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Safety and efficacy of edoxaban in patients undergoing hip fracture surgery

Takeshi Fuji [a,*], Satoru Fujita [b], Yohko Kawai [c], Mashio Nakamura [d], Tetsuya Kimura [e], Yuichi Kiuchi [f], Kenji Abe [g], Shintaro Tachibana [h]

[a] Department of Orthopaedic Surgery, Osaka Koseinenkin Hospital, Osaka, Japan
[b] Department of Orthopaedic Surgery, Takarazuka Daiichi Hospital, Takarazuka, Japan
[c] International University of Health and Welfare, Tokyo, Japan
[d] Department of Clinical Cardiovascular Research, Mie University Graduate School of Medicine, Tsu, Japan
[e] Clinical Planning Department, Daiichi Sankyo Co. Ltd, Tokyo, Japan
[f] New Drug Regulatory Affairs Department, Daiichi Sankyo Co. Ltd, Tokyo, Japan
[g] Clinical Data & Biostatistics Department, Daiichi Sankyo Co. Ltd, Tokyo, Japan
[h] Department of Orthopaedic Surgery, Mishuku Hospital, Tokyo, Japan

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ABSTRACT

Introduction: Edoxaban is an oral, direct, once-daily factor Xa inhibitor. This study evaluated the safety and efficacy of edoxaban compared to subcutaneous enoxaparin in Japanese patients undergoing hip fracture surgery.
Materials and methods: In this multicenter, randomized, open-label, active-comparator, phase 3 trial, 92 patients were randomized 2:1 to receive edoxaban 30 mg once daily (n = 62) or enoxaparin sodium (enoxaparin) 2000 IU (equivalent to 20 mg) twice daily (n = 30) for 11 to 14 days. The primary endpoints were the incidence of major or clinically relevant non-major (CRNM) bleeding and incidence of any bleeding events (major, CRNM, or minor bleeding). Secondary efficacy endpoints included the incidence of thromboembolic events, venous thromboembolism-related deaths, and all-cause deaths. Additional adverse events were recorded throughout the study.
Results: In the edoxaban and enoxaparin treatment groups, the incidence of major or CRNM bleeding was 3.4% and 6.9%, respectively, while any bleeding event occurred in 25.4% and 17.2% of patients, respectively. The incidence of thromboembolic events was 6.5% in the edoxaban group and 3.7% in the enoxaparin group. All events were asymptomatic deep vein thrombosis. The incidence of adverse events was 72.9% and 82.8% in the edoxaban and enoxaparin groups, respectively.
Conclusions: Compared to subcutaneous enoxaparin 2000 IU twice daily, oral edoxaban 30 mg once daily demonstrated similar safety and efficacy in the prevention of thromboembolic events in Japanese patients undergoing hip fracture surgery.
Clinical trials registration number: NCT01181141.

Introduction

Patients undergoing lower-limb orthopedic surgeries (LLOS) are at an increased risk for developing deep vein thrombosis (DVT) and pulmonary embolism (PE) if they are not provided with timely and adequate thromboprophylaxis [1,2]. The incidence of postoperative DVT is relatively high among patients who do not receive thromboprophylaxis undergoing total knee arthroplasty (TKA; 41%–85%), total hip arthroplasty (THA; 42%–57%), and hip fracture surgery (HFS; 46%–60%) [3]. PE, which in most cases is caused by DVT, can be fatal and is associated with a 14% in-hospital mortality rate; in serious cases accompanied by shock, the mortality rate is approximately 30% [4]. It has been reported that approximately 40% of patients who die of a PE do so within 1 hour of onset [5]. PE has been recognized as a significant

Abbreviations: ADR, adverse drug reactions; AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, every 12 hours; CI, confidence interval; CRNM, clinically relevant non-major; CT, computed tomography; DVT, deep vein thrombosis; GCP, good clinical practice; GI, gastrointestinal; HFS, hip fracture surgery; LLOS, lower-limb orthopedic surgeries; LMWH, low-molecular weight heparin; PD, pharmacodynamic; PE, pulmonary embolism; PK, pharmacokinetic; PT, prothrombin time; PT-INR, prothrombin time expressed as international normalized ratio; aPTT, activated partial thromboplastin time; SAE, serious adverse event; sc, subcutaneous injections; THA, total hip arthroplasty; TKA, total knee arthroplasty; ULN, upper limit of normal; VTE, venous thromboembolism.

