Primary Arthroplasty

Comparison of 3 Routes of Administration of Tranexamic Acid on Primary Unilateral Total Knee Arthroplasty: A Prospective, Randomized, Controlled Study

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A R T I C L E   I N F O

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A B S T R A C T

Background: The mode of administration for tranexamic acid (TXA) to significantly reduce the decrease in hemoglobin (Hb), number of transfusions, relevant costs, and side effects in patients undergoing primary unilateral total knee arthroplasty (TKA) has not been resolved.

Methods: A total of 560 patients undergoing primary unilateral TKA were randomized into 4 groups: intravenous group (140 patients receiving 2 doses of 20 mg/kg intravenous TXA), topical group (140 patients administered 3.0 g topical TXA), oral group (140 patients given 2 doses of 20 mg/kg oral TXA), and a control group (140 patients not given TXA). The primary outcomes included postoperative 48-hour Hb loss and drainage volume, number of transfusions, transfusion and TXA costs, and thromboembolic complications. Secondary outcomes were postoperative inpatient time and wound healing 3 weeks after TKA.

Results: Baseline data among the 4 groups were similar. The 48-hour Hb loss and drainage volume, number of transfusions, transfusion and TXA costs, and thromboembolic complications. Secondary outcomes were postoperative inpatient time and wound healing 3 weeks after TKA.

Conclusion: All the 3 modes of TXA administration significantly reduced postoperative Hb loss, the number of transfusions, and transfusion costs compared with those in the control group. No pulmonary embolism or infection was observed. Oral TXA is recommended because it provided a similar clinical benefit and resulted in the lowest TXA cost compared with the other 2 modes of TXA administration.

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The number of patients who undergo primary total knee arthroplasty (TKA) has gradually increased over the past several decades because life expectancy has gradually lengthened, the aging population is increasing, and medical services have considerably improved [1–3]. Some studies have shown that blood loss of 1450-1790 mL occurs without special intervention, and that transfusions are needed for 10%-38% of patients undergoing TKA [4–6], which likely results in side effects associated with anemia and allogeneic blood such as hemolysis, abnormal immunologic reactions, infection, additional costs, and morbidity and mortality [4,7–11]. Therefore, a number of strategies to minimize blood loss and decrease the risks of transfusion are performed in patients undergoing TKA. For example, deliberate hypotension [12], spinal anesthesia [13], a tourniquet [14–16], and tranexamic acid (TXA) are used during the operation [17,18]. TXA is a synthetic fibrinolytic inhibitor that competitively inhibits plasmin, plasminogen, and fibrin from combining and directly inhibits plasmin activity at a high concentration [19–21].

Intravenous, topical, and oral routes are available to administer TXA. However, the ideal route of TXA administration remains controversial [20–22]. In addition, no study has compared the 3 TXA administration routes at the same time during primary unilateral TKA. Therefore, the aim of this prospective, randomized, controlled study was to simultaneously evaluate the effects of the 3 TXA administration routes on hemoglobin (Hb) loss, total number of transfusions, additional costs, and side effects, and to...
demonstrate which route is most beneficial for patients undergoing primary unilateral TKA. We hypothesized that the oral administration route would be optimal for TXA.

Materials and Methods

This study was a prospective, randomized, controlled trial supported by the Special Research Program of the Health Care Industry (No. 201302007), Ministry of Public Health, China. It was registered in the Chinese Clinical Trial Registry (ChiCTR-ORC-16009358). Approval was obtained from the ethics committee of our hospital (Approval No: 2013-43), and written informed consent was obtained from all the patients who participated in this study. All the patients who underwent TKA at our hospital from September 2013 to June 2016 were enrolled. Inclusion criteria were osteoarthritis or rheumatoid arthritis, primary unilateral TKA, at least a 3-week follow-up, normal clotting mechanism, and effectively controlled medical diseases. The exclusion criteria were previous bilateral TKA, revision TKA, severe hepatic and/or renal diseases, coagulopathy, or a bleeding disorder.

Preoperative Protocol

Patients eligible for the study were randomized into 4 groups with a list generated by a computer at an allocation ratio of 1:1:1:1 with a maximum number of 140 per each group (intravenous, topical, oral, and control). The intravenous group received 20 mg/kg TXA administered intravenously 30 minutes before incising the skin, and the same dose 12 hours after TKA. The topical group received 3.0 g TXA (total 60 mL solution) administered after the subcutaneous tissue was sutured. The oral group received 20 mg/kg TXA orally 2 hours before the operation and the same dose 12 hours after TKA. No TXA was used in the control group. Furthermore, all the patients in the 4 groups were administered a pill (TXA for oral group, and placebos [calcium tablet] for the other 3 groups), a joint injection (TXA for the topical group, and saline for the other 3 groups), and an intravenous infusion (TXA for the intravenous group, and saline for the other 3 groups). All the patients were administered the drugs by a nurse and an anesthetist who were not involved in the surgeries, care, or assessment of outcomes. The patients, surgeons, care providers, and those assessing outcomes were blinded to the group assignments.

