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The Effect of Tranexamic Acid Administration on Perioperative Bleeding in Patients Undergoing Knee or Hip Arthroplasty: A Single-Centre Retrospective Study

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Abstract

Objective: Tranexamic acid (TXA) has been used to reduce perioperative bleeding in various surgeries because of its antifibrinolytic effect. Recently, patients undergoing orthopaedic surgery in our institution received a loading dose of TXA (1000 mg) before surgery, followed by 100 mg h^{-1} until the end of surgery. The purpose of the present study was to evaluate the efficacy of TXA administration on the perioperative blood loss in patients undergoing knee arthroplasty or hip arthroplasty.

Methods: A retrospective cross-sectional study was conducted for the records in patients who underwent surgery without TXA administration (control group) and patients who underwent surgery with TXA administration (TXA group). Amount of intraoperative blood loss, intraoperative infusion volume, intraoperative blood transfusion volume, postoperative blood transfusion volume, changes in haemoglobin concentrations (ΔHb) and estimated blood loss were collected. Data were adjusted by propensity score method.

Results: A total of 126 (63 in the control group and 63 in the TXA group) patients were included during the study period. Intraoperative infusion, postoperative transfusion, ΔHb and estimated blood loss were significantly reduced in the TXA group, although there were no significant differences in the volumes of intraoperative transfusion and blood loss.

Conclusion: The administration of TXA (loading dose of 1000 mg and continuous infusion of 100 mg h^{-1}) reduced postoperative transfusion and perioperative blood loss. These results indicated that TXA administration is useful for reducing perioperative blood loss in patients undergoing knee or hip arthroplasty.

Keywords: Arthroplasty, tranexamic acid, transfusion

Introduction

It is known that perioperative anaemia affects morbidity and mortality and increases the risk of surgical site infection (1, 2). Tranexamic acid (TXA) has been used to reduce perioperative bleeding and transfusion in various surgeries because of its antifibrinolytic effect (3-6). The number of total knee arthroplasty (TKA) and total hip arthroplasty (THA) procedures has been increasing worldwide (7). However, previous reports have shown that TKA and THA surgeries are associated with considerable blood loss, thereby necessitating perioperative blood transfusion in approximately 30% of the patients (8, 9). Allogeneic blood transfusion is expensive and accompanied with the risk of infection, transfusion-related acute lung injury and transfusion-associated circulatory overload. To reduce the need for allogeneic transfusion, some studies have reported the effect of TXA on perioperative bleeding; however, there is insufficient information about the ideal dosage, timing and continuous infusion (7). Patients who were scheduled to undergo orthopaedic surgery at our institution between July 2016 and June 2017 received a loading dose of TXA (1000 mg) before surgery, followed by 100 mg h^{-1} until the end of surgery.

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Therefore, the aim of the present study was to retrospectively investigate perioperative blood loss in patients who underwent knee arthroplasty or hip arthroplasty 1 year before and after the administration of TXA.

Methods

Study design and data source

A retrospective single-centre, cross-sectional study between January 2015 and June 2017 at our institution was conducted. The study was approved by the Akita University Ethics Committee of our institution on 18 October 2017 (approval no. 1862). All data were extracted from the clinical database in our institution.

Patients

Patients who underwent unilateral primary THA, TKA or unicompartmental knee arthroplasty (UKA) at our institution were selected. One hundred thirty-five patients were enrolled in this study. Demographic data on sex, age, height, weight, American Society of Anaesthesiologists Physical Status, duration of surgery, type of surgery (THA, TKA or UKA) and type of anaesthesia were collected. Patients who did not receive TXA (control group) were those who underwent surgery between January 2015 and December 2015, whereas those who received TXA (TXA group) underwent surgery between July 2016 and June 2017. TKA and UKA surgeries were performed using a tourniquet.

