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Optimal Route for Tranexamic Acid in Diabetics and Obese Patients Undergoing Primary Total Knee Arthroplasty – a Data from Randomized Study

Optimální způsob podání tranexamové kyseliny u diabetiků a obézních pacientů – data z randomizované klinické studie

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ABSTRACT

PURPOSE OF THE STUDY
To determine the optimal strategy for tranexamic acid (TXA) administration in diabetic patients, smokers and obese patients (BMI > 30 kg/m^2) undergoing primary total knee arthroplasty (TKA).

MATERIAL AND METHODS
The total of 400 consecutive patients indicated for primary TKA were randomised into 4 basic groups with different TXA administration regimens. Group 1 (IV1) had a single intravenous dose (15 mg TXA/kg) applied prior to skin incision. Group 2 (IV2) got two intravenous doses (15 mg TXA/kg): one prior to skin incision and one subsequently 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. Group 4 (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. Follow-up period was one year postoperatively.

RESULTS
In the group of diabetic patients (n = 87; 21.7%) the lowest TBL was observed in the order: IV1, IV2 > COMB > TOP. In the obese patients (BMI > 30 kg/m^2; n = 242; 60.5%), TBL was significantly lower in the intravenous regimens (IV1: p = 0.002; IV2: p = 0.005, respectively) than in the TOP regimen. In the smoking patients (n = 30; 7.5%), TBLs were significantly lower in the order: IV1 > IV2 > COMB > TOP.

DISCUSSION
Individualised approach to prevention and therapy is a recent trend, also because comorbidities significantly affect the result of the intervention. In the case of diabetes, obesity and smoking, there is a proven link to early post-operative infections, mainly due to poorer innate immunity. It is conceivable, though, that the occurrence of infectious complications is also contributed to by larger hematomas or hemarthroses which are largely preventable.

CONCLUSIONS
In the diabetic and obese patients (BMI > 30 kg/m^2), the combined topical/intravenous TXA application and two intravenous doses of TXA interventions were shown to be the most effective. However, no evidence of superiority of any of the TXA administration routes was obtained in the smokers. None of the TXA protocols was associated with a higher incidence of complications or early reoperation following TKA surgery.

Key words: tranexamic acid, topical application, intravenous application, combined administration, diabetes, obesity, BMI, smoking, blood loss, hidden blood loss, total knee arthroplasty, complications.

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INTRODUCTION

The haemostatic effect of tranexamic acid (TXA) is generally recognised (6, 22). The clinical effect of TXA in orthopaedics has been best demonstrated on hip and knee replacements (6, 18). However, no complete consensus exists between the studies as regards to the implementation of protocols (6, 12). No recommendation applicable to a specific patient coming to the hospital for surgery exists as of yet (21). A combination of intravenous and topical TXA administration offers optimum benefit/risk balance (9, 11, 20). Total knee arthroplasty (TKA) seems to be the ideal intervention for a combined procedure due to the large bleeding area.

Nowadays, contraindications to TKA have actually been reduced to active infection in the affected knee, ASA IV status, and a patient unable to cooperate in the postoperative regimen. This implies that individuals indicated for the surgery also very often include patients with comorbidities and obese patients. The risks of pe-

rioperative complications in such patients are well-known and good clinical practice consistently strives to eliminate them. One of the basic steps to lower the likelihood of a non-healing wound and of early infection is to reduce the haematoma size (and hence, blood loss into the tissues). This is largely under the surgeon's control.

Also, the concept of "precise" medicine is increasingly gaining acceptance in orthopaedics: this means that a precisely described procedure is applied to a specific patient with the aim to maximise the effect of the intervention while minimising the risk of harm. Many of the patients coming to the hospital for TKA are diabetic patients, overweight patients and smokers. Last year, we organised an extensive randomised clinical study assessing the clinical benefits of four TXA administration regimens in patients undergoing primary TKA. In the present study, we publish secondary results regarding the efficiency of different TXA administration regimens in diabetic patients, smokers and obese patients, with the aim to find which of the regimens is most favourable in regards to blood loss (into drains, hidden loss) and the given blood transfusion volumes. The results of this study may help improve the quality of the perioperative care in the above patient groups.

