Combined and intravenous administration of TXA reduces blood loss more than topical administration in primary total knee arthroplasty: A randomized clinical trial

Jiri Lostak[a], Jiri Gallo[a], Lubos Balaz[a], Jana Zapletalova[b]

Aim. To determine the most effective administration of tranexamic acid (TXA) in patients with primary total knee arthroplasty (TKA).

Material and Method. We enrolled a total of 400 patients (154 men and 346 women) in this randomized trial (4 groups, each of 100 patients). The first group (IV1) had a single intravenous dose (15 mg TXA/kg) prior to skin incision. Group 2 (IV2) had TXA in 2 intravenous doses (15 mg TXA/kg): prior to skin incision and 6 hours after the first dose. Group 3 (TOP) had 2 g TXA in 50 mL of saline irrigated topically at the end of the surgery. The fourth group (COMB) combined IV1 and TOP regimens. We monitored the amount of total blood loss (TBL), haemoglobin drop, use of blood transfusions (BTs), and complications in each patient.

Results. The amount of TBL was significantly lower in IV1, IV2 and COMB regimens compared to the TOP ($P<0.0001$). The lowest decrease in haemoglobin within 12 hours after surgery was observed in intravenous regimens ($P=0.045$). A significant difference in haemoglobin decrease on day 1 after the surgery was demonstrated in the COMB and intravenous regimens ($P=0.011$).

Conclusion. In primary TKA, it is preferable to administer TXA intravenously in two doses or in a combined regimen. Simple topical administration of TXA was not as effective and is indicated only in cases where systemic administration of TXA is contraindicated. No substantial complications occurred in either group of patients.

Key words: total knee arthroplasty, tranexamic acid, topical administration, intravenous administration, combined administration, randomized clinical trial

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[a]Department of Orthopaedics, University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic
[b]Department of Medical Biophysics, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic
Corresponding author: Jiri Gallo, e-mail: jiri.gallo@volny.cz

INTRODUCTION

Tranexamic acid (TXA) can be administered intravenously, orally or directly into the joint via irrigation in the perioperative period for primary total knee arthroplasty (TKA) (ref.[1]). Most studies have been performed with systemic and topical administration of TXA (ref.[1,2]). However, there are still concerns about the potential risk of thromboembolic disease in the case of intravenous administration in higher doses[3,4]. For this reason, some studies favour topical administration with the aim of transferring the maximum effect to the target area and thus avoid an overall effect on the fibrinolytic system[5,6]. It is potentially most effective to combine both routes, to reduce the intravenous dose, thereby minimizing the risk of thromboembolism and increase the effect by additional topical administration[4,5,7].

Some studies suggest that combined TXA administration have a greater effect than single topical or intravenous administration[8,9]. TKA appears to be an ideal candidate for combined procedures due to the large bleeding area. However, there are concerns about the synergy of the systemic and topical TXA effect. In our previous study, we determined the safety profile for systemic, combined and topical administration of TXA in patients undergoing primary TKA (ref.[10]). We found no significant effect on systemic markers of fibrinolysis in either regimen. Although many excellent studies have focused on search for the optimal protocol for use of TXA in TKA, differences in views on the optimal regimen of TXA administration have only increased[1,2,8]. Even large-scale randomized studies and meta-analyses do not provide consistent conclusions on the proper administration of TXA in terms of dose or number of doses[11].

The primary objective of our study was to determine which route of TXA administration has the greatest effect on the reduction of blood loss (into the drainage system, hidden loss) and use of blood transfusions. We compared postoperative haemoglobin and its decrease in the early postoperative period in individual regimens.

MATERIAL AND METHOD

Patient cohort

We enrolled a total of 400 consecutive patients into this prospective randomized trial. These were indicated for primary TKA in our department between June 2018 and October 2019. The patients received TXA during the perioperative period according to a predetermined protocol. Each group consisted of 100 patients (Fig. 1). The inclusion criteria for the enrolment in the trial were normal preoperative blood count (haemoglobin, platelets) and blood coagulation (INR, Quick, aPTT). The trial did not include patients with a history of any disease associated with blood coagulation defects, with a history of venous thromboembolism (VTE), severe kidney disease or convulsions. The basic characteristics of the 4 groups were similar (Table 1). A more detailed analysis of BMI (comparing cohorts in pairs) showed no significant difference (results of Dunn's post hoc test).

The clinical register of joint replacements has been approved by the hospital management, and its administration is regulated by an amended ethical and legal protocol. The local Ethics Committee approved the study in accordance with the latest Helsinki Declaration; all the enrolled patients agreed with the use of anonymized data for research purposes (registration number 87-67). Prior to enrolment into the study, patients signed an informed consent.

