	.9773	.9999	.9715	Ordinary 1-way ANOVA (Tukey multiple comparisons)
Body weight, kg	83.29 ± 19.65	77.90 ± 14.90	77.41 ± 16.96	.3377	.2759	.9910	Ordinary 1-way ANOVA (Tukey multiple comparisons)
Body weight, kg, male	92.72 ± 20.12	89.53 ± 15.77	92.23 ± 12.53	.8519	.9965	.9068	Ordinary 1-way ANOVA (Tukey multiple comparisons)
Body weight, kg, female	75.91 ± 16.12	71.85 ± 9.81	70.54 ± 14.19	.5412	.3377	.9305	Ordinary 1-way ANOVA (Tukey multiple comparisons)

ANOVA = analysis of variance, aTXA = topical intra-articular administration tranexamic acid, sTXA = systemic administration tranexamic acid.

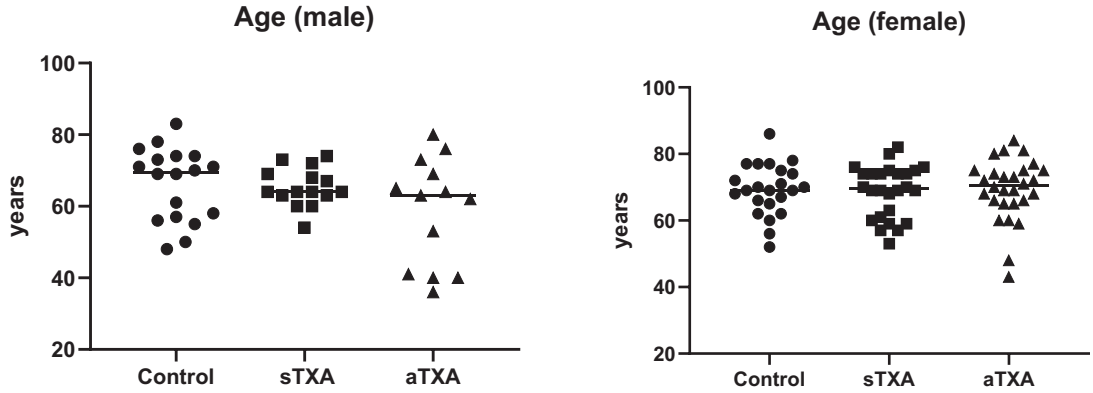

Figure 1. Age spectrum—male and female. Ordinary 1-way analysis of variance (Tukey's multiple comparisons).

3.2. Intraoperative and postoperative bleeding, transfusion requirements

One hundred twenty-three patients were included in the study. Table 2 shows averages of blood loss: intraoperative, postoperative, and transfusions requirements. The recorded intraoperative blood loss in the control group was 300.0 ± 100.0 mL, in the sTXA group 287.5 ± 103.1 mL, and in the aTXA group 218.6 ± 84.96 mL. Topical intra-articular use of TXA led to a significant reduction of intraoperative blood loss when compared to the control group ($P = .0121$).

The average postoperative blood loss represented by drainage output was 791.7 ± 302.2 mL in the control group, 474.9 ± 207.3 mL in sTXA-treated group, and 349.9 ± 219.5 mL in aTXA (Table 3). Both TXA groups had less postoperative bleeding volume in drainage (control vs sTXA $P < .0001$; control vs aTXA $P < .0001$, Table 3), without a statistically significant difference between TXA groups (sTXA vs aTXA $P = .0653$, Table 3).

Major differences were observed in transfusion requirements, with 41.46% of control group patients requiring at least one blood transfusion, while in the sTXA and aTXA groups, only 4.9% and 17.07% of patients required blood transfusions, respectively. Thus, particularly systemic administration of TXA has attributed a significant reduction of transfusion requirements (control vs sTXA $P < .0001$, control vs aTXA $P = .0278$, sTXA vs aTXA $P = .1549$, Table 2).

