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Original article

Edoxaban is effective in reducing the incidence of asymptomatic phlebographic events following closed-wedge high tibial osteotomy

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ABSTRACT

Introduction: The purpose of this study was twofold: to investigate whether edoxaban significantly decreases the rate of venous thromboembolism (VTE) following closed-wedge high tibial osteotomy (CWHTO), in terms of phlebographic event, and to determine whether edoxaban is safe or increases the rate of hemorrhagic complications. We hypothesized that edoxaban would decrease the incidence of VTE and would not increase the rate of hemorrhagic complications.

Materials and methods: We randomly enrolled 60 patients undergoing CWHTO. The patients were divided into two groups: one group receiving edoxaban (15 mg in 5 patients, 30 mg in 23 patients) and a non-edoxaban group. All patients underwent computed tomography venography on day 7 to diagnose postoperative VTE. Blood samples were obtained on the day before CWHTO and on postoperative days 1, 3, 7 and 14. The incidence of VTE and hemorrhagic events in both groups was compared using unpaired Student *t*-test or chi-square test.

Results: The incidence of VTE was significantly greater in the non-edoxaban group (31.3% versus 7.1%; $P=0.02$). The incidence of deep vein thrombosis (DVT) was also significantly greater in the non-edoxaban group (28.1% versus 3.6%; $P=0.01$). A single patient from the edoxaban group experienced major bleeding. On days 3 and 7, D-dimer levels were significantly lower in the edoxaban group ($P=0.03$ and 0.003 , respectively). On days 3, 7 and 14, activated partial thromboplastin time was significantly greater in the edoxaban group ($P=0.02$, 0.01 and 0.006 , respectively).

Conclusion: Patients undergoing CWHTO are at risk of postoperative VTE. Edoxaban helps prevent asymptomatic phlebographic VTE and DVT following CWHTO; however, the risk of major bleeding must be considered.

Level of evidence: II.

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1. Introduction

The clinical results of closed-wedge high tibial osteotomy (CWHTO) are generally good. CWHTO provides durable pain reduction and stabilization of the osteoarthritic process [1,2]. However, a variety of complications of CWHTO have been reported, such as infection, venous thromboembolism (VTE), neurovascular complications, fractures, delayed union, and non-union [3]. VTE includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Without thromboprophylaxis, DVT occurs in 40%–60% of total knee arthroplasties (TKA) and 42%–57% of total hip arthroplasties

(THA) [4–6]. Reports on the incidence of VTE following CWHTO are scarce [7–9]. VTE rates as low as 0.7% and as high as 41% have been reported [7–11]. The American College of Chest Physicians Evidence-based Clinical Practice Guidelines for the prevention of VTE stated that routine use of thromboprophylaxis is not advised for patients with isolated lower-limb surgery below the knee [6]. However, the Japanese Orthopaedic Association Guidelines for the prevention of VTE recommends mechanical thromboprophylaxis with elastic stocking or intermittent pneumatic compression [12]. Although the incidence of VTE has decreased over time due to improved surgical techniques, early rehabilitation and mechanical thromboprophylactic treatment [13], VTE remains a serious concern. Various anticoagulants have been developed. Edoxaban (Lixiana®, Daiichi Sankyo, Tokyo, Japan) is an oral direct factor-Xa inhibitor for the prevention and treatment of thromboembolic events [14,15]. The efficacy and safety of edoxaban for the

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prevention of VTE has been reported for patients undergoing hip fracture surgery, TKA, and THA [14,16–18]. We previously investigated the incidence of VTE with or without edoxaban after opening-wedge high tibial osteotomies (OWHTO) [11]. No study has evaluated the outcome of edoxaban treatment after CWHTO. The clinical diagnosis of VTE after CWHTO is difficult because of frequent calf pain and swelling associated with the fibular osteotomy. Therefore, diagnosis relied here on systematic phlebography.

We hypothesized that edoxaban would decrease the incidence of VTE and would not increase the rate of hemorrhagic complications.

Therefore, we investigated whether the use of edoxaban would significantly decrease the rate of VTE following CWHTO, in terms of phlebographic events, and whether edoxaban would increase the rate of hemorrhagic complications.

2. Materials and methods

2.1. Patients

This prospective study included 60 patients with either knee osteoarthritis (OA) or idiopathic osteonecrosis (ON). The patients provided informed consent to participate in the study. All underwent CWHTO between October 2012 and July 2016. The patients were randomized using sealed envelopes. The first group received edoxaban while in the second group thromboprophylaxis used elastic stockings and intermittent pneumatic compression only. The study was approved by our Institutional Review Board (No. B120906026), and was registered in UMIN-CTR (UMIN00018101). Patients with preoperative VTE, severe renal impairment (creatinine clearance < 30 mL/min), or using anticoagulants, antiplatelet agents, thrombolytic agents or other agents that impact thrombus formation were excluded. Preoperative duplex ultrasonography and/or computed tomography (CT) was used to confirm the absence of VTE in six patients with > 1.0 µg/mL D-dimer level prior to surgery. Sixty-one patients met our inclusion criteria and were included, 28 in the edoxaban group and 32 in the non-edoxaban group. One patient declined participation, and was therefore excluded. No significant differences were observed in gender, age, height, body weight or body mass index between the two groups (Table 1).