Collection of preoperative data

Data were collected prospectively according to a predetermined procedure. The medical data were registered by the physician during the admission interview. The physician also recorded the basic medical history, including the primary diagnosis and results of clinical examination.

Preoperative preparations

Patient preparation procedures were initiated on the day of admission, i.e. one day before the surgery. In the context of VTE prevention, we applied either low-molecular-weight heparin (Fraxiparine; Aspen Pharma Trading Limited, Dublin, Ireland), first administered subcutaneously 12 h before the surgery (at the dose recommended by the manufacturer). Alternatively, Rivaroxaban (Xarelto; Bayer AG, Leverkusen, Germany) was administered orally 6 to 8 h after the surgery. Postoperative infection prevention largely consisted in i.v. administration of 1 g of the third-generation cephalosporin antibiotic (Azepo; Sandoz, Holzkirchen, Germany). Clindamycin 600 mg i.v. was administered in case of allergy (Fresenius Kabi, Bad Homburg vor der Höhe, Germany). The antibiotic was administered intravenously 30 to 60 min before the skin incision. The additional doses of antibiotics were administered 8 and 16 h after the first administration.

Surgical procedure and the implant

The surgical procedure was performed under general or block anaesthesia. The procedure invariably used skin

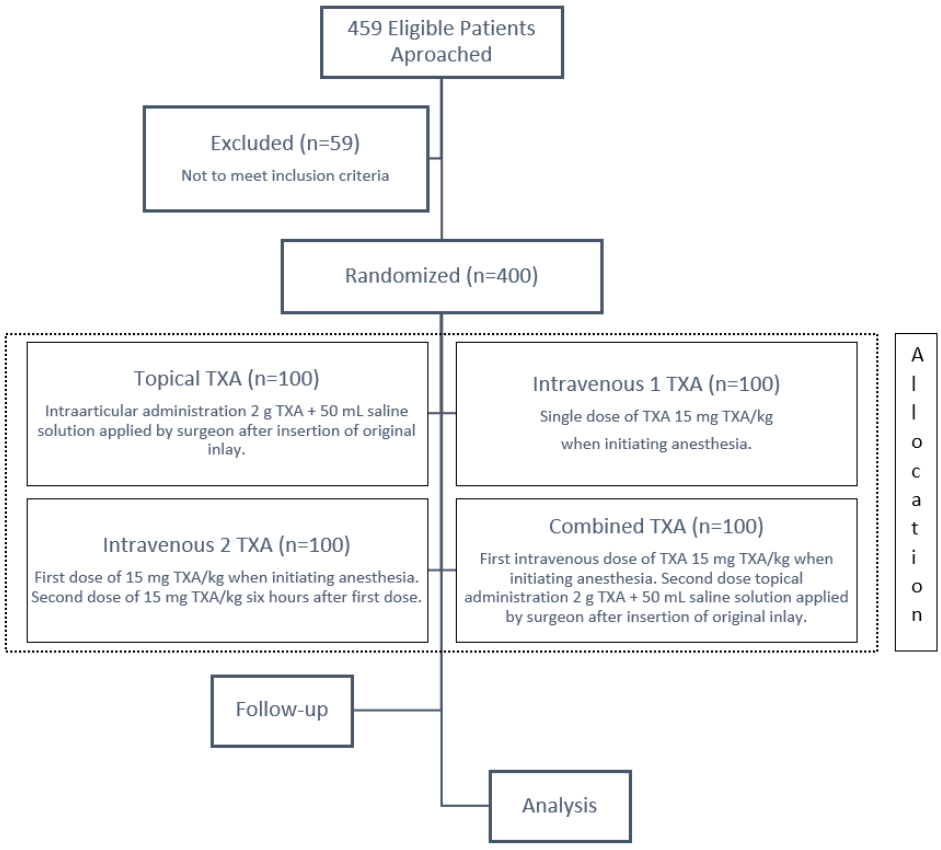

Fig. 1. Flow chart showing study subject identification, inclusion and exclusion, allocation and protocols of TXA.

Table 1. Comparison of the groups in their basic parameters.