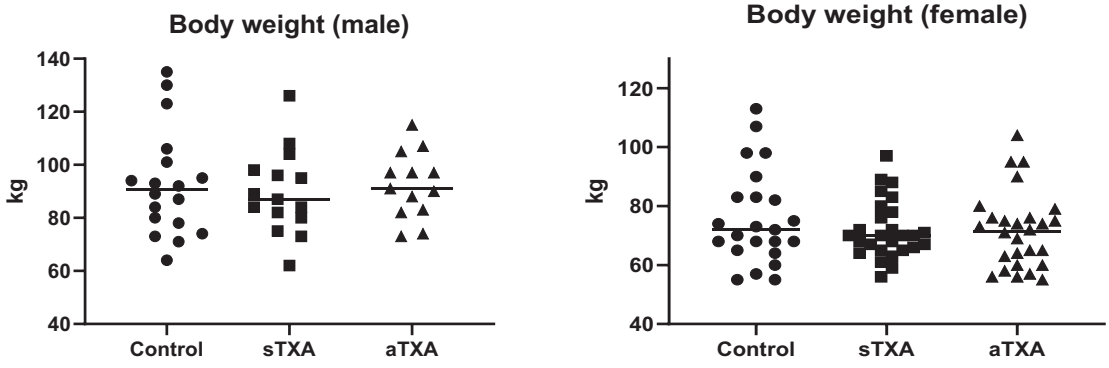

Figure 2. Body weight spectrum - male and female. Ordinary 1-way analysis of variance (Tukey multiple comparisons).

Table 2

Intraoperative and postoperative blood loss, transfusion rate.

Characteristics	Control group	sTXA	aTXA	*P*			
				Control vs sTXA	Control vs aTXA	sTXA vs aTXA	
Intraoperative blood loss	300.0 ± 100.0	287.5 ± 103.1	218.6 ± 84.96	.967	.0121	.3279	Ordinary 1-way ANOVA (Tukey multiple comparisons)
Postoperative blood loss	791.7 ± 302.2	474.9 ± 207.3	349.9 ± 219.5	<.0001	<.0001	.0653	Ordinary 1-way ANOVA (Tukey multiple comparisons)
No. of transfusion patients (yes/no)	17/24	2/39	7/34	.0001	.0278	.1549	Fisher exact test

ANOVA = analysis of variance, aTXA = topical intra-articular administration tranexamic acid, sTXA = systemic administration tranexamic acid.

Table 3

Descriptive statistics postoperative blood loss.

Characteristics in mL	Control group	sTXA	aTXA
Postoperative blood loss	791.7 ± 302.2	474.9 ± 207.3	349.9 ± 219.5
Minimum	300.0	150.0	5.0
Maximum	1750.0	1000.0	1180.0
95% CI of median	650.0–850.0	350.0–550.0	250.0–420.0
95% CI of mean	696.3–887.1	409.4–540.3	278.7–421.0

aTXA = topical intra-articular administration tranexamic acid, CI = confidence interval, sTXA = systemic administration tranexamic acid.

We measured Hb levels at several time points, specifically one day before surgery, on the day of surgery, and the first and fourth postoperative days (Table 4, Fig. 3A–D). Hb levels on the first and fourth days after surgery were higher in both groups treated with TXA than in the control group. On the first day after surgery, the control group exhibited Hb levels of 108.5 ± 12.82 g/L, whereas 115.8 ± 11.36 g/L were observed in sTXA-treated patients; $P = .0311$. On the fourth day after the surgical procedure, Hb levels in the control group were 104.0 ± 9.525 g/L, in the sTXA group 110.9 ± 10.63, and in the aTXA group 109.7 ± 12.34 g/L (control vs sTXA $P = .0134$; control vs aTXA $P = .049$). The decrease in Hb levels from the first day to the fourth day after surgery was expressed in percentage and was the highest in the control group with a 26% Hb decrease, a 22% decrease in sTXA, and 18% in aTXA. Notably, Hb levels might have been confounded by factors including preoperative anemia, serum iron levels, transfusion therapy, iron absorption, and blood transfusion. Since these factors were not controlled nor monitored, we abstain from the conclusion that the relatively higher postoperative Hb levels were a result of TXA treatment.

