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Comparison of Intravenous and Topical Tranexamic Acid in Total Joint Arthroplasty

Porovnanie celkového a lokálneho podania kyseliny tranexámovej pri totálnej náhrade bedrového a kolenného kĺbu

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ABSTRACT

PURPOSE OF THE STUDY
To compare topical and intravenous (IV) administration of tranexamic acid (TXA) 2 g in patients undergoing total hip arthroplasty (THA), or total knee arthroplasty (TKA).

MATERIAL AND METHODS
In total, 452 patients undergoing THA or TKA were randomised to 3 groups: 1) the IV TXA group received 2 doses of TXA 1 g intravenously 3 hours apart; 2) the topical TXA group received TXA 2 g topically, and 3) the NO TXA – control group. Furthermore, each group was divided in two subgroups by performed surgery (THA versus TKA). The following endpoints were used for final analysis: postoperative blood loss, transfusion requirement, haemoglobin drop and postoperative complications (haematoma, surgical site infection, thromboembolism, early surgical revision).

RESULTS
Both topical and IV administration of TXA significantly reduced postoperative bleeding (mean ± standard deviation) after THA and TKA (topical 504.4±281.0 ml, IV 497.3±251.7 ml, NO 863.1±326.4 ml, $p<0.001$). Topical use was superior to IV in reducing postoperative drainage output in THA (topical 377±213.3 ml, IV 518.1±259.0 ml, $p<0.01$). On the opposite, IV use was superior to topical in drainage output in TKA (topical 646.1±281.3 ml, IV 457.8±235.8 ml, $p<0.01$). The differences in transfusion requirement and Hb drop between these administration methods were not statistically significant ($p\geq0.05$), but any TXA administration was significantly better than no TXA in all endpoints of efficacy ($p<0.001$). The lowest complication rate was observed in the topical group (NO 24%, IV 19%, topical 7.5%).

DISCUSSION
Consensus on optimal TXA dosing regime in primary hip and knee arthroplasties is still missing. Use of TXA therapy in routine clinical practice is highly individualized in accordance with the current approach of personalized medicine. Topical application seems to be the safest route of TXA administration. However, precise application technique is essential. IV TXA is beneficial especially in patients with some bleeding coagulopathies undergoing TKA with a tourniquet. Repeat doses of TXA are not usually necessary after completed primary arthroplasties.

CONCLUSIONS
IV and topical TXA 2 g have similar effect on reduction of transfusion requirements and haemoglobin drop in THA and TKA. The IV route is superior to topical in TKA while topical TXA reduces complications in both THA and TKA.

Key words: tranexamic acid, total hip arthroplasty, total knee arthroplasty, topical administration, intravenous administration.

INTRODUCTION

The antifibrinolytic agent tranexamic acid (TXA) synthesized in 1962 is a 7–10 times more potent inhibitor of fibrinolysis than the related ε-aminocaproic acid (20). TXA inhibits fibrinolysis by blocking the lysine binding site of plasminogen to fibrin. As a result, fibrin is not cleaved from the clot. On 14 February 2012, the European Medicines Agency (EMA) completed a review of the antifibrinolytics medicines and made recommendations on the use of TXA (2). Up to the present, therapeutic indications of TXA involve prevention and treatment of haemorrhages due to general or local fibrinolysis and management of haemorrhage due to the administration of a fibrinolytic agent. Other specific indications include: menorrhagia and metrorrhagia, gastrointestinal bleeding, haemorrhagic urinary disorders, ear nose throat surgery, gynaecological surgery or disorders of obstetric origin, thoracic and abdominal surgery and other major surgical intervention such as cardiovascular surgery.

The standard TXA dose recommended by EMA is 0.5 to 1 g IV twice to 3times daily for treatment of local fibrinolysis, and 1 g IV every 6 to 8 hours or equivalent dose 15 mg/kg of body weight for treatment of general fibrinolysis. On 19 June 2012, the EMA's Committee for Medicinal Products for Human Use decided to remove a requirement for a pharmacokinetic study of TXA and informed of ongoing pharmacokinetic studies which

are to be finalised and assessed by national authorities (2). In the last years, new pharmacokinetics studies and off-label prophylactic indications of TXA use has been increasing, including the field of orthopaedic surgery.