	COMB	IV1	IV2	TOP	*P*
# of patients	100	100	100	100	-
Primary osteoarthritis	89/11	89/11	88/12	87/13	0.966
Gender (m/f)	38/62	33/67	36/64	47/53	0.203
Mean age ±SD	68.9±6.9	69.1±7.6	69.2±7.7	71.4±6.4	0.064
BMI (kg/m^2) Median (min-max)	32.3 (20.9-42.3)	31.2 (23.3-53.4)	40.4 (21.3-48.8)	30.4 (23.2-44.7)	0.028
Patient type A/B/C*	57/40/3	64/35/1	67/33/0	58/39/3	0.432
X-rays K-L II/III/IV	1/94/5	1/94/5/	3/94/3	1/96/3	0.870
X-rays IKDC C/D/O	47/46/7	52/41/7	46/48/6	50/47/3	0.817
CCI median (min-max)	2 (0-14)	1 (0-14)	0 (0-14)	2 (0-14)	<0.0001

CCI, Charlson Comorbidity Index; TOP, topical administration of TXA; COMB, combination of topical and intravenous administration of TXA; IV1, single intravenous administration; IV2, two intravenous doses of TXA; SD, standard deviation; m, male; f, female; K-L, Kellgren-Lawrence classification; IKDC, International Knee Documentation Committee; *P,* significance; *According to the degree of risk of infection (A = minimal risk; B = moderate; C = highest; modified from McPherson et al.[12])

Table 2. Overview of perioperative blood loss.

	COMB	IV1	IV2	TOP	*P*
Total blood loss into drains (mL) median	450	375	350	635	<0.0001
Hidden blood loss (mL)	192	196	178	275	0.015
Blood loss during surgery	300	300	300	300	0.268
Total blood loss (mL), (during surgery + into drainage system)	750	650	605	900	<0.0001
Maximum blood loss to drainage system	1500	1400	1500	1790	–
Minimum blood loss to drainage system	0	0	0	0	–
Total post-operative blood loss into drains including hidden blood loss	620	608	534	861	<0.0001
Total blood loss including hidden loss (mL)	979	919	819	1185	<0.0001

Median values for the data are provided in the table because blood losses did not have a normal distribution (verified by the Shapiro-Wilk test). TOP, topical administration of TXA; COMB, combination of topical and intravenous administration of TXA; IV1, single intravenous administration; IV2, two intravenous doses of TXA; *P,* significance.

Table 3. Comparison of blood loss in individual TXA regimens (results of Dunn's post hoc test).

	Total blood loss into drains	Hidden blood loss	Total loss during surgery and postoperative loss to drainage systems	Total postoperative loss to drainage systems including hidden loss	Total loss including hidden loss
TOP vs. COMB	0.004	–	0.021	0.004	0.015
TOP vs. IV1	<0.0001	–	0.004	<0.0001	0.005
TOP vs. IV2	<0.0001	0.010	<0.0001	<0.0001	<0.0001

TOP, topical administration of TXA; COMB, combination of topical and intravenous administration of TXA; IV1, single intravenous administration; IV2, two intravenous doses of TXA.

incision and the medial parapatellar approach. The bleeding was stopped during the surgery using electrocoagulation. The tourniquet was only activated for cementing (typically up to 15 min). All operations were performed by experienced surgeons. We used only cemented implants preserving the posterior cruciate ligament or replacing its function.

TXA protocols

Each group had a well-defined protocol for TXA administration and dosing (Fig. 1). Group 1 (IV1) included patients with TXA administered by the anaesthesiologist prior to skin incision as a single intravenous dose (15 mg TXA/kg). Group 2 (IV2) included patients with TXA administered in two intravenous doses (15 mg TXA/kg), the first dose as described above (IV1) and the subsequent dose 6 hours after the first administration. Group 3 (TOP) included patients with TXA administered topically by lavage with a diluted solution of 2 g TXA in 50 mL of saline. The fourth group (COMB) had TXA administered in combination, the first dose of 15 mg TXA/kg intravenously prior to skin incision and the second dose topically via irrigation using the mixture of 2 g TXA in 50 mL of saline at the end of the surgery. In all patients, the drains were left closed for 1 h from the surgery.

Endpoints

Blood loss including hidden blood loss

We evaluated the amount of blood loss during the surgery and postoperative period into the drainage system

in each patient. Hidden blood loss was calculated using a formula that includes perioperative and postoperative blood loss related to the sex and weight of the patient[13]. Briefly, hidden blood loss = true calculated red blood count (RBC) – total measured RBC volume loss – total measured RBC volume gain [True calculated RBC = PBV (patient blood volume) * (hematocrit before surgery–postoperative); total measured RBC volume loss = intraoperative blood loss + postoperative blood loss; total measured RBC volume gain = blood reinfused (recuperation) + RBC volume transfused; PBV = k1× h3 + k2 × w + k3; h, height (m); w, weight (kg); for male, k1 = 0.3669, k2 = 0.03219, and k3 = 0.6041; for female k1 = 0.3561, k2 = 0.03308, and k3 = 0.1833].

We also recorded the number of blood transfusions administered, together with the type of transfusion (autotransfusion, allogeneic blood transfusion).