Study intervention and outcomes

TXA was infused (1000 mg) before surgery as a loading dose and 100 mg h^{-1} continuously until the end of surgery in the TXA group. The total doses of TXA were confirmed from the anaesthesia records. The control group did not receive any placebo drug. Induction and maintenance of anaesthesia was entrusted to the discretion of a responsible anaesthesiologist. Similarly, the choice of epidural or femoral perineural anaesthesia was at the discretion of the anaesthesiologist. Primary outcome was perioperative estimated blood loss, which was calculated using the modified Zufferey's method (10). In brief, the value was expressed as 1000×(ΔHb×blood volume+the total amount of transfused Hb)/preoperative Hb. ΔHb was obtained by the subtraction of the Hb value on the preoperative day and postoperative day 4. Secondary outcomes included intraoperative blood loss, ΔHb, intraoperative infusion (amount of crystalloid and colloid infusion), intraoperative transfusion and postoperative transfusion. The criteria for transfusion depended on the discretion of the anaesthesiologist in charge. From postoperative day 1, all patients received 3000 IU (30 mg) of enoxaparin daily for 2 weeks as prevention against venous thromboembolism.

Main Points:

- Tranexamic acid has been used to reduce perioperative bleeding and transfusion in various surgeries.
- The ideal dosage, timing and continuous infusion of tranexamic acid has not been fully elucidated.
- Loading dose and intraoperative continuous infusion of tranexamic acid were used in patients with orthopaedic surgery.
- Tranexamic acid reduced postoperative transfusion and perioperative blood loss.
- No patient developed adverse effects.

Statistical analyses

According to our previous records of anaesthesia and other similar studies, we assumed that the difference between perioperative blood loss was 400 mL and standard deviation was 750 mL. Based on the above, we calculated that a sample size of 57 patients per group would be required to achieve a power of 80% with a two-sided α risk of 0.05. The propensity score matched pair analysis was applied to reduce the effect of confounding factors. Student's t-test, Mann-Whitney U test and McNemar test were employed for the analysis of results. Propensity score matched pair analysis for demographic data was done using EZR version 1.36 (The R Foundation for Statistical Computing, Vienna, Austria) (11). Comparison between the two groups was performed using StatView version 5.0 (SAS Institute, Cary, NC, USA) and JMP version 14.1 (SAS Institute). Normally distributed values were expressed as mean±SD, and non-normally distributed data were expressed as median (25^{th}-75^{th} percentile). A p value <0.05 was considered statistically significant.

Results

This retrospective cross-sectional study consisted of 135 (98 THA, 29 TKA and 8 UKA) patients between January 2015 and June 2017, of whom 63 were in the control group and 72 were in the TXA group (Figure 1). Demographic data are summarised in Table 1. All data except for the duration of surgery and activated partial thromboplastin time (aPTT) were similar between the two groups. To adjust this confounding factor, 87.5% (n=63) of patients in the TXA group were matched with similar patients in the control group through propensity score matching. Both matched and unmatched data are described in Table 1.

Within the matched data, perioperative estimated blood loss and ΔHb in the TXA group were significantly less than those in the control group (p=0.01) (Figure 2a and b). However, the mean intraoperative blood loss did not differ between the two groups (Figure 2c).

