Clin Orthop Relat Res (2014) 472:1552–1557
DOI 10.1007/s11999-013-3446-0

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

CLINICAL RESEARCH

Topical Tranexamic Acid Reduces Blood Loss and Transfusion Rates Associated With Primary Total Hip Arthroplasty

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Received: 30 August 2013 / Accepted: 20 December 2013 / Published online: 3 January 2014

Abstract

Background Systemic tranexamic acid can decrease blood loss and rates of transfusion in patients undergoing total hip arthroplasty (THA). However, the efficacy of topical tranexamic acid in THA has only recently been characterized in a small number of studies.

Questions/purposes The purpose of this study was to compare (1) the greatest hemoglobin decrease after surgery; (2) transfusion rates; and (3) symptomatic thromboembolic events among patients undergoing THA who did and did not receive topical tranexamic acid.

Methods We retrospectively compared 135 patients (154 THAs) who received 10 mL 5% tranexamic acid added in a topical cocktail solution during surgery between January 2009 and July 2011 with 211 patients (234 THAs) who received only the topical cocktail solution (analgesic and antibiotic agent) between January 2005 and December 2008. Contraindications for the use of tranexamic acid included a documented history of a venous thromboembolic event, an allergy to tranexamic acid, thrombophilia, or a high risk of venous thromboembolism based on the guidelines of the American Academy of Orthopaedic Surgeons; the 135 patients who received it during that period represented 99.4% of the patients undergoing THA during that time. We compared changes in Hb, transfusion rates, estimated blood loss, surgical results, and complications between the groups. The transfusion threshold was the same, when the Hb values were < 10 g/dL. Patients were screened for thromboembolic disease if symptoms or signs appeared.

Results Hb decreased less in the tranexamic acid group (1.87 ± 1.10 g/dL) than in the control group (2.2 ± 1.36 g/dL; $p = 0.01$) on the first postoperative day. The frequency of transfusion was lower in patients receiving tranexamic acid (17% as compared with 35% in the control group; $p < 0.001$). There was only one nonfatal pulmonary embolism in the control group during the study period.

Conclusions Use of topical tranexamic acid in patients undergoing THA reduces postoperative bleeding and decreases blood transfusion rates. No increase in major complications was identified in patients managed with topical tranexamic acid. This retrospective study confirms the results of a smaller randomized trial on the same topic by another group.

Level of Evidence Level III, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

One of the authors (MSL) is a consultant for Zimmer (Warsaw, IN, USA) without financial support and conflicts of interests in preparing this study.
All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research* editors and board members are on file with the publication and can be viewed on request.
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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Introduction

The need for THAs is increasing [6, 23, 25]. THAs may lead to considerable blood loss and perioperative transfusions [3, 51]. Blood transfusions are associated with risks and complications, including transfusion-related reactions, transmission of infectious agents, and immunomodulatory effects [4, 27, 49]. Many methods are used to decrease the need for postoperative blood transfusions such as epoetin administration [16, 24, 26, 31, 45, 50], fibrin spray [29, 30], patient position [37, 51], deliberate hypotension [33, 39], hemodilution [36], autologous blood transfusion [5, 10, 11, 14, 44, 53, 54], and tranexamic acid administration [9, 17–19, 28, 35, 40, 42, 43, 46, 48].

Systemic use of tranexamic acid decreases blood loss during orthopaedic surgeries [9, 17–19, 28, 35, 40, 41, 43, 46, 48]. Topical application of tranexamic acid has been used in dental [42], cardiac [1, 13, 40, 41], spine [21], and knee surgery [52]; however, topical tranexamic acid in THA has just been reported recently [3, 20]. The benefit of tranexamic acid topical application including ease of administration provides a maximum concentration of tranexamic acid at the surgical site and theoretically is associated with little systemic effect.

The purpose of this study was to analyze the THA registry data to compare the results of blood loss and the rate of transfusion in patients who had or had not had topical tranexamic acid after cementless THA. We hypothesized that topical application of tranexamic acid before closure reduces postoperative bleeding as reflected by the maximum drop in hemoglobin level during the postoperative period. The secondary objective was to analyze the transfusion rate in patients with or without topical tranexamic acid.

