The Journal of Arthroplasty xxx (2016) 1–6

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Original Article

The Efficacy of Combined Use of Rivaroxaban and Tranexamic Acid on Blood Conservation in Minimally Invasive Total Knee Arthroplasty a Double-Blind Randomized, Controlled Trial

Jun-Wen Wang, MD [a, *], Bradley Chen, MD, ScD [b], Po-Chun Lin, MD [a], Shih-Hsiang Yen, MD [a], Chung-Cheng Huang, MD [c], Feng-Chih Kuo, MD [a]

[a] Department of Orthopaedic Surgery, Kaohsiung Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Kaohsiung, Taiwan
[b] Institute of Public Health, National Yangming University, Taipei, Taiwan
[c] Department of Radiology, Kaohsiung Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Kaohsiung, Taiwan

ARTICLE INFO

Article history:
Received 9 June 2016
Received in revised form
17 August 2016
Accepted 18 August 2016
Available online xxx

Keywords:
rivaroxaban
tranexamic acid
venous thromboembolism
total knee arthroplasty
total blood loss
wound complications

ABSTRACT

Background: Tranexamic acid (TXA) was reportedly to decrease postoperative blood loss after standard total knee arthroplasty (TKA). However, the blood-conservation effect of TXA in minimally invasive TKA, in particular, receiving a direct oral anticoagulant was unclear. The aim of the study was to investigate the efficacy of combined use of TXA and rivaroxaban on postoperative blood loss in primary minimally invasive TKA.

Methods: In a prospective, randomized, controlled trial, 198 patients were assigned to placebo (98 patients, normal saline injection) and study group (100 patients, 1g TXA intraoperative injection) during primary unilateral minimally invasive TKA. All patients received rivaroxaban 10 mg each day for 14 doses postoperatively. Total blood loss was calculated from the maximum hemoglobin drop after surgery plus amount of transfusion. The transfusion rate and wound complications were recorded in all patients. Deep-vein thrombosis was detected by ascending venography of the leg 15 days postoperatively.

Results: The mean total blood loss was lower in the study group (1020 mL [95% confidence interval, 960-1080 mL]) compared with placebo (1202 mL [95% confidence interval, 1137-1268 mL]) ($P < .001$). The transfusion rate was lower in the study group compared with placebo (1% vs 8.2%, $P = .018$). Postoperative wound hematoma and ecchymosis were higher in placebo than the study group ($P = .003$). There was no symptomatic deep-vein thrombosis or pulmonary embolism in either group.

Conclusion: Systemic administration of TXA can effectively reduce the postoperative blood loss which results in lower rate of transfusion requirement and wound hematoma in minimally invasive TKA patients when rivaroxaban is used for thromboprophylaxis. Rivaroxaban has a high rate of bleeding complications when used alone in TKA patients.

Total knee arthroplasty (TKA) is the most common and effective procedure for end-stage arthritis of the knee in terms of pain relief and functional recovery [1,2]. However, this procedure is associated with substantial perioperative blood loss. An allogeneic blood transfusion rate as high as 69% was reported in patients receiving total hip and knee arthroplasty when the preoperative hemoglobin (Hb) level was <13 g/dL [3].

Both surgery and the application of a pneumatic tourniquet are considered to enhance coagulability and local fibrinolytic activity in the limb [4-6]. Tranexamic acid (TXA) is a synthetic amino acid derivative which inhibits the conversion of plasminogen to plasmin through the reversible blockade of fibrinolysin-binding sites on the plasminogen molecule [7-9]. Several clinical trials [10-13] and meta-analyses [14-17] have demonstrated that intravenous TXA reduced blood loss and the need for transfusion in primary total hip and knee arthroplasty.

No author associated with this paper has disclosed any potential or pertinent conflicts which may be perceived to have impending conflict with this work. For full disclosure statements refer to http://dx.doi.org/10.1016/j.arth.2016.08.020.

Financial support: This study was supported in part, by Ministry of Science and Technology, grant #NMRPG8136181-2.

* Reprint requests: Jun-Wen Wang, MD, Department of Orthopaedic Surgery, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University, College of Medicine, No.123, Da Pi Rd., Niao Sung Dist., Kaohsiung City, Taiwan, ROC.

http://dx.doi.org/10.1016/j.arth.2016.08.020
0883-5403/

Rivaroxaban is one of the first licensed oral factor Xa inhibitors for thromboprophylaxis in total hip and knee arthroplasty surgeries. The advantages of rivaroxaban, which include oral administration, no need to monitor blood levels, and no dosing adjustments, make this drug convenient for the short hospital stays required in contemporary TKA [18]. Its efficacy in preventing venous thromboembolism (VTE) after TKA has been shown to be superior to enoxaparin given subcutaneously in RECORD (Regulation of Coagulation in Orthopaedic surgery to prevent Deep-vein thrombosis and pulmonary embolism) 3 and 4 studies [19,20].

Despite its clinical efficacy in VTE prophylaxis, orthopedic surgeons are still skeptical regarding the routine use of rivaroxaban in knee and hip surgery and, in particular, the increased risk of bleeding complications [21]. A higher reoperation rate from wound complications within 30 days of hip and knee arthroplasty in the rivaroxaban group compared with the tinzaparin group (2.94% vs 1.8%) was also recently reported [22]. Similar concerns have been raised by other authors [21,23-26]. However, none of these studies used TXA as bleeding prophylaxis after hip and knee arthroplasty surgery. Owing to its antifibrinolytic effects, there is an increased risk of VTE after TXA use [27-29]. Furthermore, most of the studies reporting the blood-conservation effect of TXA in total knee and hip arthroplasty used low–molecular weight heparin for thromboprophylaxis [10-12,30].

