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ORIGINAL ARTICLE • KNEE - ARTHROPLASTY

Intra-articular 1 g tranexamic acid administration during total knee arthroplasty is safe and effective for the reduction of blood loss and blood transfusion

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Abstract

Introduction The effect of tranexamic acid (TXA) on the incidence of venous thromboembolic events (VTEs) in total knee arthroplasty (TKA) as assessed by contrast-enhanced computed tomography (CT) is unclear. Thus, we investigated the efficacy and safety profiles of TXA administration during TKA. We hypothesised that intra-articular 1 g TXA administration would have a sufficient effect on the reduction of blood loss and transfusion rates without increasing VTE risk.

Materials and methods We retrospectively analysed 86 patients who underwent primary TKA from January 2014 to September 2017. The study comprised control ($n=45$) and TXA ($n=41$) groups. All patients underwent navigation-assisted TKA via the medial parapatellar approach. In those who received TXA, 1 g of intra-articular TXA was injected via a drain immediately following wound closure. The drain was clamped for 2 h and then reopened. Contrast-enhanced CT was performed 5–6 days after surgery to detect deep venous thrombosis (DVT) and pulmonary embolism (PE). Blood loss was calculated using the haemoglobin balance method.

Results The mean postoperative volume of blood loss was 900 ± 296 mL vs 1216 ± 445 mL in the TXA vs control group ($p<0.01$). Allogeneic blood transfusion was required for 0 (0%) vs 6 (13.3%) patients in the TXA vs control group ($p=0.013$). There were no significant inter-group differences regarding DVT and PE incidence ($p>0.05$). No case of symptomatic PE occurred.

Conclusions This study demonstrated that intra-articular 1 g TXA administration during TKA is safe and effective for reducing blood loss and blood transfusion without increasing VTE risk.

Keywords Total knee arthroplasty · Tranexamic acid · Contrast-enhanced computed tomography · Venous thromboembolism · Blood loss · Blood transfusion

Introduction

Total knee arthroplasty (TKA) is one of the most commonly performed procedures for patients with intolerable pain associated with osteoarthritis or rheumatoid arthritis. According to a previous study, the average perioperative blood loss per procedure in TKA is greater than 1000 mL [1]. Patients who undergo TKA often require blood transfusion, and the transfusion rate ranges from 10 to 22% [2–4]. Despite notable improvement compared to previous years, blood transfusions have an impact on increased risks of infection, immunological reactions, alloimmunisation, transfusion-related acute lung injury, and 90-day mortality [5–7]. Furthermore, overall malaise related to low blood counts and the subsequent need for transfusion may not only lead to conditions such

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as hypotension, fatigue, weakness, and loss of balance but also to prolonged recovery and delayed discharge from the hospital, resulting in higher costs. In recent years, the use of tranexamic acid (TXA), which is a synthetic antifibrinolytic agent that competitively inhibits plasminogen activation, has become widespread for reducing blood loss and transfusion in primary TKA [8–10]. Currently, there are various dosing regimens for TXA administration but no consensus regarding the optimal route and amount. Although the most common administration route for TXA in published studies regarding TKA is the intravenous route, several meta-analyses revealed that both topical TXA and intravenous TXA are equally effective in reducing blood loss and blood transfusion rates in patients who undergo TKA [11–13]. The topical dosage is commonly between 1.5 g and 3 g with/without a drain clamp [14–19], and even 1 g of topical TXA demonstrated a sufficient effect [20, 21].

One of the most concerning complications in the use of TXA is the potential risk of increased thrombosis. TXA is contraindicated in patients with a history of venous or arterial thrombosis and in those with an intrinsic risk of thrombosis or thromboembolism [22]. However, this increased risk has not been reported in a randomised clinical trial using TXA in patients with bleeding trauma [23]. Poeran et al. [24] demonstrated that TXA was not associated with an increased risk of perioperative venous thromboembolic events (VTEs) and acute renal failure in patients who underwent total hip arthroplasty or TKA. However, in these studies, patients were diagnosed with VTE only when there was clear clinical evidence. The effect of TXA on the incidence of VTEs in TKA as assessed by contrast-enhanced computed tomography (CT) remains unclear. Therefore, a study that investigates the association between TXA administration during TKA and the incidence of VTE using an imaging modality such as contrast-enhanced CT is required to establish evidence regarding the safety of treatment using TXA.

