Intravenous Combined with Topical Administration of Tranexamic Acid in Primary Total Hip Arthroplasty: A Randomized Controlled Trial

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Objective: Although there are still some controversies, large previous studies have confirmed that intravenous (i.v.) tranexamic acid (TXA) can effectively reduce blood loss and transfusions in total hip arthroplasty (THA) without increasing the risk of deep venous thrombosis. However, few studies have investigated the combination of i.v. and topical application of TXA in primary THA. The purpose of our current study is to examine whether i.v. combined with topical administration of TXA decreases postoperative blood loss and transfusion rates after THA.

Methods: From December 2013 to May 2014, all adult patients undergoing primary THA at our arthroplasty center were considered for inclusion in the present study. Included patients were randomly assigned to two groups by computer-generated list number: a TXA group and a placebo group. Patients in the TXA group received i.v. (15 mg/kg) combined with topical administration (1.0 g) of TXA during the THA procedure, and patients in the other group received the same dosage of normal saline both i.v. and topically. Our primary outcome measures were total blood loss (calculated using Gross’s equation), hemoglobin, hematocrit and platelet concentration changes on the third postoperative day, the amount of drainage, the amount of intraoperative blood loss, the frequency of transfusion, and the number of blood units transfused. Secondary outcome measures were the length of postoperative stay, range of hip motion (measured by goniometer), Harris hip scores (HHS), and any perioperative complications or events such as infection, DVT or PE. Range of motion and HHS were measured at 3 week follow-up and compared with preoperative values.

Results: This trial included 100 patients (50 in each group). Patients in the TXA group had significantly higher postoperative hemoglobin (103 vs 87.7 g/dL, P < 0.01), lower hemoglobin changes (32.2 vs 44.9 g/dL, P < 0.01), higher postoperative hematocrit (0.32 vs 0.27 L/L, P < 0.01), lower hematocrit changes (0.1 vs 0.14 L/L, P < 0.01), lower total blood loss (822 vs 1100 mL, P = 0.004), lower drainage (117.8 vs 242.4 mL, P < 0.01), lower intraoperative blood loss (193.8 vs 288.2 mL, P < 0.01), and lower transfusion rate (2% vs 34%, P < 0.01) compared with those in the placebo group. No statistical difference was found in postoperative platelets between the two groups. There were no differences in perioperative complications or venous thromboembolism (VTE) events.

Conclusions: The combined administration of i.v. and topical TXA resulted in a clinically relevant reduction in blood loss, compared with placebo group. No thromboembolic complications were observed. This randomized controlled trial supports the combined i.v. and topical administration of TXA in primary THA.

Key words: Blood loss; Topical administration; Total hip arthroplasty; Tranexamic acid; Transfusion
Introduction

Total hip arthroplasty (THA) is one of the most common orthopedic operations and is used for end-stage osteoarthritis and other hip diseases, such as osteonecrosis of the femoral head. However, severe perioperative blood loss during THA operative procedures is a major surgical concern. It is estimated that one-third of patients who received THA required transfusion of one to three units of blood, and the reported range of transfusion rates are between 25% and 84%. The risks of blood transfusion include immunological reactions, volume overload, infection, intravascular hemolysis, renal failure, and even death. Therefore, determining how to reduce bleeding and, therefore, transfusions following THA has become an important and urgent problem to be resolved for orthopedist.