Haemoglobin, haematocrit

The first blood sample was collected from each patient on the day of admittance to the ward in order to determine the preoperative haemoglobin level. The second sample was collected 4 hours after the surgery. The blood picture was also checked on post-operative day 1 and, in certain patients, also on post-operative day 2. Since we had available the initial preoperative levels, we were able to determine haemoglobin decrease (difference between the preoperative level and postoperative level) induced by the surgical procedure. The blood picture was routinely examined on a Sysmex XN 3000 analyser (Sysmex, Kobe, Japan).

Incidence of haematomas, secretion from the wound after 4th post-operative day

We evaluated the frequency of early postoperative complications (occurrence of haematomas, wound secretion 4 days after the surgery). Upon discharge from the ward, we recorded the incidence, size and location of the haematoma. Secretion from the wound was recorded if persisting after post-operative day 4.

Statistics

The distribution of the quantitative data was subjected to the Shapiro-Wilk normality test. Data with a normal distribution are presented as means and standard deviations. ANOVA was used to test differences between the groups for normally distributed data. Data that were not distributed normally are shown as medians and minimum and maximum values and analysed using the non-parametric Kruskal-Wallis test with Dunn's post-hoc correction. Qualitative data are described as absolute and relative frequencies and were analysed by the exact Fisher test. The IBM SPSS Statistics, version 23 (Armonk, NY; IBM Corp.) was used for the analysis. The statistical level of significance was 0.05 in all cases.

RESULTS

Primary objectives of the trial

Blood loss after the surgery

There was a significant difference in total postoperative blood loss in the following order: IV2, IV1 <COMB <TOP (P<0.0001). On average, the lowest drainage discharge was achieved in intravenous regimens (IV2 = 350 mL and IV1 = 375 mL) and combined administration

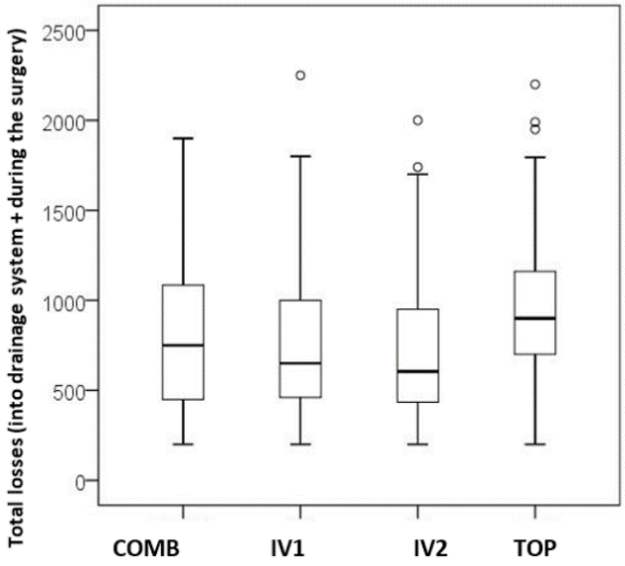

Fig. 2. Graphical representation of the range of blood loss during surgery and postoperative period into drainage systems in individual groups.
TOP, topical administration of TXA; COMB, combination of topical and intravenous administration of TXA; IV1, single intravenous administration; IV2, two intravenous doses of TXA.

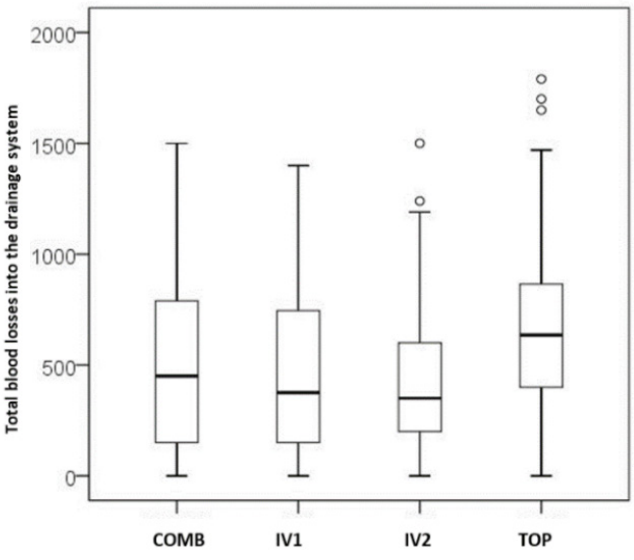

Fig. 3. An illustration of the range of blood loss to drainage systems in each group.
TOP, topical administration of TXA; COMB, combination of topical and intravenous administration of TXA; IV1, single intravenous administration; IV2, two intravenous doses of TXA.