This study aimed to investigate efficacies and safety profiles of intra-articular TXA. We hypothesised that intra-articular 1 g TXA administration during TKA would have a sufficient effect in reducing blood loss and transfusion rates without an increased risk of VTE.

Methods

This study was approved by our Institutional Review Board, and patients provided informed consent prior to participation. We retrospectively reviewed patients who underwent primary TKA by a single senior surgeon (M.S.) at our hospital from January 2014 to September 2017. The study comprised the control ($n=45$) and TXA ($n=41$) groups. The patients were divided into the two groups according to study period; patients in the control group underwent TKA from January 2014 to September 2015, while those in the TXA group underwent TKA from October 2015 to September 2017. All patients underwent navigation-assisted TKA via the medial parapatellar approach. Patients were excluded from the study for any of the following reasons: re-replacement, use of augmentations such as femoral or tibial stems, undergoing TKA by other surgeons, non-use of navigation-assisted TKA, non-evaluation of VTE by contrast-enhanced CT, and a past history of venous or arterial thrombosis. Haemoglobin concentration levels were measured preoperatively and on days 1, 3, 5, 7, and 14 after TKA. D-dimer levels were measured preoperatively and on day 5 after TKA. Patient medical records were reviewed to determine the age, desease, sex, height, body weight, body mass index, operation time, tourniquet time, and the presence of blood transfusion. The patient demographics are summarised in Table 1.

Calculation of blood volume, haemoglobin loss, and blood loss

Blood volume was first calculated using the formula by Nadler et al. [25]: blood volume (men) (L) $=(0.3669\times\text{height}^3\ (\text{m}))+(0.03219\times\text{weight (kg)})+0.6041$; and blood volume (women) (L) $=(0.3561\times\text{height}^3\ (\text{m}))+(0.03308\times\text{weight (kg)})+0.1833$. The loss of haemoglobin was estimated according to the following formula [26]: Hb_{loss} (g) = blood volume (L) $\times(\text{Hb}_i-\text{Hb}_e)$ (g/dL) $\times 0.1+\text{Hb}_t$ (g). Hb_{loss} (g) is the amount of haemoglobin lost up to 5 days after the surgery, Hb_i (g/dL) is the haemoglobin concentration before surgery, Hb_e (g/dL) is the haemoglobin concentration on the fifth day after surgery, and Hb_t (g) is the amount of haemoglobin transfused. The total blood loss (mL) was calculated as follows [27]; blood loss (mL) $=100\times\text{Hb}_{\text{loss}}/\text{Hb}_{i.}$

Table 1 Patient demographics

	Control ($n=45$)	TXA ($n=41$)	p value
OA/RA	38:7	35:6	n.s.
Male/female	9:36	12:29	n.s.
Age (years)	62.3 ± 8.2	70.8 ± 8.3	n.s.
Height (m)	1.52 ± 0.09	1.53 ± 0.09	n.s.
Weight (kg)	60.8 ± 12.7	62.7 ± 12.6	n.s.
Body mass index (kg/m^2)	26.3 ± 5.2	26.7 ± 3.9	n.s.
Blood volume (L)	3.53 ± 0.65	3.67 ± 0.66	n.s.
Preoperative Hb (g/dL)	12.9 ± 1.4	13.0 ± 1.2	n.s.
Preoperative D-dimer (g/dL)	1.3 ± 1.4	1.5 ± 2.1	n.s.
Operation time (min)	161 ± 25	173 ± 31	n.s.
Tourniquet time (min)	74 ± 26	81 ± 36	n.s.

Control control group, *TXA* tranexamic acid group, *OA* osteoarthritis, *RA* rheumatoid arthritis, *Hb* haemoglobin, *n.s.* no significance

Data are displayed as a mean ± SD. *$p<0.05$

Surgical procedure

All patients received a cemented posterior cruciate substitute TKA (Attune PS, DePuy Synthes, Warsaw, IN; or FINE PS, Teijin Nakashima Medical, Okayama, Japan) with a CT-free navigation system (BrainLab CI-System, Munich, Germany) by the same surgeon. A midline skin incision followed by a medial parapatellar approach was used. Anchoring pins were inserted into the distal femur and proximal tibia, and then navigation trackers were attached. After registration, bone resections were performed. In principle, the bone resections were matched to implant thicknesses to restore the original joint line level. Patellar replacements were performed in all patients. Before cementing, the tourniquet was inflated to between 280 and 320 mmHg after the elevation of the limb and exsanguination with an Esmarch bandage. The polyethylene liner was inserted. After sufficient irrigation and electrocoagulation, an intra-articular drain was placed followed by the removal of the pins and closure of the wound. After wound dressing, the tourniquet was deflated. In the patients who received TXA, 1 g of intra-articular TXA was injected via a drain just after wound closure and the drain was clamped for 2 h and then opened. However, the patients in the control group did not receive any injection via a drain. The drain was connected to a vacuum drain bottle.

