Effect of Intra-articular Injection of Tranexamic Acid on Postoperative Hemoglobin in Total Hip Arthroplasty

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abstract

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Postoperative anemia is a significant risk factor in total hip arthroplasty, leading to increased length of hospital stay and delayed mobility and rehabilitation, and is poorly tolerated by patients with peripheral vascular and cardiovascular disease. Intravenous tranexamic acid, an antifibrinolytic drug, has been shown to reduce postoperative anemia in total joint replacement. Intra-articular administration eliminates the risk of systemic effects, the most concerning of which is thrombosis. Although this method of administering tranexamic acid has been studied in total knee replacement, currently no literature has been published on its efficacy in primary total hip replacement. The purpose of this study was to examine postoperative hemoglobin decrease and the transfusion rate following intra-articular tranexamic acid administration in primary total hip arthroplasty. The authors conducted a retrospective review of 181 consecutive total hip replacements, 91 of which received tranexamic acid. No statistical significance was found between these groups in any of the demographic variables. Postoperative hemoglobin decrease in the control group was 4.4±1.0 g/dL compared with a decrease of 3.6±1.1 g/dL in the tranexamic group, demonstrating an 18% reduction in blood loss (P<.001). No significant difference was found between the number of patients transfused (P=.777) or the number of units used (P=.993). No clotting events were seen in either group. Overall, the study demonstrates that intra-articular tranexamic acid in primary total hip arthroplasty is associated with a significant improvement in postoperative hemoglobin decrease without systemic hypercoagulability.

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Total hip arthroplasty (THA) is growing at an exponential rate in the United States and postoperative anemia is a significant risk factor of particular importance in elderly patients undergoing THA, who already have a higher prevalence of preoperative anemia and comorbid medical conditions. In addition, up to half of patients undergoing THA have received an average of 2 units of blood postoperatively. However, allogenic blood transfusion has potential risk and cost implications.

Antifibrinolytic drugs, such as tranexamic acid, have been found to reduce blood loss in THA. Tranexamic acid is a synthetic analog of the amino acid lysine that acts by competitively blocking the lysine-binding site of plasminogen, leading to inhibition of fibrinolysis. Several studies have shown the effectiveness of intravenous tranexamic acid use on reducing blood loss in THA. However, concerns about the safety of the systemic administration of tranexamic acid and the risk of thromboembolic events, such as deep vein thrombosis or pulmonary embolism, in the high-risk THA patient population have hindered the wide adoption of this medication in the setting of total joint arthroplasty. In view of such safety concerns, intra-articular injection of tranexamic acid during THA may be a safer route of administration that will reduce postoperative bleeding while not increasing the hypercoagulable state associated with THA.

Intra-articular injection of tranexamic acid in total knee arthroplasty has been shown to be more effective than an intravenous injection in reducing the amount of blood lost and needed for transfusion. In addition, in patients undergoing total knee arthroplasty, intra-articular tranexamic acid has been shown to reduce postoperative swelling, leading to improved wound healing, reduced pain, and more rapid rehabilitation. Intra-articular injection of tranexamic acid at the surgical site provides a direct and straightforward means of application with the potential mechanism and the advantage of directly targeting the bleeding site just before wound closure but after surgical hemostasis has been achieved. Currently, no published investigations have been made of the intra-articular use of tranexamic acid in primary THA. The purpose of this study was to retrospectively examine the effectiveness of intra-articular injection of tranexamic acid in THA following joint capsule closure on postoperative hemoglobin decrease and the blood transfusion rate.

**METHODS AND MATERIALS**

The authors retrospectively reviewed the records of all patients who underwent unilateral primary THA by a fellowship-trained total joint specialist (J.H.) in private practice in a consecutive series from September 2011 to September 2012. No routine patient care or surgical practices were altered during this time, with the exception of the implementation of the use of tranexamic acid beginning in March 2012. During this time, all patients were given the drug regardless of their risk for bleeding. The only exclusion criteria was known allergy to tranexamic acid, which no patient had.

Patient data were retrieved from a private database kept by the performing surgeon. All identifying data were removed prior to the study and the institutional review board at the authors’ institutions granted approval. A total of 181 patients were found during the study period, and all were included in the study. The control group consisted of 90 patients who received nothing, whereas the experimental group contained 91 patients who received 1 g of tranexamic acid (Pfizer, New York, New York) in 10 mL of sterile saline injected following fixation of the implants and closure of the hip capsule. In all patients, a Smith & Nephew (London, England) cementless R3 acetabular cup with an Anthology porous femoral stem, Oxinium femoral heads, and highly cross-linked R3 poly liner were implanted.