Before implementation of blood management strategies, 57% of THA patients underwent transfusion therapy (3). Total joint arthroplasty (TJA) is characterized by relatively mild intraoperative but excessive postoperative blood loss up to 1000 ml. Dosing of IV TXA 1 g to reduce acute haemorrhage is a convenient method of administration. The meta-analysis from 40,138 patients with acute severe bleeding confirmed that delay of TXA administration reduces the treatment benefit ($p<0.0001$), while immediate treatment improves survival by more than 70% (odds ratio – OR 1.72, 95% confidence interval 1.42–2.10; $p<0.0001$). Precisely, the survival benefit decreased by 10% for every 15 min of treatment delay until 3 hours, after which there is no benefit (10). In lower limb arthroplasty, approximately 90% of blood loss occurs between skin closure and postoperative 24 hours (16). Since the TXA elimination half-time is about 3 hours, we decided to repeat bolus administration of TXA 1 g in 3 hours to extend the drug effect. TXA is available in IV and oral dosage forms. Topical administration of diluted IV TXA solution is an alternative off-label method and further investigation is needed to determine the optimal dose and dosing regimen.

The aim of our study is to compare efficacy and safety of TXA in total dose of 2 g administered IV versus topically in patients undergoing total hip or knee arthroplasties. Reduction in postoperative blood loss, transfusion requirements, haemoglobin (Hb) drop and complication rate were evaluated as study endpoints.

MATERIAL AND METHODS

Study population and design

The open, prospective, randomized study was conducted at the Faculty Hospital Trencin from November 2016 to April 2019. The study was approved by the hospital ethics committee and all patients signed an informed consent form before their enrolment.

Overall, 550 adult patients with end-stage arthrosis scheduled for primary unilateral total hip (THA) or knee (TKA) arthroplasties were assessed for eligibility.

The following exclusion criteria were applied:
- a coronary or vascular stent placed within the last six months,
- deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI) or ischemic stroke within the last 12 months,
- hypercoagulable state/disorder,
- history of convulsions or epilepsy,
- creatinine clearance < 30 ml/h,
- colour vision impairment.

Out of 512 enrolled patients who met eligibility criteria, 452 patients successfully completed study participation and were included in the final analysis The baseline characteristic of the study population is shown in Table 1.

Enrolled patients were randomised to 3 groups: 1) the IV TXA group received 2 doses of TXA 1 g intravenously 3 hours apart; 2) the topical TXA group received TXA 2 g topically, and 3) the NO TXA group was used as no TXA treatment control group. Furthermore, each group was divided in two subgroups by performed surgery (THA versus TKA).

Figure 1 shows patient flow during the study. Out of 550 screened patients, 38 patients did not meet eligibility criteria or declined to participate. There were 60 patients who were withdrawn prematurely due to administration of lower TXA dose than planned. All withdrawn patients were from the topical TXA group. Overall, 452 patients were included in the final analysis.

Perioperative regime

Routine DVT prophylaxis was initiated with subcutaneous nadroparin a day before surgery or alternatively with 10 mg of rivaroxaban in accordance with approved dosing up to 6 weeks postoperatively. To prevent postoperative infection, patients received cefuroxime 1.5 g IV, (clindamycin 600 mg in case of allergy), with subsequent two doses 8 hours apart .

