The Knee 24 (2017) 1206–1212

Contents lists available at ScienceDirect

The Knee

Combined intravenous, topical and oral tranexamic acid administration in total knee replacement: Evaluation of safety in patients with previous thromboembolism and effect on hemoglobin level and transfusion rate

Joris A. Jansen *, Joost R.C. Lameijer, Barbara A.M. Snoeker

Department of Orthopedics, Alrijne Hospital Leiden, Simon Smitweg 1, 2353 GA Leiderdorp, The Netherlands

ARTICLE INFO

Article history:
Received 25 November 2016
Received in revised form 2 June 2017
Accepted 5 July 2017

Keywords:
Tranexamic
Knee
Dosage
Safety
Topical
Oral administration

ABSTRACT

Background: The aims of this study were to investigate the safety of combined intravenous, oral and topical tranexamic acid (TXA) in primary total knee replacement. We assessed dose-related efficacy on hemoglobin level, transfusion, length of stay and thromboembolic complications. In addition, TXA safety in patients with previous history of thromboembolism >12 months ago was monitored specifically.

Methods: From January 2013 until January 2016, 922 patients were included who received TXA after primary total knee replacement. Patients without TXA administration or with thromboembolic events <12 months ago were excluded. TXA dosage groups were divided into ≤10 mg/kg, >10–25 mg/kg and >25–50 mg/kg.

Results: Between the three TXA groups no significant difference was found in thromboembolic complications (deep venous thrombosis (DVT) and pulmonary embolism (PE)), wound leakage and transfusion rate. For patients with DVT or PE in their history >12 months ago specifically, no more complications were noted in higher-TXA-dosage groups compared to the low-dosage group. Length of stay was shorter in the highest-TXA-dosage group compared with lower-dosage groups (median two vs three days). With high TXA dose a smaller difference between pre- and postoperative Hb was found: the >25–50 mg/kg TXA group had a 0.419 mmol/l smaller decrease in postoperative hemoglobin compared to the lowest-dosage group ($P < 0.05$).

Conclusion: Combined intravenous, oral and topical TXA is effective in knee replacement and can safely be given to patients with a thromboembolic history >12 months ago. High dosage (>25–50 mg/kg) TXA resulted in the smallest decrease in postoperative hemoglobin.

1. Introduction

Multiple studies have shown that tranexamic acid (TXA) gives a significant reduction in blood loss after knee replacement, and results in lower blood transfusion rates [1–3]. Consensus is lacking though regarding the administration route and optimal dose of TXA administration after total knee arthroplasty (TKA) [4]. Intravenous TXA is most often used, and has been found to be very safe and effective [5]. Oral TXA has been shown to give an equivalent reduction in blood loss, and has a lower cost than intravenous use [6,7]. Besides oral and intravenous administration, topical TXA offers the advantage of intra-articular administration at

* Corresponding author.
E-mail address: jajansen@alrijne.nl (J.A. Jansen).

http://dx.doi.org/10.1016/j.knee.2017.07.004
0968-0160/

the site of bleeding and minimizes its systemic absorption [1,2,8,9]. Topical TXA administration during joint replacement surgery has been described as a safe and cost-effective alternative to intravenous use [1,2,10,11]. For transfusion rates a similar odds ratio is found with significantly less transfusion in the topical as well as in the intravenous TXA groups when compared with control groups [8,10,11]. No increased risk of deep venous thrombosis (DVT) or pulmonary embolism (PE) has been reported in several meta-analysis studies on the use of TXA in arthroplasty, even at higher and repeated dosages [1,2,11–15]. Combined intravenous and topical administration has also been studied, and a further reduction in blood loss and transfusions was found [16–18]. Recent meta-analysis of different methods of tranexamic acid administration did not show any significant differences, but more studies on efficacy are warranted [19]. Subgroup analysis on the dose-related effect of tranexamic acid has shown that a higher and repeated dose of TXA may be better at reducing bleeding and transfusions than a lower single TXA dose [20,21]. Although TXA is widely administered in different administration forms, no previous study has been performed to investigate the combined effect of intravenous, oral and topical use in order to achieve a prolonged anti-fibrinolytic effect. Besides determination of its dose-related efficacy, also the safety profile has not been studied before in patients with thromboembolic events in the past. Therefore, the present study was conducted to assess the effect of different TXA dosages on the outcomes of hemoglobin (Hb) decrease, transfusion rates, length of stay (LoS), thromboembolic and wound complications, and referral to home or a care facility. In addition, the effect of TXA in patients that had a DVT or PE longer than 12 months ago was monitored specifically and incidence of thromboembolic complications in this group was compared with patients without a previous thromboembolic event in the past.