A variety of blood-conserving techniques have been developed to reduce blood loss and postoperative transfusion rates, including controlled hypotension, regional anesthesia, autologous blood transfusion, intraoperative blood salvage, and the use of erythropoietin and anti-fibrinolytic agents. Tranexamic acid (TXA), a synthetic antifibrinolytic agent, can retard fibrinolysis and blood clot degradation by reversible blockade of the lysine-binding sites of plasminogen, plasmin, and tissue plasminogen activator, and has been used to decrease blood loss in various surgical settings. It has been used successfully to stop bleeding after dental extraction, tonsillectomy, prostate surgery, heavy menstrual bleeding, and cardiac surgery, and in patients with hemophilia. The trauma of surgery can activate fibrinolysis by promoting the release of tissue plasminogen activator. The body will naturally inhibit fibrinolysis by 24 h after surgery but TXA may block the activation of plasminogen to plasmin and, therefore, decrease perioperative blood loss. In 1995, TXA was first used in total knee arthroplasty (TKA) and showed good results in reducing blood loss. Since then, many other studies have demonstrated that the administration of TXA, given intravenously (i.v.), reduces postoperative bleeding and the need for transfusion with little or no noticeable side effects in both THA and TKA. Several meta-analyses have also confirmed the previous results and recommended that TXA should be considered for routine use in primary THA and TKA to decrease blood loss.

However, the majority of these studies utilized i.v. administration of TXA. In the literature, it is generally agreed that only a small percentage of the i.v. injected TXA reaches the target location to inhibit tissue fibrinolysis and stabilize clots. It has also been reported that the i.v. administration of TXA decreases external blood loss but not hidden blood loss. Furthermore, the safety of i.v. administration of TXA and the risk of thromboembolic events such as deep vein thrombosis (DVT) or pulmonary embolism (PE) in patients have received increasing attention. Topical administration of TXA leads to 70% lower systemic absorption, and may, therefore, be a safer alternative to giving it systemically. Comparing with application of i.v. TXA in THA, topical TXA was considered with little or no systemic absorption of the TXA; therefore, topical TXA could avoid the potential complications of i.v. TXA administration. Akizuki et al. first reported topical use of TXA in orthopedic surgery in 1997, reporting no postoperative blood transfusion in 42 simultaneous bilateral cementless TKA patients and 64 unilateral cementless TKA patients. The technique did not appeal to many surgeons, or they were not aware of it, because it was not until 2000 that another group reported on the use of topical TXA in THA. In 2005, Yamasaki et al. performed a study with 21 patients who underwent staged bilateral THA for the treatment of osteoarthritis of the hip. The results showed that the postoperative blood loss in the TXA group was significantly lower than that in the control group. Nowadays, some surgeons prefer topical administration of TXA in arthroplasty surgery (e.g. wound irrigation or intraarticular injection), and they have proved that the topical application of TXA to the joint at the time of surgery may be a safer and easier route of administration that achieves similar results to i.v. administration. Some surgeons proposed that the use of topical TXA may be preferable due to the potential reduction of systemic side effects such as DVT and PE.

For consideration of the benefit of i.v. and topical administration of TXA, we hypothesized that low dose i.v. combined with topical administration of TXA may decrease postoperative blood loss and transfusion rates without adversely affecting the overall treatment protocol. The purpose of this prospective, randomized placebo-controlled trial was to assess the efficacy and safety of low dose i.v. combined with topical application of TXA on postoperative blood loss, the transfusion of blood products, and complications in patients undergoing a primary unilateral THA without cement. The primary hypothesis was that i.v. combined with topical administration of TXA in patients undergoing a primary unilateral THA can reduce blood loss and transfusion rates significantly without increasing DVT and PE risk. To our knowledge, no previous study has reported on this combined administration of TXA in THA.

Materials and Methods

The present study was registered in the Chinese Clinical Trial Registry (ChiCTR-TRC-14004474). Approval was obtained from the Clinical Trials and Biomedical Ethics Committee of West China Hospital, and written informed consent was obtained from all participants.

Patients

From December 2013 to May 2014, all adult patients (aged between 18 and 90 years) undergoing primary unilateral THA at West China Hospital were considered for inclusion in this trial. Patients were eligible for participation if they had end-stage joint disease and the treating surgeon believed their pre-morbid activity profile and general condition made them suitable for a THA. The exclusion criteria included allergy to TXA, preoperative hepatic or renal dysfunction, preoperative use of anticoagular medication 7 days prior to surgery, history of fibrinolytic disorder or blood dyscrasia,
cerebrovascular accident, myocardial infarction, New York heart association class III or IV heart failure, atrial fibrillation, history of deep vein thrombosis or pulmonary embolus, preoperative international normalized ratio (INR) >1.4, activated partial thromboplastin time (aPTT) >1.4X normal, platelets <140 000/mm³, and failure to give consent.