MATERIAL AND METHODS

Patient cohort

A total of 400 consecutive patients indicated for primary TKA were enrolled in this prospective study. The subjects were administered TXA based on a predefined protocol during the perioperative period. The patients were divided into 4 groups based on the TXA administration routes. Prior to surgery, the minimum number of subjects in each group was postulated to be 100 in order to ensure statistical credibility. The patients were assigned to the groups randomly. The TXA administration patterns were determined by each patient's position in the sequence as follows: 1 – TOP, 2 – IV1, 3 – IV2, 4 – COMB. If the TXA sequence was not completed on the same day, the randomisation procedure was resumed the next day. The surgeon had no opportunity to subsequently change the schedule in any way. The subject inclusion criteria were as follows: patient coming for TKA, with normal preoperative blood panel (haemoglobin, thrombocytes etc.) and blood coagulation (INR, Quick, aPTT) parameters. Exclusion criteria included patients with a history of any blood coagulation disorder-related disease or VTE; who had a serious renal disorder; or suffered from preoperative cramps. The basic characteristics of the 4 groups were identical (Table 1). Obesity was defined as BMI ≥30. A detailed overview of the proportions of diabetic patients, overweight patients and smokers of the basic study is presented in Table 2.

The clinical register of joint replacements is approved by the hospital management, and its administration is regulated by the amended ethical and legal protocol (registration number 87-67). The local Ethical Committee approved this study in accordance with the Helsinki Declaration; all the enrolled patients agreed with the use

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 TXA application, COMB – combined topical/intravenous TXA application, IV1 – single intravenous application, IV2 – two intravenous doses of TXA administration, SD – standard deviation, m – male, f – female, IKDC – International Knee Documentation Committee, K-L – Kellgren-Lawrence classification, p – significance, TXA – tranexamic acid, BMI – body mass index, * Based on the infection risk (A = minimal risk; B = medium risk; C = highest risk; modified McPherson et al. [13].

Table 2. Proportions of diabetic patients, BMI and smokers in the TXA cohorts

	COMB	IV1	IV2	TOP	p
Diabetes	32	24	27	28	0.720
Diabetes on OHA	23	14	16	19	0.838
Diabetes on insulin	2	6	3	4	
Diabetes on a diet	7	4	8	5	
BMI (kg/m^2)					0.119
Overweight BMI 25–30	29	28	35	39	
Class 1 obesity BMI 30–35	33	43	32	39	
Class 2 obesity BMI 35–40	23	16	14	10	
Class 3 obesity BMI > 40	9	10	7	6	
Smoking					
Non-smokers	91	91	93	95	0.663
Smokers	9	9	7	5	

TOP – topical TXA application, COMB – combined topical/intravenous TXA application, IV1 – single intravenous application, IV2 – two intravenous doses of TXA application, OHA – oral hypoglycemic agents, p – significance, TXA – tranexamic acid, BMI – body mass index.

of anonymized data for the research purpose of this study. Prior to enrolment into the study, the patients signed a specific informed consent.

Data collection

Data was collected prospectively based on a predefined protocol. Medical information was recorded by the physician within the primary visit. This also included basic medical history, along with the primary diagnosis and clinical examination results. The blood loss data, laboratory results and information concerning any complications during the patient's stay in the hospital and within 1 year of the surgery were input into the database by a specifically trained healthcare professional (i.e. follow-up period was one year postoperatively).

Preoperative preparations

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

Surgical procedure and the implant

The surgical procedure was performed in general or block anaesthesia. The procedure used invariably skin incision and the medial parapatellar approach. Haemostasis was applied continually by electrocoagulation during the procedure. The tourniquet was only activated for cementing (typically for 10 to 15 minutes). All surgeries were done by experienced surgeons. We used only cemented implants preserving the posterior cruciate ligament or replacing its function. In all cases, only one drain was applied intraarticular and extracted on the 1st or at the latest the 2nd postoperative day according to the blood loss.

TXA administration

Each group had its precisely defined TXA administration/dosage protocol. Group 1 (IV1) included patients to whom TXA was administered by the anaesthesiologist as a single intravenous dose (15 mg TXA/kg) during induction of anaesthesia. Group 2 (IV2) included patients to whom TXA was administered in two intravenous doses (15 mg TXA/kg) on induction of anaesthesia and subsequently 6 hours after the first administration. Group 3 (TOP) included patients to whom TXA was administered only topically by lavage with a diluted solution of 2 g TXA in 50 ml of saline. The diluted solution was applied into a joint (allowed to act for 10 minutes) before closing the joint capsule. Group 4 (COMB) included patients to whom TXA was administered by a combined scheme: the first dose of 15 mg TXA/kg, intravenously on induction of anaesthesia; the second dose, topically by lavage with a diluted solution 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 hour from the surgery. The flow chart of the study randomization and TXA protocols is shown in Fig. 1.