Patients were grouped based on risk factors for bleeding and clotting. Patients with liver disease, platelet dysfunction or thrombocytopenia, or coagulopathy and those taking anticoagulation medications were considered to be at risk for bleeding. Patients with history of deep vein thrombosis or pulmonary embolism, cancer, smoking, and previous stroke or myocardial infarction were considered to be at an increased risk for clotting.

All patients were given a spinal anesthetic and fascia iliaca block, with use of a laryngeal mask airway being at the discretion of the anesthesiologist. Most surgeries (n=162; 89.5%) were done through a direct anterior approach with a small hemovac drain placed just under the tensor fasciae latae, with the remaining surgeries (n=19; 10.5%) being done through a posterior approach. In addition, most patients received aspirin alone for their postoperative anticoagulation medication; however, a small group of patients at high risk for deep vein thrombosis received warfarin. Both of these decisions were at the discretion of the surgeon.

Preoperative hemoglobin levels were drawn as part of the preadmission process. Postoperative hemoglobin levels were drawn routinely as part of a complete blood cell count on each postoperative day until the patient left the hospital. The preoperative hemoglobin level was compared with the lowest postoperative value to determine the hemoglobin decrease. The decision and quantity to transfuse were at the discretion of a hospitalist, who comanaged all postoperative surgical patients. The transfusion trigger was a hemoglobin level of 7.0 g/dL or lower unless the patient had a known cardiac disease or was symptomatic. Only banked blood was used for transfusion. Complications were defined by clotting events, which included deep vein thrombosis, pulmonary embolism, myocardial infarction, and cerebrovascular accident, or as blood loss–related events, which included significant hematoma formation or syncopal episodes.
A mathematician associated with the practice conducted all statistical analyses. He used parametric tests (t test) and a nonparametric test (Mann-Whitney U test) when appropriate.

**RESULTS**

Patients’ demographic data with continuous variables are found in Table 1, and no statistical significance was found in any category. Table 2 provides the distribution of the nominal patient variables. No statistical significance was found between these groups in any of these variables. Patients with known hypercoagulable states and those at an increased risk for bleeding are summarized in Table 3, with no statistical difference seen between the 2 groups. Regarding complications, no clotting events were seen in either group. However, the control group had 1 patient with a thigh hematoma that did not require surgical evacuation and another patient with a syncopal episode in the hospital.

The postoperative hemoglobin decrease in the control group was 4.4±1.0 g/dL (range, 1.8-6.8 g/dL), whereas the tranexamic acid group had a mean hemoglobin decrease of 3.6±1.1 g/dL (range, 1.3-7.5 g/dL). Therefore, the use of tranexamic acid was associated with a significantly (P<.001) reduced decrease of 18% in postoperative hemoglobin. Six (6.7%) patients in the control group were transfused a total of 11 units of blood (range, 1-2 each), whereas 7 (7.7%) patients in the tranexamic acid group were transfused a total of 13 units (range, 1-3 each). No significant difference was found in the number of patients transfused (P=.777) or in the number of units used (P=.993) between the 2 groups.

**DISCUSSION**

In this study, the current authors retrospectively reviewed 181 patients undergoing primary THA to assess the effectiveness of intra-articular tranexamic acid use on postoperative hemoglobin decrease and transfusion rate. To the authors’ knowledge, this is the first study in the literature that reviews the topical administration of tranexamic acid during a primary THA. The authors found that intra-articular administration of tranexamic acid to the hip joint following closure of the capsule significantly reduced postoperative blood loss in patients having a primary unilateral THA.

Postoperative anemia in patients who underwent joint replacement leads to increased length of hospital stay and delayed mobility and rehabilitation and is poorly tolerated by patients with peripheral vascular and cardiovascular disease. Treatment for this anemia is most commonly through homologous blood transfusions; however, this is associated with the risk of transfusion-related adverse events. Tranexamic acid is a synthetic, non-competitive and reversible inhibitor of plasmin, which has been shown to reduce the risk of postoperative anemia in this study and others. 