Table 4. Comparison of haemoglobin level, its decrease.

HAEMOGLOBIN	COMB	IV1	IV2	TOP	*P*
Preoperative (average, g/L)	130	131	131	134	0.283
Post-operative 3 h (average, g/L)	123	121	122	124	0.266
Post-operative 6 h (average, g/L)	123	120	119	125	0.256
Post-operative 12 h (average, g/L)	118	115	115	118	0.657
Post-operative day 1. (average, g/L)	113	113	113	112	0.996
Post-operative day 2.	104	104	107	104	0.387
Difference pre-operative – day 1. (average, g/L)	17	18	18	21	0.011
Difference pre-operative – 6 h postop. (average, g/L)	11	10	10	11	0.932
Difference post-operative 3 h – 6 h postop. (average, g/L)	5	1	4	3	0.054
Difference post-operative 6 h – 12 h postop. (average, g/L)	5	5	5	7	0.629
Difference post-operative 3 h – 12 h postop. (average, g/L)	10	5	9	11	0.045

TOP, topical administration of TXA; COMB, combination of topical and intravenous administration of TXA; IV1, single intravenous administration; IV2, two intravenous doses of TXA; *P,* significance.

Table 5. Comparison of the use of allogeneic blood transfusions.

USE OF BLOOD TRANSFUSIONS	COMB	IV1	IV2	TOP	*P*
Allogeneic blood transfusions	15	20	9	23	0.044
Total allogeneic + autologous blood transfusions	24	35	23	30	0.198

Allogeneic blood transfusions, substitution by red cell mass from a donor; autologous, substitution by the patient's own blood transfusion collected during pre-operative preparation. TOP, topical administration of TXA; COMB, combination of topical and intravenous administration of TXA; IV1, single intravenous administration; IV2, two intravenous doses of TXA; *P,* significance.

(450 mL) compared to topical administration (635 mL). A more detailed overview of perioperative loss is given in Table 2. Intravenous and combined administration lead to the significantly lowest total blood loss, including hidden loss, compared to isolated topical administration ($P<0.0001$). Blood loss during surgery did not differ between cohorts ($P=0.268$). A detailed overview of the results is given in Tables 2 and 3. A graphical representation of blood loss range is given in Fig. 2 and 3.

Hidden blood loss

Topical administration lead to the numerically highest hidden blood loss, i.e. loss to dead space, but a significant difference was found between TOP and IV2 ($P=0.010$).

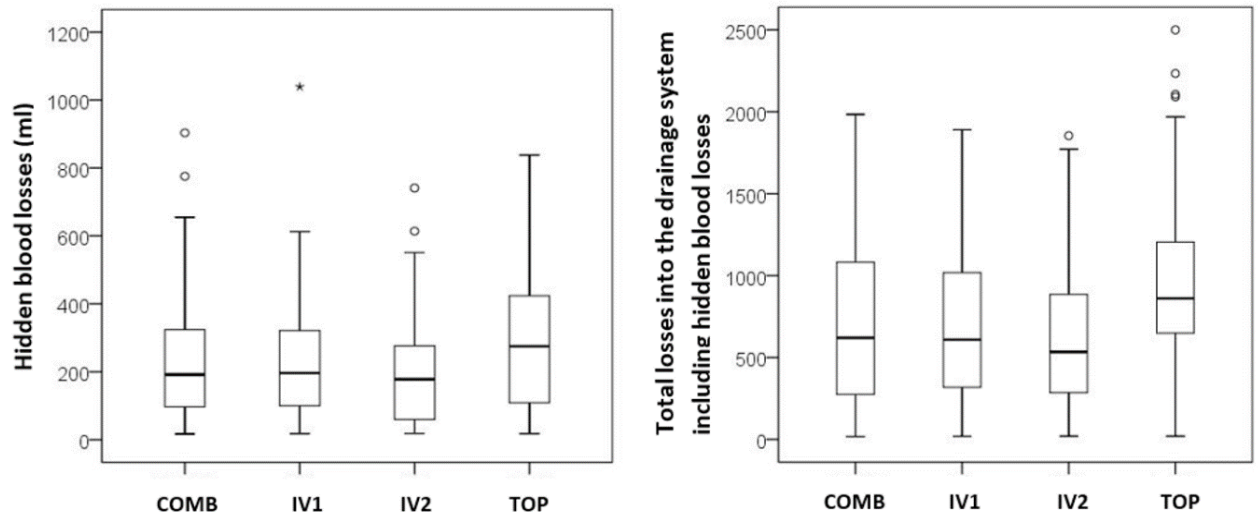

Fig. 4. Range of hidden blood loss during surgery (a) and in addition to postoperative blood loss to the drainage system (b) for each group.
TOP, topical administration of TXA; COMB, combination of topical and intravenous administration of TXA; IV1, single intravenous administration; IV2, two intravenous doses of TXA.

