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The combined administration of systemic and topical tranexamic acid for total hip arthroplasty: Is it better than systemic?

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ABSTRACT

Obective: The aim of this study was to evaluate the effect of combined intravenous and topical use of tranexamic acid (TXA) on total blood loss and transfusion rate in total hip arthroplasty.
Methods: This prospective randomized study included 57 patients who had undergone total hip arthroplasty between September 2016 and September 2017. The IV administration group (Group 1) consisted of 26 patients (mean age: 63.73 ± 10.29 years), while the IV and topical administration group (Group 2) consisted of 22 patients (62.82 ± 8.31 years). Demographic data and outcomes were obtained through a review of individual medical records. Medical comorbidities, body mass index (BMI), ASA and CCI, preoperative and postoperative hemoglobin levels, postoperative transfusion records and 90-day joint-related (implant subsidence, dislocation, postoperative anemia, deep infection, hematoma and/or wound problem, postoperative periprosthetic fracture) readmission rate and complication rate were compared between the groups.
Results: No significant differences were observed between the 2 groups in terms of age, gender, height, weight, body mass index (BMI), the level of preoperative Hb values, and the American Society of Anesthesiologists (ASA) and Charleson Comorbidty Index (CCI) rating ($p > 0.05$). The mean postoperative Hgb in the group 2 was higher by a small amount compared to the group 1. No statistically significant difference was determined between the groups in respect of the Hgb values ($p = 0.562$). Hgb Delta in the group 2 was lower than that of the group 1. The difference between the groups in the Hgb Delta values was not statistically significant ($p = 0.268$). The mean total blood loss was lower in the group 2 than in the group 1 but the difference was not statistically significant ($p = 0.788$). There was no significant difference observed in terms of any adverse complications among the 2 groups ($p > 0.05$).
Conclusion: The combined administration of IV and topical TXA compared with IV alone can decrease total blood loss and the number of blood transfusions required without increasing the risk of DVT or/and PE in total hip arthroplasty. But the statistical analysis and clinical relevance is not significant.
Level of Evidence: Level I Therapeutic Study.

Introduction

Total joint arthroplasty is an excellent option for patients suffering from painful hip arthritis. The number of primary arthroplasty has steadily increased over the past years due to the increase in life expectancy, the aging population, and improved perioperative medical management.[1,2]

Total hip arthroplasty (THA) can produce significant blood loss necessitating a transfusion. Perioperative blood loss and subsequent allogenic blood cell transfusions are common in arthroplasty surgery

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and present a potential for adverse outcome including transmission of infectious agents, hemolytic transfusion reaction, short-term mortality and prolonged hospital stay in addition to increased costs.[3,4] Several methods have been described in literature to reduce the need for allogenic blood transfusion, such as hypotension anesthesia, regional anesthesia, autologous blood transfusion, and antifibrinolytic agent tranexamic acid (TXA) administration.[5–8]

There is wide-spread use of TXA in orthopedic surgery, especially in arthroplasty procedures. TXA is an antifibrinolytic agent that acts by blocking the lysine binding sites on plasminogen molecules, inhibiting the formation of plasmin.[9] Therefore, TXA stabilizes fibrin clots, which results in more stable hemostasis. The use of perioperative TXA has dramatically lowered blood loss and the need for postoperative transfusions, almost eliminating the need for these other strategies.[10,11]

Previous clinical studies which have examined the use of TXA in arthroplasty surgery, have found that the administration of TXA was strongly associated with reduced blood loss and decreased transfusion rates without increasing the risks of deep vein thrombosis (DVT) or/and pulmonary embolism (PE).[12–15] In studies by Huang et al[13] and Wu et al[2] the combined administration of TXA was observed to have satisfactory results in reducing blood loss and transfusion rates compared to either regimen alone.

In the present study, an analysis of the outcomes of total blood loss and the transfusion rate was made in patients with primary THA. It was hypothesized that combined (IV + Topical) TXA reduced total blood loss and transfusion rate compared to IV alone TXA following THA.

Patients and methods

A total of 57 patients scheduled for elective unilateral primary TKAs were assessed during the period between September 2016 and September 2017 for the eligibility. This study was approved by the Hospital Ethical Committee. All patients were required to sign an informed consent prior to participation in the study. One senior surgeon (DG) performed all surgeries. Preoperative teaching and perioperative management were the same for patients in two groups. Of the 57 patients assessed, 5 patients were excluded for the following reasons: 2 patients for diagnoses other than primary OA, and 3 patients with prior history of DVT. The IV administration group was named Group 1, and the IV and topical administiration group was named Group 2. Randomization was undertaken using a computer-generated method by the study coordinator. Patients were randomized in a 1:1 fashion to receive only IV TXA (n = 26) or IV + TOPİCAL (n = 26) TXA. The surgeon and anesthetist were notified of the treatment assignment via randomization notification placed on the patient's hospital medical record before surgery. The patients and principal investigator were blinded as to the regimen of TXA during the surgery. Demographic data and outcomes were obtained through a review of individual medical records. Medical comorbidities, body mass index (BMI), ASA (American society of Anesthesiologists) and CCI (Charlson Comorbidity Index) score, preoperative and postoperative hemoglobin levels, postoperative transfusion records and 90-day joint-related (implant subsidence, dislocation, postoperative anemia, deep infection, hematoma and/or wound problem, postoperative periprosthetic fracture) readmission rate and complication rate were analyzed.