Minimally invasive techniques for TKA are increasing recently in orthopedic service. The advantages of minimally invasive TKA are less wound pain [31,32], faster rehabilitation [32,33], shorter hospital stay [33], and possible less blood loss [31] compared with conventional TKA. However, it is unclear that whether there is a blood-conservation effect of TXA in patients who undergo minimally invasive TKA and receive modern oral anticoagulants for thromboprophylaxis. The aim of this study was to conduct a prospective, randomized, double-blind study to assess the blood-conservation effect of TXA and wound hemotoma related to postoperative blood loss when rivaroxaban is used for thromboprophylaxis in minimally invasive TKA patients.

Methods

Patients were included in the study if they were 18 years of age, or older, and were scheduled for unilateral primary TKA. Patients were excluded from the study if they had a coagulopathy, severe renal impairment (creatinine clearance, <30 mL/min), concomitant use of protease inhibitors of human immunodeficiency virus, or fibrinolytic agents that contraindicated the use of rivaroxaban, prior surgery on the affected knee, a history of thromboembolic disease requiring life-long anticoagulant therapy or antiplatelet drugs that could not be stopped before operation, previous allergic history to TXA, or contrast medium for radiographic examination or a preoperative Hb level less than 10 g/dL.

The present study was registered in the public ClinicalTrials.gov registry (NCT02458729) and was approved by the institutional review board of our institution. Written informed consent was obtained from all participating patients before randomization.

Between August 2013 and April 2015, 250 patients scheduled for primary unilateral TKA were assessed for eligibility. Fifty patients were excluded because of ineligibility. The remaining 200 patients were randomly assigned, by means of a computer-generated randomization method, to either placebo (100 patients) or the study group (100 patients, 1 g TXA intravenous injection intraoperatively) (Table 1). Two patients in placebo group refused to participate after allocation. Thus, a total of 198 opaque, sealed envelopes which contained appropriate study medications and placebo were randomly numbered from 1 to 198 by means of a computer-generated method at the Institutional Clinical Trial Pharmacy. The 198 envelopes included 98 envelopes containing 2 ampoules of 20 mL of normal saline (placebo group) and 100 envelopes containing one ampoule of 20 mL of normal saline and four ampoules of 250 mg/5 mL TXA (China Chemical and Pharmaceutical Co, Taiwan) (study group).

Table 1
Patients Included and Excluded for Analyses.

Enrollment of Patients	Placebo (%)	Study Group (%)
Randomized	100 (100)	100 (100)
Patients underwent surgery and took study medication	100 (100)	100 (100)
Patients in primary and secondary safety outcome analysis	98 (98)	100 (100)
Refused to participate after randomization	2 (2)	0 (0)
Patients in primary safety outcome analysis	98 (98)	100 (100)
Patients in radiographic evaluation for deep-vein thrombosis	66 (66)	67 (67)
Refused venographic examination	21 (21)	21 (21)
Inadequate renal function (GFR <60 mL/min/1.73m^2)	7 (7)	6 (6)
Failure of venography	4 (4)	6 (6)

GFR, glomerular filtration rate.

All patients underwent unilateral primary TKA using the mini-midvastus technique according to Haas et al [31] under general anesthesia. They described: the skin incision was made along the medial border of mid-to-distal tibial tubercle, and the vastus medialis oblique muscle was split approximately 2-cm inline with its fibers from the superior medial pole of the patella [32]. A pneumatic tourniquet was inflated to a pressure of 300 mmHg before the incision and released at the end of surgery after skin closure. All TKAs were cemented using the same prosthesis (NexGen, Legacy, Posterior-Stabilized Prosthesis; Zimmer, Warsaw, IN). Before wound closure, 2 drain tubes were placed into the knee joint and connected to the vacuum bag. Then, the envelop was sequentially opened by circulating nurse not involved in this study before each surgery. The attending anesthetists and the nurse in charge, who were not involved in the study, administered the study medications according to the groupings. Thus, patients in placebo received 20-mL saline intravenously, 5 minutes before deflation of the tourniquet, and patients in the study group received 1 g TXA by slow intravenous infusion 5 minutes before deflation of the tourniquet. Patients, surgeons, research assistant participating in clinical evaluation were blinded as randomization until data analysis was completed. The length of wound in full extension of the knee was recorded at the end of operation in all patients. All patients received 10 mg of oral rivaroxaban (Xarelto, Bayer Shering Pharma AG, Wuppertal, Germany) once daily starting from postoperative day (POD) 1 to POD 14 for VTE prophylaxis. No other anticoagulants or antiembolic devices were used in all patients.

Preoperative data, including Hb level, hematocrit, prothrombin time, activated partial thromboplastin time, D-dimer levels, and platelet count were collected. The demographics of the patients, including age, gender, body mass index, American Society of Anesthesiologists grade [34], and blood indices were similar between the 2 groups (Table 2).

Safety Outcomes

Postoperative Hb levels were recorded on the first, second, and fourth days postoperatively. The drop of Hb level on POD1, POD2, and POD4 compared with the preoperative Hb level of all patients were recorded. It was assumed that blood volume was normalized