3.3. Incidence of complications

We did not observe any convulsion, color vision impairment, cerebral stroke, MI, PE, or hypersensitivity reaction during TXA treatment in this study (Table 5). We noticed more oozing of the wound in the control group compared with sTXA and aTXA groups. In terms of thromboembolic events, we recorded only 1 case of DVT (popliteal vein thrombosis) in the control group. Overall, the lowest rate of complications was in the aTXA group.

4. Discussion

TXA is an antifibrinolytic agent with the potential to fundamentally change blood management strategies in total joint arthroplasty by reducing the high demand for transfusion. Although TXA is used in THA since 2000,[12] it has not yet become the standard of care. In the literature, excessive variability exists in the method of administration, dosage, timing, and the number of doses required.

Goldstein et al[10] performed a meta-analysis of five randomized controlled trials (RCTs) of IV TXA prophylaxis in hip joint replacement, using the PubMed and Cochrane Library databases. The authors reported that the use of TXA resulted in a reduction in total blood loss by 289 to 369 mL, intraoperative blood loss by 86 to 190 mL, and postoperative blood loss by 172 to 341 mL. Moreover, the number of transfusions was reduced by 12.2% to 24.6%.[10] Furthermore, the meta-analysis evaluated the dose of TXA (1–4 g/24 hours), thromboembolism prophylaxis method and the transfusion requirement criteria. After bolus administration of 10 mg/kg body weight, >90% of the substance was excreted in the urine within 24 hours. Accumulation effects occurred only in patients with renal insufficiency, but not in patients with hepatic insufficiency.[10,13]

Table 4

Hb levels.

Characteristics	Mean ± SD, g/L			*P*			
	Control group	sTXA	aTXA	Control vs sTXA	Control vs aTXA	sTXA vs aTXA	
Hb 1 day before surgery	139.0 ± 12.04	140.8 ± 13.94	132.9 ± 15.10	.832	.1167	.0298*	Ordinary 1-way ANOVA (Tukey multiple comparisons)
Hb on the day of surgery	123.1 ± 13.52	124.5 ± 21.28	120.5 ± 15.08	.9286	.7611	.5363	Ordinary 1-way ANOVA (Tukey multiple comparisons)
Hb 1st day after surgery	108.5 ± 12.82	115.8 ± 11.36	114.4 ± 13.38	.0311*	.0975	.8732	Ordinary 1-way ANOVA (Tukey multiple comparisons)
Hb 4th day after surgery	104.0 ± 9.525	110.9 ± 10.63	109.7 ± 12.34	.0134*	.0490*	.8701	Ordinary 1-way ANOVA (Tukey multiple comparisons)

ANOVA = analysis of variance, aTXA = topical intra-articular administration tranexamic acid, Hb = hemoglobin, sTXA = systemic administration tranexamic acid.

