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Tranexamic acid is effective in lower doses with infusion in total knee arthroplasty

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ABSTRACT

Objective: To identify the most effective intravenous regimen with reduced doses of tranexamic acid (TXA).

Methods: We retrospectively evaluated the two most frequently used TXA regimens (infusion and divided-dose regimens) in total knee arthroplasty in comparison with patients not treated with TXA, in three groups. Group NO (n = 134; 19 men and 115 women; mean age: 66.48 ± 7.66) (patients who were not treated with TXA); group DIV (n = 158; 14 men and 144 women; mean age: 65.67 ± 7.98) (total dose of 10 mg/kg intravenous TXA divided into two doses: 15 minutes before tourniquet inflation and 15 minutes before tourniquet deflation), an extra 5 mg/kg intravenous TXA dose was administered 2 hours after surgery in the orthopedic ward, if needed; and group INF (n = 193; 33 men and 160 women; mean age: 67.08 ± 7.2) (10 mg/kg TXA perioperative intravenous infusion starting 15 minutes before surgery until closure of the wound, and 5 mg/kg additional intravenous dose was administered 12 hours after surgery). Pre-postoperative hemoglobin (Hb) and hematocrit (Htc) difference, total blood loss (TBL), number of transfused packed red blood cells (pRBC), and length of hospital stays (LOS) were compared between the groups.

Results: TBL was lower in group INF (531.61 ± 316.76 mL) in comparison with group DIV (999.91 ± 352.62 mL). TBL was statistically significantly higher in Group NO (1139.23 ± 43 mL). The mean number of transfused pRBC was significantly higher in the control group (1.22 ± 0.58 units) than the in the other TXA groups. The mean number of transfused pRBC was significantly lower in INF group (0.33 ± 0.56 units) than DIV group (0.75 ± 0.63 units). The number of patients requiring transfusion was significantly lower in INF group (28.5%) than DIV group (65.2%). Group NO had the highest number of patients requiring transfusion (96.3%). Pre-postoperative Hb and Htc difference was significantly lower in INF group (−1.19 ± 0.9 gr/dL and −3.74 ± 2.96%). The mean LOS of the control group, group DIV and group INF were 7.16 ± 2.29, 6.93 ± 2.39 and 5.06 ± 1.24 days, respectively. Group INF had the lowest hospital stay time in comparison with the other groups ($p < 0.005$). There was no statistically significant difference between the control group and group DIV in the LOS.

Conclusion: A total dose of 10 mg/kg of TXA perioperative intravenous infusion starting 15 minutes before the surgery until wound closure can significantly decrease TBL. Intraoperative infusion regimen is more effective than the divided-dose regimen.

Level of Evidence: Level III, Therapeutic Study.

Introduction

Orthopedic surgery can cause significant blood loss that requires blood transfusion. Even though blood transfusion can help to prevent surgery-related complications, it is associated with many adverse effects, including risk of bacterial/viral infections, allergic

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reactions, immune sensitization, transfusion-related acute lung injury, and even mortality.[1–3]

Early activation of fibrinolysis is common after trauma and is associated with increased mortality.[4] Trauma triggers the release of tissue plasminogen activator, the enzyme that converts plasminogen to plasmin.[5,6] TXA, is a lysine analog that inhibits plasmin activation, which in turn inhibits fibrinolysis and stabilizes clots. TXA has been shown to have both antifibrinolytic and anti-inflammatory properties.[7,8] The studies of the effect of TXA from time of injury to the initiation of treatment showed that early treatment was essential. TXA reduced death due to bleeding in patients treated within 3 h of injury, but there was no benefit when it was given after 3 h.[9,10]

There has been much debate and controversy about the optimal regimen of TXA in primary total knee arthroplasty (TKA). The most common practice is to administer TXA at an intravenous dose of 10–15 mg/kg before the deflation of the tourniquet, which is followed by a continuous infusion or repeated boluses. Dosing regimens range from 10 to 135 mg/kg,[11] but the regimen duration ranges from a single shot to multiple injections, to continuous infusion after surgery for up to 3 days.[12,13] There has also been controversy about the optimal administration route of TXA in primary TKA. Intravenous, oral, and topical use of TXA has been compared in numerous studies, but none of them have been superior to the other.[14–19] Currently, the ideal route of TXA administration remains controversial.[20]

TXA is being used in our institute since it was recommended for bleeding control in the guidelines. The total amount of TXA used in our daily practice is at much lower doses than is being used typically. The 2 frequently used TXA regimens (infusion and divided-dose regimens) in our institute were observed in this study. We aimed to identify the most effective TXA regimen with greatly reduced doses.

