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Efficacy Study of the COmbination of Edoxaban and Physiotherapy on the PRevention of Venous-Thromboembolism in patients after Total Knee Arthroplasty (ESCORT-TKA Trial): Study protocol for a randomized controlled trial

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ABSTRACT

Background: Deep vein thrombosis (DVT) after total knee arthroplasty (TKA) often results in a fatal pulmonary thromboembolism (PTE). Edoxaban is an activated factor X inhibitor, which has been shown to prevent thromboembolic events in venous thromboembolism (VTE). Recently, the Total-Thrombus-formation Analysis System (T-TAS™), a microchip-based flow chamber system capable of evaluating thrombogenicity, was developed. In this study, utilizing the T-TAS™, we will examine the incidence of VTE after TKA and evaluate how thromboses form.

Methods/design: This study will be a prospective, single-center, open-label, randomized, controlled clinical trial aimed at exploring the efficacy of edoxaban in reducing the incidence of VTE after TKA.

A total of 80 patients who will undergo TKA will be randomly and evenly divided into groups receiving edoxaban plus physiotherapy or physiotherapy alone. The primary outcome measures will include the incidence rate of VTE as detected by ultrasonography 7 days after TKA and the changes in T-TAS™ parameters. The secondary outcome measures will include the changes in prothrombin time and activated partial thromboplastin time, incidence of major/minor bleeding events and adverse effects of edoxaban.

Discussion: This study will provide clinical evidence on the combined efficacy and safety of edoxaban and physiotherapy compared with that of physiotherapy alone. This is will be the first prospective trial designed to explore how thrombus formation after TKA can be predicted by the T-TAS™.

1. Introduction

One of the major complications after orthopedic surgery is venous thromboembolism (VTE). In addition, fetal pulmonary thromboembolism (PTE) often occurs in this surgery. It is thought that most occurrences of PTE are derived from a deep vein thrombosis (DVT). It has been reported that PTE occurs in 50–60% [1,2] of DVT patients and that DVT occurs in 50–80% [3,4] of symptomatic VTE patients. It is important to inhibit the occurrence of PTE and prevent its origin from DVT.

According to Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (Japanese Circulation Society 2009) [5], the incidence rates of DVT in total knee arthroplasty (TKA) are high, and TKA is considered to be as high a risk factor for VTE as total hip arthroplasty (THA) and hip fracture surgery (HFS). The prevention of VTE due to these high-risk operations by physiotherapy has been recommended, including by the use of elastic stockings [6,7] or intermittent pneumatic compression (IPC) [8–11]. Although the merit of physiotherapy is that there is no possibility of bleeding, the efficacy of physiotherapy is lower than that of anticoagulation therapy [12].

Edoxaban (DU-176b, trade names: Savaysa® and Lixiana®, Daiichi Sankyo, Inc.) is an oral direct factor Xa (FXa) inhibitor [13,14], which has been shown to be effective in the treatment and prevention of thromboembolic events in atrial fibrillation [15] and VTE [16,17]. A multicenter, phase II study in patients undergoing TKA demonstrated that edoxaban was safe and effective for thromboprophylaxis across a wide range of doses [18]. The phase III study (the Studying Thrombosis After Replacement Surgery (STARS) E-3 Trial) demonstrated that edoxaban (30 mg, once daily) was more effective for

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thromboprophylaxis than subcutaneous enoxaparin (2000 IU, twice daily) following TKA and demonstrated a similar incidence of bleeding events in Japanese and Taiwanese patients [19]. However, the evaluations of VTE in edoxaban clinical development tests have been performed using venography, and VTE has not been evaluated by ultrasonography or contrast-enhanced computed tomography (CT) scanning, which is what are used in real clinical situations.

Recently, the Total-Thrombus-formation Analysis System (T-TAS™) [20,21], a microchip-based flow chamber system capable of evaluating whole blood thrombogenicity, was developed as an easy-to-use system for the quantitative analysis of thrombus formation. We have previously demonstrated the usefulness of the AR10-AUC30 levels determined by the T-TAS™ in distinguishing the pharmacological effects of edoxaban in patients undergoing TKA [22]. However, we did not compare these effects to the results from a control group (non-edoxaban-receiving group). Thus, the possibility that the operation affected the measured outcomes could not be ruled out.