2. Patients and methods

2.1. Study design

Data was prospectively gathered in all consecutive primary TKA patients from January 2013 until January 2016, and retrospectively analyzed. Data was collected by the Department of Orthopedics at the Alrijne Hospital Leiden, The Netherlands. Data was extracted from patient files until six months after total knee replacement surgery. Subjects were included in case of primary total knee replacement surgery in which TXA was administered. Subjects that had revision knee arthroplasty, unicondylar knee replacement, fracture or tumor prosthesis were excluded from the study. Exclusion was also the case if no TXA was given or with a recent thromboembolic event less than 12 months ago. Consecutive series of subjects with total knee replacement surgery were compared in the following dosages: ≤10 mg/kg, >10–25 mg/kg, and >25–50 mg/kg administration of TXA. The retrospective cohorts consisted of a group with only a single dose of intravenous TXA administration, a group with combined intravenous and oral administration, and a group with combined intravenous, oral and topical administration.

2.2. Study procedure

From 2013 until 2014 pre-operative intravenous TXA was administered, from 2014 to 2015 patients received pre-operative intravenous and postoperative oral TXA, and from 2015 until 2016 topical administration of TXA was added intra-articularly after closure of the knee joint in addition to the intravenous and oral administration as per earlier time periods. The method of TXA administration and the total dosage of TXA were recorded for every patient. The anesthetist administered 10 mg/kg intravenous TXA just before the start of surgery, and one gram of oral TXA was given postoperatively after transfer from the recovery room. Topical TXA was administered in the joint during surgery after closure of the knee capsule in the standard dose of two grams. Three consultant orthopedic surgeons performed all surgeries through a medial parapatellar approach using a cemented Nexgen posterior stabilized high flex total knee prosthesis (Zimmer Biomet, Warsaw, US). All patients had rehabilitation by the same enhanced recovery protocol including multimodal opioid sparing pain management, a pre-operative dose of intravenous dexamethasone, per-operative local infiltration analgesia, and in the case of spinal anesthesia a low dose enabling early mobilization out of bed within three hours after operation. An upper-leg tourniquet was used during surgery to achieve a bloodless field, so no blood loss was seen during operation. As no postoperative wound drains were used, the amount of lost blood was assessed by measuring the difference in pre-operative and postoperative Hb levels, which was checked the month before and the day after surgery in every patient. A daily subcutaneous dose of low-molecular-weight heparin was used for one month as DVT prophylaxis in all patients. No urinary catheters, and no patient-controlled anesthesia pain pumps were used in any of these patients. To investigate the incidence of postoperative symptomatic DVT and PE, the hospital electronic patient data files of each patient were surveyed including the regional general practitioners' referral system with a follow-up of six months postoperatively. In addition, the radiology patient database was checked for positive results on ultrasound or computed tomography scans for proven DVT and PE.

2.3. Statistical analysis

To summarize continuous data, a mean and standard deviation was used. If data was not normally distributed, a median and range was reported. Absolute and relative frequencies were used to summarize categorical data. To evaluate differences between the TXA dosage groups (≤10 mg/kg, >10–25 mg/kg, and >25–50 mg/kg) and the primary outcomes, the appropriate statistical test for each outcome was used. Differences were significant if $P < 0.05$. As we identified body mass index (BMI), age, gender and pre-operative Hb levels as possible confounders between TXA dosage and the outcome measures Hb level and referral to home or facility care, we first assessed whether these variables were significantly associated with TXA dosage and with the

Table 1
Baseline characteristics 922 patients with combined intravenous, topical and oral tranexamic acid.