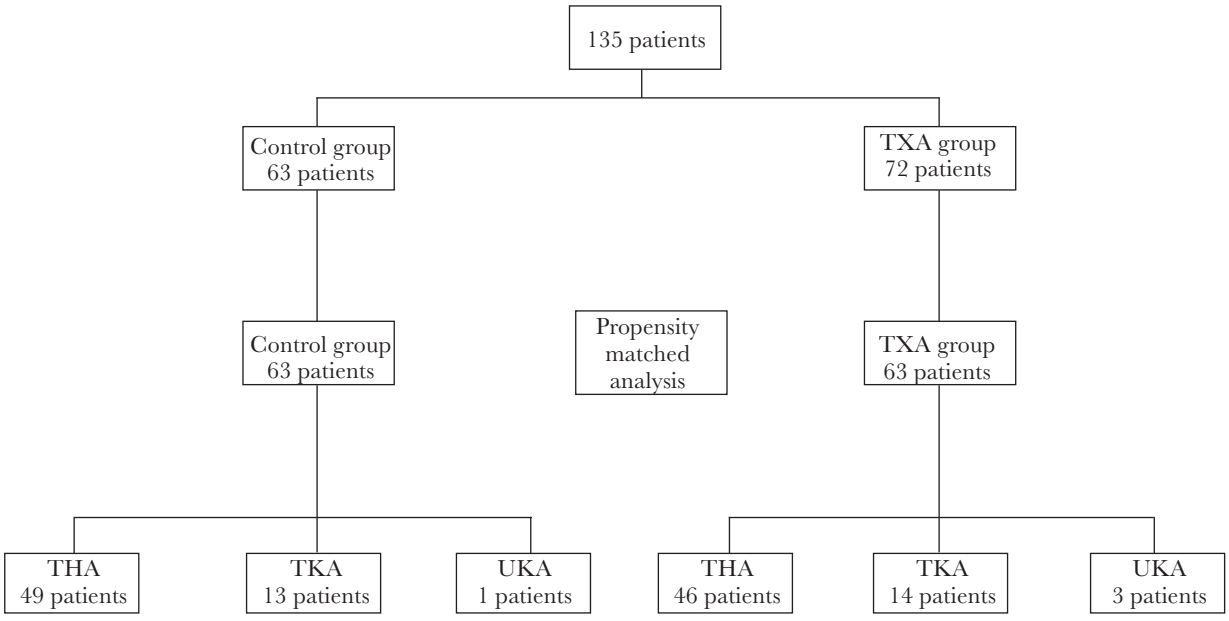

Figure 1. Flowchart of the study population. We used propensity matched analysis to reduce confounding factors. After the matched analysis, 63 (87.5%) patients, with similar demographic data, in the TXA group were extracted to be compared to 63 patients in the control group. Patients in the TXA group received TXA as a loading dose of 1000 mg and continuous infusion of 100 mg h^{-1}

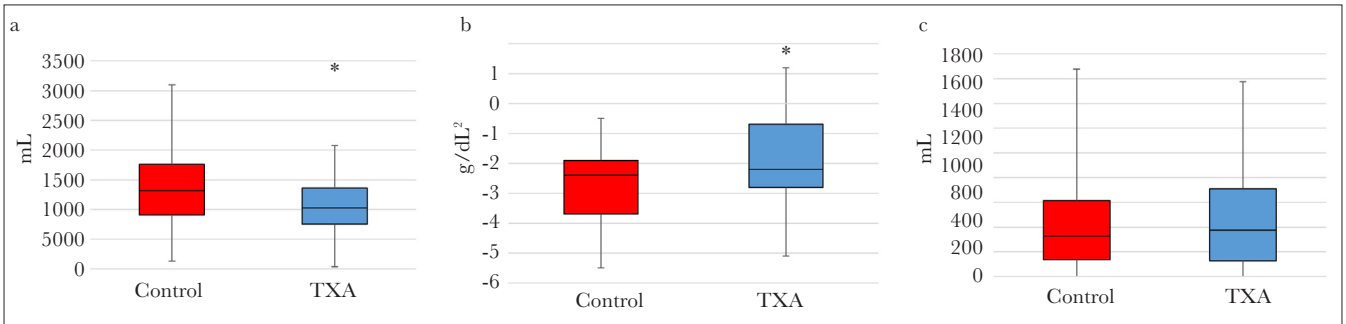

Figure 2. a-c. Perioperative blood loss. (a) Perioperative estimated blood loss. (b) ΔHb indicates the difference in haemoglobin between preoperative and day 5 values. (c) Intraoperative blood loss. Perioperative estimated blood loss in the TXA group was significantly lower than that in the control group. ΔHb in the TXA group was significantly lower than that in the control group. Intraoperative blood loss between the two groups was not significantly different. The box-and-whisker plots show minimum and maximum values, 25th and 75th percentiles and medians. White box presents data of the control group, and black box presents data of the TXA group. *p<0.05 versus control group

Although the volumes of intraoperative red blood cell transfusion were similar between the two groups, the volume of postoperative transfusion was significantly less in patients given TXA (Table 2). There was no significant difference in the number of patients who required at least 1 U of allogeneic red blood cells in the perioperative period (21 patients in the TXA group and 22 patients in the control group). No patient received other blood products, such as fresh frozen plasma and platelet concentrate.

