Intra-Articular Injection of Tranexamic Acid on Perioperative Blood Loss During Unicompartmental Knee Arthroplasty

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Background: Tranexamic acid (TXA) is safe and effective in total knee arthroplasty (TKA) for the prevention of bleeding. However, the role of TXA during unicompartmental knee arthroplasty (UKA) remains unclear. This study aimed to compare operative blood loss in patients undergoing UKA treated with an intra-articular injection of TXA with controls undergoing UKA without TXA.

Material/Methods: The prospective study included 101 patients who underwent UKA between January 2014 to March 2018. All patients completed a preoperative routine examination and were randomized to the study group (n=54) and the control group (n=47). The study group was given an articular injection of TXA (1.5 g in 50 ml normal saline) after the fascia was closed; the control group was injected with the same volume of normal saline. Blood volumes were measured from the drainage tube of the two groups during 48 hours. Total blood loss, postoperative drainage, hidden blood loss, blood transfusion rates, postoperative hemoglobin values, indicators of coagulation function, and the rates of wound complications were recorded.

Results: Total blood loss in the study group was 745.6±105.1 ml, total drainage volume was 353.9±79.5 ml, and the hidden blood loss was 391.7±80.5 ml, which were all significantly lower when compared with the control group (P<0.05). None of the patients in the two groups suffered complications of surgery.

Conclusions: Intra-articular injection of TXA significantly reduced the total blood loss in patients who underwent UKA and did not increase the rate of complications.

MeSH Keywords: Arthroplasty, Replacement, Knee • Blood Loss, Surgical • Knee Joint • Tranexamic Acid

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Background

Tranexamic acid (TXA) is an antifibrinolytic agent that promotes the formation of stable hemostasis and is effective in reducing blood loss during total knee arthroplasty (TKA) and total hip arthroplasty (THA) [1–3], TXA has been successfully used in orthopedic surgery to reduce perioperative bleeding [4–6]. The routes of administration of TXA include intra-articular or intravenous treatment or a combination of both. Currently, the use of TXA in TKA is recommended as it has been shown to reduce hemorrhage during TKA effectively and to reduce the need for postoperative blood transfusion.

Compared with TKA, unicompartmental knee arthroplasty (UKA) is less invasive and is usually associated with reduced postoperative hemorrhage [7,8]. However, some patients undergoing UKA still require a blood transfusion, and it has been reported that the blood transfusion rate in minimally invasive UKA surgery can be as high as 7.4% [9]. Blood transfusion can be associated with complications that include a febrile reaction, transmission of viral infection, hemolysis and allergic reactions, which can increase postoperative morbidity [10,11]. Hemorrhage associated with surgery can cause delayed postoperative rehabilitation and mobility and delays improvement in the function of the knee.

Currently, there have been few studies to evaluate the effect of TXA on postoperative hemorrhage in UKA. In 2016, the findings from a retrospective study showed that the degree of postoperative hemorrhage was not affected by intravenous administration of TXA in minimally invasive UKA surgery [12]. However, the effect of intra-articular injection of TXA on postoperative hemorrhage in UKA surgery remains unclear.

Therefore, this prospective study aimed to compare operative blood loss in patients undergoing UKA treated with intra-articular injection of TXA with controls undergoing UKA without TXA.

Material and Methods

Inclusion and exclusion criteria

The study inclusion criteria were patients with osteoarthritis of the knee who were scheduled to undergo elective UKA surgery in two hospitals from January 2014 to March 2018, who could tolerate surgery and cooperate with postoperative functional exercises. Patients included in the study were informed of the treatment plan and the risks of surgery and signed informed consent.

The study exclusion criteria were patients with infectious arthritis, flexure contracture >15 degrees, the preoperative range of motion (ROM) <90 degrees, varus deformity >10 degrees or valgus deformity >5 degrees. Patients were excluded if they had severe destruction of cartilage in the contralateral compartment with an associated anterior cruciate ligament (ACL) and subchondral bone exposure of the patella, patients with osteonecrosis and severe varus deformity, a history of prior knee surgery, and any contraindication for treatment with tranexamic acid (TXA) [13].