* Corresponding author at: Osaka Koseinenkin Hospital, 4-2-78, Fukushima, Fukushima-ku, Osaka, 553–0003, Japan. Tel.: +81 6 6441 5451; fax: +81 6 6445 8900.
E-mail address: fuji-th@umin.ac.jp (T. Fuji).

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cardiovascular disease in Japan in recent years [2]. As such, current guidelines from the Japanese Circulation Society and the American College of Chest Physicians underscore the importance of preventing postoperative thrombosis and strongly recommend the use of adequate anticoagulant therapy soon after surgery [1,2].

Traditional anticoagulants (like heparin and warfarin) have limited use for venous thromboembolism (VTE) prevention in Japan because little is known about their efficacy in postoperative DVT prevention, adverse drug reactions (ADRs), and bleeding risks in this patient population. Enoxaparin, a low-molecular weight heparin (LMWH), and fondaparinux, an indirect factor Xa inhibitor, are efficacious in preventing VTE in patients undergoing LLOS, compared to placebo [6,7], and have both been approved in Japan for thromboprophylaxis in patients undergoing lower-limb orthopedic surgery [2]. Both drugs require subcutaneous injections (sc) administered once or twice daily, which may hinder patient adherence to therapy [8,9].

Edoxaban is an oral, once-daily, selective, direct factor Xa inhibitor that demonstrates a linear pharmacokinetic (PK) profile, a rapid onset of action with approximately 62% oral bioavailability [10], and low intra-subject variability [11]. Previous phase 2 studies in patients undergoing TKA [12] and THA [13,14] have demonstrated that edoxaban is associated with dose-dependent reductions in VTE with a low incidence of bleeding events that do not significantly increase with dose. In addition, edoxaban demonstrated efficacy and safety profiles similar to sc enoxaparin sodium for the prevention of thromboembolic events in patients undergoing THA [13]. The objective of this phase 3 study was to investigate the safety and efficacy of edoxaban in Japanese patients undergoing HFS.

Materials and Methods

Study Design

This was a multicenter, open-label, active-comparator, phase 3 trial (ClinicalTrials.gov Identifier: NCT01181141). Japanese patients were randomized 2:1 to receive an oral dose of edoxaban 30 mg once daily or the active control, enoxaparin 2000 IU sc every 12 hours (BID), which is the approved dosing regimen in Japan [15]. Edoxaban was initiated within 6 to 24 hours after surgery; enoxaparin was initiated within 24 to 36 hours after surgery (the standard of care in Japan). Both treatments were continued for 11 to 14 days. Concomitant use of mechanical physiotherapy (intermittent pneumatic compression or elastic stockings) was permitted.

Venography of both lower limbs was performed within 24 hours after the end of study treatment or treatment discontinuation; however, if it could not be performed within 24 hours for reasons such as difficulty establishing an intravenous line, it was performed within 96 hours. If DVT was suspected during the study, it was visually confirmed with diagnostic imaging. Similarly, suspected PE was confirmed by pulmonary scintigraphy or arteriography, computed tomography (CT) scan, or other appropriate imaging techniques. Study treatment was immediately discontinued if a suspected DVT or PE was confirmed and appropriate interventions were taken.