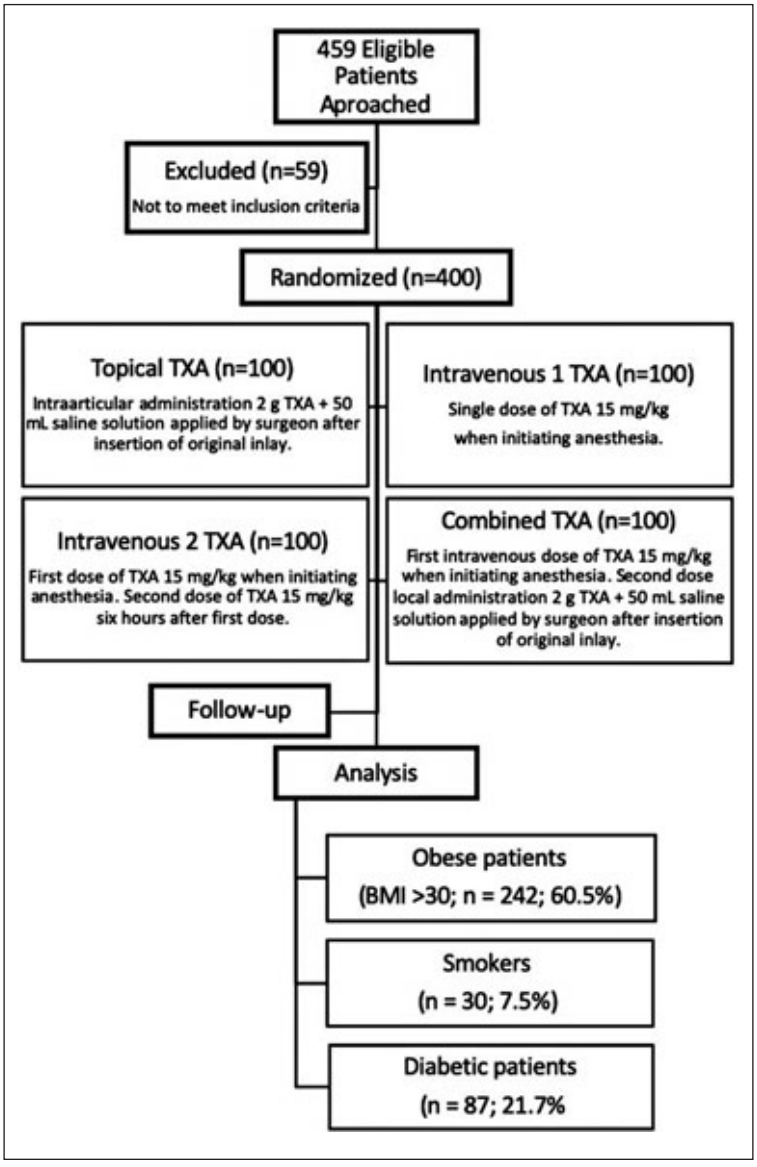

Fig. 1. Flow diagram showing study randomization and TXA protocols; TXA – tranexamic acid, BMI – body mass index.

Primary outcomes

Blood loss including hidden blood loss

We recorded the blood loss during the surgical procedure (waste + drape estimate) and postoperatively into drains for each patient. We also recorded the number of blood transfusions administered, together with the type of transfusion (autotransfusion, allogeneic blood transfusion). Hidden blood loss (Hbloss) was calculated by using a formula

(Hb_{loss} = True calculated Red Blood Cell Count (RBC) – Total measured RBC volume loss – Total measured RBC volume gain)

that includes perioperative and postoperative loss, change of haemoglobin and haematocrit before and after surgery, in relation to patient's gender and body weight (8).