Patients and Methods

We retrospectively reviewed those cases by sequential series study. From January 2009 to July 2011, 155 patients (180 THAs) were treated with topical tranexamic acid during surgery as the study group. The patients received a local injection of a cocktail solution containing 10 mg levobupivacaine (20 mL), 1 mg epinephrine (1 mL), 5 mg morphine (1 mL), 1 g cefazolin sodium, 80 mg gentamicin sulfate (2 mL), and 5% tranexamic acid (10 mL). One-third of the cocktail was injected into soft tissue including capsule and muscles around the joint, and two-thirds of the cocktail was injected intraarticularly after fasciae closure. All surgeries were performed by a single surgeon (MSL) using a modified Watson-Jones approach. Topical tranexamic acid was used in all patients in this group, except those with a documented history of a venous thromboembolic event, an allergy to tranexamic acid, thrombophilia, or a high risk of venous thromboembolism based on the guidelines of the American Academy of Orthopaedic Surgeons for use of intravenous tranexamic acid [38]; there are no guidelines available to our knowledge on use of the topical preparation. Based on those contraindications, one patient who had previous asymptomatic pulmonary embolism did not receive tranexamic acid during the study period (a total of 99.4% of the 180 patients undergoing THA during the period in question received it). The control group consisted of 253 patients with a total of 287 THAs performed by the same surgeon using the same surgical approach and identical topical cocktail solution without tranexamic acid between January 2005 and December 2008. All patients followed the same clinical pathway, including standard postoperative care and a protocol of blood transfusion. No other blood conservation strategies were implemented during the study period.

After institutional review board approval (No. 100-2208B), clinical records were retrieved from the electronic database. The following data points were collected: age, sex, body mass index, diagnosis, American Society of Anesthesiology (ASA) status, operation time, preoperative hemoglobin (Hb), hematocrit (Hct) and platelet counts, intraoperative blood loss, intraoperative blood transfusion, the lowest postoperative Hb and Hct, length of hospital stay, and any intraoperative or postoperative complications. We excluded patients who underwent bilateral simultaneous THAs (18 hips), intraoperative blood loss of $\geq$ 1000 mL (13 hips), and intraoperative fracture (four hips). Patients who received blood transfusions either before or during the surgery were also excluded (44 hips in 37 patients). In total, 79 hips in 63 patients were excluded from the final analysis. The excluded patients were followed for the occurrence of complications including infection, dislocation, neurovascular injury, or venous thromboembolic events.

All surgeries were standardized using the same cementless prosthesis (Triology cup, Prolong polyethylene, Versys Fiber Metal Taper stem; Zimmer, Warsaw, IN, USA) without a suction drain. The need for intraoperative transfusion of blood products was not standardized and was determined by the surgeon and the anesthesiologist based on the physiologic conditions to maintain a mean arterial pressure of 70 mmHg. Fluid requirements and third-space losses were replaced with balanced crystalloid solutions, either pentastarch (Pentaspan; Bristol-Myers Squibb, Montreal, Canada) or hydroxyethyl starch (Voluven; Fresenius Kabi, Mississauga, Ontario, Canada). The amount of crystalloid solutions was not recorded. At the conclusion of surgery, Hb and Hct levels were measured. On postoperative day 1, Hb and Hct were measured again.

Transfusion of allogeneic packed red blood cells was performed in patients when the Hb values were $<$ 10 g/dL (based on the clinical pathway).

No chemical prophylaxis for thromboembolism was administered during the study period. No systematic

screening for thromboembolic disease was performed; however, patients with symptoms or signs of thromboembolism of legs (such as swelling, ecchymosis, and pain) were screened using venous duplux scan or venous angiography; dyspnea, desaturation, or syncope was screened using CT angiography for pulmonary embolism.

Estimated blood loss was calculated using the following formula: estimated blood loss = estimated blood volume × (final Hct reduction/mean Hct) [15, 32].

The final analysis included 338 patients with a total of 388 hips divided into the control group (211 patients with 234 THAs) and the tranexamic acid group (135 patients with 154 THAs). Eight patients had one hip in the tranexamic acid group and the other in the control group. There were no statistically significant differences in the patient demographics, body mass index, ASA status, and diagnosis between the two groups (Table 1). The surgical results, including total operating time, wound length, position of acetabular and femoral components, and the length of hospital stay, were not significantly different between the two groups (Table 2). The preoperative Hb and Hct levels were not statistically different between the two groups (Table 3).

A Student's t-test, analysis of variance, and chi-square test were used to analyze the data. A p value of < 0.05 was considered statistically significant (as per SPSS 17.0; SPSS Inc, Chicago, IL, USA).

