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Full Length Article

Single-dose tranexamic acid for reducing bleeding and transfusions in total hip arthroplasty: A double-blind, randomized controlled trial of different doses

Changde Wang [a,b,1], Pengde Kang [a,1], Jun Ma [a], Chen Yue [a], Jinwei Xie [a], Fuxing Pei [a,*]

[a] Department of Orthopedic Surgery, West China Hospital, West China Medical School, Sichuan University, Chengdu, Sichuan Province 610041, China
[b] Department of Orthopedic Surgery, Affiliated Hospital, Northwest University for Nationalities, Lanzhou, Gansu Province 730030, China

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ABSTRACT

Background: Tranexamic acid can be effective at decreasing blood loss and transfusion requirements associated with total hip arthroplasty (THA), but few studies have compared the efficacy of different intravenous dosing regimes. This double-blind, randomized controlled trial compared the ability of two doses of intravenous TXA (IV-TXA, 10 or 15 mg/kg) to reduce bleeding and transfusions associated with THA.
Materials and methods: A total of 124 patients scheduled for THA were consecutively randomized 1:1:1 into three parallel arms: control (placebo), 10 mg/kg IV-TXA and 15 mg/kg IV-TXA.
Results: The proportion of patients who experienced bleeding and required transfusions was significantly lower in the 15 mg/kg IV-TXA group (1 of 42, 2.4%) than in the 10 mg/kg IV-TXA group (8 of 39, 20.5%; $P = 0.012$) and in the control group (10 of 38, 26.3%; $P = 0.002$). In fact, this proportion was similar between the 10 mg/kg IV-TXA and control groups ($P = 0.547$). Ultrasound examination on postoperative day 3 revealed only one case of asymptomatic deep vein thrombosis (in the femoral vein) in the 10 mg/kg IV-TXA group, which was managed by administering low-molecular-weight heparin. No cases of deep-vein thrombosis were observed in the other two groups. No cases of symptomatic pulmonary embolism were observed.
Conclusion: IV-TXA at 10 mg/kg significantly reduced blood loss and mitigated the decrease in hemoglobin and hematocrit after THA, but it did not significantly reduce the need for transfusions. In contrast, a dose of 15 mg/kg reduced both bleeding and transfusion requirements. Our results argue for a dose of 15 mg/kg when using single-dose IV-TXA.
Level of evidence: Therapeutic Level I

1. Introduction

Total hip arthroplasty (THA) is associated with significant blood loss necessitating subsequent allogeneic blood transfusion [1,2,3,9,10] in 16–37% of patients [1]. Clinicians have studied several methods to reduce bleeding and transfusion requirements, including autologous blood donation, hypotensive anesthesia, perioperative blood salvage and synthetic antifibrinolytic therapy [5–7]. The synthetic antifibrinolytic agent tranexamic acid has been shown in numerous studies to be safe and effective at reducing bleeding and transfusion requirements associated with THA [7–19]. Tranexamic acid works by blocking the conversion of plasminogen to plasmin on the surface of fibrin, thereby inhibiting fibrinolysis and reducing bleeding [4]. In 2001, Benoni et al. [8] showed that 10 mg/kg intravenous tranexamic acid (IV-TXA) reduced blood loss associated with THA, which subsequent studies confirmed [10,12]. In 2005, Johansson et al. [9] showed that 15 mg/kg intravenous tranexamic acid (IV-TXA) reduced blood loss and transfusion requirements associated with THA, which was also confirmed in subsequent studies [7,11,13]. Similar results were obtained with single dosing of 1 g IV-TXA [17,18] and multi-dose IV-TXA [15,16,19]. Table 1 summarizes key characteristics and findings from randomized controlled trials (RCTs) using IV-TXA.

Despite this substantial evidence base, we are unaware of parallel efficacy comparisons of different single-dose regimens of IV-TXA. Therefore, we conducted this double-blind RCT to assess the relative abilities of single-dose IV-TXA at 10 or 15 mg/kg to reduce bleeding and transfusion requirements associated with THA.