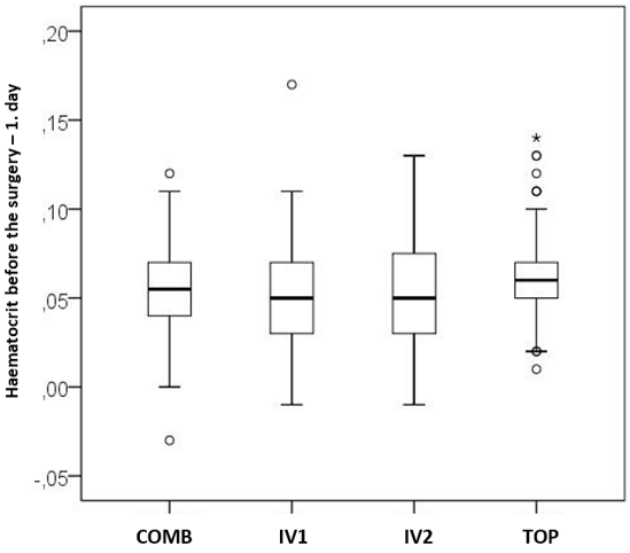

Fig. 5. Graphical representation of the difference between pre-operative haematocrit and post-operative day 1.
TOP, topical administration of TXA; COMB, combination of topical and intravenous administration of TXA; IV1, single intravenous administration; IV2, two intravenous doses of TXA.

A comparison of the individual regimens in terms of the amount of hidden blood loss is shown in Fig. 4.

Decrease in haemoglobin levels

The mean postoperative haemoglobin level did not differ between groups. The distribution of differences in haemoglobin decrease from the preoperative value is shown in Table 4. Dunn's post hoc tests revealed differences in haemoglobin decrease only in the comparison of topical and combined TXA (P=0.028) to topical and IV2 regimens (P=0.033).

Haematocrit

A significantly greater difference was found between pre-operative haematocrit and haematocrit on the post-operative day 1 in the topical TXA regimen compared to a single intravenous administration (P=0.010) and compared to the combined administration (P=0.048, Fig. 5). Further, there was a significantly greater difference between haematocrit measured 3 and 6 h after the surgery when the topical administration regimen is compared to the IV1 regimen (P=0.033). There were no differences in other haematocrit values.

Consumption of allogeneic blood transfusions (EBR)

The lowest use of blood transfusions was found after double intravenous administration of TXA (9/100). Conversely, the highest EBR use was found after topical administration (23/100). Details are given in Table 5.

Post-operative complications (haematoma, wound secretion, early surgical revision)

There were no differences in wound secretion and early postoperative revisions between groups. The lowest incidence of haematomas was found in IV2, but the difference was not statistically significant (P=0.291) compared to the other groups. There was a very low incidence of wound secretion cases (2–3%) in all groups. There was also no difference in postoperative knee flexion measured at discharge (P=0.332). Neither regimen showed a significantly higher frequency of early repeated surgeries (P=0.905). A more detailed overview is given in Table 6.

Combined administration vs. other regimens

We demonstrated that combined administration of TXA leads to significantly lower blood loss to the drainage (P=0.004) and lower total blood loss including the drainage (P=0.015) than topical administration of TXA. However, there was no significant difference compared to the intravenous regimens. We also found that combined administration of TXA leads to a significantly smaller haemoglobin decrease on day 1 compared to TOP (P=0.028). No significant difference was found in comparison with the intravenous regimens.

Table 6. Comparison of hospitalization complications – haematoma, secretion, swelling, revision.

	COMB	IV1	IV2	TOP	*P*
Haematoma occurrence	24	22	16	27	0.291
Haematoma based on the size					
up to 10x10 cm	6	7	4	12	0.265
over 10x10 cm	18	13	12	15	
almost the entire limb	0	2	0	0	
Wound secretion	3	2	2	3	1.000
Limb oedema	23	22	23	24	0.990
Average duration of hospitalisation	7.9	8.0	7.9	7.9	0.452
Knee flexion at the discharge (median)	80 (40–100)	80 (50–100)	80 (60–100)	80 (40–100)	0.332
Surgical revision	0	1	1	2	0.905

TOP, topical administration of TXA; COMB, combination of topical and intravenous administration of TXA; IV1, single intravenous administration; IV2, two intravenous doses of TXA; *P,* significance.