Inclusion criteria were patients aged >18 years undergoing elective total hip surgery. Patients with blood clotting problems, cardiac stents, a history of thromboembolic disease, chronic renal or hepatic failure, bilateral joint arthroplasty, revision surgery, acute subarachnoid hemorrhage, TXA allergy, and cerebrovascular disease and patients with a diagnosis other than primary OA were also excluded.

Our protocol for administering TXA is 1000 mg TXA mixed in 100 ml of isotonic sodium chloride solution and given as a slow intravenous injection in 30 min before the skin incision and the same dose repeated 3 h later. In the group 2, in addition to the intravenous preoperative and postoperative doses, 3 g of TXA diluted in 30 ml of isotonic sodium chloride solution was applied intra-articularly for about 5 min after closure of the arthrotomy.

Surgical procedure

All surgical procedures in both groups were performed by the same senior author (D.G.). A posterolateral surgical approach with spinal anesthesia was used in all cases. Each patient received a prophylactic antibiotic injection before the skin incision. Moreover, no drain was applied in any patient following THA. All patients received 0.4 ml (4000 IU) enoxaparin (Clexane, 4000 anti-Xa IU/0.4 ml, Sanofi-Aventis, Gentilly, France) dose of low molecular-weight heparin at 6 h postoperatively and this was repeated at 24-h intervals in the subsequent days until discharge and continued to 30 days after discharge to prevent DVT or/and PE.[16] In addition, antiembolic socks were routinely applied to all patients. To reduce the risk of thrombosis, all patients were encouraged with early rehabilitation exercise. The patients had a standardized preoperative and postoperative employment of a pain management ladder.

Total blood loss (TBL) was calculated using the modified Gross formula[17]: TBL = PBVx (Hctpre−Hctpost)/Hctave, PBV = k1 x height (m) + k2 x weight (kg) + k3, k1 = 0.3669, k2 = 0.03219, and k3 = 0.6041 for men; and k1 = 0.3561, k2 = 0.03308, and k3 = 0.1833 for females, where Hctpre was preoperative day 1 Hct level, Hctpost was defined as the minimum postoperative Hct level, Hctave was the average of the Hctpre and Hctpost, and PBV was the patient's blood volume (mL). If blood transfusion was performed, the TBL was considered equivalent to the loss calculated from the change in hematocrit plus the volume transfused.[17]

The maximum Hb drop was defined as the difference between the Hb level before surgery and the minimal Hb level drawn postoperatively during the hospitalization period and the lowest Hb level before any blood transfusion.

Postoperative care and follow-ups

A standardized postoperative pain management ladder was employed (contramol 50 mg 2 × 1, voltaren 2 × 1). Hemoglobin levels were obtained preoperatively and daily thereafter until postoperative day 3. All patients stayed 3 or more days. The primary outcome was the transfusion rate. A standardized postoperative transfusion protocol was used. All patients were transfused if the Hb level was <80 g/L or the patient showed symptoms of anemia (such as dizziness and fatigue) as decided by the senior orthopedic surgeon. The secondary outcomes were the maximum Hb drop, the length of hospital stay, and other complications.

There was no routine screening for thromboembolic events. However, all clinically suspicious scenarios were investigated by either duplex ultrasound or CT angiography for suspected deep vein thrombosis (DVT) or pulmonary embolism (PE), respectively.

Any evidence of erythema, swelling, wound drainage or surrounding cellulitis was considered as a wound complication. This parameter was assessed by an orthopedic junior.

Postoperative rehabilitation

Postoperatively, mobilization was early and aggressive. Static quadriceps exercises, straight leg rising exercise, and range of

motion exercises were started immediately. All patients were allowed full weight bearing.

Statistical analysis

To test the significance of the difference between the groups in the variables of the proportional scale according to the use of transamine, the Independent Samples t-test for means was used. The analysis of the Independent Samples t-test was tested with the SPSS 15.0 software program.

To test the significance of the difference between the groups in the variables of the nominal scale according to the use of transamine, the Independent Samples t-test for proportions was used. The analysis of the Independent Samples t-test was tested with the STATA 12.0 software program.