Surgery was performed in a supine position using the anterolateral (in THA) or the medial parapatellar (in TKA) approach. In TKA tourniquet was deflated after polymerization of the bone cement. In accordance with assigned group, we administered TXA (Exacyl® 5x5 ml (0.5 g), Sanofi, France) to reduce surgical bleeding. In

Table 1. Baseline characteristics of patient population

Characteristics	Gender	*n*	$\bar{x}$	*sd*	x_m	*min.*	*max.*	p_{MW}
Age	Male	176	65.2	8.2	65.0	37	83	<0.001
	Female	276	68.4	8.0	69.0	44	86	
	Total	452	67.2	8.2	68.0	37	86	–
Body weight (kg)	Male	176	93.2	15.7	92.0	62	155	<0.001
	Female	276	77.9	14.0	76.0	38	114	
	Total	452	83.9	16.4	82.5	38	155	–

n – sample size, $\bar{x}$ – arithmetic mean, *sd* – standard deviation, x_m – median, *min.* – minimal value, *max.* – maximal value, p_{MW} – p-value of Mann-Whitney test;

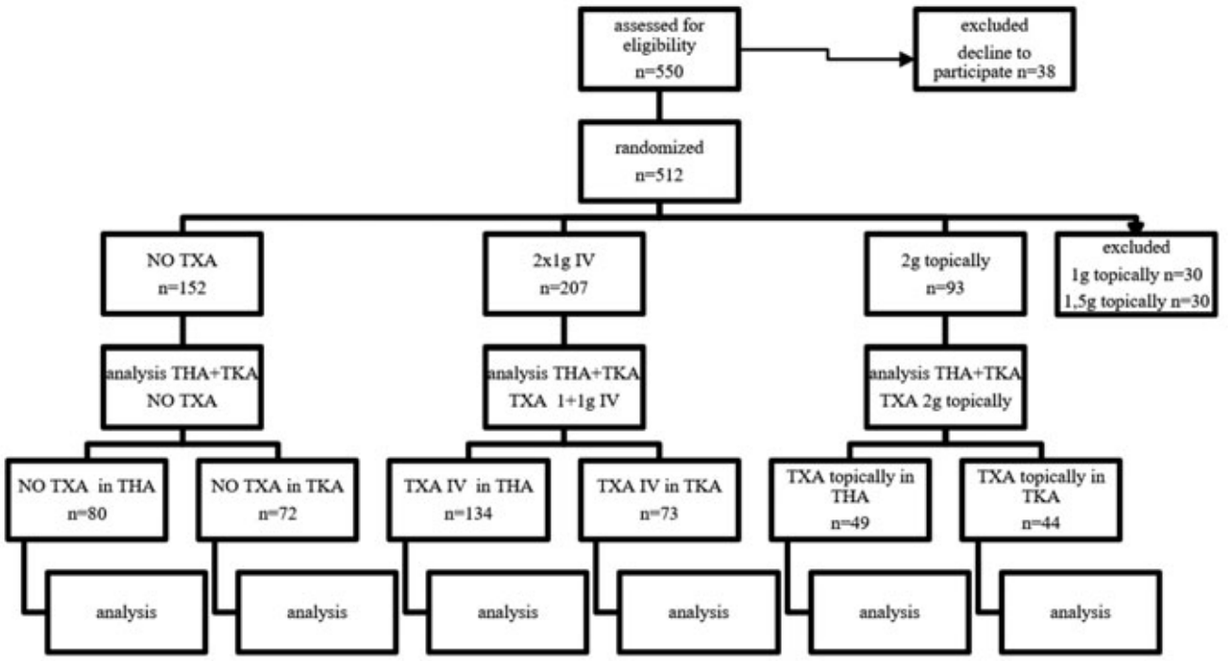


Fig. 1. Diagram showing flow of patients through the study.

the IV TXA group, patients received 1 g of TXA diluted in 100 ml of saline IV before skin incision with additional same 1 g bolus administered 3 hours later. In the topical TXA group, 2 g of TXA (20 ml Exacyl®) were diluted in 50 ml of saline. About ¼ of the solution was applied topically into the acetabulum and periacetabular tissue using a syringe with a needle for the best irrigation effect before implantation of the acetabular cup. The remaining solution was used to irrigate all areas of the wound after the final reduction of hip prosthesis. In TKA, we irrigated all potentially bleeding areas after the final haemostasis following tourniquet release. TXA stayed in place for at least 5 minutes. The remaining fluid has been suctioned before finishing fascial or capsular closure, while the suction drain was inserted in surgical site. The drain was left closed for 30 minutes after surgery and it was removed the next morning after surgery.