Haemoglobin

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. Blood panel was also checked on 1st post-operative day and, in

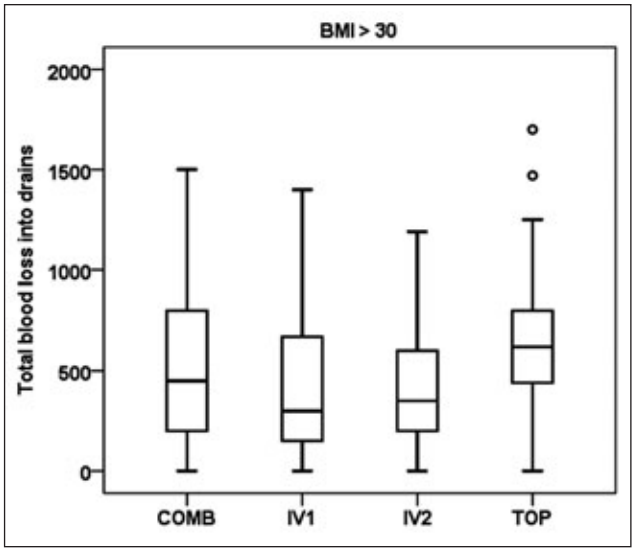

Fig. 2. Blood loss comparison between the regimens in obese patients;
TOP – topical TXA application, COMB – combined topical/intravenous TXA application, IV1 – single intravenous application, IV2 – two intravenous doses of TXA application, BMI – body mass index.

Table 3. Summary overview of perioperative blood losses in the BMI classes, in smokers and in diabetic patients

	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*
BMI 25–30 *kg/m²*	430	425	400	740	***0.021***	166	185	172	282	*0.136*	970	1250	1500	1650	–	991	913	920	1256	**0.026**
BMI 30–35 *kg/m²*	350	400	310	630	**0.003**	197	221	195	207	0.879	1500	1400	1000	1700	–	825	955	747	1123	**0.036**
BMI 35–40 *kg/m²*	450	300	400	645	0.263	262	123	133	409	**0.048**	1250	800	1190	870	–	985	734	740	1240	0.193
BMI > 40 *kg/m²*	650	150	400	500	0.071	218	170	183	405	0.611	1500	1150	740	1070	–	1406	758	974	1205	0.305
Diabetic patients (insulin + OHA)	500	260	300	600	**0.013**	151	169	152	206	0.338	1500	1050	1240	1470	–	585	469	534	796	**0.012**
Smokers	710	150	300	750	**0.034**	286	168	138	391	0.146	1210	950	750	1100	–	1156	318	454	1141	**0.026**

TOP – topical TXA application, COMB – combined topical/intravenous TXA application, IV1 – single intravenous application, IV2 – two intravenous doses of TXA application, OHA – oral hypoglycemic agents, p – significance, TXA – tranexamic acid, BMI – body mass index.

certain patients, also on 2nd post-operative day. 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 post-operative day 4

We examined both the wound condition and the presence, size and location of haematoma. The condition was assessed by the attending physician. Secretion from the wound was recorded if persisting after post-operative day 4.

Statistics

Distribution of the quantitative data was examined by the Shapiro-Wilk normality test. Data exhibiting normal distribution were represented by the mean and standard deviation. Analysis of variance (ANOVA) was used to assess the differences between the patient groups. Data that did not exhibit normal distribution were characterised by the median and the minimum and maximum values. The non-parametric Kruskal-Wallis test and post-hoc Dunn's tests were used to make a comparison between the groups. Qualitative data were described via the absolute and relative frequencies and analysed by the exact Fisher test. IBM SPSS Statistics software version 23 (Armonk®, NY: IBM Corp.) was used for statistical analysis. The statistical significance level of 0.05 invariably applies.

RESULTS

Obese patients (BMI > 30 kg/m²)

For the obese patients (BMI > 30), significantly lower blood loss into drains and lower total blood loss into drains including hidden loss were observed in the group with the intravenous administration regimen than in the group with the topical administration regimen. The difference between the intravenous regimens and the combined administration regimen was not significant. A detailed comparison is presented in Tables 3–5 and in Fig. 2. The groups exhibited no differences in the frequency of secretion from the wound, incidence of post-operative haematoma or early post-operative revision.

When dividing the groups in more granularity based on the degree of obesity, Class 1 obese patients (BMI 30–35; n = 147) exhibited significantly lower blood losses into drains and lower total blood losses (into drains including hidden loss) in the intravenous and combined regimen groups than in the topical administration group (p = 0.018). The blood loss reduction decreased in the order: IV2 > COMB > IV1 > TOP. The IV2 regimen exhibited significantly the lowest blood losses in all the endpoints compared to topical administration. Combined administration attained significantly lower blood losses into drains than topical administration.