The sample size estimation thus calculated with Hgb D:1.21, SD: 1.4, α:0.05, β:0,20 and power of 80% showed that a sample of 23 patients would be required for the IV-alone and combined IV and IA group, respectively.

Results

The demographic data and results of the preoperative blood tests are summarized in Table 1 and the postoperative results in Table 2. No significant differences were observed between the 2 groups in terms of age, gender, height, weight, body mass index (BMI), the level of preoperative Hb values, and the American Society of Anesthesiologists (ASA) and Charleson Comorbidty Index (CCI) rating.26 patients in group 1 and 22 patients in group 2 were completed the study, 4 patients in group 2 were lost during follow-up.

The mean postoperative mean Hgb in the group 2 was higher by a small amount compared to the group 1. No statistically significant difference was determined between the groups in respect of the Hgb values ($\mu_{IV}\pm\sigma_{IV} = 10.05 \pm 1.20$, $\mu_{IV+TOP} \pm \sigma_{IV+TOP} = 10.27 \pm 1.43$ $p = 0.562$). Hgb Delta in the group 2 was lower than that of the group 1. The difference between the groups in the Hgb Delta values was not statistically significant ($\mu_{IV}\pm\sigma_{IV} = 3.16 \pm 0.82$, $\mu_{IV+TOP} \pm \sigma_{IV+TOP} = 2.87 \pm 0.98$, $p = 0.268$).

The mean Blood Transfusion was higher in the group 1 than in the group 2 but the difference was not statistically significant ($\mu_{IV}\pm\sigma_{IV} = 0.12 \pm 0.33$, $\mu_{IV+TOP} \pm \sigma_{IV+TOP} = 0.09 \pm 0.294$ $p = 0.788$). The mean operation time was longer in the group 2 but there was no statistically significant difference between the two groups ($\mu_{IV}\pm\sigma_{IV} = 113.46 \pm 14.06$, $\mu_{IV+TOP} \pm \sigma_{IV+TOP} = 116.82 \pm 11.71$ $p = 0.379$). The mean postoperative length of stay in hospital was similar in both groups ($\mu_{IV}\pm\sigma_{IV} = 4.46 \pm 1.21$, $\mu_{IV+TOP} \pm \sigma_{IV+TOP} = 4.46 \pm 0.91$ $p = 0.982$).

Table 1
Demographic and pre-operative clinical data.

	IV(n = 26)	IV + TOP(n = 22)	Significance
Age	63.73 ± 10.29	62.82 ± 8.31	0.740[a]
Sex (Male rate)	0.42 ± 0.49	0.41 ± 0.49	0.922[b]
Height	1.69 ± 0.11	1.72 ± 0.06	0.234[a]
Weight	82.46 ± 11.78	85.05 ± 9.43	0.412[a]
BMI	29.09 ± 1.91	28.82 ± 1.83	0.622[a]
Side (Right rate)	0.58 ± 0.48	0.55 ± 0.50	0.827[b]
PreopHgb	13.43 ± 1.21	12.96 ± 1.10	0.167[a]
CCI	1.31 ± 0.68	1.18 ± 0.85	0.572[a]
ASA	2.27 ± 0.67	2.18 ± 0.85	0.692[a]

BMI: Body Mass Index, CCI: Charlson Comorbidity Index, ASA: American Society of Anesthesiologists.
[a] Independent samples t test for means.
[b] Paired samples t test for proportions.

Table 2
Post-operative clinical data.

	IV(n = 26)	IV + TOP(n = 22)	Significance
Post op Hgb	10.27 ± 1.43	10.05 ± 1.20	0.562[a]
Hgb Delta	3.16 ± 0.82	2.87 ± 0.98	0.268[a]
Blood Transfusion	(3)0.12 ± 0.33	(2)0.09 ± 0.29	0.788[a]
Complications			
DVT	(2) 0.08 ± 0.27	(2)0.09 ± 0.29	0.861[b]
Operation Time	113.46 ± 14.06	116.82 ± 11.71	0.379[a]
Hospital stay (days)	4.46 ± 1.21	4.46 ± 0.91	0.982[a]
TBL (ml)	848.81 ± 224.10	772.22 ± 322.07	0.353[a]

DVT: Deep venous trombophelibitis, TBL: Total Blood Loss, () number of patients.
[a] Independent samples t test for means.
[b] Paired samples t test for proportions.

The mean TBL was lower in the group 2 than in the group 1 but the difference was not statistically significant ($\mu_{IV} \pm \sigma_{IV} = 848.81 \pm 224.10$, $\mu_{IV+TOP} \pm \sigma_{IV+TOP} = 772.22 \pm 322.07$ $p = 0.353$) (Table 2).

There was no significant difference observed in terms of any adverse complications among the 2 groups. Two patient in each group had clinical suspicion of DVT; however, they were found to be negative on duplex Doppler study. Moreover, therewas no case of clinical thromboembolic event among the 2 study groups. Neither infection nor transfusion-related complications were seen in both groups.