Intraoperative Protocol

General anesthesia was adopted, and TKA was performed through a standard medial parapatellar approach by the same group of senior surgeons. A tourniquet was applied from the incision of the skin until a prosthesis was fitted. The same type of drainage tube was clamped for 2 hours and removed 48 hours after TKA.
The extremity venous pump was applied the first day after TKA. Means and standard deviations were calculated for quantitative data, and frequencies or percentages were determined for qualitative data. One-way analysis of variance was performed to compare continuous variables, and the chi-square test was used to compare categorical variables. A P value <.05 was considered statistically significant.

Results

A total of 161 of 721 patients undergoing TKA were excluded because they failed to meet the inclusion criteria of this study (Fig. 1). The remaining 560 patients were eligible and divided randomly into 4 groups (n = 140 per group) according to the TXA administration route. Among the patients, 46% (258 of 560) were male and 97.5% (546 of 560) were diagnosed with osteoarthritis or rheumatoid arthritis. The baseline data among the 4 groups were similar (P > .05; Table 1).

**Primary Outcomes**

According to Tables 2-5, no difference was observed in preoperative Hb concentration among the 4 groups (P = .51). The 48-hour Hb loss and drainage volume, the ratio of patients transfused, total number of transfused units, and the transfusion costs in the control group were 3.34 ± 0.48 g/dL, 441.50 ± 48.29 mL, 25.7%, 81 U, and ¥34,830.0, respectively, which were significantly higher than those in the other 3 groups (P < .05). The oral group had the lowest cost for TXA (¥1936.6) compared with that in the intravenous (¥6062.4) and topical (¥6048.0; P < .05) groups. There were 30 cases of intramuscular venous thrombosis, 4 of DVT, and no PE cases (P = .53).

**Secondary Outcomes**

Table 6 shows that no difference was observed in mean postoperative inpatient time among the 4 groups (P = .39). One patient...
in the topical group stayed for 8 days because of wound dehiscence and continuous wound discharge. Although no infection occurred in any wound and no difference was detected in wound healing among the 4 groups, it is notable to consider 1 patient in the topical group. The knee joint of this patient was full of a large number of blood clots at the first surgical debridement. The continuous wound discharge was eliminated thoroughly and the wound healed well on day 8 after TKA.

Discussion

Many studies have reported the potential mechanism of action for TXA, which is a synthetic derivative of lysine that competitively inhibits plasminogen and the binding between plasmin and fibrin, stabilizes blood clots, and decreases the fibrinolysis rate [19,21,25]. TXA has been frequently used to reduce the risks of blood loss and the number of blood transfusions in surgeries that activate fibrinolysis by release of tissue plasminogen activator [26,27]. In particular, the efficacy of TXA for minimizing the risks of anemia and transfusion during TKA and total hip arthroplasty has been investigated and is associated with mortality and morbidity [8,9,28,29]. Some studies have also assessed different administration routes for TXA. However, the best administration route for TXA has remained unclear and controversial, until now [18,30]. For example, TXA is administered intravenously because this method widely, rapidly, and uniformly distributes TXA into the knee joint [31,32]. Compared with intravenous TXA, topical TXA is convenient to administer, reaches a local maximum concentration quickly, and decreases systemic side effects caused by intravenous TXA [6,33].

We performed this prospective, randomized, controlled study to address this issue. This is the first study to evaluate the effects of TXA administration route on patients compared with a proper control group. Our results show that TXA significantly reduced Hb loss and the number of transfusions compared with the control group in patients undergoing primary unilateral TKA, and no differences were observed in thromboembolic complications or wound healing. One previous trial reported a significant increase in thromboembolic complications (eg, DVT and PE) in patients receiving intravenous TXA during hemiarthroplasty surgery [34].