	≤10 mg/kg	>10–25 mg/kg	>25–50 mg/kg	*P*
Subjects, n	238	474	210	NA
Age, mean (SD)	69.51 (9.47)	68.34 (8.88)	65.69 (8.92)	<0.0001
Gender, male (%)	55 (23.11)	134 (28.27)	79 (37.62)	0.003
BMI, mean (SD)	27.22 (3.38)	29.11 (4.54)	31.81 (4.34)	<0.0001
Pre-operative Hb level, mean (SD)	8.44 (0.65)	8.61 (0.66)	8.75 (0.74)	<0.0001
ASA score, frequencies (%)	1. 31 (13.0)	1. 59 (12.4)	1. 21 (10.0)	NE
	2. 193 (81.1)	2. 378 (79.8)	2. 173 (82.4)	
	3. 14 (5.9)	3. 37 (7.8)	3. 16 (7.6)	
	4. 0 (0.0)	4. 0 (0.0)	4. 0 (0.0)	

ASA, American Society of Anesthesiology; BMI, body mass index; Hb, hemoglobin; NA, not applicable; NE, not estimable; SD, standard deviation.

outcome. Then, we compared univariate regression analysis with multivariable regression analysis, and we added these variables into a multivariate model for each outcome to adjust for the identified confounders. In subgroup analysis, we created subgroups by American Society of Anesthesiology (ASA) score (ASA scores 1 and 2 versus ASA scores 3 and 4), and type of anesthesia (spinal versus general). Differences between subgroups within the different dosage groups were analyzed univariately for all outcome measures. All analyses were performed in R Studio Statistics program (version 3.0.2).

3. Results

In total, 1546 patients underwent knee replacement surgery between January 2013 and January 2016 of which 922 were eligible for this study. We only included patients who received TXA before, during or after primary total knee replacement. Therefore 624 patients were excluded because no TXA was used due to a recent thromboembolic event within 12 months, or because of unicondylar or revision knee arthroplasty. In total, 922 patients were included in the analysis and were divided by dosage into three groups: 238 patients received a low dose of ≤10 mg/kg TXA, 474 patients received an intermediate dose of >10–25 mg/kg TXA, and 210 patients received a high dose of >25–50 mg/kg TXA. Baseline characteristics of all 922 patients with TXA use are summarized in Table 1. In the highest-dosage group, patients were significantly younger, more frequently men, had a higher BMI and higher pre-operative Hb levels. In total, 73 patients were on pre-operative use of anti-coagulant medication already, but this number was evenly distributed over all groups.

In univariate analysis, we found no significant difference in thromboembolic complications (DVT and PE), wound leakage and transfusion rates between the three dosage groups (Tables 2–5). There were 31 patients with DVT and 12 patients with PE in their history >12 months ago specifically, but in this specific group no more complications were noted with the higher-dosage TXA compared to the low-dosage TXA. In the highest-dosage group, no transfusions after surgery were necessary compared to two transfusions in both lower-dosage groups. This result was not significantly different though. LoS had a median of two days in the highest dosage group, and was significantly shorter compared with a median of three days in both lower dosage groups.

Table 2
Deep venous thrombosis: no significant difference between tranexamic acid dosage groups.

	DVT +	DVT −	
TXA ≤10 mg/kg	0	238	238
TXA >10–25 mg/kg	1	473	474
TXA >25–50 mg/kg	0	210	210
	1	921	922

DVT, deep venous thrombosis; TXA, tranexamic acid. Fisher's exact test: $P = 0.999$.

Table 3
Pulmonary embolism: no significant difference between tranexamic acid dosage groups.

	PE +	PE −	
TXA ≤10 mg/kg	1	237	238
TXA >10–25 mg/kg	1	473	474
TXA >25–50 mg/kg	0	210	210
	2	920	922

PE, pulmonary embolism; TXA, tranexamic acid. Fisher's exact test: $P = 0.999$.

Table 4
Wound leakage: no significant difference between tranexamic acid dosage groups.

	WL +	WL −	
TXA ≤10 mg/kg	41	197	238
TXA >10–25 mg/kg	64	410	474
TXA >25–50 mg/kg	35	175	210
	140	782	922

TXA, tranexamic acid; WL, wound leakage. Fisher's exact test: $P = 0.328$.

Table 5
Transfusion rates: no significant difference between tranexamic acid dosage groups.

	Transfusion +	Transfusion −	
TXA ≤10 mg/kg	2	236	238
TXA >10–25 mg/kg	2	471	473
TXA >25–50 mg/kg	0	210	210
	4	917	921

TXA, tranexamic acid. Fisher's exact test: $P = 0.549$.