All procedures were performed by surgeons with appropriate experience and training and as per standard of care. We recorded postoperative bleeding volume in drainage and the number of blood transfusions administered if the following indications were met: acute blood loss of 700 ml and Hb level ≤90 g/l. Hb levels were measured in each patient the day before surgery, 1 hour after the surgery, and on the 1st and 4th postoperative day. We focused our postoperative monitoring up to 6 weeks after surgery on detection of surgical site infections, the presence of limb swelling and haematoma and arterial and venous thrombotic events for calculation of complication rate.

Table 2. Postoperative drainage output

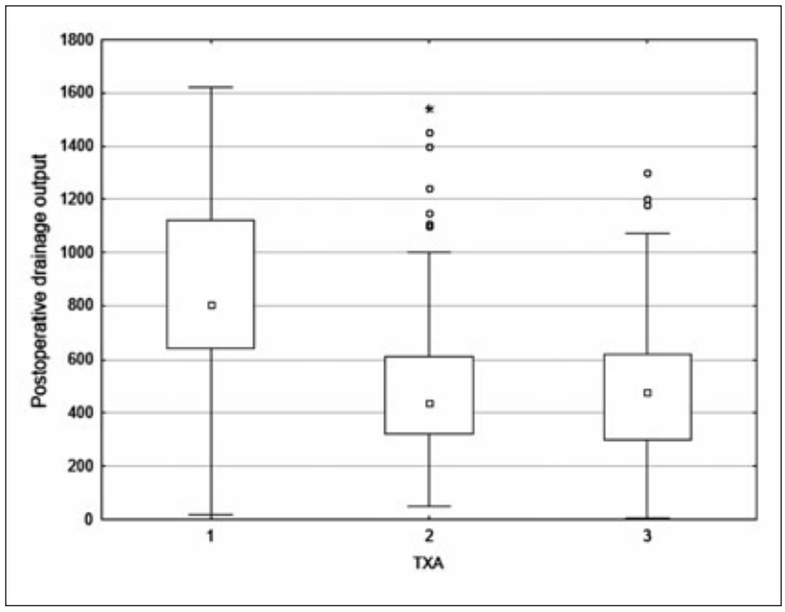
Procedure	**TXA**	***n***	$\bar{x}$	***sd***	x_m	***min.***	***max.***	p_{KW}	p_D		
									No	*IV*	*Top.*
Total arthroplasties (THA+TKA)	NO TXA	148	863,1	326,4	805	20	1620	<0.001	–	***	***
	IV TXA	207	497,3	251,7	440,0	50	1540		***	–	ns
	Topical TXA	93	504,4	281,0	480.0	5	1300		***	ns	-
THA	NO TXA	80	788,3	279,5	750.0	300	1600	<0.001	–	***	***
	IV TXA	134	518.1	259.0	450.0	100	1540		***	–	**
	Topical TXA	49	377.0	213.3	340.0	5	1180		***	**	–
TKA	No TXA	68	956,4	356,5	950,0	20	1620	<0.001	–	***	***
	IV TXA	73	457,8	235,8	400.0	50	1450		***	–	**
	Topical TXA	44	646.1	281.3	600.0	120	1300		***	**	–

Legend: THA – total hip arthroplasty, TKA – total knee arthroplasty, TXA – tranexamic acid, IV TXA – intravenous tranexamic acid, Top. TXA – topical tranexamic acid; NO TXA – control group, *n* – sample size, $\bar{x}$ – sample mean, *sd* – sample standard deviation, x_m – median, *min.* – minimal value, *max.* – maximal value, p_{KW} – Kruskal-Wallis test p-value, p_D – Dunn's test p-value: ns – *not significant*; * – $p<0.05$; ** – $p<0.01$; *** – $p<0.001$

Statistical analysis

Data were analysed by software In-Stat®, version 3.02, 32 bit, GraphPad Software, Inc., USA, and software Statistica 12®, 64 bit, StatSoft/TIBCO Software, USA. No imputation methods (deletion, replacement by any of the measures of centre or by zero value) was applied to replace missing data. Non-parametric tests (Mann-Whitney test and Kruskal-Wallis test with the Dunn post-test) on the level of 0.05 significance were used for statistical analysis of numerical data. Box plots were used to graphically show median as a point within the central square of 1st -3rd quartiles and lines marking the range.