2.2. Surgical procedure

Surgeries were performed by two experienced orthopedic surgeons (Y.A., T.S). After arthroscopy, the tourniquet was inflated and the tibial osteotomy was performed. Fixation was achieved using Osteotomy W Locking (Mizuho, Tokyo, Japan) and TomoFix (Synthes, Bettlach, Switzerland) plate and locking screws (Fig. 1).

Table 1
Clinical data on patient subgroups.

	Edoxaban group	Non-edoxaban group	P value
Cases	28	32	
Female/male	21/7	21/11	n.s.
Edoxaban 15 mg/30 mg	5/23		
Age (years) ^a	66	69	n.s.
	63–70	66–72	
Body height (cm) ^a	155.0	157.2	n.s.
	151.7–158.3	154.8–159.7	
Body weight (kg) ^a	64.5	62.6	n.s.
	60.4–68.6	58.3–66.8	
Body mass index (kg/m ²) ^a	26.8	25.2	n.s.
	25.5–28.1	23.9–26.4	

^a Data are expressed as means with 95% confidence intervals.

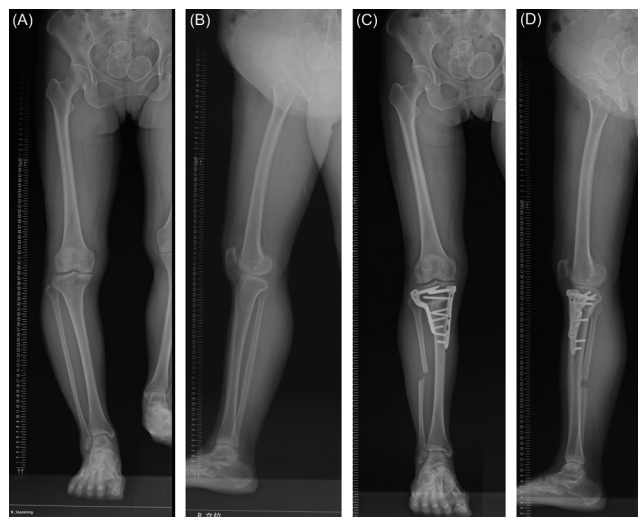


Fig. 1. Radiographs of the right leg of a 54-year-old female patient with knee osteoarthritis. Preoperative anteroposterior (A) and lateral (B) standing whole-leg radiograph. Postoperative anteroposterior (C) and lateral (D) standing whole-leg radiograph.

2.3. Postoperative rehabilitation program

All patients underwent postoperative physical therapy. Twenty-three patients in the edoxaban group received 30 mg edoxaban daily for 14 days, starting on postoperative day 1. Five other patients received 15 mg edoxaban, either because they were ≥ 75 years of age or due to renal impairment (creatinine clearance 30–50 mL/min). Patients in the non-edoxaban group underwent mechanical thromboprophylaxis only. All patients respected non-weight-bearing for 3 weeks, then progressively resumed weight bearing until achieving full weight-bearing 4 weeks after surgery.

2.4. Outcome measures

To detect postoperative VTE, angiography of the pulmonary artery and deep veins of the lower limbs was performed on postoperative day 7 using 64-slice multi-detector-row computed tomography (MDCT) (Aquilion CXL (Toshiba, Japan), Aquilion 64 (Toshiba, Japan), or SOMATOM Definition AS+ [Siemens, Erlangen, Germany]). The diagnostic criterion was the presence of a defect in intraluminal filling in the pulmonary artery or deep vein of the lower limbs due to thrombosis. Because of renal dysfunction, duplex ultrasonography was performed instead of CT analysis in three patients. If asymptomatic PE was detected, heparin and warfarin were administered. If DVT was detected, only physical therapy, warfarin, or edoxaban with physical therapy was prescribed, depending on the size and location of the DVT. Patients were evaluated for clinical symptoms of VTE, including chest pain, acute dyspnea and syncope, and VTE-related mortality.

Incidence of major and clinically relevant non-major (CRNM) bleeding was assessed. Major bleeding was defined as life-threatening bleeding, bleeding requiring reoperation, bleeding into critical organs (e.g., retroperitoneal, intracranial, intraocular or intrathecal bleeding), or clinically overt bleeding leading to a decrease of more than 2 g/dL in hemoglobin level or requiring blood transfusion of > 800 mL. CRNM bleeding was defined as bleeding not meeting the criteria for major bleeding, with either ≥ 5 cm diameter hematoma, epistaxis or ≥ 5 minutes' gingival bleeding, gastrointestinal bleeding, or gross hematuria persisting 24 hours after onset.

Blood samples were obtained preoperatively and on postoperative days 1, 3, 7, and 14. Hemoglobin (Hb) levels were measured,

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