**Surgical Technique and Drug Delivery**

The THA was undertaken by one senior author under general anesthesia. The patient was positioned laterally and a posterolateral approach was performed. The patients were randomized into two groups by computer-generated list number: TXA group and placebo group. The TXA group received i.v. (15 mg/kg, 15 mg TXA) in 1.5 mL normal saline (NS) combined with topical administration (1000 mg TXA in 100 mL NS) of TXA during THA procedure, and the placebo group received the same dosage of NS (100 mL NS i.v. combined with 100 mL NS topical). For patients in the TXA group, 15 mg/kg TXA was applied i.v. ly 5 min before the skin incision. Then, after acetabular preparation the acetabulum was bathed with 20 mL (200 mg) of the TXA solution (point one). An acetabular component was fixed tightly with a 1-mm press-fit. After femoral canal broach preparation, 20 mL (200 mg) of the TXA solution was placed within the femoral canal (point two). After reduction of the final hip components, 60 mL (600 mg) of the TXA solution was applied to the open joint surfaces and was left in contact with the tissues for 5 min (point three). The wound was then closed without any irrigation or manipulation. Topical administration of TXA in the above three points was reported on in prior studies and was found to be effective and safety.²³,²⁹ The external rotators and capsule points was reported on in prior studies and was found to be effective.

**Blood Transfusion Protocol**

A transfusion protocol based on the guidelines for perioperative transfusion by the Chinese Ministry of Health was utilized to standardize the application of blood transfusions. Blood transfusion was indicated when the hemoglobin concentration was <7 g/dL; blood transfusion was indicated when the hemoglobin concentration was <8 g/dL in a patient who tolerated anemia poorly, and was indicated when the hemoglobin concentration was <10 g/dL in a patient who developed any anemia-related organ dysfunction.

**Thromboembolism Prophylaxis and Venous Thromboembolism Screening**

Prophylaxis against VTE was administrated as per standard practice at our department. All patients were started with passive and active physiotherapy after anesthesia awareness. An inflatable lower extremity venous pump was applied on the first day after surgery. On the second day after surgery, all patients were required to leave their bed and walk, bearing full weight, at least two times. Low molecular weight heparin was first administrated 8 h after surgery, and then applied every 24 h until discharged. After discharge from hospital, rivaroxaban was administration for 15 days to prophylaxis VTE (10 mg/d).

While in the hospital, patients were examined daily for any clinical symptoms of VTE. A diagnosis Doppler ultrasound examination of both legs was performed on postoperative day 3 for all patients. Ultrasound examination was applied at any time if a patient had VTE symptoms. Any thromboembolic events or medical adverse events occurring during the 3 weeks after surgery were recorded at the time of the 3-week follow-up visit.

**Outcome Measures**

Our primary outcome measures were total blood loss, hemoglobin, hematocrit and platelet concentration changes on the third postoperative day, the amount of drainage, the amount of intraoperative blood loss, the frequency of transfusion, and the number of blood units transfused. Total blood loss was calculated using equations described by Gross et al.³¹,³². Secondary outcome measures were the length of postoperative stay, range of hip motion (measured by goniometer), Harris hip scores (HHS), and any perioperative complications or events such as infection, DVT, or PE. Range of motion and HHS were measured at 3 weeks follow-up and compared with preoperative values.

**Statistical Analysis**

Data were recorded as mean, standard deviation (SD) and range. Categorical outcomes were analyzed with use of the x²-test. Continuous outcomes were analyzed with use of the independent-sample t-test. All statistical analysis was performed using SPSS software (version 13.0, SPSS, Chicago, Illinois) and P < 0.05 was considered statistically significant.