Methods

The study was approved by the Kocaeli University Ethics Committee of Noninvasive Investigations (26.04.2017; protocol #2017/131; decree #2017/6.25). A total number of 485 patients with osteoarthritis who were scheduled to undergo primary unilateral TKA between 2016 January and 2017 May were included and evaluated retrospectively.

Exclusion criteria were revision or bilateral TKA; American Society of Anesthesiologists (ASA) level 3–4, renal or hepatic dysfunction; if antiplatelet, anticoagulant, and non-steroid anti-inflammatory drugs were not stopped 7 days prior to surgery; coagulopathy; additional or different interventions performed instead of the planned surgical procedure; if a surgical complication occurred during surgery; use of an alternative regimen of TXA administration different from the protocols that were planned to be compared; and patients whose hospital data could not be acquired.

A total of 485 patients who met the inclusion criteria to the study were divided into 3 groups (Fig. 1). (1) Patients who were not treated with TXA because of any reason comprised group NO (n = 134). (2) Method 1: A total 10 mg/kg intravenous TXA dose was divided into two and administered 15 minutes before tourniquet inflation as preoperative, and 15 minutes before tourniquet deflation as intraoperative. An extra 5 mg/kg intravenous TXA dose was administered 2 hours after the surgery at the orthopedic ward, if needed (total dose of 10–15 mg/kg TXA) (group DIV, n = 158). (3) Method 2: 10 mg/kg TXA perioperative intravenous infusion was started 15 minutes before surgery until closure of the wound, and 5 mg/kg an additional intravenous dose was administered 12 hours after surgery (total dose of 15 mg/kg TXA) (group INF, n = 193).

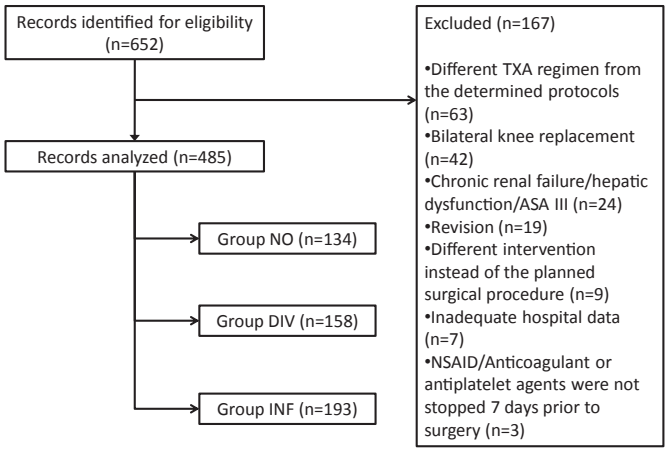

Fig. 1. Study flow diagram.

Routine preoperative patient preparations were made. Patients underwent elective surgery under optimum conditions. Spinal anesthesia was the preferred anesthetic technique, and all surgical procedures were similar. Tourniquet was used in all cases, from the start of the surgery until wound closure (approximately 30–70 min). All prostheses were similar (Zimmer, NexGen, LPS-Flex Mobile). Cement with gentamicin was used for fixation of the prosthesis. In each knee, one intraarticular drain was placed and connected to vacuum bottles. Drains were removed 48 hours after surgery. No blood salvage system was used. All patients received subcutaneous low-molecular-weight heparin (enoxaparin) twice daily was initiated on the night of surgery and continued until discharge.