In the multivariate analysis we presented the difference in Hb level unadjusted and adjusted for BMI and pre-operative Hb level (Table 6). We concluded that with a higher TXA dosage, the difference between pre-operative and postoperative Hb levels becomes smaller: in the group treated with >25–50 mg/kg TXA the decrease in postoperative Hb was 0.419 mmol/l less compared to the group treated with ≤10 mg/kg TXA ($P < 0.05$). For referral to home or a care facility in unadjusted analysis, subjects in the lower-dosage group were referred less often to home compared to subjects in the highest-dosage group, but adjusted for age, gender, BMI, and pre-operative Hb level this result was not significant (Table 7).

In the subgroup analysis, we compared low ASA score patients (1 and 2) with high ASA score patients (3 and 4), and only found a difference in the median LoS that differed between the ASA scores in the dosage groups of >10–25 mg/kg and of >25–50 mg/kg. In both dosage groups, the median LoS was two days for low ASA score patients and three days for high ASA score patients. In the comparison of general versus spinal anesthesia, we found in the dosage group of >10–25 mg/kg median LoS of three days (range two to six days) for general anesthesia versus a median LoS of two days (range one to 13 days) for spinal anesthesia. No other important differences were found in the subgroup analyses.

4. Discussion

This study has demonstrated the safety of combined intravenous, oral and topical TXA administration in total knee replacement. Using a higher dose of >25–50 mg/kg TXA in this combined manner resulted in a smaller decrease in postoperative hemoglobin. Patients with a thromboembolic history specifically did not have more complications in the high TXA dosage group compared to the low dosage group.

Table 6
Length of stay with different dosages of tranexamic acid.

	LoS	Range
TXA ≤10 mg/kg	3	2–15
TXA >10–25 mg/kg	3	1–13
TXA >25–50 mg/kg	2	1–9

LoS, length of stay; TXA, tranexamic acid. Kruskal–Wallis test: $P < 0.0001$.

Table 7
Multivariate regression analysis for hemoglobin and referral to home or care facility.

	Hb difference mmol/l (95% CI) Unadjusted	Hb difference mmol/l (95% CI) Adjusted	Referral to home versus care facility (95% CI) Unadjusted	Referral to home versus care facility (95% CI) Adjusted
TXA >10–25 mg/kg	0.279 (0.173–0.385)*	0.345 (0.246–0.444)*	0.856 (0.458–1.648)^{NS}	1.082 (0.557–2.164)^{NS}
TXA >25–50 mg/kg	0.419 (0.294–0.545)*	0.543 (0.418–0.668)*	0.681 (0.292–1.516)^{NS}	1.318 (0.507–3.283)^{NS}
Adjusted for	NA	BMI, pre-operative Hb	NA	Age, gender, BMI, pre-operative Hb

The postoperative hemoglobin (Hb) differences in tranexamic acid (TXA) groups >10–25 mg/kg and >25–50 mg/kg are compared to the reference TXA group ≤10 mg/kg. Likelihood of referral to home versus care facility is presented as an odds ratio. BMI, body mass index; CI, confidence interval; NS, not significant.
* Significant ($P < 0.05$).

Previous meta-analyses have not shown an increased thromboembolic risk with TXA use in general, however the effect in patients with a previous history of thromboembolic events in the past has not been reported before [12,13,15]. In our study TXA was also given to a group of patients who had a DVT or PE longer than 12 months ago, and no significant difference was seen in comparison with TXA administration to patients without a thromboembolic history. From our data, it can be concluded that by combined intravenous, oral and topical administration a dose of >25–50 mg/kg TXA can be safely given to patients with a thromboembolic event more than 12 months ago.

With regard to safety of high TXA doses, evidence can also be derived from randomized studies in cardiac surgery that showed a further reduction of blood loss without side effects if a total dose of up to 50 mg/kg TXA was used, resulting in fewer transfusions and fewer re-operations due to cardiac bleeding complications [22]. Higher TXA doses of more than 100 mg/kg have been associated in observational studies with an increased risk of postoperative seizures after cardiopulmonary bypass surgery [23], but no data from prospective trials is available on this subject. Pharmacokinetic studies in cardiac surgery have shown that high TXA doses of 100 mg/kg are not required though to achieve adequate fibrinolytic inhibition [24]. The actual TXA plasma level with a dose of 50 mg/kg was found to be significantly higher than expected based on pharmacokinetic models [25], resulting in a complete inhibition of fibrinolysis. From this study, it was concluded that patients with a high risk of bleeding after cardiac surgery should receive high dose TXA [24]. This conclusion is also compatible with the results from this current study that showed better efficacy of higher TXA doses after knee replacement, which was even more significant after adjustment for BMI and pre-operative Hb levels. Our study shows that in clinical practice it is better to give patients a repeated and higher dose of TXA after knee replacement.