**Results**

During the recruitment period, 100 eligible patients were recruited and formed the study cohort. A total of 50 patients were randomized to the TXA group and the other 50 patients were included in the placebo group. The two groups were similar at baseline (Table 1).

**Primary Outcomes**

Table 2 shows details of our primary outcomes regarding perioperative blood loss and transfusion. The postoperative hemoglobin and hematocrit level on postoperative day 3 were significantly higher in the TXA group compared with the placebo group (P < 0.01). Similarly, the postoperative hematocrit level was significantly higher in the TXA group compared with the placebo group (P < 0.01). The postoperative platelet level showed no significant difference between the two groups (P = 0.89). The mean drain blood loss and intraoperative blood loss was 117.8 and 193.8 mL in the TXA group and 242.4 and 288.2 mL in the placebo group, with significant difference between the two groups (P < 0.01).
Estimating using Gross’s formula, the mean total blood loss was 822 mL in the TXA group and 1100 mL in the placebo group, which showed significant difference (P = 0.004).

Two patients (4%) in the TXA group and 17 (34%) in the placebo group required blood transfusions. Four units (800 mL) of concentrated red blood cells (CRBC) were transfused into 2 patients in the TXA group compared with 35 units (7000 mL) into 17 patients in the placebo group (P < 0.01).

Secondary Outcomes
The mean range of motion of prosthetic hips was increased significantly after THA (Table 3). The mean HSS score increased to 91 points in the TXA group and 92 points in the placebo group, which showed no significant difference (P = 0.08). Patients who received the TXA had a mean postoperative hospital stay of 6.2 days compared with 6.8 days for patients who received the placebo (P = 0.14).

There were two complications in the TXA group (one calf muscular venous thrombosis and one periprosthetic fracture) and one in the placebo group (one periprosthetic fracture). Both periprosthetic fractures were calcar split and occurred when implanting the stem prosthesis during surgery. Cerclage wiring was used to fix the fractures and postoperative X-ray examination showed stable implant positions. The muscular venous thrombosis was treated with rivaroxaban for 35 days (10 mg/d) and the periprosthetic fracture was treated with wire internal fixation. No PE or infection occurred in either of the two groups.

Discussion
Perioperative blood loss and subsequent blood transfusion during THA operative procedures is a major surgical concern, and can have a detrimental effect on the surgical outcome. In the present study, i.v. combined with topical administration of TXA significantly reduced postoperative
blood loss in patients having a primary unilateral THA. The calculated blood loss was 25% lower in patients who were managed with TXA as compared with the placebo, with a mean difference of approximately 300 mL. Our results of reduced postoperative bleeding are consistent and comparable with the findings of a previous meta-analysis of individual studies of TXA administration in patients undergoing THA, which demonstrated a reduction of blood loss of about 300 mL per case\textsuperscript{7}.

Tranexamic acid is an inhibitor of fibrinolysis that blocks the lysine-binding site of plasminogen to fibrin and inhibits the activation of plasminogen by plasminogen activators\textsuperscript{6}. Several studies have demonstrated that preoperative i.v. administration of TXA reduces blood loss and transfusion rates in THA. Claes\textit{ et al.} performed a randomized controlled trial and showed that TXA 15 mg/kg given as a single preoperative bolus dose reduced postoperative and total blood loss in primary THA\textsuperscript{33}. Niskanen and Korkala showed a significant relationship between TXA administration and blood loss reduction\textsuperscript{34}. The randomized controlled study from Yamasaki\textit{ et al.} also supported the administration of TXA in THA for reducing blood and transfusion\textsuperscript{35}. Furthermore, in a recent systematic review and meta-analysis of 11 randomized controlled trials, i.v. TXAs was found to reduce blood loss and transfusion needs significantly\textsuperscript{7}.