Postoperative management

Immediately after surgery, all patients wore elastic stockings and used an intermittent pneumatic compression device. On the first postoperative day, all patients began ambulation and gait training. The drain was removed on the 2nd postoperative day. In a case with excess bleeding from the drain on the 2nd postoperative day, we delayed drain removal. The stitches were removed on the 14th postoperative day. When patients were able to walk with or without a T cane, they were discharged from hospital 3 weeks after TKA.

Anticoagulant agents were used according to the following protocol. All patients received subcutaneous injections of low molecular weight heparin (LMWH) (enoxaparin, 40 mg/day) starting on the evening of the first postoperative day, which was continued for 10 days. The dose was reduced for patients with compromised renal function. When patients were diagnosed with VTE using contrast-enhanced CT, they were referred to a cardiologist, withdrawn from LMWH injections, and administered direct oral anticoagulants such as edoxaban for 3–6 months. The criteria for blood transfusion were a haemoglobin concentration < 8 g/dL and the presence of signs of anaemia (e.g. chest pain of suspected cardiac origin, congestive heart failure, and unexplained tachycardia or hypotension unresponsive to fluid replacement).

Contrast-enhanced CT evaluation

Contrast-enhanced CT images were obtained from the pulmonary apex to the foot in all cases, and the incidences of pulmonary embolism (PE) and deep venous thrombosis (DVT) were compared. Contrast-enhanced CT was performed 5–6 days after surgery, using a 64-row multi-slice CT (Aquilion 64®; Toshiba Medical Systems, Tochigi, Japan). The contrast agent Iopamiron® (Bracco, Milan, Italy) was injected into an upper extremity vein (100 mL, 4 mL/s). During the arterial phase, for 22 s after the injection, imaging was performed from the pulmonary apex to the costophrenic angle. During the venous phase, i.e. 300 s after the injection of contrast agent, imaging was performed from the diaphragm to the foot. All images were acquired as 2-mm horizontal axial sections, from which coronal and sagittal sections were reconstructed [28]. Two radiologists evaluated the images to determine the presence of VTEs.

Statistical analyses

The mean ± standard deviation was calculated for each group. Differences between the control and TXA groups were evaluated with Welch's t test. The Chi-square test was used to compare the findings between deseases, sexes, blood transfusion rates and incidences of VTE. p values of < 0.05 were considered statistically significant. Statistical calculations were performed using EZR-WIN (Saitama Medical Center, Saitama, Japan).

Results

During the 3.5-year period, we retrospectively analysed 86 patients who underwent cemented primary TKA by a single surgeon at our hospital. Demographic data for the patients are shown in Table 1. The two groups were well matched, showing no significant inter-group differences. The mean postoperative blood loss was 900 ± 296 mL in the TXA group and 1216 ± 445 mL in the control group ($p < 0.001$) (Table 2). The mean postoperative reduction in haemoglobin levels was significantly less in the TXA group than in the control group (Fig. 1). Allogeneic blood transfusion was required for 0 (0%) and 6 (13.3%) patients in the TXA and

Table 2 Estimated blood loss and ratio of blood transfusion

	Control ($n = 45$)	TXA ($n = 41$)	p value
Blood loss (mL)	1216 ± 445	900 ± 296	0.0001*
Blood transfusion [n (%)]	6 (13.3)	0 (0)	0.013*