2. Materials and methods

The study was designed as a double-blind RCT and approved by the Institutional Review Board of West China Hospital, Sichuan University (No. 201302007). From September 2014 to November 2014, patients

* Corresponding author at: Department of Orthopedics, West China Hospital, Sichuan University, No. 37 Guoxue Road, Chengdu, Sichuan Province, China.
E-mail addresses: wangchangde76@163.com (C. Wang), kangpd@163.com (P. Kang), 492385233@qq.com (J. Ma), 596681500@qq.com (C. Yue), 154762995@qq.com (J. Xie), pfxhuaxi@sina.com (F. Pei).
[1] These authors contributed equally to this work.

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Table 1
Randomized controlled trials analyzing effects of intravenous tranexamic acid on transfusion and complications associated with total hip arthroplasty.

Study	N	IV-TXA dose	Transfusion	Thrombotic complications	DVT prophylaxis	Type of prosthesis
Claeys et al. (2007) [7]	40	15 mg/kg before surgery	1/20	DVT 3/17	LMWH	Hybrid
Garneti and Field (2004) [14]	50	10 mg/kg at induction of anesthesia	0/25	0	Mechanical	Cemented
Singh et al. (2010) [12]	42	10 mg/kg before surgery	0/21	0	LMWH	Cemented or cementless
Ekbäck et al. (2000) [15]	40	10 mg/kg at end of operation and 3 h later	0/20	DVT 1/20	LMWH	Cemented
Benoni et al. (2001) [7]	40	10 mg/kg before the surgery	4/18	0	LMWH	Cemented
Jamie et al. (2011) [9]	66	10 mg/kg when the operation began	0/22	0	Aspirin	Cemented
Johansson et al. (2005) [9]	100	15 mg/kg before surgery	8/47	0	LMWH	Cemented
Yamasaki et al. (2004) [17]	40	1 g before surgery	0/20	0	Not mentioned	Cementless
Rajesparan et al. 2009 [20]	73	1 g before surgery	3/36	0	LMWH	Cemented, cementless
Kazemi et al. (2010) [11]	64	15 mg/kg before surgery	0/32	0	LMWH	Cementless
Malhotra et al. (2011) [12]	50	15 mg/kg at 15 min before incision	0/25	0	LMWH and mechanical	Cementless

Abbreviations: DVT, deep-vein thrombosis; IV-TXA, intravenous tranexamic acid; LMWH, low-molecular-weight heparin.

diagnosed with osteoarthritis and scheduled to undergo primary unilateral THA were recruited into the study. Patients were excluded from this study if they had a history of any of the following: hemophilia, deep vein thrombosis, pulmonary embolism, stents, ischemic heart disease, anticoagulant medication, serious liver or renal dysfunction, or allergy to tranexamic acid.

Enrolled patients were consecutively randomized into three groups in a 1:1:1 ratio: control (placebo), 10 mg/kg IV-TXA (median dose, 650 mg) and 15 mg/kg IV-TXA (median dose, 960 mg). The group to which patients were assigned was indicated in numbered, sealed envelopes that were prepared by a researcher and opened by non-research clinical staff assigned to the study after enrollment was completed. The two IV-TXA groups received total doses based on their weight, and infusion was complete before the THA procedure began. The control group received a placebo of normal saline before surgery at a dose of 10 or 15 mg/kg, which was decided by the non-research clinical staff.

The necessary sample size was estimated based on the results of a pilot study involving 40 patients scheduled for THA, of whom 20 received placebo and 20 received 15 mg/kg IV-TXA. Transfusions were necessary in 40% of the control patients, compared to 5% of the patients receiving IV-TXA. Power analysis of the Wilcoxon rank sum test and the difference-in-proportions test indicated that control and intervention groups with 30 patients would be needed to confirm this difference with 90% power at a 5% significance level.