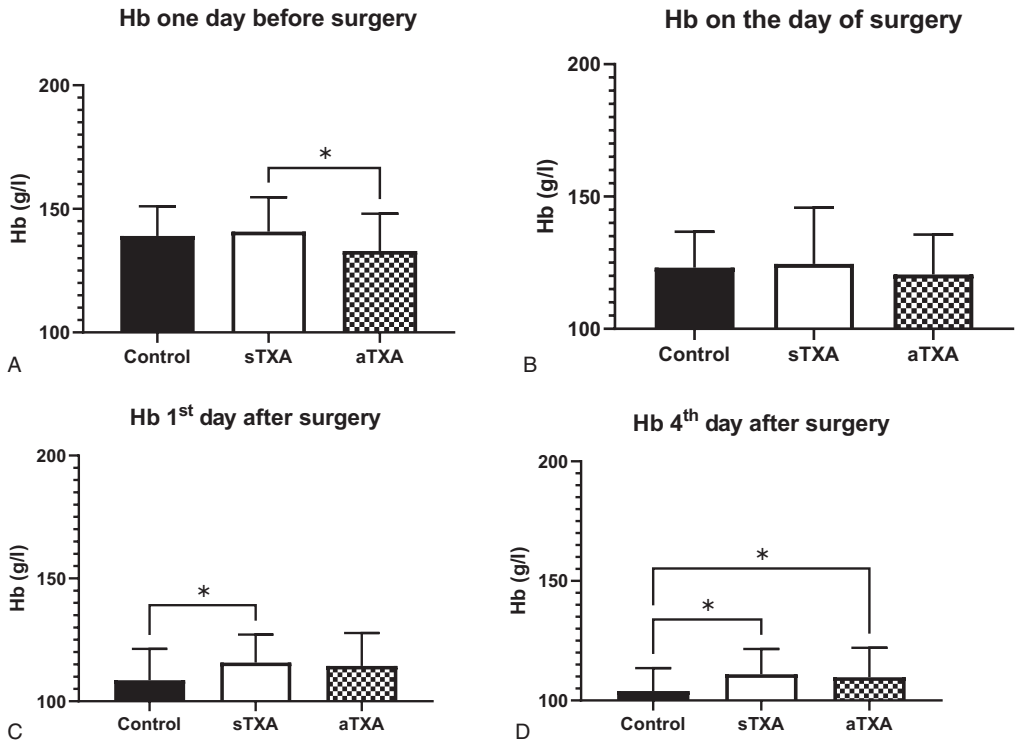

Figure 3. (A–D) The measurement of hemoglobin. Ordinary 1-way analysis of variance (Tukey multiple comparisons).

Our study evaluated 2 administration routes of TXA, namely systemic and local intra-articular, each with a different dosing regimen. Systemic TXA was administered before a skin incision by first injecting 1 g TXA diluted in 100 mL saline, and 3 hours later followed by a 1 g bolus. The 3-hour interval was based on the elimination half-life of TXA which is approximately 3 hours,[10] and repeated dosing was expected to produce a more pronounced clinical effect than a single bolus. For local intra-articular administration, we diluted 2 g TXA in 50 mL saline solution, applied approximately one-fourth of the liquid topically intra-articularly, and the remainder was applied to all wound areas with a risk of bleeding after the hip prosthesis was finally reduced. Presently, the most common topical TXA administration routes are joint irrigation and installation into the standard drain, alternatively combined with epinephrine.[14] In clinical practice, topical irrigation doses of TXA range from 0.5 to 3 g in 20 to 100 mL saline. Lostak et al[15] administered 3 g of TXA in 100 mL saline topically to the bleeding bone bed before the implantation of final joint components, as well as before wound closure.

Table 5

The types of complications.

Types of complications	Control	sTXA	aTXA
Pneumonia	0	0	1
Febrility	0	1	0
Positive microbial cultivation (wound, the tip of the drain)	3	6	3
Wound oozing	10	3	1
org.psychosis	0	0	1
Thrombosis	1	0	0
Without complication	19	31	32

aTXA = topical intra-articular administration tranexamic acid, sTXA = systemic administration tranexamic acid.

By using these 2 methods, we found that the reduction in intraoperative blood loss was least significant in aTXA group (compared with control $P = .0121$, compared with sTXA $P = .3279$), and postoperative blood loss (postoperative drainage output) was significantly decreased in the aTXA and sTXA groups compared with the control group ($P < .0001$). Postoperative blood loss was decreased by 56% in the aTXA group, and by 40% in the sTXA group when compared to the control group. These findings were similar to those found by Vijay et al.[4]

There is still no clear consensus if multiple boluses of systemic TXA have an additional benefit in terms of blood loss or transfusion requirements. Iwai et al[16] found that administration of a repeated bolus of TXA reduced postoperative blood loss and the need for transfusion after total knee arthroplasty without association with the risk of DVT or PE. Oppositely Fillingham et a[9] demonstrated no additional benefit of multiple doses of IV TXA in primary THA. Using TXA reduced the transfusion rate in our study. Only 2 patients of 39 in sTXA group and 7 patients of 34 in aTXA group needed transfusion compared with 71% of patients in the control group. We propose that this positive effect was a result of repeated dosing.