Patient randomization

The study included 101 patients, 36 men and 65 women, an age range of 44–83 years (average, 65.86 years). Routine preoperative examinations were performed, including routine blood tests, coagulation tests, and color Doppler ultrasound examination of the lower limbs. All patients were consecutively numbered from 1–101, sequentially on hospital admission, and randomly divided into the study group (n=54) and the control group (n=47) using random allocation software for parallel group randomized. The process of selecting the two groups of patients is shown in Figure 1.

Surgery and anesthesia

All patients received general anesthesia. Before surgery, a lower extremity inflatable tourniquet was applied and the pressure was initially adjusted to 60 kPa to ensure intraoperative hemostasis. Using the medial patella approach, a 7–10 cm incision was made. Proximal tibia and distal femoral osteotomies could tolerate surgery and cooperate with postoperative function and mobility. Using the medial patella approach, a 7–10 cm incision was made. Proximal tibia and distal femoral osteotomies were performed using standard methods. The appropriate type of UKA prosthesis and meniscus pad (Zimmer Biomet, Warsaw, IN, USA) were selected and installed. None of the patients received patella replacement or trimming. A drainage tube was placed in the knee joint cavity attached to an ordinary drainage bag. The incision was sutured in layers and a pressure dressing was applied using an elastic bandage.

Local administration of TXA

The surgeons were unaware of the patient groups and treatment regimens as each patient was assigned a uniquely numbered
On postoperative day 3, a walking aid was used to enable weight-bearing walking. If the patient did not have complications requiring intervention, they were discharged 3–4 days after the operation. All patients, whether or not they participated in this study, used the same postoperative rehabilitation regime after UKA surgery. The patients without complications and who could walk with a walking aid on postoperative day 3 were discharged home.

Performance during postoperative rehabilitation and the blood test results of the patients during and after surgery were used to determine whether a blood transfusion was needed. If the patients had signs of anemia or the hemoglobin was <70 g/L, they were given a blood transfusion. In accordance with the 2009 Guidelines for Prevention Of Venous Thromboembolism in Chinese Orthopedic Surgery [14], subcutaneous injection of low molecular weight heparin, 4000 IU once per day, was commenced at 12 h after surgery, and oral rivaroxaban (5 mg/day) was continued after hospital discharge. To prevent deep venous thrombosis of the lower extremities, the anticoagulation therapy was continued for a minimum of two weeks. Patients underwent routine Doppler color ultrasonography of both lower limbs at postoperative day 7 and day 14. The stitches were removed at postoperative day 14.

**Preoperative and postoperative parameters**

In addition to height and weight of all patients, the preoperative hemoglobin, hematocrit (Hct), partial thromboplastin time (PTT), prothrombin time (PT), and International Normalised Ratio (INR) were recorded. The operation time, postoperative complications, the total volume of blood loss, postoperative drainage volume, hidden hemorrhage, the requirement for blood transfusion, postoperative hemoglobin values, PTT, PT, INR, postoperative rates of deep vein thrombosis (DVT), and pulmonary embolism (PE) and the incidence of wound complications were recorded.

The degree of hemorrhage was calculated as:

\[
\text{total hemorrhage} = \text{preoperative blood volume} + \left( \text{preoperative hematocrit} - \text{postoperative hematocrit} \right) + \text{blood transfusion volume}
\]

Preoperative blood volume was calculated using the Nadler equation [15–17]:

\[
\text{Male (L)} = \text{height (m)}^3 \times 0.3669 + \text{weight (kg)} \times 0.03219 + 0.6041
\]

\[
\text{Female (L)} = \text{height (m)}^3 \times 0.3561 + \text{weight (kg)} \times 0.03308 + 0.1833.
\]

The amount of hidden hemorrhage was calculated according to the Gross equation [18]:

\[
\text{Hidden hemorrhage} = \text{total hemorrhage} - \text{revealed hemorrhage} - \text{allogeneic blood transfusion volume} + \text{return volume of autologous blood or drained blood.}
\]
The method of examination of deep venous thrombosis included vascular ultrasonography of the lower extremities that was performed on one or two days before surgery and on postoperative day 7 and 14. The examinations were performed by the same person using color Doppler ultrasound.