Graph 1. Postoperative drainage output – all patients



Legend: 1 – NO TXA, 2 – IV TXA, 3 – Topical TXA

RESULTS

Postoperative drainage output

Table 2 summarizes the volume of postoperative drainage output per TXA treatment group and performed procedure. The use of TXA significantly reduced postoperative bleeding in comparison to no TXA treatment ($p<0.001$, Graph 1). In the surgery with the highest postoperative bleeding – TKA with tourniquet (median 950 ml and mean 956.4 ml), the IV route of administration was statistically significantly more effective than topical (Dunn's test: $p<0.01$). On the opposite, topical route of administration was statistically significantly more effective than IV in THA (Dunn's test: $p<0.01$).

Transfusion requirements

Table 3 shows the total number of transfusion requirements per TXA treatment group and performed procedure. Our data suggest that transfusion need is an infrequent event if TXA is used. The difference between topical and IV route of administration is not statistically significant, but both differences between topical TXA and no TXA as well as between IV TXA and no TXA were statistically significant (both Dunn's test: $p<0.001$).

Haemoglobin decrease

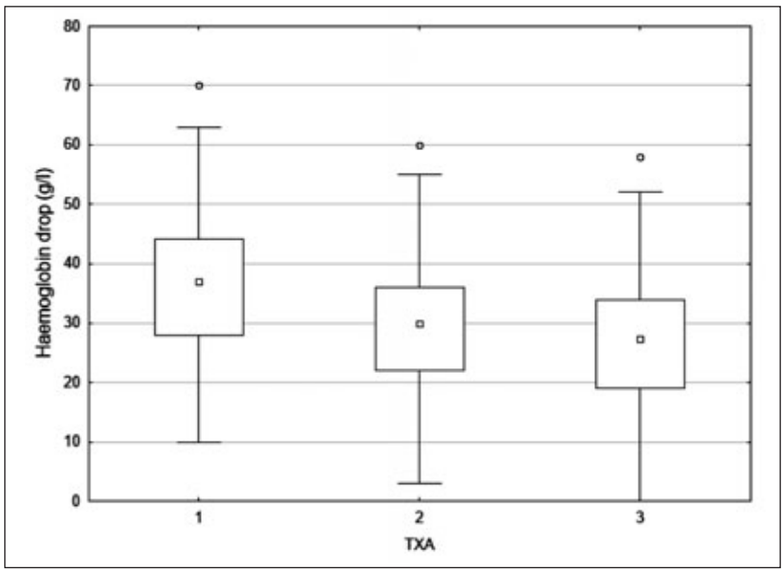
Table 4 and Graph 2 show a Hb drop between preoperative Hb level and Hb level on the 4th postoperative day in patients without transfusion therapy. There is no statistical difference between topical and IV TXA. Both administration routes significantly reduced Hb drop between preoperative and postoperative Hb levels in comparison to no treatment (Dunn's test: $p<0.001$).

Table 3. Transfusion requirements

Procedure	TXA	*n*	*sum*	$\bar{x}$	*sd*	x_m	*min.*	*max.*	p_{KW}	p_D		
										No TXA	*IV*	*Top.*
Total arthroplasties (THA+TKA)	NO TXA	152	87	0.6	0.9	0	0	5	<0.04	–	***	***
	IV TXA	207	26	0.1	0.4	0	0	3		***	–	ns
	Topical TXA	93	12	0.1	0.4	0	0	3		***	ns	–
THA	NO TXA	80	54	0.7	1.1	0	1	5	<0.04	–	***	***
	IV TXA	134	19	0.1	0.4	0	0	3		***	–	ns
	Topical TXA	49	10	0.2	0.5	0	0	3		***	ns	–
TKA	NO TXA	72	33	0.5	0.8	0	0	3	<0.04	–	***	***
	IV TXA	73	7	0.1	0.3	0	0	2		***	–	ns
	Topical TXA	44	2	0.0	0.2	0	0	1		***	ns	–