Sex differences

Total blood loss was 200 mL higher (on average) in men than women. The greatest difference was demonstrated with topical administration (500 mL vs. 800 mL). In women, there was a significant difference in total blood loss, including hidden loss, between different TXA regimens (*P*=0.0001), while the difference was not significant in men. In men, there were significant differences in hidden blood loss (*P*=0.019) and in the reduction of hidden loss in favour of dual intravenous administration (*P*=0.020). In the context of the overall results, the lowest perioperative blood loss in both intravenous and combined administration was demonstrated in both sexes compared to topical administration alone (Table 7).

DISCUSSION

This prospective trial presents the comparison of the effects of four most common TXA regimens on blood loss reduction and use of blood transfusions in 400 patients following primary TKA. We found that the volume of blood loss increased in order: IV2, IV1 <COMB <TOP. Blood loss was higher in men by 200 mL on average than in women, with the greatest difference in the topical TXA regimen. The pattern seen in the whole cohort was maintained in both sexes, i.e., intravenous regimens lead to lower overall blood loss compared to combined and topical TXA. The differences in haemoglobin decrease depending on the route of TXA administration were not as clear as in blood loss. The lowest use of blood transfusions was seen with double administration of TXA.

According to recent meta-analyses of RCTs, intravenous administration is preferred for primary TKA due to its rapid onset of action and longer stability of therapeutic TXA concentration in the bleeding site[2,11]. Compared to topical administration, the effect of intravenous administration in the bleeding site is up to 5 h longer[2]. However, this is associated with higher systemic dose, which, in some patients, may induce VTE or other thrombotic complications. In our trial, we tested two forms of intravenous administration. In the first group, we administered a single intravenous dose of TXA (15 mg TXA/kg) at the induction of anaesthesia. In the second group, we administered an additional intravenous dose (15 mg TXA/kg) 6 hours after the first administration. Differences in blood loss volume between IV1 and IV2 were not significant in our trial, similarly to the differences in other endpoints. We may state, consistent with recent studies, that even the single dose regimen achieves an acceptable clinical benefit for patients undergoing primary TKA (ref.[14]). On the other hand, administration of 2x15 mg TXA/kg did not increase the risk of serious perioperative complications according to our and other studies[4]. The effect was slightly better than the combined administration especially in the case of double administration, but this difference was not statistically significant.

Topical administration of TXA was the least effective approach for almost all endpoints (blood loss, haemoglobin decrease) in our trial. TXA is topically administered most often via irrigation of the surgical wound (intra-articular application) or less frequently via TXA infiltration directly into surrounding soft tissues, the so-called periarticular application[2,15]. However, recent meta-analysis has shown that the method of topical administration does not play a significant role[2]. The advantage of topical application is the maximal concentration at the application site, minimal resorption into the bloodstream. In our trial, we administered 2 g of TXA topically in a mixture with 50 mL of saline to irrigate the wound. Our previous trial also provided detailed reports on topical administration[6]. The reason for the lowest efficacy of topical administration in primary TKA is the fact that the topical effect is based on stopping the bleeding from soft tissues, not from spongy bone. Based on these findings, it seems most advantageous to combine both the routes in one procedure to stop bleeding from both soft tissues (topical administration) and bone marrow (intravenous administration). A recent meta-analysis (6 RCTs, 701 patients) showed very good results of combined administration on the reduction of total blood loss[4]. A combined administration was associated with less drainage to the drainage system and minimal haemoglobin decrease. On the other hand, the significant decrease in post-operative blood loss is not

Table 7. Comparison of perioperative blood loss by regimen and sex (data presented as median blood loss).

	Total blood loss into drains (mL)					Hidden blood loss (mL)					Maximum blood loss (mL)					Blood loss into drains including hidden loss (mL)				
	COMB	IV1	IV2	TOP	*P*	COMB	IV1	IV2	TOP	*P*	COMB	IV1	IV2	TOP	*P*	COMB	IV1	IV2	TOP	*P*
Female	375	280	300	550	<0.0001	151	172	152	146	0.658	1200	1250	1050	1250	-	525	475	406	760	0.001
Male	650	600	575	800	0.168	285	299	254	380	0.019	1500	1400	1500	1790	-	939	916	759	1141	0.081

TOP, topical administration of TXA; COMB, combination of topical and intravenous administration of TXA; IV1, single intravenous administration; IV2, two intravenous doses of TXA; *P*, significance.