Blood transfusion was administered at the Hb threshold of 8 g/dL in patients without comorbidities, and a threshold of 10 g/dL in patients with preexisting cardiac insufficiency, coronary heart disease or symptomatic anemia.[21] All patients' hemoglobin levels were assessed preoperatively, on the 5th postoperative day, and additionally on the variable times if needed.

Drains are routinely used in TKA, but drain collections were not routinely recorded in our practice; therefore, drain loss could not be calculated. It has been reported that TXA decreases external blood loss, but intraoperative and hidden blood loss should be accounted for.[22] Therefore, we chose the hemoglobin balance method for the total blood loss (TBL) calculation, which was suggested to better establish combined external loss (intraoperative loss, drain loss, and hidden (internal) loss).[23,24]

Pre-postoperative Hb and hematocrit (Htc) differences were recorded. Patients' blood volumes were calculated using the formula of Nadler et al.[25] TBL were calculated using the hemoglobin balance method.[26] (Table 1) Requirement for blood transfusion, the units of packed red blood cells (pRBC), and length of hospital stay were recorded in order to determine the efficacy of TXA on reducing blood loss.

Statistical analysis

IBM SPSS Statistics Version 24 program was used for the statistical analyses of the data. The intergroup comparison of the categorical data was analyzed using Pearson's Chi-square test, and intergroup continuous data were analyzed using one-way analysis of variance (ANOVA) (*post hoc* Bonferroni) testing. Repeated-measures ANOVA was used to compare the changes of the first and last Hb and Htc values. The Results were evaluated as statistically significant at a level of $p < 0.05$.

Table 1
Formulas used for calculation of blood volume and total blood loss.

Nadler Formula:
Males:$BV = (0.3669 \times H^3) + (0.03219 \times W) + 0.6041$
Females: $BV = (0.3561 \times H^3) + (0.03308 \times W) + 0.1833$
BV (ml): Blood Volume, **H (mt)**: Height, **W (kg)**: Weight
Hemoglobin Balance:

$$\textbf{Hb loss total} = \textbf{BV} \times \frac{\textbf{Hb i} - \textbf{Hb e}}{\textbf{1000}} + \textbf{Hb t}$$

$$\textbf{V loss total} = \textbf{1000} \times \frac{\textbf{Hb loss total}}{\textbf{Hb t}}$$

Hb loss total (gr): Amount of hemoglobin lost, **Hb i (gr/L)**: The hemoglobin value before surgery, **Hb e**: The hemoglobin value after surgery, **Hb t (gr)**: Total amount transfused hemoglobin with blood transfusion[a], **V loss total (mL)**: Total blood loss

[a] 1 U bank blood is considered to contain 52 ± 5.4 gr Hb.

Results

The three patient groups were comparable in terms of sex, age, body mass index, blood volume, and other demographic and clinical variables (Tables 2 and 3). The demographic variables of all groups were similar. The majority of patients were females in all groups. No adverse effects regarding TXA administration were observed.

All three groups showed comparable TBL values. TBL was lower in the treatment groups according to the control group. In the treatment groups, TBL was lower in group INF (531.61 ± 316.76 mL) in comparison with group DIV (999.91 ± 352.62 mL). The highest value of TBL (1139.23 ± 43 mL) was observed in control group NO. All intergroup comparisons of TBL was statistically significant ($p < 0.005$).

The mean number of transfused pRBC was significantly higher in the control group (1.22 ± 0.58 units) than the in the other TXA groups. The mean transfused pRBC count was significantly lower in INF group (0.33 ± 0.56 units) than DIV group (0.75 ± 0.63 units). In comparison of the both treatment groups, the number of patients requiring transfusion was lower in INF group (with a rate of 28.5%) than DIV group (with a rate of 65.2%). Control group NO had the highest number of patients requiring transfusion (with a rate of 96.3%). All intergroup comparisons of transfused pRBC count and rate of patients requiring transfusion was statistically significant ($p < 0.005$).