The authors combined IV and topical TXA administration, and they concluded that the combination could be more effective than IV and topical alone. Moreover, Yoon et al[5] evaluated 25 RCT to assess the comparative efficacy and safety of 3 TXA administration routes. They identified the most effective interventions in terms of reducing the need for transfusion as follows: combined = 98.2%, IV single dose = 54.0%, IV multiple doses = 78.6%, topical = 66.1%, placebo = 0.0%, with no differ-

ence in the rate of occurrence of DVT and PE. However, the results of this study Fillingham et al in the Clinical Practice Guidelines on the use of TXA in primary total joint arthroplasty did not identify the superior method or combination of methods for administering TXA.[9] Our study found that the use of 2 g TXA topically intra-articularly led to significant decreases in intra-and postoperative blood loss and the transfusion requirements compared to the control group. Using systematic TXA significantly reduced postoperative blood loss and the number of transfusions. So, in our study, topical use was more effective in the reduction of drainage volume. However, IV use was more effective in the reduction of transfusion requirements. We assess in the topical use of TXA surgeon is more concerning with hemostasis during the procedure. The efficacy of the use of TXA in the reduction of transfusion requirements was admirable in our study. Postoperative bleeding volume in the drain was in the control group, 791.7 mL, compared with 474.9 mL in the sTXA group and 349.4 mL in the aTXA group. In clinical practice, acute loss of 700 mL of the blood indicates transfusion therapy.[17] The use of TXA prevents overshooting this limit. The cost of 2 g TXA in our hospital is 2.87 € compared to the cost of packed red blood cells 79.30 € per concentrate. Allogenic blood transfusion carries various risks, including immune modulation, prosthesis infection, transfusion reactions, and the transmission of known and potentially as-yet-unknown pathogens.[18] Off-label use of TXA in total joint arthroplasty reveals significant benefits for the patients and the hospital.[19]

Nevertheless benefits we need to concern with the risks of the use of TXA in THA. The using TXA based on its inhibition of fibrinolysis is theoretically assumed to activate coagulation with an increased tendency for thrombosis.[5] Numerous studies prove the safety of systemic and topical TXA use in total joint arthroplasty.[9,10,20–22] The present state of knowledge suggests that the thromboembolic risk does not increase with low-dose, short-term administration with standard clinical use of postoperative DVT prophylaxis. Patients considered to be at high risk for arterial and venous thrombosis, such as those with a history of stroke, DVT, PE, MI, cardiac stents, have generally been excluded from studies of TXA.[23] These patients were excluded from our study too. Topical TXA administration results in low plasma levels and to have a reduced risk of complications without affecting wound healing. Presently, the amount of information from RCTs on the risk of adverse effects of TXA in high-risk patients is limited.[9,10] As a consequence, each patient with known risk factors should be considered individually in a multidisciplinary approach when deciding whether to administer TXA.[9,22] With regards to complications due to TXA treatment in our study, we did not observe any statistical differences. Thrombotic events in both TXA groups were not observed, and only one case of DVT was recorded in the control group (popliteal vein thrombosis), which together support the safety of TXA. In the literature, only case reports recorded that systemic TXA use could be associated with arterial or venous thrombosis, although such observations were very rare in orthopedic surgery.[24,25]

5. Conclusion

The use of TXA to reduce blood loss and transfusion requirements in THA is an effective and relatively safe concept in practice. The dose of TXA given topically intra-articularly (2 g), and by a repeated bolus systemically (1 g) led to lower intra- and postoperative bleeding and significantly fewer transfusion events than in the control group. Topical intra-articular administration of TXA is therefore proposed as a reasonable choice for high-risk patients.

Author contributions

Resources: MD. Masaryk Juraj, MD. Vidan Jaroslav, Andrea Gažová, PaedD. Viera Žufková.
Supervision: PharmD. Ján Kyselovič, Ass.Prof. MD. Boris Šteňo.

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