Results

The final Hb and Hct reduction in the tranexamic acid group was less than that in the control group ($p = 0.01$). The intraoperative blood loss and early Hb and Hct level reduction were similar between the control and tranexamic acid groups (Table 3). Further analysis showed that the reduction in final Hb and Hct levels was less in cases with preoperative Hb levels of < 12 g/dL than in those with preoperative Hb ≥ 12 g/dL (Table 3). The reduction in final Hb and Hct levels was the least in the subgroup that had preoperative Hb levels of < 12 g/dL and received tranexamic acid. The estimated blood loss was 695 ± 499 mL in the tranexamic acid group; this was less than that of the control group (819 ± 695 mL). Subgroup analysis of the group that did not receive tranexamic acid revealed that the estimated blood loss was lower in patients with preoperative Hb < 12 g/dL than in those with preoperative Hb ≥ 12 g/dL. The amount of blood loss was the lowest in the subgroup that had preoperative Hb < 12 g/dL and received tranexamic acid. The intraoperative estimated blood loss in the control group was not different from the tranexamic acid group (409 ± 198 mL and 388 ± 163 mL, respectively; Table 3). Each group was further divided into two subgroups using a preoperative Hb level of 12 g/dL as the cutoff value. There were no differences in intraoperative blood loss among the four subgroups.

The blood transfusion rate was lower in the tranexamic acid group (17%) than in the control group (35%) ($p < 0.001$). The highest blood transfusion rate (60%) was found in the subgroup that had preoperative Hb < 12 g/dL and did not receive tranexamic acid. The lowest blood transfusion rate (15%) was found in the subgroup that had preoperative Hb ≥ 12 g/dL and received tranexamic acid.

There was one symptomatic nonfatal pulmonary embolism in the control group. No symptomatic deep vein thromboses were noted in either group.

Table 1. Baseline demographic and clinical data

Demographic and clinical data	Control group	Tranexamic acid group	Significance*
Number	234	154	
Age (years)†	56.7 ± 14.6	57.2 ± 14.3	0.747
Sex (female/male)	111/123	79/75	
Weight (kg)†	64.1 ± 10.6	64.7 ± 12.6	0.573
Body mass index (kg/m^2)†	25.3 ± 4.6	25.2 ± 4.3	0.742
ASA status (I/II/III)	35/153/46	12/111/31	
Diagnosis			
Osteoarthritis and dysplasia	105	81	
Osteonecrosis	114	65	
Miscellaneous	15	8	

* Student's t-test; †mean ± SD; ASA = American Society of Anesthesiologists.

Table 2. Surgical results and hospital course

Surgical result	Control group (N = 234)	Tranexamic acid group (N = 154)
Operation time (minutes)	125 ± 30	136 ± 34
Wound length (cm)	8.9 ± 2.0	9.5 ± 1.7
Acetabular component		
Inclination (degrees)	46.2 ± 5.6	47.8 ± 6.4
Anteversion (degrees)	14.4 ± 5.4	13.7 ± 1.8
Femoral component		
Stem alignment (degrees)	0 ± 1	0 ± 0.2
Canal fill ratio (%)	0.94 ± 0.05	0.99 ± 0.01
Length of hospital stay (days)	5.2 ± 1.9	5.7 ± 1.9

Values are mean ± SD.

Table 3. Blood loss, hematologic data, and allogeneic blood transfusion

Preoperative Hb subgrouping	Control group (n = 234)		Tranexamic acid group (n = 154)		Significance
	Hb ≥ 12 g/dL (n = 199)	Hb < 12 g/dL (n = 35)	Hb ≥ 12 g/dL (n = 132)	Hb < 12 g/dL (n = 22)	
Intraoperative blood loss (mL)	409 ± 198		388 ± 163		0.274
	414 ± 199	380 ± 191	394 ± 165	355 ± 150	0.402
Preoperative Hb (g/dL)	13.5 ± 1.6		13.3 ± 1.4		0.229
Preoperative hematocrit (%)	40.5 ± 4.8		40.0 ± 4.1		0.229
Early Hb reduction (g/dL)	0.24 ± 0.12		0.23 ± 0.12		0.541
Early hematocrit reduction (%)	1.1 ± 0.4		1.1 ± 0.4		0.454
Final Hb reduction (g/dL)	2.20 ± 1.36		1.87 ± 1.10		0.010†
	2.34 ± 1.37	1.37 ± 0.93	2.00 ± 1.10	1.07 ± 0.68	0.000‡
Final hematocrit reduction (%)	6.6 ± 4.1		5.6 ± 3.3		0.010†
	7.02 ± 4.10	4.11 ± 2.80	6.01 ± 3.30	3.22 ± 2.04	0.000‡
Estimated blood loss (mL)	819 ± 695		695 ± 499		0.041†
	865 ± 726	561 ± 402	736 ± 507	448 ± 371	0.002‡
Packed RBC transfusion	82 (35%)		26 (17%)		0.000*
	61 (31%)	21 (60%)	20 (15%)	6 (27%)	0.000*

Values are mean ± SD; * chi-square test; †Student's t-test; ‡analysis of variance (post hoc Bonferroni test); Hb = hemoglobin; Hct = hematocrit; RBC = red blood cells.