THA was performed by two experienced orthopedic surgeons using the posterolateral approach and cementless cups and stems. Anesthesia methods were decided by anesthetists, with general anesthesia being the first option at our medical center. Blood pressure was controlled to remain within 90–110 mm Hg/60–70 mm Hg throughout the procedure. During surgery, no hemostatic medication except tranexamic acid was given to reduce bleeding. A drainage catheter was routinely inserted at the end of the operation, which was not clamped.

Patients were given a blood transfusion if their hemoglobin was <70 g/L, or if their hemoglobin was 70–100 g/L with symptomatic anemia, such as tachycardia, pallor and lethargy, poor eating, and fatigue. Total blood loss was calculated using the gross formula [21–22]. The drainage catheter was removed on the morning after the operation, and the blood volume in the vacuum collectors was recorded as the postoperative drainage. Hemoglobin and hematocrit levels were tested on postoperative day 3, as per routine procedure at our hospital.

As chemical thromboprophylaxis, all patients received a half-dose of low-molecular-weight heparin (LMWH; 2000 IU in 0.2 ml; Clexane, Sanofiaventis, France) starting at 6 h postoperatively, followed by a full dose (4000 IU in 0.4 ml) at 24-h intervals. As mechanical thromboprophylaxis, all patients were hooked up to an intermittent foot slope pump system. As prophylaxis after discharge, patients were instructed to take 10 mg Rivaroxaban (Xarelto, Bayer, Germany) orally once a day for 14 days.

Before surgery and at 5–7 days after surgery, all patients were screened in-hospital for deep vein thrombosis (DVT) events by experienced ultrasound technicians using B-mode ultrasonography (iU22 Philips Medical System, Royal Philips Electronics, Netherlands) with compression and color Doppler flow imaging. At 3 months after discharge, all patients were screened for asymptomatic DVT on an outpatient basis.

Primary outcomes were the proportions of patients in each group (a) requiring blood transfusion, (b) experiencing deep vein thrombosis (DVT) or (c) experiencing pulmonary embolism (PE). Secondary outcomes were total blood loss, drained blood loss, decrease in hemoglobin and hematocrit as well as other complications.

Staff performing data analysis was blinded to group allocations. Data were analyzed using SPSS 19.0 (IBM, Chicago, IL, USA). One-way ANOVA was used to assess the significance of inter-group differences in normally distributed data, while the chi-squared or Fisher's exact test was used to assess qualitative variables. The threshold of significance was defined as $P < 0.05$, except in the case of multiple inter-group comparisons on qualitative variables. These comparisons were made using chi-squared decomposition, and the significance threshold was defined as $P' \leq 0.0125$.

3. Results

During the recruitment period, 173 patients were scheduled for primary unilateral THA at our hospital and were therefore considered for inclusion in our study. Of these, 49 refused to participate, so the remaining 124 were randomly allocated into one of the three study arms. All were treated as planned, but three patients in the control group and two in the 10 mg/kg IV-TXA group were lost to follow-up after discharge. Therefore, they were excluded from all analyses as withdrawals/drop-outs. The patient flow diagram is shown in Fig. 1. All three study arms showed similar baseline characteristics, including age, gender, body mass index, anesthesia method, and preoperative levels of hemoglobin and hematocrit (Table 2).

3.1. Primary outcomes

3.1.1. Blood transfusions

Ten of 38 patients (26.3%) in the control group, eight of 39 patients (20.5%) in the 10 mg/kg IV-TXA group and one of 42 patients (2.4%) in the 15 mg/kg IV-TXA group needed transfusions (Table 3). The transfusion proportion was significantly lower in the 15 mg/kg IV-TXA group than in the control group ($P = 0.002$) and in the 10 mg/kg IV-TXA group ($P = 0.012$). The proportion was similar between the 10 mg/kg IV-TXA and control groups ($P = 0.547$).

3.1.2. DVT and PE

Ultrasound examination on postoperative day 3 detected only one case of asymptomatic DVT, which occurred as proximal femoral vein thrombosis in the 10 mg/kg TXA group. This was managed using low-molecular-weight heparin therapy. No DVT events were observed in the other two groups. The proportion of patients experiencing DVT