reflected in lower use of blood transfusions compared to other TXA routes. Importantly, TXA dose (>1.5 g) is critical for topical administration and the number of doses (i.e., more than one administration of TXA) plays a role in intravenous administration. Lin et al. published a systematic review and meta-analysis (15 studies, 1,495 patients) comparing the combined, intravenous and topical administration of TXA (ref.[16]). They report that combined TXA administration is mildly more effective in reducing blood loss compared to simple intravenous or topical administration of TXA. Blood loss was reduced in combined administration by almost 458 mL. It was significantly more effective than intravenous administration in blood loss comparison (P=0.034). According to Nielsen et al., the combined administration resulted in nearly 37% reduction in blood loss compared to simple intravenous administration within 24 hours after surgery and two days after the surgery[17]. Therefore, there is a question why the superiority of combined administration of TXA was not demonstrated in our and several other studies. One explanation may be the difficulty of standardizing the process of topical TXA administration. The effect of topical administration substantially depends on maintaining the TXA contact with the bleeding bed (tissue contact time) for at least five minutes[18]. It can also be assumed that the highest effect of topical TXA irrigation will be seen in surgeries when a tourniquet has been used since the beginning of the procedure. Bleeding starts once the tourniquet is released and the highest activation of fibrinolysis starts. At this point, the fastest haemostatic effect is achieved by the immediate topical antifibrinolytic effect of TXA administered directly on the bleeding bed. In our sample, the tourniquet was filled only during cementing of the implant (usually for 10–15 min). The formation of clot in topical administration may cause clogging of the drain and thereby mask the amount of visible blood loss to the drainage system. The difference should be reflected mainly in the decrease in haemoglobin or in the amount of hidden blood loss. Significant difference in hidden blood loss was shown only 12 h after the surgery in the IV2 regimen with an additional dose 6 h after the first administration.

Conversely, the difference in endpoints between topical and combined administration is clearly caused by a systemic dose of TXA, which is effective on its own. Jain et al. report a significant reduction of blood loss in combined use when compared to simple topical administration (590.69 ± 191.1 vs. 385.68 ± 182.5, P<0.001) (ref.[19]). The greater effect of combined TXA administration may be explained by the initial intravenous dose administered at the start of anaesthesia, thus covering the entire surgical period from the initial incision (especially for surgeries without a tourniquet). At the same time, the combined administration of TXA has a dual effect, as opposed to simple topical irrigation by affecting the systemic activation of fibrinolysis thanks to the intravenous dose[18].

Sex could play an important role in the extent of blood loss. The number of women in TKA indications has long been higher than in men. The number of women in our cohort was also higher and their blood loss volume was on average 200 mL lower compared to men. However, the basic efficacy structure, i.e. from intravenous through combined to topical administration was seen in both sexes. A larger bleeding area can be assumed in men due to the size of the joint, affecting blood loss. Hormonal changes and/or greater prevalence of obesity may play an important role in women. Rajesparan et al. showed a higher effect of intravenous dose of 1 g TXA in total hip arthroplasty in women (P=0.05) than in men[20]. There are no studies on total knee arthroplasty that address the different effect of TXA on sex basis.

We found no significant postoperative complications associated with TXA administration in this trial, similar to the previous trial on safety of TXA administration[10]. There were no thromboembolic complications in the study groups. Other meta-analyses have not shown any risk association with TXA administration. Thus, it can be stated that all tested routes of TXA administration are safe in selected group of patients.

Study limitations

The present study has certain limitations. We are aware of the fact that the data are crude estimates, particularly as concerns perioperative blood loss. In fact, there are no validated protocols enabling the volume of blood in drapes, dressings, wastes, etc., to be precisely measured. A second drawback is the difference between the physicians' approaches to the make-up for post-operative blood loss. Some physicians indicate administration of allogeneic blood at a haemoglobin level as high as 95–99 g/L whereas others are reluctant even when the level approaches 90 g/L and less if the circumstances are otherwise favourable (young patient, no signs of the anaemic syndrome, etc.). Therefore, in theory the blood transfusion savings could be even higher.

CONCLUSION

The intravenous and combined regimens of TXA administration in primary TKA lead to a more significant reduction in blood loss than topical administration. The effect on blood loss into the drainage system can be expressed in the following order: IV2, IV1 <COMB <TOP. Intravenous and combined administration leads to the lowest total blood loss, including hidden loss, compared to topical administration (P<0.0001). In contrast, the decrease in haemoglobin on the first postoperative day did not show the most advantageous intervention. The number of blood transfusions was highest in the group with topical TXA administration. In primary TKA, it is preferable to administer TXA intravenously in two doses or in a combined regimen. Simple topical administration is not as effective as other regimens and is indicated in case of contraindications to systemic administration. Follow-up studies should show whether it is possible to balance the effect of TXA in individual subgroups of patients according to the principles of precision medicine.

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