Pre-postoperative Hb and Htc difference was significantly lower in INF group (−1.19 ± 0.9 gr/dL and −3.74 ± 2.96%). There were statistically significant differences pre-postoperative Hb and Htc values in the intergroup comparison of group INF and the other groups ($p < 0.005$). But the intergroup comparison of pre-postoperative Hb and Htc differences of the control group with group DIV was not statistically significant. Transfusion rates were found to be higher in each group; therefore, we observed relatively higher Hb and Htc values in all groups on the postoperative 5th day.

The mean length of hospital stays of the control group, group DIV and group INF were 7.16 ± 2.29, 6.93 ± 2.39 and 5.06 ± 1.24 days, respectively. Group INF had the lowest hospital stay time in comparison with the other groups ($p < 0.005$). There was no statistically significant difference between the control group and group DIV in the length of hospital stay.

Postoperatively, acute renal dysfunction developed in one patient, and coronary vasospasm developed in one patient in the NO group. No other major complications were observed in any group during their hospital stay.

Discussion

There was a significant difference in TBL, and transfusion rates between the two TXA protocols. Both TXA regimens showed lower transfusion rates, but this reduction was more significant in the intraoperative infusion regimen. The most important finding of the study was that, both treatment groups receive 10 mg/kg TXA with two different regimen and bleeding is more in the divided-dose regimen group. Although lower doses of TXA were used, the intraoperative infusion regimen produced similar, or even lower TBL values compared with studies that used higher doses of TXA.[17,27]

Some studies have shown that TBL of 1450–1790 mL occurs without special interventions of patients undergoing TKA.[22,28] In our study, we calculated a TBL of 1139.231 mL in the control group without TXA administration. Benoni et al. achieved 730 ± 280 mL TBL with a divided-dose regimen (1st dose was given shortly before the release of the tourniquet, and the 2nd dose was repeated 3 hours later).[29] A study that aimed to show the most effective regimen of TXA in TKA demonstrated that a three-dose regimen (preoperative dose of 10 mg/kg 20 min before surgery; 10 mg/kg as an intraoperative dose; 10 mg/kg 3 hours after surgery as a postoperative dose) produced the least TBL of 688 mL.[17] The timing of this regimen was similar to our 1st method in the divided-dose regimen group, however we administered a total dose of 10 mg/kg TXA and TBL was recorded as 999.9 mL in this group.

Many studies have shown a wide range of dosing regimens with higher dosages. Hourlier et al. showed 1.163 ± 589 mL of TBL with

Table 2
Demographic and preoperative variables.

		NO (n = 134)	DIV (n = 158)	INF (n = 193)	p
		M.±SD	M.±SD	M.±SD	
SEX	Male	19 (14,2)	14 (8,9)	33 (17,1)	0,079
	Female	115 (85,8)	144 (91,1)	160 (82,9)	
Age (years)		66,48 ± 7,66	65,67 ± 7,98	67,08 ± 7,2	0,223
ASA I		21 (15, 7%)	29 (18, 3%)	37 (19, 2%)	0,710
BMI (kg/m^2)		29,57 ± 4,25	31,05 ± 4,4	30,11 ± 4,32	***0,013***
BV (mL)		4225,54 ± 659,68	4344,22 ± 515,6	4381,48 ± 630,87	0,066
Preoperative Hb (gr/dL)		13,24 ± 1,45	13,04 ± 1,45	13,08 ± 1,32	0,450
Preoperative Htc (%)		39,4 ± 4,01	38,81 ± 3,7	39,03 ± 3,84	0,414

Pearson Chi-Square, One Way Anova; ***p < 0.05***
ASA American Society of Anesthesiologists, *BMI* Body Mass Index, *BV* Blood Volume.

Table 3
Postoperative data analysis.