However, concerns about the safety of systemic administration of TXA and the risk of DVT or PE have hindered the wide adoption of TXA in arthroplasty surgery\textsuperscript{23}. In view of these safety concerns, topical administration of TXA to the joint closure at the time of TKA or THA has become an optimal alternative that will reduce postoperative bleeding yet will not increase the hypercoagulable state associated with TKA or THA\textsuperscript{24,27–30}. The potential mechanism and advantage of topical administration of TXA is to directly target the site of brin clot dissolution and increase its volume and strength at the raw surgical surfaces, thus enhancing microvascular hemostasis\textsuperscript{36,37}. Once injected intra-articularly, TXA is rapidly absorbed and maintains a biological half-time of approximately 3 h within joint fluid\textsuperscript{38,39}. Since 2010, increasing numbers of researchers have preferred topical administration of TXA in TKA or THA, and have demonstrated that topical application of TXA may produce the same efficacy, but with much lower systemic absorption and, thus, much lower risk of VTE complications\textsuperscript{24,27–30}.

Alshryda\textit{ et al.} performed two randomized controlled trials to demonstrate that topical application TXA was effective in reducing blood loss and the need for blood transfusion following THA and TKA\textsuperscript{24,27}. Other studies have identical results to Alshryda\textit{ et al.}\textsuperscript{24,27,28–30}. In our study, we combined i.v. and topical administration of TXA together in THA. We believe this combined regimen of TXA may inhibit fibrinolytic activity in both a systemic and local way, which can reduce blood loss and transfusion rates without increasing DVT and PE risk. To our knowledge, no previous study has reported on this combined administration of TXA in THA.

The present study had several limitations. First, the 3-week follow-up period was thought to be adequate to identify known adverse events like DVT or PE, but it might be inadequate to detect longer-term safety issues, such as accelerated wear of the joint due to exposure to TXA. Patients included in this study were diagnosed with different end-stage joint disease, which might decrease the statistical significance between the two groups. Second, another limitation of the study is that the Doppler ultrasound studies were performed 3 days after surgery, rather than at the peak of clinically evident thrombosis (6–7 days after surgery)\textsuperscript{40}. Third, ultrasound examination was applied at follow-up if a patient had VTE symptoms, which might ignore asymptomatic DVT. Fourth, we only compared the TXA group with the placebo group, which might not reflect the advantage of a combined regimen of mostly TXA. Patients who received i.v. or topical administrations of TXA alone need to be included in another controlled group: a TXA i.v. group and a TXA topical group. Finally, the study population was relatively small. For the low DVT or PE incidence, we believe that the sample size was large enough to reach the conclusion that combined administration of TXA in patients undergoing a primary unilateral THA significantly reduces postoperative bleeding; studies with more patients are needed to determine whether this combined application approach might increase VTE risk.

In conclusion, i.v. combined with topical administration of TXA in patients undergoing a primary unilateral THA reduces postoperative bleeding by 25% in comparison with the values in the placebo group. No increase in thromboembolic or other complications was identified in patients managed with TXA. Larger trials are needed to further confirm whether this promising strategy to reduce bleeding and assess the need for blood transfusion in patients undergoing THA is safe with regard to thromboembolic complications.

### Table 3: Secondary outcomes for both the TXA group and the placebo group (mean ± SD)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Extension (°)</th>
<th>Abduction (°)</th>
<th>Adduction (°)</th>
<th>HHS score (points)</th>
<th>Length of stay after surgery (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TXA group (n = 50)</td>
<td>98.5 ± 2.7</td>
<td>35.7 ± 4.8</td>
<td>21.4 ± 5.4</td>
<td>91.2 ± 5.4</td>
<td>6.2 ± 1.7</td>
</tr>
<tr>
<td>Placebo group (n = 50)</td>
<td>96.0 ± 6.4</td>
<td>40.6 ± 3.8</td>
<td>19.6 ± 4.5</td>
<td>92.3 ± 6.1</td>
<td>6.8 ± 2.0</td>
</tr>
<tr>
<td>P value*</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>0.09</td>
<td>0.08</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*Independent-sample t-test.; TXA, tranexamic acid.
References

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