Statistical analysis

Data were analyzed using SPSS version 13.0 statistical software. Data were expressed as the mean ± standard deviation (SD). Comparison between two sets of data was performed using a group design t-test. The count data were analyzed using the chi-squared ($\chi^2$) test. The dual $\alpha$ value was set as 0.05. A $P$-value $<$0.05 was considered to be statistically significant.

Results

Preoperative and intraoperative data (Table 1)

A total of 101 patients were included in the study and none were lost to follow-up. There was no statistical difference in gender, age, body mass index (BMI), comorbidity, preoperative hemoglobin, hematocrit, coagulation function, preoperative mechanical axis, and physical activity between the study group and the control group ($P$$>$$0.05$) (Table 1).

Postoperative data

There was no significant difference in the operation time, incision length, or length of hospital stay between the study group and the control group ($P$$>$$0.05$) (Table 2). The hemoglobin level was significantly greater in patients undergoing unicompartmental knee arthroplasty (UKA) treated with tranexamic acid (TXA) compared with the control group on postoperative days 1, 3, and 7 ($P$$<$$0.05$) (Table 2). In the study group, there were two cases that required a blood transfusion, while in the control group there were six patients who received a blood transfusion, but there was no significant difference between the two groups ($\chi^2$=1.723; $P$$>$$0.05$) (Table 2). There were no postoperative complications such as deep venous thrombosis (DVT), pulmonary embolism (PE), or surgical site infection in the study group or control group.

Comparison of postoperative blood loss between the study group and the control group

The total blood loss in the study group and the control group was $745.6\pm105.1$ ml and $921.4\pm106.2$ ml, respectively, with a significant difference between the two groups ($t$=8.345; $P$$=0.001$) (Table 3). Compared with the control group, hidden blood loss in the study group ($391.7\pm80.5$ ml) was significantly lower compared with the control group ($509.1\pm85.7$ ml) ($t$=7.097; $P$$=0.001$) (Table 3). In the study group, the postoperative drainage volume at 0–8 h and 8–24 h was significantly lower than in the control group but there was no significant difference in drainage volume after 24 hours between the study group and

### Table 1. General information of patients.

|                | Experiment group (n=54) | Control group (n=47) | $P$ value |
|----------------|-------------------------|----------------------|-----------|
| Gender (Female/Male) | 35/19                   | 30/17                | 0.918     |
| Age (year)       | 64.8±9.6                | 67.1±7.4             | 0.178     |
| BMI (kg/m$^2$)   | 26.5±2.7                | 27.4±4.5             | 0.196     |
| Comorbidity      |                         |                      |           |
| DM (n, %)        | (6, 11.1%)              | (4, 8.5%)            | 0.190     |
| HT (n, %)        | (34, 63%)               | (32, 68%)            | 0.589     |
| Hemoglobin (g/dl)| 13.1±1.5                | 13.0±1.3             | 0.963     |
| Hematocrit (Hct) | 41.4±3.1                | 42.5±3.5             | 0.104     |
| PT-INR           | 0.96±0.03               |                      |           |
| APTT-INR         | 0.93±0.01               | 0.93±0.1             | 0.507     |
| Mechanical axis  | 5.1° Varus              | 4.9° Varus           | 0.070     |
| Activity         | 113.0±22.7              | 111.4±18.8           | 0.708     |

$n$ – number; DM := diabetes mellitus; HT = hypertension; PT-INR – international normalized ratio of prothrombin time; APTT-INR – international normalized ratio of activated partial thrombin time; BMI = body mass index=Weight $(kg)$/Height $(m)^{2}$

There was no statistical difference in gender, age, body mass index (BMI), comorbidity, preoperative hemoglobin, hematocrit, coagulation function, preoperative mechanical axis, and activity between the two groups ($P$$>$$0.05$).
Table 2. Postoperative patient data.