### Table 1

<table>
<thead>
<tr>
<th>Continuous Patient Variable</th>
<th>Tranexamic, Mean±SD</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.9±9.0</td>
<td>61.4±10.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.7±5.8</td>
<td>30.1±5.4</td>
</tr>
<tr>
<td>Incision, cm</td>
<td>11.9±1.2</td>
<td>12.0±1.1</td>
</tr>
<tr>
<td>Operative time, min</td>
<td>92.3±16.7</td>
<td>91.5±15.6</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>2.4±0.8</td>
<td>2.3±0.7</td>
</tr>
</tbody>
</table>

**Abbreviation:** BMI, body mass index.

### Table 2

<table>
<thead>
<tr>
<th>Nominal Patient Variables</th>
<th>Tranexamic, No. (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46 (51.1)</td>
<td>47 (51.6)</td>
</tr>
<tr>
<td>Female</td>
<td>44 (48.9)</td>
<td>44 (48.4)</td>
</tr>
<tr>
<td>Side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>47 (52.2)</td>
<td>45 (49.5)</td>
</tr>
<tr>
<td>Right</td>
<td>43 (47.8)</td>
<td>46 (50.6)</td>
</tr>
<tr>
<td>Approach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>79 (87.8)</td>
<td>84 (92.3)</td>
</tr>
<tr>
<td>Posterior</td>
<td>11 (12.2)</td>
<td>7 (7.7)</td>
</tr>
<tr>
<td>Anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral block</td>
<td>87 (96.7)</td>
<td>84 (92.3)</td>
</tr>
<tr>
<td>None</td>
<td>3 (3.3)</td>
<td>7 (7.7)</td>
</tr>
<tr>
<td>DVT prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>85 (94.4)</td>
<td>83 (91.2)</td>
</tr>
<tr>
<td>Coumadin</td>
<td>5 (5.6)</td>
<td>8 (8.8)</td>
</tr>
</tbody>
</table>

**Abbreviation:** DVT, deep vein thrombosis.
of infection and viral transmission, as well as hemolysis, immunosuppression, transfusion related acute lung injury, fluid overload, and even death. In addition, allogeneic transfusion is independently associated with a 1.5-fold increase in the risk of development of thromboembolism postoperatively. Therefore, obvious medical and financial advantages are found in reducing transfusion to a minimum.

Various methods have been used to reduce the amount of bleeding intraoperatively, including blood conservation programs, intraoperative red cell salvage, autologous retransfusion, use of erythropoietin, and use of antifibrinolytic drugs. Despite aggressive attempts to reduce perioperative transfusion rates through blood conservation program, Ralley et al\(^6\) reported that they have reached a plateau in the program’s effectiveness. Autologous transfusion is a relatively safe and effective option for these patients, but the collection and transfusion of autologous blood carry risks, including compartment syndromes, bacterial contamination, febrile nonhemolytic and septic reactions, phlebitis, and clerical error. Predonation is also difficult to organize, and units collected are often discarded, making it relatively expensive. In addition, patients least likely to require transfusion are those most suitable for predonation. Cell salvage requires specialized equipment and suitably trained staff, whereas the yield of erythrocytes from postoperative autotransfusion is typically low. Although effective in reducing postoperative transfusion, erythropoietin is expensive.

Antifibrinolytics are believed to potentiate inhibition of fibrinolysis at an earlier stage by competitively inhibiting the activation of plasminogen to plasma. They promote hemostasis and reduce bleeding and the need for allogeneic transfusion. Specifically, tranexamic acid is an affordable and selective intravenous fibrinolytic inhibitor that carries a reduced risk of anaphylaxis. A meta-analysis by Sukeik et al\(^7\) demonstrated a significant reduction in intraoperative, postoperative, and total blood loss, as well as allogeneic blood transfusion, following use of intravenous tranexamic acid in THA. In addition, they demonstrated a dose response curve with tranexamic acid use and blood loss.

Intra-articular administration of tranexamic acid provides a novel therapeutic approach for decreasing bloodshed from the surgical wound after THA. Although it has only been shown in nonorthopedic literature, the current authors believe a concern still exists for tranexamic acid to promote a hypercoagulable state when used intravenously in the study’s patients, leading to cerebral, pulmonary, mesenteric, and retinal thrombosis. In addition, the effect of intravenous tranexamic acid on disrupted endothelium remains unknown. However, the complication rate following tranexamic acid administration is small because systemic absorption is low when administered intra-articularly.

A large number of studies discuss the cost-effectiveness of different intravenous tranexamic acid protocols; however, intra-articular use limits the dose required, and thus the cost, making its use more significant. This is because only a small portion of the drug reaches the target location when injected intravenously; therefore, intra-articular administration would provide a more efficient method of delivery. In addition, multiple factors contribute to therapeutic effectiveness following intravenous administration of a drug, including factors related to the patient, medication, disease, surgeon, duration of surgery, and method of anesthesia. In addition, the half-life of 1 g of intravenous tranexamic acid was found to be 1.9 hours, meaning that at 10 mg/kg body weight, tranexamic acid in plasma remains at or over the minimum therapeutic level for approximately 3 hours after intravenous administration. However, when used intra-articularly, tranexamic acid enters the tissue space and accumulates for up to 17 hours. Furthermore, dosing schedules of either an initial bolus of tranexamic acid followed by 6- to 12-hour infusion or multiple intravenous bolus doses are cumbersome and labor-intensive, making them difficult to introduce into a busy operating room schedule.