The intraoperative infusion in the TXA group (1489±808 mL) was significantly less than that in the control group (1880±851 mL, p<0.01). No patient was diagnosed with pulmonary embolism (PE), deep vein thrombosis (DVT) or myocardial infarction using spiral computed tomography or electrocardiogram.

Table 1. Preoperative patient's characteristics

	Unmatched		Matched	
	Control	TXA	Control	TXA
No. of cases	63	72	63	63
Female	52	57	52	51
Age (year)	64.7±11.2	67.4±12.6	65.3±11.2	67.0±12.7
Height (cm)	154.0±8.5	155.3±9.6	154.0±8.5	153.9±8.5
Weight (kg)	57.8±10.8	58.7±12.9	57.8±10.8	57.0±11.8
ASA I/II/III	10/51/2	6/64/2	10/51/2	6/56/1
Duration of surgery (min)	178±49	146±55*	178±49	153±53*
Diagnosis				
OA	56	62	56	54
RA	1	4	1	4
RDC	6	6	6	5
Preoperative				
Hb (g dL^{-1})	12.2±1.3	12.0±1.5	12.2±1.3	12.0±1.6
aPTT (s)	29.5±3.4	26.9±4.1*	29.5±3.4	27.0±4.4*
PT (%)	113.9±14.6	113.3±14.1	113.9±14.6	113.1±13.5
Plt ($\times 10^3/\mu L$)	270.6±78.8	258.7±75.1	270.6±78.8	263.7±76.7
Type of surgery				
THA	49	49	49	46
TKA	13	16	13	14
UKA	1	7	1	3
Type of anaesthesia				
General	22	22	22	20
General+epidural	39	45	39	40
General+nerve block	2	5	2	3

The duration of surgery and aPTT have significant differences between the TXA and the control groups. Matched data which is adjusted by the propensity matched analysis is shown at the right side of the table. Data are expressed as mean±SD and numbers.
*p<0.05 versus control group.
TXA: tranexamic acid; ASA: American Society of Anesthesiologists; OA: osteoarthritis; RA: rheumatoid arthritis; RDC: rapidly destructive coxopathy; THA: total hip arthroplasty; TKA: total knee arthroplasty; UKA: unicompartmental knee arthroplasty; aPTT: activated partial thromboplastin time; PT: prothrombin time; Plt: platelet; Hb: haemoglobin

Table 2. Perioperative transfusion

	Control group	TXA group
Intraoperative transfusion (mL)	0 (310, 0)	0 (300, 0)
Postoperative transfusion (mL)	0 (280, 0)	0 (280, 0)*

Data are expressed as median (25^{th}–75^{th} percentile). *p<0.05 versus control group.
TXA: tranexamic acid

Discussion

In the present study, we found that perioperative blood loss (estimated blood loss and ΔHb) and volume of postoperative transfusion were less in patients who were given TXA, whereas the volumes of intraoperative blood loss and transfusion were similar between patients with and without TXA. These results were consistent with previous similar studies showing that TXA decreased not only blood loss but also need for perioperative infusion (12). In addition, our results showed significant reduction in need for intraoperative infusion in the TXA group due to decrease in intraoperative blood loss.