In the present study, we will examine the potential benefits of a combination of edoxaban and physiotherapy on the incidence rate of DVT in the lower extremities following surgery utilizing ultrasonography and contrast-enhanced CT scanning. Moreover, we will evaluate how well thrombosis formation in the lower extremities following surgery is predicted using the T-TAS™. We will obtain data to test the hypothesis that this combined therapy can ameliorate the incidence rate of VTE in the lower extremities following surgery.

2. Methods/design

2.1. Study design

This study is a prospective, single-center (Kumamoto University Hospital, Kumamoto, Japan), open-label, randomized, controlled trial on the efficacy of edoxaban on preventing VTE in patients who have undergone TKA. Consecutive patients who will undergo TKA will be randomly and evenly assigned to groups receiving edoxaban plus physiotherapy or conventional physiotherapy alone. TKAs will be conducted at the Department of Orthopedic Surgery (Kumamoto University Hospital) as described in detail below. Ultrasonography of the operated lower limb will be performed 7 days after the TKA operation by examiners blinded to the treatment group. The study design is summarized in Fig. 1. This study has been registered at UMIN000020627, according to the statement of the International Committee of Medical Journal Editors.

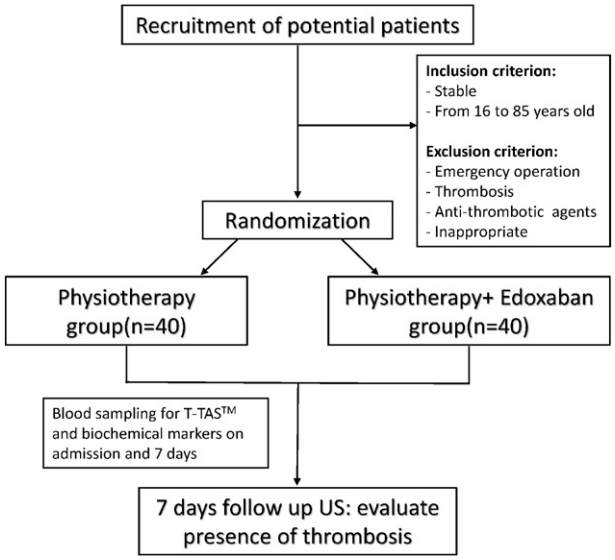

Fig. 1. Flow chart. (T-TAS™; Total-Thrombosis Analysis System, US; ultrasonography).

2.2. Recruitment and consent

A target sample size of 80 patients who are scheduled to undergo TKA operations at the Department of Orthopedic Surgery in Kumamoto University Hospital will be recruited. All candidates will go through a standardized interview process and will receive more information about the study and the treatments. The purpose, procedures, and potential risks and benefits of the study will also be thoroughly explained to the participants. The participants will be able to withdraw from the study at any time without any consequences. The entire trial, including enrollment and follow-up, will be conducted from April 2015 to December 2016.

2.3. Ethical consideration

All procedures will be conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol has been approved by the human ethics committee of Kumamoto University and written informed consent will be obtained from each patient or from the family of the patient.

2.4. Inclusion criteria

Participants meeting the following criteria will be included:

- Meet the diagnostic criteria for TKA.
- 16 to 85 years of age
- Willingness to give written informed consent and willingness to participate in, and comply with, the study

2.5. Exclusion criteria

Participants meeting one or more of the following criteria will be excluded:

- Emergent operation
- Serious infection
- Allergy to the drug used in the study
- Current thrombosis
- Taking any anti-thrombotic agents, including aspirin, P2Y12 inhibitor, warfarin, or non-vitamin-K oral anticoagulants (NOACs)
- Unwilling to give informed consent

2.6. Interventions

All TKAs will be performed by the same surgeon, who will use a measured resection technique as previously reported in detail [23]. In brief, the patella will be not resurfaced. Using a mobile-bearing TKA (NexGen LPS Flex Mobile, Zimmer, Warsaw, IN), a device will be employed intraoperatively to place four 0.8-mm tantalum beads at predefined sites in a polyethylene insert. The Hospital for Special Surgery (HSS) score will be used for preoperative and postoperative clinical evaluations. Radiographic evaluations will be performed using standing AP radiographs for the tibiofemoral angle and the Knee Society rating system for component alignment [24].

2.7. Periprocedural anticoagulation regimen and collection of blood samples

Oral administration of edoxaban (30 mg, once daily) will be initiated from the second day after the TKA operation to prevent VTE, as described in the to The STARS E-3 Trial [25]. Blood samples will be obtained the day before (anticoagulant-free point) and 7 days after the TKA operation (trough point).