For the patients with Class 2 obesity (BMI 35–40; n = 63) the degree of reduction of blood loss into drain decreased in the order: IV1 > IV2 > COMB > TOP. No significant difference in the amounts of perioperative losses was demonstrated.

For the patients with Class 3 obesity (BMI > 40; n = 32, the lowest number among the groups), no significant difference in the amounts of perioperative losses was demonstrated. The blood loss reduction order was as follows: IV1 > IV2 > TOP > COMB. When making a detailed comparison in pairs, the significantly lowest decrease in post-operative haemoglobin was in the IV2 regimen group compared to the topical administration group (p = 0.044). A detailed comparison of the perioperative blood losses and post-operative haemoglobin decrease is presented in Tables 3–5.

Table 4. Blood loss comparison between the regimens, in pairs, for the BMI classes (post hoc test results)

	Norm BMI <25 kg/m²		**Overweight** BMI 25–30 kg/m²		**Obesity** BMI >30 kg/m²	
	Blood loss into drains	Total postoperative blood loss into drains including hidden loss	Blood loss into drains	Total postoperative blood loss into drains including hidden loss	Blood loss into drains	Total postoperative blood loss into drains including hidden loss
COMB vs. IV1	1.000	1.000	1.000	1.000	1.000	1.000
COMB vs. IV2	0.365	0.250	1.000	1.000	1.000	1.000
COMB vs. TOP	1.000	1.000	**0.036**	**0.040**	0.094	0.141
IV1 vs. IV2	0.090	0.092	1.000	1.000	1.000	1.000
IV1 vs. TOP	1.000	1.000	0.204	0.374	**0.002**	**0.006**
IV2 vs. TOP	0.301	0.183	0.097	0.097	**0.005**	**0.005**

TOP – topical TXA application, COMB – combined topical/intravenous TXA application, IV1 – single intravenous application, IV2 – two intravenous doses of TXA application, TXA – tranexamic acid, BMI – body mass index.

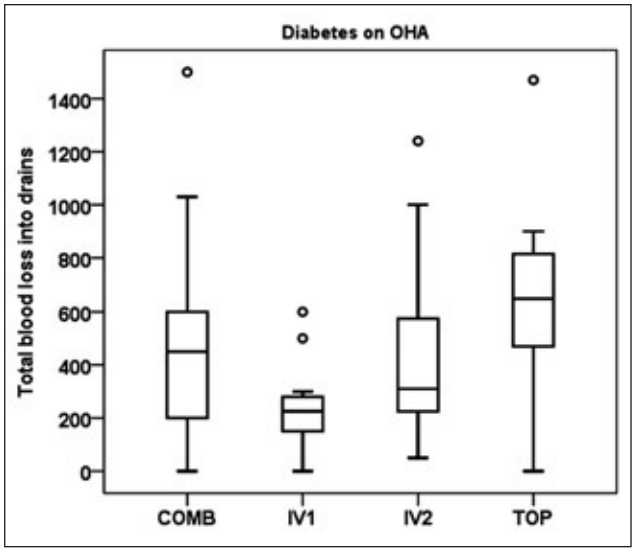

Fig. 3. Ranges of blood loss into drains for the 4 groups of diabetic patients;
TOP – topical TXA application, COMB – combined topical/intravenous TXA application, IV1 – single intravenous application, IV2 – two intravenous doses of TXA application, OHA – oral hypoglycemic agents, TXA – tranexamic acid.