	NO (n = 134)	DIV (n = 158)	INF (n = 193)	p	Post-Hoc		
	M.±SD	M.±SD	M.±SD		NO-DIV	NO-INF	DIV-INF
TBL (mL)	1139,23 ± 426	999,91 ± 352,62	531,61 ± 316,76	***0,000***	*0003*	*0,000*	*0000*
pRBC (units)	1,22 ± 0,58	0,75 ± 0,63	0,33 ± 0,56	***0,000***	*0000*	*0,000*	*0000*
LOS (days)	7,16 ± 2,29	6,93 ± 2,39	5,06 ± 1,24	***0,000***		*0,000*	*0000*
Hb difference (gr/dL)	−2,14 ± 1,19	−2,17 ± 1,09	−1,19 ± 0,9	***0,000***		*0,000*	*0000*
Htc difference (%)	−6,43 ± 3,6	−7,2 ± 3,6	−3,74 ± 2,96	***0,000***		*0,000*	*0000*
Postoperative Hb (gr/dL)	11,09 ± 1,05	10,86 ± 1,26	11,88 ± 1,19	***0,000***		*0,000*	*0000*
Postoperative Htc (%)	32,98 ± 2,96	31,98 ± 3,61	35,23 ± 3,36	***0,000***	*0,33*	*0,000*	*0000*
Patients requiring transfusion (n, %)	129 (96,3)	103 (65,2)	138 (28,5)	***0,000***	*0000*	*0,000*	*0000*

One Way Anova; $\boldsymbol{p < 0.05}$.
TBL Total Blood Loss, *pRBC* packed red blood cell, *LOS* Length of Stay.

an intraoperative infusion of 30 mg/kg TXA.[27] This regimen was similar to our 2nd method in the INF group in which we achieved a lower total blood loss of 531.6 mL with a single dose of 10 mg/kg of TXA. The effectiveness of TXA in TKA when given as a single 30 mg/kg infusion or as a multiple dose regimen of total 50 mg/kg (including 20 hours' of continuous infusion following the surgery) was investigated and it was shown that a single injection during the intraoperative period was as effective as a continuous infusion during perioperative period in patients undergoing TXA.[27] Previous studies suggested that a single and low-dose regimen was not as effective as multiple-dose regimens.[11] However, as a result of our study we thought that lower doses were enough and an infusion regimen during surgery is superior to a divided-dose regimen because of maintaining a stabilized plasma concentration. Additionally, TXA reaches its maximum plasma levels in 5–15 minutes, then it diffuses rapidly into soft tissues.[30,31] Because of this reason, it would be better to start the infusions 15 minutes prior to surgery. The half-life of an intravenous TXA dose is 2–3 hours, so additional postoperative TXA doses are usually needed to reduce the reactionary hemorrhage following intraoperative primary bleeding.[32]

Similar to other studies, length of hospital stay was found to be lower in patients who were treated with TXA.[13] In addition, length of hospital stay was significantly shorter in the intraoperative infusion group. However, there was no statistically significant difference between the control and the divided-dose group.

We accept that there has been variability in transfusion decisions depending on the physician's view of symptomatic anemia when Hb levels are lower than 10 g/dL. Patients' Hb levels on discharge confirm unnecessary transfusions and over-treatment. This research enabled us to review the transfusion decisions in our institution. Even so, when we analyzed the data on hand, there was a significant reduction in transfusion rates with intraoperative infusion of TXA.

There are several potential limitations of our study. First, this is a retrospective study. Second, the procedures were performed by different surgeons. Nevertheless, all of the surgeons work in collaboration in the operating theatre and their surgery techniques were similar. Third, was that we did not use erythropoietin or iron preparations before surgery, which Results in more symptomatic postoperative anemia and increased transfusion rates. Therefore, we thought that the higher transfusion rates in our institution may be the result of the excessive symptoms of postoperative anemia. Another limitation of the study is that we could not evaluate the long-term outcomes of the patients because we screened the inpatient hospital files. However, the short-term outcomes were evaluated in terms of complications and length of hospital stay.

The strengths of our study include strict patient selection for standardization and to avoid bias, and the large number of patients. All procedures were performed using a similar approach, similar implants, and uniform perioperative medical care procedures.

Conclusion

A total dose of 10 mg/kg of TXA perioperative intravenous infusion starting 15 minutes before the surgery until wound closure can significantly decrease total blood loss. At the same doses, the intraoperative infusion regimen is more effective than the divided-dose regimen.

Conflicts of interest

None.

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