Discussion

THAs may cause considerable blood loss. Postoperative anemia can lead to increased mortality and morbidity [8, 22], a longer hospital stay [47], and delayed rehabilitation [12], especially in patients with vascular disease [7]. Blood transfusion is associated with several well-recognized risks and complications, including transfusion-related acute lung injury, hemolytic transfusion reactions, transfusion-associated sepsis [49], and transmission of infectious agents [4, 27]. Many studies report that intravenous use of tranexamic acid can reduce blood loss and blood transfusion in patients undergoing primary arthroplasty [9, 17–19, 28, 35, 40, 41, 43, 46, 48]. The potential advantages of topical application of tranexamic acid are (1) direct targeting of the site of bleeding; and (2) prevention of systemic side effects. To our knowledge, there has been only one small randomized trial [3] and another study [20] evaluating topical tranexamic acid in THA. These favored its use; we sought to validate these findings in a larger, although retrospective, study. The dosage of tranexamic acid used in our study (0.5 g) was lower than that used in other studies in which the systemic dosage ranged from 1 to 3 g [9, 17–19, 28–30, 35, 41, 43, 46]. Although the dosage of tranexamic acid was low, we may effectively reduce the amount of total blood loss and the need for blood transfusion in our patients by using the topical administration route.

The present study had several limitations. First, this was not a randomized study but a sequential series study. However, we did not preselect the patients for this study, which might decrease the selection bias. Second, the case number was not equal between the two groups. Third, the blood loss was estimated by a validated method [15, 32]; although it was not accurate, it was simple and practicable. We also excluded the patients who had blood loss more than 1000 mL intraoperatively or received blood transfusion before or during surgery to avoid the confounding effect. Fourth, the need for blood transfusion was arbitrarily determined based on the clinical pathway. Fifth, venography or CT scan was not routinely performed to screen for pulmonary embolism or thromboembolic complications. Some asymptomatic venous thromboembolism might be overlooked. Finally, we used a topical cocktail solution that contained levobupivacaine, epinephrine, morphine, and antibiotics; the tranexamic acid mixed into this cocktail during the study period. We were not aware of any drug-drug interaction of the tranexamic acid with the topical cocktail solution, although it is conceivable that there might be such an interaction. However, we did observe that the addition of low-dose tranexamic acid was effective in decreasing blood loss after THA without an apparent increase in symptomatic thromboembolic events.

When tranexamic acid is administered intravenously, it is widely distributed through the extracellular and intracellular compartments [34]. When a high dose of systemic tranexamic acid is administered, the drug rapidly diffuses into the joint and has a biological half-life of approximately 3 hours [2]. To address the potential risk of thromboembolism with

high doses of tranexamic acid, low-dose tranexamic acid has been topically used in dental surgery [42], cardiac surgery [1, 13], and spine surgery [21]. Similar to our findings, the results of these studies have demonstrated that topical use of tranexamic acid significantly decreases the amount of blood loss. One other study that we know of in THA has evaluated topical tranexamic acid [3]. In this small, randomized trial, the authors found–much as we did–less bleeding, fewer transfusions, and no increase in postoperative complications, although we use a different way of topical application of tranexamic acid (intramuscular and intracapsular versus intraarticular injection).

In conclusion, the use of low-dose topical tranexamic acid in patients undergoing THA effectively reduced postoperative bleeding and blood transfusion rates. Although the study was retrospective, it is worth noting that the surgical procedures and perioperative care were similar in both groups and that the number of patients included was quite large (approximately twice as large as the only other study on this topic of which we are aware [3]). Our findings largely confirmed theirs, lending strength to the major findings in both studies. The addition of tranexamic acid to a local cocktail solution did not lead to an observable increase in symptomatic thromboembolic events. We suggest that the use of low-dose topical tranexamic acid in combination with a topical cocktail solution is safe and effective in decreasing blood loss in cementless THAs, especially in patients with preoperative Hb < 12 g/dL.

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