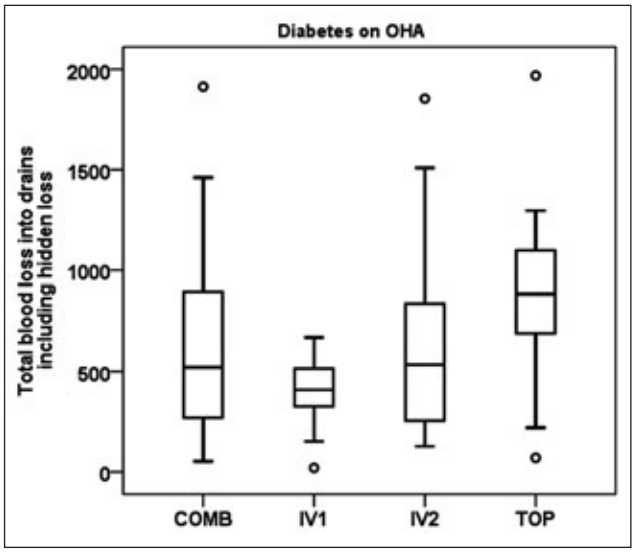

Fig. 4. Ranges of total blood loss into drains including hidden loss for the 4 groups of diabetic patients;
TOP – topical TXA application, COMB – combined topical/intravenous TXA application, IV1 – single intravenous application, IV2 – two intravenous doses of TXA application, OHA – oral hypoglycemic agents, TXA – tranexamic acid.

Diabetic patients

The group of diabetic patients exhibited significantly lower blood loss into drains (p = 0.013) and lower total blood loss into drains including hidden loss (p = 0.012) in the intravenous regimens than in the topical administration regimen. The degree of reduction of blood loss into drains including hidden loss decreased in the order: IV1, IV2 > COMB > TOP. The above results apply to diabetic patients on oral hypoglycemic agents (OHA). The numbers of diabetic patients on insulin in the groups were low and statistically non-evaluable. A detailed comparison of the perioperative blood losses and post-operative haemoglobin decrease is presented in Tables 3, 5 and 6 and in Figs 3 and 4.

Table 5. Post-operative haemoglobin level decrease with time granulated by the BMI classes, diabetic patients and smokers

	Haemoglobin diff. preoper. – postoper. day 1					Haemoglobin diff. preoper. – 6 hours postoper.					Haemoglobin diff. postoper 6 hours – 12 hours postoper.				
	COMB	IV1	IV2	TOP	*p*	COMB	IV1	IV2	TOP	*p*	COMB	IV1	IV2	TOP	*p*
BMI 25–30 *kg/m²*	17.0	17.0	18.0	22.0	**0.043**	13.0	8.0	6.0	12.5	0.820	6.0	7.0	7.5	3.0	0.929
BMI 30–35 *kg/m²*	17.0	19.0	15.0	21.0	0.084	10.0	14.0	11.0	12.0	0.632	6.5	4.5	4.0	7.0	0.336
BMI 35–40 *kg/m²*	16.5	15.5	19.5	18.5	0.113	9.5	10.5	11.5	16.5	0.473	6.0	2.5	3.0	8.0	0.729
BMI > 40 *kg/m²*	19.0	13.5	23.0	13.0	**0.037**	10.0	7.5	25.5	-3.0	0.284	6.0	7.0	7.0	15.5	0.482
Diabetic patients (insulin + OHA)	15.0	16.0	16.0	18.0	0.357	9.0	7.0	11.5	7.0	0.871	6.0	6.0	4.0	5.0	0.909
Smokers	16.0	16.0	14.0	23.0	0.110	3.5	13.0	8.5	7.5	0.700	10.5	5.0	10.5	0.0	0.124

TOP – topical TXA application, COMB – combined topical/intravenous TXA application, IV1 – single intravenous application, IV2 – two intravenous doses of TXA application, TXA – tranexamic acid, p – significance, BMI – body mass index, OHA – oral hypoglycemic agents.

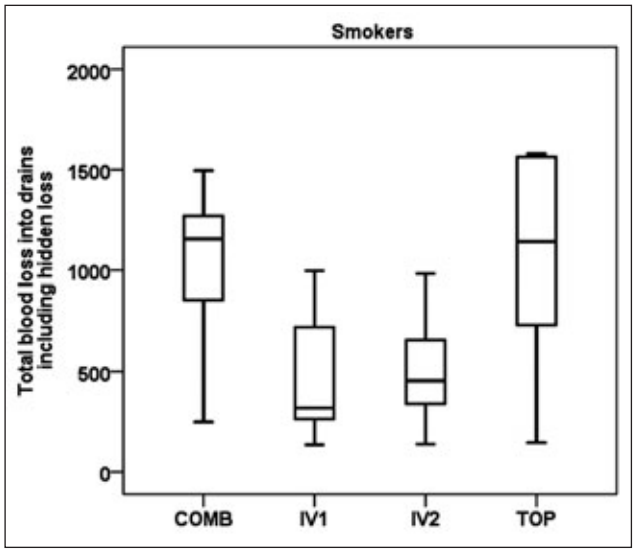

Fig. 5. Ranges of total blood loss including hidden loss for the 4 groups of smokers;
TOP – topical TXA application, COMB – combined topical/intravenous TXA application, IV1 – single intravenous application, IV2 – two intravenous doses of TXA application, TXA – tranexamic acid.