|                          | Experiment group (n=54) | Control group (n=47) | P value |
|--------------------------|-------------------------|----------------------|---------|
| Operation time (min)     | 71.4±11.2               | 71.7±12.7            | 0.916   |
| Incision length (cm)     | 8.2±1.0                 | 8.4±1.2              | 0.387   |
| Hospital stay time (day) | 4.1±1.6                 | 4.2±1.2              | 0.568   |
| Hemoglobin (g/dl) Postop (1 d) | 11.8±0.8             | 11.2±1.8             | 0.027   |
| Postop (3 d)             | 9.3±0.6                 | 8.9±0.8              | 0.004   |
| Postop (7 d)             | 8.5±0.3                 | 8.3±0.4              | 0.003   |
| Blood transfusion (n)    | 2                       | 6                    | 0.189   |
| DVT (n)                  | 0                       | 0                    |         |

n – number; min – minute; DVT – depth venous thrombosis. There was no significant difference in the operation time, incision length, or length of hospital stay between the two groups (P>0.05). Hemoglobin was significantly higher in patients treated with TXA than those in the control group on day 1, 3, and 7 after surgery. (P<0.05).

Table 3. Postoperative drainage and total blood loss.

|                          | Experiment group (n=54) | Control group (n=47) | P value |
|--------------------------|-------------------------|----------------------|---------|
| Drainage (ml) 0–8 h      | 156.3±56.2              | 197.8±61.9           | 0.001   |
| 8–24 h                  | 105.9±29.3              | 127.1±39.0           | 0.002   |
| >24 h                   | 91.6±48.0               | 87.4±34.1            | 0.615   |
| Total drainage (ml)      | 353.9±79.5              | 412.3±80.9           | 0.001   |
| Hidden blood loss (ml)   | 391.7±80.5              | 509.1±85.7           | 0.001   |
| Total blood loss (ml)    | 745.6±105.1             | 921.4±106.2          | 0.001   |

n – number. The total blood loss in the experiment and control groups was 745.6±105.1 ml and 921.4±106.2 ml, respectively, with a statistically significant difference between the two groups (t=8.345, P=0.001, Table 3). Compared with the control group, hidden blood loss of the experimental group (391.7±80.5 ml) was significantly lower than the control group (509.1±85.7 ml) (t=7.097, P=0.001, Table 3). In the experimental group, the drainage volume at 0–8 h and 8–24 h after operation was lower than that of the control group. The difference was statistically significant, but there was no significant difference in drainage volume after 24 hour between the experiment group and the control group.

Table 4. Range of motion (ROM) and HSS score.

|                          | Experiment group (n=54) | Control group (n=47) | P value |
|--------------------------|-------------------------|----------------------|---------|
| ROM                      |                         |                      |         |
| Preop                    | 112.6±4.4               | 113.6±5.1            | 0.302   |
| Postop (1 y)             | 124.7±5.0               | 126.0±5.2            | 0.277   |
| HSS                      |                         |                      |         |
| Preop                    | 58.3±4.5                | 57.8±4.2             | 0.607   |
| Postop (1 y)             | 84.9±3.5                | 85.0±3.2             | 0.846   |

n – number; y – year. There was no significant difference in range of motion (ROM) and HSS score between the two groups (P>0.05). The two groups had shown a very good functional outcome.
the control group (t=0.504; P=0.615) (Table 3). There was no significant difference in the range of motion (ROM) and the Hospital for Special Surgery (HSS) knee score between the two groups (P>0.05) (Table 4).

Discussion

The most suitable surgical procedure for the treatment of isolated medial compartment arthritis remains controversial, but unicompartmental knee arthroplasty (UKA) can be used for patients with limited activity, who are non-obese and older than 60 years [19]. However, UKA surgery can be associated with 7.4% blood transfusion rates, which may result in complications associated with blood transfusion. Tranexamic acid (TXA) has been reported to significantly reduce perioperative blood loss and blood transfusion rates in orthopedic surgery and has been shown to be relatively safe, but there are few reports of its use in UKA [20,21]. The aim of this retrospective study was to compare operative blood loss in patients undergoing UKA treated with an intra-articular injection of TXA with controls undergoing UKA without TXA. The findings showed that the total blood loss of the study group and the control group was found to be 745.6±105.1 ml and 921.4±106.2 ml, respectively. The difference between the two groups was statistically significant (P<0.05), indicating that local application of TXA reduced total blood loss after UKA.