TXA has been used in TKA surgery for over 20 years to decrease blood loss and transfusions [26]. Most TXA publications have described the effect of a single intra-operative intravenous TXA dose in ranges of often 10–20 mg/kg [26,27] in order to minimize weight-related dose variability, and compared the effect with a cohort of patients in whom this protocol was not used. Also, in revision knee arthroplasty and bilateral knee replacement, the safety and effectivity of an intra-operative TXA administration within the same dosage range were published [28,29]. Under a contemporary blood saving protocol, the clinical value of a higher and repeated total TXA dose of up to 30 mg/kg was described more recently in randomized controlled trials in which also simultaneous bilateral TKA patients were studied [21,30,31]. Even in minimally invasive TKA surgery the positive effect of intra-operative TXA use resulting in less peri-operative blood loss was reported [32]. Single intravenous TXA administration has been described though to decrease more the external blood loss than the hidden blood loss after TKA [33], which may be explained by the form of administration and the relatively short half-life of TXA. For this reason, we investigated the combined oral and topical TXA administration forms specifically as well, and in higher dose ranges than previously studied.

Previous studies that investigated the effect of TXA after knee replacement did find a significant difference in transfusions between groups with TXA and without TXA use [8,12–14]. Our study did not have a comparison group without TXA though, and no significant difference in transfusions was found between the groups with high and low TXA administration. In subgroup analysis, a difference in median LoS was found between low ASA (1 & 2) score and high ASA (3 & 4) score groups, which is a finding that has also been reported in another knee arthroplasty study [34]. After adjustment for age, gender, BMI, and pre-operative Hb level, no significant difference was found in our study between high and low TXA dosage groups with regard to discharge to home or a care facility. A recent study on this subject has already shown that advanced age and functional status before surgery are the strongest predictors for postoperative facility discharge [35]. Given the positive effect of high dose TXA on Hb levels and LoS in our study, it does have an effect on medical cost reduction and improved patient wellbeing too.

With regard to the pharmacokinetics it is known from intravenous studies that TXA elimination half-life is approximately two hours, and the oral TXA bioavailability is 34% of the dose [36]. Topical TXA provides an attractive route for administration specifically because of lower systemic absorption, so in comparison with intravenous use very low plasma levels of just 4.5 mg/l can be found 80 min after an intra-articular TXA administration of 1.5 g [37]. Because of TXA's relatively short half-life, the efficacy of repeated postoperative TXA administration was also found in other studies previously [38].

Besides being retrospective and non-randomized, our study has some limitations. For calculation of the dose effect the amount administered in different forms was simply added to a total. No adjustment was made with regard to possible differences in absorption by different administration forms affecting TXA serum peak levels, and half-life of the drug systemically was not taken into account. However, previous studies of intravenous and topical use have not shown any differences in efficacy [9,16]. Also, it must be noted that the current study with high dose TXA administration has been performed within an established enhanced recovery protocol setting with a short LoS due to early mobilization and a low incidence of thromboembolic events already. The enhanced recovery protocol was implemented in the Alrijne Hospital several years before the start of this study in 2013, and due to functional discharge criteria and better focus on compliance to transfusion barriers, a gradual decrease in LoS and transfusions can usually be seen in this process as well. Nevertheless, in our study the smallest significant postoperative decrease in Hb and a shorter LoS were found in the highest TXA group anyway. Further research regarding the exact dosage and timing of combined intravenous, oral and topical TXA use will be necessary in the future.

5. Conclusion

Our study describes for the first time in literature the efficacy of combined use of intravenous, oral and topical TXA in total knee replacement and its safety in patients with a thrombo-embolic history more than 12 months ago. A combined TXA dose of >25–50 mg/kg is recommended, resulting in a smaller change in postoperative Hb level.

Conflict of interest

The authors have no conflicts of interest to report.

Author contributions

JJ designed the study, operated on the patients, and wrote the manuscript. JL assisted in writing the study protocol, collected data and edited the manuscript. BS performed statistical analysis, assisted in writing the discussion, and edited the manuscript.

Acknowledgments

Financial support for this study was given by the Alrijne Hospital Scientific Committee (20150601) in order to create a research database of all primary knee arthroplasties.

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