Legend: THA – total hip arthroplasty, TKA – total knee arthroplasty, TXA – tranexamic acid, IV TXA – intravenous tranexamic acid, Top. TXA – topical tranexamic acid; NO TXA – control group, *n* – sample size, *sum* - number of administered transfusion units, $\bar{x}$ – sample mean, *sd* – sample standard deviation, x_m – median, *min.* – minimal value, *max.* – maximal value, p_{KW} – Kruskal-Wallis test p-value, p_D – Dunn's test p-value: ns – not significant; * – $p<0.05$; ** – $p<0.01$; *** – $p<0.001$

Graph 2. Differences in haemoglobin level (g/l) between day 0 and 4th post-surgery day with respect to the method of TXA application – patients without transfusion need only



Legend: 1- NO TXA, 2 – IV TXA, 3 – Topical TXA

Complication rate

Table 5 summarizes complications observed during the study. With respect to thromboembolic events alone, the following complications were reported: 2 DVTs and 1 arterial thrombotic event in the TXA IV group, 1 DVT in the topical TXA group and 2 DVTs in the NO TXA group.

DISCUSSION

Up to date, consensus on optimal TXA dosing regime in primary THA and TKA is still missing. In the network meta-analysis of Fillingham et al. (8), 2113 publications of TXA use in THA underwent critical appraisal with 34 publications identified as representing the best available evidence for inclusion in the analysis. Topical, IV, and oral TXA formulations provided reduced blood loss and risk of transfusion compared to placebo, but no formulation was clearly superior. No specific TXA routes of administration, dosage, dosing regimen, or time of administration were identified to provide superior blood-sparing properties (8, 9). In the network meta-analysis, the dose-response relationship for higher doses of TXA was observed in TKA (9). The high dose of TXA corresponds to ≥20 mg/kg or >1g IV and >1.5 g topically (9). For both TXA groups in our study, we administered high doses – TXA topically as joint irrigation and IV low dose bolus was repeated in 3 hours what could be considered as high dose of TXA in a prolonged regime. We chose the 3hour interval because the elimination half-time of TXA in the joint fluid is about 3 hours (1). As a result, the prolonged regime ensured a decrease of fibrinolysis up to 6 hours from the beginning of the surgery.

In our study comparing topical and IV TXA, we observed equivalent efficacy of both administration routes in terms of transfusion requirements and Hb drop, but statistically significant difference between these two methods in postoperative drainage output and complication rate. IV TXA was superior to topical route in decrease of postoperative drainage output in TKA. Ischaemisation of the limb caused by tourniquet results in hypoperfusion of the endothelial territory distal to com-

Table 4. Haemoglobin drop (g/l) – all patients without transfusion therapy

TXA group	*n*	$\bar{x}$	*sd*	x_m	*min.*	*max.*	p_{KW}	p_D		
								No TXA	*IV*	*Top.*
NO TXA	94	35.6	9.9	36.0	10	63	<0.001	–	***	***
TXA IV	184	29.2	10,5	30.0	3	60		***	–	ns
Topical TXA	85	27.2	11.2	28.0	0	58		***	ns	–

Legend: TXA – tranexamic acid, TXA IV – intravenous tranexamic acid, NO TXA – control group, *n* – sample size, $\bar{x}$ – sample mean, *sd* – sample standard deviation, x_m – median, *min.* – minimal value, *max.* – maximal value, p_{KW} – Kruskal-Wallis test p- value, p_D – Dunn's test p-value: ns – *not significant*; * – $p<0.05$; ** – $p<0.01$; *** – $p<0.001$