Investigations, observations, examinations, and urine and blood sample collections (for urinalysis, edoxaban plasma concentration measurements, pharmacodynamic [PD] indices assessments, and hematology tests) were performed during the presurgical evaluation, pretreatment (postsurgery), on day 7, and on the completion day of treatment. Follow-up examinations were performed 25 to 35 days after the last dose of the study drug. The occurrence of thromboembolic events, bleeding, and all other adverse events (AEs) were recorded throughout the study and the follow-up period. If applicable, site, duration, and total time of physiotherapy use were recorded throughout the course of the study. The study was conducted in compliance with the ethical principles in the Declaration of Helsinki, the Pharmaceutical Affairs Law Articles 14–3 and 80–2, and the Ministry of Health and Welfare Ordinance on Good Clinical Practice (GCP). All study protocols, information for patients, and informed consent forms received approval from an independent review board.

Patient Selection

Men and women of at least 20 years of age who provided written informed consent and were scheduled to undergo surgery within 10 days for inner or outer femoral neck (trochanteric or subtrochanteric) fracture were eligible for enrollment. Prior to surgery, patients were considered ineligible if they were at increased risk for bleeding (e.g., a history of intracranial bleeding or recent gastrointestinal [GI] bleeding) or increased risk for VTE (i.e., had a prior VTE, history of fracture or prosthetic replacement of lower limbs within 6 months, or recent occurrence of myocardial infarction, cerebral infarction, or transient ischemic attack). Additional reasons for exclusion included body weight of <40 kg, current use of antithrombotic therapy for another indication, severe renal impairment (creatinine clearance <30 mL/min) or evidence of hepatic impairment, conditions preventing bilateral venography, pregnancy or lactation, and any contraindications to enoxaparin. After surgery, patients could also be excluded if they experienced any abnormal bleeding at the site of spinal anesthesia administration, experienced abnormal or excessive bleeding during or immediately after surgery, were unable to take oral medications, or required additional surgery after the initial HFS until the start of study drug administration.

Study Endpoints

The primary endpoints were the incidence of major or clinically relevant non-major (CRNM) bleeding and the incidence of any bleeding event (major, CRNM, or minor bleeding) from the start of treatment to completion day of treatment, inclusive. Secondary safety endpoints included the incidence of individual bleeding events, AEs, ADRs, vital signs and laboratory test data. AEs were reported from the start of the treatment up to the end of the follow-up period (25–35 days after treatment).

Secondary efficacy endpoints included the proportion of patients who experienced the composite of asymptomatic DVT detected by the end-of-study venography, confirmed symptomatic DVT, or confirmed symptomatic PE; the proportion of patients who experienced the composite of symptomatic or proximal DVT, symptomatic PE, or VTE-related mortality; the incidence of asymptomatic or symptomatic DVT; the incidence of symptomatic or proximal DVT; the incidence of confirmed, symptomatic PE; the incidence of VTE-related mortality; and the incidence of all-cause mortality. To ensure objectivity, independent committees assessed bleeding events and thromboembolic events under blinded conditions.

Major bleeding was defined as fatal bleeding, clinically overt bleeding accompanied by a decrease in hemoglobin of >2 g/dL, clinically overt bleeding requiring transfusion (excluding predonated autologous blood) with more than 4 units of blood (1 unit = approximately 200 mL), retroperitoneal bleeding, intracranial bleeding, intraocular bleeding or intrathecal bleeding, and bleeding requiring repeat surgery. CRNM bleeding was defined as bleeding that did not fall under the category of major bleeding but corresponded to any of the following: hematoma of ≥ 5 cm in longest diameter, epistaxis or gingival bleeding that occurred in the absence of external factors and lasts ≥ 5 minutes, GI bleeding, gross hematuria that is persistent after 24 hours of onset, and other bleeding that was assessed to be clinically significant by the investigator or sub-investigator. Any bleeding event that did not meet major or CRNM criteria was categorized as a minor bleeding event.

In addition to safety and efficacy outcomes, PD indices (prothrombin time [PT], prothrombin time expressed as international normalized ratio [PT-INR], and activated partial thromboplastin time [aPTT]), and edoxaban plasma concentrations were measured at various time points as described below.