Discussion

There is increasing evidence from the use of TXA in orthopaedic arthroplasty surgery that IV or topical administration has a substantial impact on blood loss and the need for post-operative transfusion following primary THA. The main finding of this study was that compared with the IV administration of TXA alone, the combined IV and topical administration of TXA is able to reduce transfusions, TBL and Hb drops without increasing the risk of DVT and PE in THA surgery.

In a study by Wind et al,[11] they reported that IV administration of TXA reduced postoperative blood loss and transfusion need. In that study, the transfusion rate was 4.39% in the TXA group, and 19.86% in the control group. In an another study by Wei and Wei,[10] the transfusion rate was significantly low in the TXA group, with transfusion reported in 26 of 100 patients (26%) in the non-TXA group, in 6 of 102 (5.88%) in the topical TXA group and in 6 of 101 (5.94%) in the IV TXA group. In a prospective, randomized control study by Wu et al[2] of total hip revision arthroplasty surgery, it was reported that the transfusion rate was significantly low in the IV + topical group (21.4%) compared with the IV alone group (45.2%). In the present study, the transfusion rate was 9% (2/22) in the group 2, and 12% (2/26) in the group 1. Although the transfusion rate was higher in the group 1, it was not statistically significant. Finally, intraoperatively, the bone bed was not flushed with TXA solution after preparation of the acetabulum and femoral canal according to the method described by Konig et al.[18] This may have resulted in greater intraoperative blood loss than has been reported.[19,20]

In a study by Akgul et al[21] the total volume of blood loss was significantly reduced in the TXA group (634.03 ± 182.88 ml) compared to the control group (1166.42 ± 295.92 ml) ($p < 0.001$). In a prospective randomized study by Wei and Wei[10] comparing patients undergoing total hip arthroplasty, the TBL was determined as 1364.2 ± 278.6 ml in the non- TXA group, which was significantly higher than in the TXA groups [963.4 ± 421.3 ml in the topical TXA group and 958.5 ± 422.1 ml in the IV TXA Group]. In the present study, the TBL was lower in the group 2 compared to the group 1, but the difference was not statistically significant ($p = 0.353$) with

TBL calculated as 772.22 ± 322.07 ml in the group 2 and 848.81 ± 224.10 ml in group 1. In this trial, the topical TXA was administered to the hip joint after closure of the joint capsule and short external rotator tendons whereas Wei and Wei[10] delivered topical TXA to the three main bleeding sites (acetabulum, femoral canal and hip joint cavity) during surgery. It was considered that one of the main causes of the blood loss in the combined group was related to inadequate administration of topical TXA, when delivered only to the hip joint cavity. We recommend that topical TXA be administered not only to the hip joint, but also to the acetabulum and femoral canal as they are the main bleeding sites as mentioned in previous studies.[18,20]

DVT or/and PE are known to be the most frequent complications in THA surgery.[22,23] Several methods to prevent DVT or/and PE have been reported in many studies.[14,15,18] In the current study, there were no statistically significant differences noted in terms of DVT o between the groups ($P = 0.861$). Two patients in the group 1 and two patients in the group 2 developed DVT. This low DVT or/and PE rate can be attributed to the following reasons. First, patients in both groups received chemical thromboprophylaxis with low-molecular weight heparin during hospitalization and after discharge for 30 days to prevent DVT. Second, patients were actively encouraged with early rehabilitation exercise to reduce the risk of thromboembolism. Numerous publications have also shown no difference in the incidence of thromboembolic events when TXA is used during hip arthroplasty.[24–26] However, most published studies have been of insufficient power to detect small differences, as in the present study. Prospective randomized cohort studies with large numbers could be designed to determine clinicial relevance for DVT and PE complications. There were no dislocations, periprosthetic fractures, wound hematoma, or pulmoner embolism reported in the first 90 days.

The strengths of the present study are that, the study groups had similar patient characteristics although there were minor biases which could not be controlled, all operations were performed by the same surgical team, and the same type of hip prothesis (was used to eliminate any bias of different types of prothesis which could result in different degrees of tissue damage and bone surface infiltration). The limitations of the study were that, the observations of the study were limited to hospitalized patients with no long-term follow-up. In addition, DVT was documented based on clinical presentation only but might have been undetected in asymptomatic patients.

In conclusion, The combined administration of IV and topical TXA compared with IV alone can decrease TBL and the number of blood transfusions required without increasing the risk of DVT or/and PE in total hip arthroplasty. But the statistical analysis and clinical relevance is not significant.

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Ethical approval: The present study was approved by the ethical Committee of Saglik Bilimleri University, Umraniye Training and Research Hospital. (2018/119).

Informed consent: Informed consent was obtained from all individual participants included in the study.

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