However, administration within a narrow and restricted joint cavity creates a high drug-concentration at raw surgical surfaces. While at therapeutic concentrations, the antifibrinolytic action of tranexamic acid involves competitive inhibition of fibrinolysis; at a higher concentration, it also acts as a weak noncompetitive inhibitor of fibrinolysis. Given its competitive and noncompetitive inhibition of fibrinolysis, a distinct probability exists that it facilitates persistent clot stabilization secondary to noncompetitive inhibition.

### Table 3

**Patient Bleeding Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tranexamic Acid, No. (%)</th>
<th>( P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=90)</td>
<td>Yes (n=91)</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>90 (98.9)</td>
<td>87 (96.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (1.1)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Hypercoagulable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>77 (84.6)</td>
<td>84 (93.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>14 (15.4)</td>
<td>6 (6.7)</td>
</tr>
</tbody>
</table>
hilation of fibrinolysis, which effectively decreases ooz-related blood loss from the raw surgical surfaces. In addition, intra-articular tranexamic acid injection has the advantage of inducing partial microvascular hemostasis by stopping fibrin clot dissolution in the affected area.

Although the current authors were able to show a significant improvement in the postoperative hemoglobin decrease, they were unable to show an improvement in the rate or number of units needed to transfuse. Because no clear parameters were defined in either group for the indications for transfusion, it was likely susceptible to bias. In addition, although no difference in blood use was noted, it was very small in both groups compared with previously published requirements. Given the significant reduction in the postoperative decrease in hemoglobin following intra-articular tranexamic acid use, the current authors believe that, although this may not be sufficient to keep all patients transfusion-free, with a defined transfusion protocol, it would be effective in reducing the number of patients receiving blood, as well as the total number of blood units used.

The authors acknowledge the retrospective nature of this review and the limitations associated with that. In addition, they recognize that their database has an inherent limitation to the quality of the data available for collections. However, they matched for variables believed most likely to influence outcomes, namely age, surgeon, procedure, and anesthesia. Although no difference was found in patient characteristics in the 2 groups, selection bias was not completely excluded.

The authors did not evaluate visual estimates of blood loss intraoperatively because they have been shown to be imprecise. The authors did not use blood drainage levels because if blood loss is to be measured accurately, it should also quantify loss through hematoma formation and extravasation. However, ultrasonographic examination of hematomas has suggested that they are often inaccurately measured. In addition, it has been shown that the drain contents are less than 50% blood. Given this, equating drain volume to blood loss is methodologically incorrect. Thus, obtaining hemoglobin levels is a more accurate method than directly measuring drainage fluid.

In using the greatest decrease in hemoglobin levels as a surrogate for blood loss, other factors might contribute to this, including hemodilution from perioperative fluid resuscitation and the type of anesthetic used. The patients were followed with daily complete blood counts while hospitalized, as is the standard practice. Although a time frame for the postoperative hemoglobin trough has not been established in the literature, in a nationwide study involving 2363 patients undergoing primary THA, 88% requiring transfusion had this done by postoperative day 2. Overall, despite potential limitations, the advantage of this study is that it is the only study to date looking at intra-articular use of tranexamic acid in THA.

**CONCLUSION**

Overall, the study demonstrates that intra-articular use of tranexamic acid in patients undergoing primary THA is associated with a significant improvement in their postoperative hemoglobin decrease. The clinical relevance of the study results may have a positive clinical effect for the daily practice of orthopedic surgery. Intra-articular tranexamic acid use is economical, easy to administer, and does not require any significant change in postarthroplasty wound care management. In addition, the favorable effects on postoperative hemoglobin are likely to decrease the overall cost of the operation. However, given the retrospective nature of this data, a large randomized placebo-controlled trial is warranted to examine blood loss, transfusion, and thromboembolic complications when using intra-articular tranexamic acid in primary THA. Such a study must be powered to assess the effect of intra-articular tranexamic acid on blood loss and transfusion as primary efficacy outcomes and the effect on thromboembolic complication as the primary safety outcome.

**REFERENCES**

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