On the other hand, in this study, 1 patient who received topical TXA suffered from an incision that did not heal properly because a large number of blood clots formed in the knee joint, leading to swelling and seepage that resulted in a longer inpatient time (8 days) and increased exposure to nosocomial pathogenic bacteria [8,35]. Thus, we doubt that topical administration of TXA was thoroughly distributed locally, resulting in clots in the knee joint and blocked drainage tubes, which prevented blood and other fluids from being discharged. In addition, the topical group tended to have a smaller mean drainage volume (399.07 mL) than the intravenous (400.71 mL) and oral groups (399.21 mL). Blocking fluid from draining properly affects primary healing of the incision after TKA and can create a passage for infection, which is often disastrous for patients who have undergone joint arthroplasty [31,36]. Therefore, this kind of side effect caused by topical TXA administration should be considered carefully.

The medical costs during the inpatient period are also a special concern in patients undergoing TKA. Therefore, studies are needed to determine how to reduce patients’ medical costs effectively and safely. Use of TXA during surgery, particularly total joint arthroplasty, has become increasingly popular because it saves money. Several studies have demonstrated that using TXA significantly lowers transfusion costs by reducing blood loss and the number of transfusions [37,38]. Gillette et al [39] reported that 1 patient saved $879 when taking all inpatient costs into account. These findings are consistent with the results of our study. In our study, the control group had higher costs associated with transfusion ($34,830.0) than the other 3 groups. Moreover, the oral group had the greatest cost savings compared with the intravenous and topical groups ($1936.6, $604.8, and $6062.4, respectively). More patients will be undergoing primary TKA considering the gradual increase in the aging population. Consequently, the administration of oral TXA will help patients undergoing primary TKA to save money.

Several limitations of our study should be mentioned. First, the follow-up time of 3 weeks may have been too short to evaluate the long-term safety of TXA because DVT sometimes occurs within 5 weeks after arthroplasty. However, the peak time for thrombosis is 10–11 days after surgery [40,41]. In addition, the half-life of TXA is only a few hours, and it is all nearly excreted within 24 hours, which may be adequate to assess thromboembolic complications caused by TXA in a 3-week follow-up. But to fully confirm whether some DVT occurring in a longer time after TKA is caused by TXA, a longer follow-up may be required. Second, based on previous studies, we administered 2 doses of 20 mg/kg TXA before the operation and 1 dose after the operation in the intravenous and oral groups, and 1 dose of 3.0 g TXA intraoperatively in the topical group. However, this may not be the best regimen. Further studies should evaluate the effects of different frequencies and doses of TXA and even a combination of different administration routes.

Table 3
Comparison of 48-h Hb Loss Between 2 of 4 Groups.

<table>
<thead>
<tr>
<th>P Value*</th>
<th>Intravenous Group</th>
<th>Topical Group</th>
<th>Oral Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous group</td>
<td>—</td>
<td>1.00</td>
<td>.78</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Topical group</td>
<td>1.00</td>
<td>—</td>
<td>.78</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oral group</td>
<td>.78</td>
<td>—</td>
<td>—</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Control group</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>—</td>
</tr>
</tbody>
</table>

The P value represents the result of Bonferroni test for comparison of mean values between 2 of the 4 groups in additional cost after 1-way analysis of variance. *P < .05 was significantly different.

Hb, hemoglobin.

Table 4
Comparison of Transfusion Units Between 2 of the 4 Groups.

<table>
<thead>
<tr>
<th>P Value*</th>
<th>Intravenous Group</th>
<th>Topical Group</th>
<th>Oral Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous group</td>
<td>—</td>
<td>.69</td>
<td>.87</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Topical group</td>
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<td>.58</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oral group</td>
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<td>—</td>
<td>—</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Control group</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>—</td>
</tr>
</tbody>
</table>

The P value represents the result of Bonferroni test for comparison of mean rank sums between 2 of the 4 groups in transfusion units after 1-way analysis of variance. *P < .05 was significantly different.
In conclusion, our clinical findings support that TXA can effectively, safely, and significantly decrease Hb loss and the number of transfusions without severe side effects in patients undergoing TKA in a 3-week follow-up (e.g., DVT, PE, and infection). In addition, oral TXA may be superior considering the clinical benefit and cost savings compared with those in the intravenous or topical TXA group.

Acknowledgments

The authors thank all the volunteers for participating in this study.

References


Table 6

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Intravenous Group</th>
<th>Topical Group</th>
<th>Oral Group</th>
<th>Control Group</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection/ (wound dehiscence/ fat liquefaction/ subcutaneous ecchymosis)</td>
<td>3</td>
<td>0/0/2/9</td>
<td>3</td>
<td>0/0/3</td>
<td>0/0/2</td>
</tr>
</tbody>
</table>

The P value represents the result of 1-way analysis of variance for the continuous variables compared among groups and the chi-square test for the categorical variables comparison.

*P < .05 was significantly different.

Postop, postoperative.


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