Many studies have reported the effect of TXA on perioperative blood loss and transfusion. However, the doses of TXA evaluated were different among the studies that included patients undergoing THA or TKA. We used 1000 mg TXA before surgery as loading dose and 100 mg h^{-1} continuous infusion until the end of surgery. Oremus et al. (13) showed that TXA reduces perioperative blood loss but not intraoperative blood loss in patients who underwent THA and TKA. Clave et al. (14) also indicated the same effect of TXA in patients who underwent THA. Although our results also indicated reduction in perioperative blood loss, the dose of TXA in their literature was greater than that of our study. Oremus et al.

(13) and Clave et al. (14) used 2 g and 4 g of TXA on the day of surgery, respectively, whereas the average dose of TXA in our study was 1.27 g. According to a previous in vitro study, plasma TXA concentration sufficient to inhibit fibrinolysis was 10 μg ml^{-1}; however, no complete literature has reported the most suitable dose of TXA for THA and TKA (15). Fiechtner et al. demonstrated that the plasma concentration is >10 μg mL^{-1} when TXA is infused at a dose of 10 mg kg^{-1}, 20 min prior to surgery, followed by 1 mg kg^{-1} h^{-1} of continuous infusion until 1 h at the end of treatment in cardiac surgery (16). We inferred that the method of administration of TXA in our study was sufficient to attain effective plasma concentration, because our primary dose was >10 mg kg^{-1} and continuous infusion was >1 mg kg^{-1} h^{-1}. In other words, the results of our study indicated the sufficient dose of TXA to achieve antifibrinolytic effect.

According to a network meta-analysis for primary TKA (17, 18), as well as THA (17, 19, 20), pre-incision administration of TXA and combination of pre-incision and continuous infusion during surgery tended to be the optimal timing as compared to post-incision administration, pertaining to blood loss and risk of transfusion. Moreover, continuous infusion of TXA during surgery failed to show a significant difference compared to post-incision administration (17, 19, 20). Thus, these studies recommended pre-incision administration of intravenous TXA to reduce the need for transfusion and blood loss (17-20). Therefore, the dose and timing of administration in the present study is one of the optimal methods in light of recent reports.

TXA binds to the lysine binding site of plasminogen to prevent fibrinolysis (21). However, some studies in the literature have raised concerns regarding the safety of TXA (22, 23). Nonetheless, a recent large meta-analysis study proved that TXA did not increase the risk of DVT and PE (7). A retrospective observational report of 6 years also indicated that TXA did not significantly affect thromboembolic complications (24). In our study, we examined patients for chest pain or difficulty in breathing by spiral computed tomography or electrocardiogram; however, no thromboembolic disease was diagnosed during hospitalisation.

Our study has some limitations. First, we could not completely adjust the duration of surgery and the aPTT between the two groups, although we used the propensity score analysis. The main reason is that the surgical time acts as an intermediate rather than a confounding variable. Although the aPTT in the TXA group was statistically less significant than that in the control group, both values were within the normal range. Thus, this difference may be ignored clinically. Second, the surgical position for THA was different in the two groups. It was the transition period of the surgical position from the end of 2015 to 2016. Almost all patients in the control group underwent surgery in the lateral decubitus position, whereas patients in the TXA group were in the jack knife position. Third, there were no exact criteria for blood transfusion in our retrospective study. Most of us considered red blood cell transfusion in cases with Hb <8 g dL^{-1} though it depended on the decision of the anaesthesiologist. Additional prospective or systematic large study should be conducted to reduce these confounding factors.

Conclusion

We observed that infusion of TXA decreased perioperative blood loss and the need for transfusion without any adverse events in patients undergoing TKA and THA. These results indicated that TXA administration is useful for reducing perioperative blood loss.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Akita University (Approval no. 1862).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.G.; Design - A.N., T.G.; Supervision - T.G.; Resources - T.G.; Materials - T.G.; Data Collection and/or Processing - A.N., K.M.; Analysis and/or Interpretation - A.N., T.G.; Literature Search - A.N.; Writing Manuscript - A.N., T.G.; Critical Review - T.G., K.M.

Conflict of Interest: The authors have no conflicts of interest to declare.

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