Original article

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


Department of orthopaedic surgery, school of medicine, Yokohama City University, 3–9, Fukuura, Kanazawa, Yokohama, Kanagawa 236-0004, Japan

ARTICLE INFO

Article history:
Received 9 December 2016
Accepted 31 July 2017

Keywords:
Closed-wedge high tibial osteotomy (CWHTO)
Venous thromboembolism (VTE)
Deep vein thrombosis (DVT)
Pulmonary embolism (PE)
Eodoxaban

ABSTRACT

Introduction: The purpose of this study was twofold: to investigate whether eodoxaban significantly decreases the rate of venous thromboembolism (VTE) following closed-wedge high tibial osteotomy (CWHTO), in terms of phlebographic event, and to determine whether eodoxaban is safe or increases the rate of hemorrhagic complications. We hypothesized that eodoxaban 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 eodoxaban (15 mg in 5 patients, 30 mg in 23 patients) and a non-eodoxaban 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-eodoxaban group (31.3% versus 7.1%; P=0.02). The incidence of deep vein thrombosis (DVT) was also significantly greater in the non-eodoxaban group (28.1% versus 3.6%; P=0.01). A single patient from the eodoxaban group experienced major bleeding. On days 3 and 7, D-dimer levels were significantly lower in the eodoxaban group (P=0.03 and 0.003, respectively). On days 3, 7 and 14, activated partial thromboplastin time was significantly greater in the eodoxaban group (P=0.02, 0.01 and 0.006, respectively).

Conclusion: Patients undergoing CWHTO are at risk of postoperative VTE. Eodoxaban 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. Eodoxaban (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 eodoxaban for the

* Corresponding author.
E-mail address: hi-deo@live.jp (H. Kobayashi).

http://dx.doi.org/10.1016/j.otsr.2017.07.016
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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 (UMIN000018101). 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

Surgical procedures 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.

<table>
<thead>
<tr>
<th>Edoxaban group</th>
<th>Non-edoxaban group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Female/male</td>
<td>21/7</td>
<td>21/11</td>
</tr>
<tr>
<td>Edoxaban 15 mg/30 mg</td>
<td>5/23</td>
<td></td>
</tr>
<tr>
<td>Age (years)*</td>
<td>66</td>
<td>69</td>
</tr>
<tr>
<td>Body height (cm)*</td>
<td>155.0</td>
<td>157.2</td>
</tr>
<tr>
<td>Body weight (kg)*</td>
<td>64.5</td>
<td>62.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>26.8</td>
<td>25.2</td>
</tr>
</tbody>
</table>

* 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 intrathoracic 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,
as were coagulation and fibrinolysis marker levels: i.e., platelets, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, D-dimer (a proteolytic fragment resulting from degradation of a fibrin clot), soluble fibrin (SF: a complex of fibrin monomer and fibrinogen derivatives), thrombin anti-thrombin complex (TAT: a marker of thrombin generation), and plasminogen activator inhibitor 1 (PAI-1: a principal regulator of the fibrinolysis system) [19].

2.5. Statistical analysis

Statistical analysis used SPSS software for Windows. Data were expressed as means with 95% confidence intervals (CIs). Blood sample results and patient characteristics (age, height, body weight, and body mass index) were compared on non-paired Student t-test. VTE incidence and gender were compared on chi-square test. P values < 0.05 were considered statistically significant. Sample size was determined on G*Power 3.1 [20]: for alpha error = 0.05, power level = 0.80 and effect size = 0.7, the minimum number of subjects per group for the chi-square test used to compare the incidence of VTE was 26.

3. Results

The incidence of VTE and of DVT was significantly greater in the non-edoxaban group (respectively, 31.3% versus 7.1%; P = 0.02 [Table 2], and 28.1% versus 3.6%; P = 0.01 [Tables 2–3]). The incidence of PE was not significantly different between the two groups (7.4% versus 6.7%; P = 1.00) (Table 2). There were no symptomatic PE and no VTE-related deaths.

One patient in the edoxaban group experienced major bleeding (P = 0.28). The aspiration drain inserted at the osteotomy site

Table 2
Incidence of venous thromboembolism.

<table>
<thead>
<tr>
<th>Group</th>
<th>Site of VTE</th>
<th>Cases</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban group</td>
<td>Operated side</td>
<td>Soleus v.</td>
<td>1 (+)</td>
</tr>
<tr>
<td>Non-edoxaban group</td>
<td>Operated side</td>
<td>Soleus v.</td>
<td>3a (−)</td>
</tr>
<tr>
<td></td>
<td>Operated side</td>
<td>Fibular v.</td>
<td>3 (−)</td>
</tr>
<tr>
<td></td>
<td>Unoperated side</td>
<td>Soleus v., fibular v.</td>
<td>1 (+)</td>
</tr>
<tr>
<td></td>
<td>Unoperated side</td>
<td>Popliteus v.</td>
<td>1 (−)</td>
</tr>
<tr>
<td></td>
<td>Both sides</td>
<td>Soleus v.</td>
<td>1b</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism.