Table 5. Number of reported complications

TXA group	n	Arterial or venous thrombosis		Haematoma, surgical site infection		Early surgical revision	
		n	%	n	%	n	%
NO TXA	152	2	1.32	34	22.37	2	1.32
IV TXA	207	3	1.45	36	17.39	4	1.93
Topical TXA	93	1	1.08	6	6.45	0	0.00

Legend: TXA – tranexamic acid, IV TXA – intravenous tranexamic acid, NO TXA – control group, n – sample size

pression. It also induces the endothelial release of fibrinolytic activators which, after tourniquet relief, circulate and act systemically until they are cleared by the liver (17). Fahmy and Patel (7) observed significantly increased systemic fibrinolytic activity after tourniquet release during the knee arthrotomy. This hyperfibrinolysis could be lowered by systemic TXA use. Definitely, TKA with tourniquet is a surgery with higher postoperative bleeding than THA (in control group without TXA in our study, it was 956.4±356.5 ml in TKA and 788.3±279.5 ml in THA). Systemic (IV) TXA administration has immediate desired effect on reduction of fibrinolysis. Goh et al. (11) retrospectively reviewed 2123 primary TJAs (975 knees and 1148 hips) performed in patients with a preoperative coagulopathy. Patients who received TXA had less intraoperative blood loss and 2.3 times decreased risk of 90-day complications especially cardiovascular (2.92% vs 12.1%, p <0.001) and wound complications (0.0% vs 1.59%, p = 0.042). Lostak at al. (15) analysed an optimal strategy of TXA administration in diabetic and obese patients undergoing primary TKA. Two IV doses and the combined topical/IV administration of TXA was more effective than topical administration (15). A secondary benefit of TXA is reduction of the heterotopic ossification ratio after primary THA (5). Generally, these benefits must be considered in respect with the risks of TXA administration. Inhibition of fibrinolysis induced by administered TXA theoretically assumes an increased tendency for thrombosis (6, 7, 17). Numerous studies proved the safety of TXA use in TJA (9, 12, 13, 19, 23, 24). The current state of knowledge suggests that the risk of thromboembolic event does not increase with a short term low dose TXA administration and with the routine use of postoperative DVT prophylaxis. Out of 452 patients who completed our study, we observed only six thrombotic events. Specifically, DVT was experienced by 1 patient in the topical TXA group, by 2 patients in the NO TXA group, and by 2 patients in the IV TXA group. One patient in the IV TXA group experienced arterial thrombosis. More specifically, thrombotic occlusion of the superficial femoral artery in the non-operated leg caused acute limb ischaemia in a 64-year-old male who underwent THA. In the detailed assessment, we detected a neglected and untreated limb artery disease, the symptoms of which were overshadowed by severe hip pain that masked the claudication pain. Except arterial disease, repeated TXA IV administration, surgery, obesity and hypertension were also identified as predisposing factors of occlusion (18). Porter et al. retrospectively analysed 38 220 high-risk patients undergoing primary THA and TKA. They reported no differences in rates of mortality, readmission rate and 90-day postoperative occurrence of DVT, PE, MI and cerebrovascular accidents between high-risk patients receiving IV TXA and high-risk patients who did not receive TXA (21). There are only case reports indicating that systemic TXA use could be associated with arterial thrombosis, but they are very rare in orthopaedic surgery (4). Topical administration of TXA notably decreased complication rate in our study and it seems to protect patients from complications. TXA plasmatic level after topical administration is lower of up to 70% in comparison to plasmatic levels after equivalent IV doses (14). Sukeik et al. reviewed 25 randomized controlled trials evaluating wound complication after primary THA with the use of TXA. Administration of TXA reduced the risk of developing wound complications of 2% in comparison to the control group (22). The proper technique of the topical TXA administration is essential. Nevertheless, we need further investigation of the TXA impact on wound healing.

CONCLUSIONS

Topically or IV administered TXA 2 g has a similar beneficial effect on reducing transfusion requirements in primary TJA. In prophylactic use, IV TXA is more effective than topical TXA in the surgery with high postoperative bleeding as TKA with tourniquet use. Topical TXA reduces number of complications after TJA.

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