Smokers

The degree of reduction of total blood loss including hidden loss in the smokers decreased in the order: IV1 > IV2 > COMB > TOP. No significant difference was found by a detailed analysis using post-hoc tests (Table 7).No differences were found between the groups as regards the parameters: secretion from the wound ($p = 1.000$) or incidence of post-operative haematoma ($p = 0.948$). None of the patients had to undergo early revision. A detailed picture can be derived from Tables 3, 5 and 7 and Fig. 5.

DISCUSSION

This article presents the results of the follow-up study evaluating the relation between blood losses and TXA administration routes in obese patients, DM patients and smokers undergoing primary TKA. The lowest blood losses in obese patients were found in the intravenous administration routes and combined administration route, when compared to the topical administration route (with the highest blood losses). The patterns encountered with the diabetic patients and smokers were similar. The lowest blood losses into drains were seen in the intravenous

Table 6. Comparison of blood loss between the different TXA administration regimens for diabetic patients (results of Dunn's post hoc tests)

Diabetic patients on OHA	Total blood loss into drains	Total blood loss (during the surgery + into drains)	Total post-operative blood loss into drains including hidden blood loss	Total blood loss including hidden blood loss
COMB VS. IV1	0.184	0.140	0.949	0.618
COMB VS. IV2	1	1	1	1
COMB VS. TOP	0.441	1	0.146	0.460
IV1 VS. IV2	0.456	1	1	1
IV1 VS. TOP	**0.002**	**0.006**	**0.005**	**0.011**
IV2 VS. TOP	0.360	0.277	0.154	0.187

TOP – topical TXA application, COMB – combined topical/intravenous TXA application, IV1 – single intravenous application, IV2 – two intravenous doses of TXA application, TXA – tranexamic acid, OHA – oral hypoglycemic agents.

Table 7. Comparison of blood loss including hidden loss in smokers between the TXA administration routes (Dunn's post hoc tests)

Smokers	Total blood loss into drains	Total blood loss (during surgery + into drains)	Total post-operative blood loss into drains including hidden blood loss	Total blood loss including hidden blood loss
COMB VS. IV1	0.073	0.092	0.083	0.111
COMB VS. IV2	0.296	0.190	0.183	0.131
COMB VS. TOP	1	1	1	1
IV1 VS. IV2	1	1	1	1
IV1 VS. TOP	0.299	0.434	0.285	0.351
IV2 VS. TOP	0.740	0.649	0.462	0.361

TOP – topical TXA application, COMB – combined topical/intravenous TXA application, IV1 – single intravenous application, IV2 – two intravenous doses of TXA application, TXA – tranexamic acid.

TXA administration regimens whereas the least favourable data in this respect were found for the topical administration route (efficiency formula: IV2, IV1 < COMB < TOP). In accordance with this trend has the data of haemoglobin decrease, compared to the preoperative level, and of the volume of blood transfusions. We found no difference in the incidence or size of haematoma or in secretion from the wound.

Diabetic patients undoubtedly constitute a risk group with respect to post-operative complications after TKA (higher incidence of wound healing disorders, risk of early infection, etc.). The proportion of diabetic patients among patients indicated for joint replacement has been increasing constantly. According to U.S. national statistics, 9.4% U.S. population are diabetic patients (17). The IAF (Institute for Alternative Futures) model expects a 54% increase in the numbers of people with Type 1 and Type 2 diabetes in the U.S. during the 2015–2030 period (17). Over 900 thousand diabetic patients were registered in the Czech Republic in 2016 (source: Institute of Health Information and Statistics – ÚZIS). The proportion of diabetic patients included in the present study was 21.7% (87/400), in other words, one of every five patients was treated for diabetes. Similar proportions of diabetic patients were found in a number of other studies. Tew et al. examined the quality of life for patients after TKA, of whom nearly one-fifth (319/1553) were diabetic patients (19). Aguilera et al., who compared topical and intravenous administration of TXA in patients undergoing knee replacement, reported a proportion of 19.3% (29/150) diabetic patients (2). Diabetic patients are frequently subject to the development of macrovascular or microvascular changes which can significantly affect perioperative haemostasis (3). The risk of lower limb ischaemia is also twofold to fourfold higher in diabetic patients, the incidence increasing 15fold to 20fold in Type 2 diabetic patients (1). Therefore, the problem of efficacy of TXA in such patients is highly relevant, as is the question as to which of the TXA administration routes is more efficient. The present study gave evidence that in diabetic patients the intravenous administration regimens were associated with significantly lower blood loss into drains ($p = 0.013$) and lower total blood loss into drains including hidden loss ($p = 0.012$) compared to the topical administration regime. The lowest data of total blood loss into drains including hidden loss were observed in the order: IV1, IV2 > COMB > TOP. We found no study in existing literature dealing in detail with the issue of TXA administration in diabetic patients. Some papers consider diabetes on insulin to be contraindication to the administration of TXA, presumably because of potential nephropathic changes and an increased TEN risk in diabetic patients (16).