Control control group, *TXA* tranexamic acid group

*$p < 0.05$

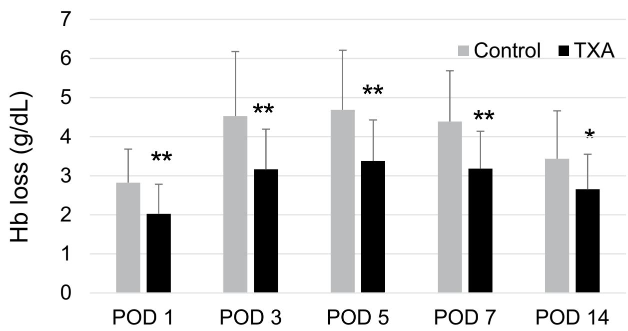

Fig. 1 Postoperative reduction of haemoglobin levels. The mean postoperative reduction in haemoglobin levels was significantly less in the TXA group than in the control group. *Hb* haemoglobin, *POD* postoperative day, *Control* control group, *TXA* tranexamic acid group. $*p < 0.001$, $**p < 0.0001$

Table 3 Postoperative D-dimer and incidence of venous thromboembolism (VTE)

	Control ($n=45$)	TXA ($n=41$)	p value
Postoperative D-dimer (µg/mL)	6.7 ± 3.3	6.6 ± 2.9	n.s.
VTE [n (%)]	26 (57.8)	18 (43.9)	n.s.
Symptomatic PE [n (%)]	0 (0)	0 (0)	n.s.
Asymptomatic PE [n (%)]	11 (24.4)	9 (22.0)	n.s.
DVT [n (%)]	25 (55.6)	17 (41.5)	n.s.

Control control group, *TXA* tranexamic acid group, *PE* pulmonary embolism, *DVT* deep venous thrombosis

control groups, respectively ($p=0.013$) (Table 2). Postoperative D-dimer levels and frequency of DVT and PE are shown in Table 3. The mean postoperative level of D-dimer was 6.7 ± 2.9 µg/mL in the TXA group and 6.6 ± 3.3 µg/mL in the control group ($p=0.965$). DVT occurred in 18 (41.9%) and 25 (55.6%) patients in the TXA and control groups, respectively ($p=0.199$). PE occurred in 9 (20.9%) and 11 (24.4%) patients in the TXA and control groups, respectively ($p=0.694$) (Table 3). There were no cases of symptomatic PE.

Discussion

The most important finding of our study was that intra-articular 1 g TXA administration during TKA had a sufficient effect on the reduction of blood loss and blood transfusion. Furthermore, contrast-enhanced CT demonstrated that intra-articular 1 g TXA administration during TKA did not increase the incidence of VTE.

Several meta-analyses reported that both topical TXA and intravenous TXA were equally effective in reducing blood loss and transfusion rates in patients who underwent TKA [11–13], and some studies showed that even 1 g of topical TXA had a sufficient effect [20, 21]. In this study, intra-articular administration of 1 g of TXA just after wound closure produced sufficient effect on decreasing blood loss and blood transfusion. TXA administration is easy and inexpensive.

Furthermore, in this study, we used contrast-enhanced CT to examine the incidence of VTE after TKA. To our knowledge, no study has investigated the effect of TXA on the incidence of VTEs using contrast-enhanced CT. Two studies evaluated VTEs after TKA using contrast-enhanced CT. Miyagi et al. [29] reported that VTEs occurred in 38.9% (21/54) of patients. In another study, VTE was detected in 97 of 194 patients (50.0%) [28]. In the present study, we detected VTE in 44.2% and 57.8% of the patients in the TXA and control groups, respectively. These incidences are similar to those in the above-mentioned reports. At least, the incidence of VTE did not increase in the TXA group. This finding is supported by previous reports noting that the intravenous or intra-articular administration of TXA did not affect VTE incidence, although most of them diagnosed VTE mainly based on clinical findings without imaging studies like contrast-enhanced CT.

There were several limitations in this study. First, this was a retrospective study. Second, a preoperative CT scan to detect VTEs was not performed. Third, the patients in the control group did not have any drain clamp time after surgery. In the TXA group, the drain was clamped for 2 h after TXA administration via a drain. However, it was not clear how long a drain should be clamped or whether a drain needed to be placed in the knee after TKA. Further examinations regarding this are required.

Conclusions

This study demonstrated that intra-articular TXA administration during TKA is safe and effective for the reduction of blood loss and blood transfusion without increasing the incidence of VTE. Our results suggest that even 1 g of TXA administered intra-articularly was effective.

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Compliance with ethical standards

Conflict of interest Associate professor Miyazawa declares that his salary is supported by Teijin Nakashima Medical Co. Ltd. The other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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