TXA is a synthetic derivative of lysine and is a potent anti-fibrinolytic agent that competes to saturate the lysine binding site of plasminogen, which inhibits binding of plasmin and plasminogen to fibrin to effectively inhibit fibrinolysis [22]. The TXA molecule injected into the knee joint can control the active bleeding point, increase the stability of fibrin clot, and effectively reduce blood loss on the damaged tissue surface. In 2013, Blanié et al. reported that the fibrinolytic effect of TXA reached a peak at around six hours after arthroplasty [23]. Therefore, the best time to administer TXA is from the beginning of surgery to six hours after surgery to minimize blood loss. In the present study, the drainage tube was clamped for four hours after the injection of TXA into the joint to maintain the local drug concentration in the intra-articular cavity, so that TXA had sufficient time to exert its effect.

In this study, the drainage volume of the study group in the first eight hours (156.3±56.2 ml) was significantly lower than that in the control group (197.8±61.9 ml) (P<0.05). This finding supported that the local use of TXA could significantly reduce the drainage volume in the first eight hours after UKA. The drainage volume in the first eight hours after surgery in both the study group and the control group was significantly greater than the drainage volume between 8–24 h, indicating that the peak of hemorrhage after UKA surgery occurred within the first eight hours after surgery. Hemorrhage may be related to release of the tourniquet and activation of plasminogen, which promotes fibrinolytic reactions and increases the amount of bleeding, or due to active hemorrhage into the joint due to insufficient hemostasis. After 24 hours, there was no statistical difference in the drainage volume between the study group and the control group (P=0.615). This finding may be related to a reduced concentration of the TXA in the tissues due to the metabolism of the compound. Pharmacological studies have shown that the half-life of TXA in the knee joint is three hours [24]. In the current study, the amount of hidden blood loss in the study group was 391.7±80.5 ml, which was significantly lower than that in the control group (509.1±85.7 ml). Local administration of TXA reduced the intraoperative hidden blood loss. However, the mechanism of hidden blood loss remains unclear, which usually manifests as an effusion into the joint and extravasation of blood into the interstitial space. Also, an increased postoperative intraarticular dose of TXA after surgery, results in a greater hemostatic effect, indicating a dose-dependent effect [25]. However, Liu et al. studied the use of low-dose TXA in TKA and showed that low-dose TXA used during the perioperative period was an effective strategy to prevent blood loss after TKA [26]. However, the relationship between the dose of TXA and blood loss was not evaluated in the present study and so whether or not TXA had a dose-dependent effect in TKA requires further study.

All the procedures used in this study were performed using standard surgical methods. Six patients in the control group required a blood transfusion, while two patients in the study group required a blood transfusion. This difference was not statistically significant. However, Schwab et al. reported that the transfusion rate during minimally invasive surgery with UKA could be as high as 7.4% [9]. In a prospective study, Yang et al. [27] found that the average hemoglobin level after UKA was 11.5 g/dl [27]. In the present study, the average hemoglobin level UKA 8.7 g/dl in the control group and 10.5 g/dl in the study group on postoperative day 7. The surgical procedures, the small surgical incision required, and the reduced soft tissue injury of minimally invasive surgery will reduce the amount of blood loss and lead to less reduction in the hemoglobin level.

This study had several limitations. The number of patients included in this study was relatively small, as the study was conducted in two orthopedic centers. The relationship between different doses of TXA and blood loss was not analyzed in this study. Also, the correlation between blood loss and injection time, the need for drainage tube clamping, and the time between clamping were not analyzed in this study. Although there were some limitations, this study demonstrated that intra-articular injection of TXA could significantly reduce the total blood loss after UKA surgery. The local injection of TXA into the articular cavity is simple to perform, rapid, and has...
no complications such as postoperative venous thrombosis of the lower extremity, and has a good effect with the potential for future clinical use.

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Conclusions

The findings of this prospective clinical study showed that for patients undergoing elective unicompartamental knee arthroplasty (UKA), intra-articular injection of tranexamic acid (TXA) significantly reduced the total blood loss and hidden blood loss, did not increase the rate of complications, and was associated with functional recovery.