The proportion of obese patients indicated for TKA has been increasing sharply. While a high BMI used to be absolute contraindication in the past, nowadays it is only relative contraindication, a patient with BMI > 35–40 indicated to TKA being no exception today. This current trend of increased numbers of obese patients indicated for TKA is confirmed by other studies as well (10). Our cohort also included more obese patients, the median BMI was 31.7. A major problem in obese patients is hyposaturation of peripheral tissues (3). Oxygenation disorder in turn enhances the risk of wound healing disorder, associated with a potential risk of development of infection. Certain papers describe a rather strong relationship between TKA reoperation and appreciable obesity (5). We were able to provide evidence that intravenous TXA administration is more beneficial than topical administration in obese patients (BMI > 30). The degree of reduction of blood losses into drains decreased in the order: IV2 > COMB > IV1 > TOP. Intravenous administration was also associated with lowest hidden blood losses compared to the topical administration route. Meng et al. reported that TXA in obese patients reduced blood loss and blood transfusion requirement significantly ($p < 0.05$) compared to patients without TXA (15). They applied TXA intravenously in 2 doses at a dose of 10 mg/kg. According to Meftah et al., intravenous application significantly reduced the amount of transfused blood in obese patients ($p < 0.0001$), (14). They found by subanalysis that TXA reduced the requirement of blood transfusions even more in Class 2 and Class 3 obese patients. However, no other studies corroborating the above results are available.

Smoking is undoubtedly also a potential risk factor for a number of post-operative complications. Nicotine causes vasoconstriction, stimulates release of proteases which can accelerate tissue degradation, and suppresses immune reaction, leading to a higher risk of infection (3). In a recent study, smokers had a 1.8% incidence of wound healing complications after total hip or knee arthroplasty, compared to 1.1% in non-smokers (4). Gallo et al. reported that smokers had an up to 3.2fold chance of being reoperated (probability increased by 220%) compared to non-smokers (7). This means that smokers are handicapped by their addiction as regards the post-operative period. The proportion of smokers in our cohort was 7.5% (30/400). The degree of reduction of total blood loss including hidden loss in smokers decreased in the order: IV1 > IV2 > COMB > TOP. Perhaps, due to low number of smokers a detailed analysis gave no evidence of a significant difference in the blood loss data between the TXA administration regimens in this study. Similarly like for diabetic patients, no other study examining in detail which TXA administration route is most beneficial in smokers currently exists.

Study limitations

The present study has certain limitations. We are aware of the fact that the data are crude estimates, particularly concerning perioperative blood loss. In fact, there exists no validated protocol providing guidelines and enabling the volume of blood in drapes, dressings, wastes, etc., to be precisely measured. The next drawback is in a certain difference between the physicians' approaches to the substitution for post-operative blood losses. Some physicians indicate administration of allogeneic blood at a haemoglobin level as high as 95–99 g/l whereas other physicians are reluctant even when the level ap-

proaches 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. From the detailed aspect of DM compensation, it would be more to the point to follow the level of glycated haemoglobin (HbA1c) as a "long-time glycaemia" indicator. The low number of smokers in our cohort is another drawback we are aware of.

CONCLUSIONS

In this study we found that combined TXA and two intravenous doses of TXA interventions appeared most beneficial both in diabetic patients and in obese patients (BMI > 30). No significant differences in this respect, however, were found in smokers. None of the regimens was associated with an enhanced incidence of early postoperative complications including reoperations.

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