Table 3
Detailed description of deep vein thrombosis (DVT).

<table>
<thead>
<tr>
<th>Group</th>
<th>Site of VTE</th>
<th>Cases</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban group</td>
<td>Operated side</td>
<td>Soleus v.</td>
<td>1 (+)</td>
</tr>
<tr>
<td>Non-edoxaban group</td>
<td>Operated side</td>
<td>Soleus v.</td>
<td>3a (−)</td>
</tr>
<tr>
<td></td>
<td>Operated side</td>
<td>Fibular v.</td>
<td>3 (−)</td>
</tr>
<tr>
<td></td>
<td>Unoperated side</td>
<td>Soleus v., fibular v.</td>
<td>1 (+)</td>
</tr>
<tr>
<td></td>
<td>Unoperated side</td>
<td>Popliteus v.</td>
<td>1 (−)</td>
</tr>
<tr>
<td></td>
<td>Both sides</td>
<td>Soleus v.</td>
<td>1b</td>
</tr>
</tbody>
</table>

DVT: deep vein thrombosis; PE: pulmonary embolism.

* Duplex ultrasonography was performed in 1 case.

† Duplex ultrasonography was performed in the case.

Fig. 2. Blood sample data of the edoxaban (n = 28) and non-edoxaban groups (n = 32) are shown. D-dimer levels, activated partial thromboplastin time (APTT), soluble fibrin (SF) level, and thrombin anti-thrombin complex (TAT) level were measured preoperatively (Preop) and on postoperative days 1 (PO1D), 3 (PO3D), 7 (PO7D), and 14 (PO14D).

* P < 0.05, ** P < 0.01 between the edoxaban and non-edoxaban groups by using non-paired Student t-test. Error bars represent standard deviations.
produced 262 mL on postoperative day 1 and 650 mL on postoperative day 2, reducing hemoglobin levels by more than 2 g/dL. Edoxaban administration was stopped on postoperative day 2. Blood transfusion was not needed and recovery continued uneventfully.

Day 3 and day 7 D-dimer levels were significantly lower in the edoxaban group (Fig. 2; P = 0.03 and 0.003, respectively). On days 3, 7 and 14, APTT levels were significantly greater in the edoxaban group (P = 0.02, 0.01 and 0.006, respectively). Decreases in SF and TAT levels were significantly greater in the edoxaban group (day 3-7: P = 0.03, day 3, 7 and 14: P = 0.04, 0.02 and 0.005, respectively). No significant differences between groups were found in platelet, PT, fibrinogen, PAI-, or Hb levels.

4. Discussion

We found that edoxaban significantly decreased the rate of VTE following CWHTO. One case of major bleeding occurred in the edoxaban group (3.6%). Our findings are in agreement with previous studies [18,21] using coagulation and fibrinolysis markers, which indicated that edoxaban inhibited secondary fibrinolysis and thrombin formation, and accelerated fibrinolysis.

The thromboprophylactic effect of edoxaban was investigated in THA and TKA, and was found to be significantly greater than that of enoxaparin [21,22]. Few studies have reported the incidence of VTE after CWHTO [3,7,9,23]. In 65 patients undergoing CWHTO, the incidence of VTE was 10.8%, and involved the inguinal region, popliteal vein and calf vein [7]. A meta-analysis showed no statistically significant differences in DVT incidence between 165 CWHTOs and 148 CWHTOs, although detailed descriptions of the method and timing of VTE diagnosis and the number and sites of DVT were not mentioned [24].

In previous investigations, the risk of major bleeding due to edoxaban was not found to be significant. In a randomized double-blind study of 264 patients undergoing THA, the incidence of major or CRNM bleeding was 2.2%, 1.2% and 2.3% for edoxaban 15 mg and 30 mg and enoxaparin, respectively [21]. Similarly, in a randomized double-blind double-dummy study of 716 patients undergoing TKA, the incidence of major or CRNM bleeding was 6.2% and 3.7% for 30 mg edoxaban and enoxaparin, respectively (P = 0.129) [22].

The current study has several limitations. Firstly, patients were evaluated for VTE only until postoperative day 7. Secondly, patients at risk were excluded. Other studies in this patient population may provide more information regarding the role of edoxaban in preventing major VTE such as PE.

5. Conclusion

Edoxaban significantly decreased the rate of phlebographic VTE following CWHTO, but did not influence the incidence of PE. Because all VTEs were asymptomatic and none resulted in fatal PE, the clinical relevance of systematic edoxaban thromboprophylaxis remains controversial in patients without risk factors.

Role of the funding source

The authors did not receive benefits or grants in any form from any commercial party related directly or indirectly to the subject of this article.

Disclosure of interest

The authors declare that they have no competing interest.

References