Multicenter, Open-Label, Randomized Controlled Trial of Warfarin and Edoxaban Tosilate Hydrate for the Treatment of Deep Vein Thrombosis in Persons with Severe Motor Intellectual Disabilities

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Abbreviations: Ccr, creatinine clearance; DVT, deep vein thrombosis; PTE, pulmonary thromboembolism; PT-INR, prothrombin time-international normalized ratio; SMID, severe motor and intellectual disabilities; TTR, time in therapeutic range.
INTRODUCTION

It has been reported that sudden death accounts for about 4.2% of the causes of death in children (patients) with severe motor intellectual disabilities (hereinafter referred to as SMID patients) [1]. One of the causes of this sudden death is pulmonary thromboembolism (PTE), and deep venous thrombosis (DVT) has drawn attention as a possible embolic source [2-6].

Although the incidence of DVT is high in SMID patients [3-6], the currently established DVT-PTE guidelines [4] are targeted for adults who have the ability to walk, and do not take into account adults with poor mobility who are often bedridden due to muscle tension abnormality resulting from cerebral palsy and developmental movement disorders from early childhood [1, 3-6].

In addition, although DVT-PTE guidelines recommend administration of oral anticoagulant warfarin, warfarin requires a strict dose control based on the international normalized ratio of prothrombin time (PT-INR) to ensure adequate efficacy and prevention of bleeding complications [4]. Nowadays, evaluation of time in therapeutic range (TTR) has been proposed as an index to evaluate whether the control is good or bad, and it is considered important to maintain TTR as much as possible. However, it is not always easy to control TTR within the range of PT-INR specified in the guideline and to maintain TTR appropriately. Moreover, many SMID patients have paralysis of the extremities, which is accompanied by spinal deformities and joint contractures, due to muscle tension abnormality resulting from cerebral palsy and developmental movement disorders, etc. For this reason, it is difficult to conduct blood-sampling tests for PT-INR measurement, and it is currently difficult to manage treatment of DVT with warfarin.

On the other hand, edoxaban tosilate hydrate, a non-vitamin K antagonist oral anticoagulant, which has newly been approved for insurance coverage for the treatment of DVT, is not listed in the DVT-PTE guidelines at the present time. The dose regulation of edoxaban is easier than warfarin, and its efficacy and safety in DVT treatment have also been reported [16-18]. The aim of this study is to evaluate the efficacy and safety of anticoagulation therapy (warfarin vs. edoxaban) in DVT treatment in SMID patients by means of an open-label, randomized controlled trial. The primary endpoint is the incidence of hemorrhagic events during 12 months of follow up.

METHODS

Study Design

This is a randomized controlled trial that takes into account the DVT characteristics of SMID patients. It was designed to provide an unbiased comparison of warfarin and edoxaban tosilate hydrate in DVT treatment in SMID patients. The presence of DVT in SMID patients will be confirmed by lower extremity venous ultrasound.

Participants

Inpatients in participating institutions and home care patients, particularly adult SMID patients with Oshima’s classification [19] grade 1 to 4, with very poor mobility, who have DVT in the lower extremities.
Inclusion criteria

1) Adult (aged 20 years or older) SMID patients with Oshima’s classification [19] grade 1 to 4
2) Patients with DVT evaluated by lower extremity venous ultrasound
3) Those who provided written informed consent through a legally acceptable representative

Exclusion criteria

1) Those who were determined by the principle investigator and the sub-investigator to be ineligible for the study
2) Patients whose Ccr fell below 15 ml/min
3) Patients taking agents contraindicated for coadministration with the study drug

Intervention

Warfarin group:

After DVT incidence, oral administration of warfarin will be initiated. If necessary, an appropriate initial treatment such as heparin will be used in combination. Following once daily oral administration of the initial dose of warfarin, the dose will be adjusted to ensure that it is within the target therapeutic range using a blood coagulation test over a few weeks, and a maintenance dose will be determined. Because individual differences in sensitivity to warfarin are large and the sensitivity may change even in the same individual, blood coagulation tests will be regularly performed, and maintenance dose will be adjusted as necessary.

Specifically, according to the DVT-PTE guidelines, the dose of warfarin will be adjusted to keep PT-INR at about 2.0 while paying close attention to bleeding tendency in the first month. After one month, the dose of warfarin will be adjusted to keep PT-INR within a range of 1.5-2.0 [3, 5, 6].

Edoxaban tosilate hydrate group:

Oral administration of edoxaban tosilate hydrate (Lixiana®) will be initiated after the diagnosis of DVT. If necessary, an appropriate initial treatment such as heparin will be administered first. The daily normal dose is 60 mg taken once orally. If one or more of the following applies, indications will be carefully considered, and the dose will be reduced to 30 mg orally once daily: body weight of 60 kg or less, Creatinine Clearance (Ccr) 15-50 ml/min, concomitant use of a P-glycoprotein inhibitor (Quinidine Sulfate Hydrate, Verapamil Hydrochloride, Erythromycin, Cyclosporine, Azithromycin, Clarithromycin, Itraconazole, Diltiazem, Amiodarone, Human Immunodeficiency Virus protease inhibitor). After one month of treatment, dose will be adjusted to 30 mg orally once daily.

Schedule

Design of this trial is shown in Figure 1. Follow-up period is 12 months.

We will observe in detail the clinical symptoms of DVT in subjects who meet the eligibility criteria. In addition, lower extremity venous ultrasound, which is a noninvasive examination, and coagulation markers (D-dimer etc.) will be measured, and the presence or absence of DVT of the lower extremities will be confirmed. Patients determined to have DVT will be included in the study.

If necessary, chest X-ray examination, electrocardiogram, echocardiography (especially evaluation of the influence of right heart load due to pulmonary artery lesion), pulmonary scintigraphy (at facilities that can perform it), and chest contrast Computed Tomography (patients in whom large vascular access can be secured) will be performed to determine the presence or absence of complications of PTE. In patients with DVT, evaluation of swelling, pain and skin color change of lower extremities, and hardening and tenderness of lower leg muscles will be performed depending on clinical symptoms. The subjects will be randomized to a warfarin group and an edoxaban tosilate hydrate group.

![Fig. 1. Design of this trial.](image-url)
Randomization and blinding

Subjects will be randomized 1:1 to a warfarin group and an edoxaban tosylate hydrate group by block randomization method, using the following allocation adjustment factors: presence of tracheostomy, gastric tube insertion, or urethral balloon insertion/absence of any factors

This is a non-blind study.

Endpoints

Primary endpoint: the incidence of hemorrhagic events (major bleeding and clinically important bleeding) during 12 months follow up [20, 21]

Major hemorrhage is defined as being clinically evident and applies to one of the following:
- hemorrhage that triggers a decrease of ≥2 g/dL (i.e. 1.25 mmol/L) in hemoglobin level, or where transfusion of at least 2 units of packed red blood cells or whole blood is required (one unit of packed red blood cells is defined as the volume of red cells that can be obtained from approximately 500 ml of whole blood, or red blood cells equivalent to that amount)
- hemorrhage in significant sites, that is, intracranial, intraspinal, intraocular, retroperitoneum, intra-articular, and pericardial sites, or an intramuscular site accompanying compartment syndrome
- hemorrhage which is a cause of death

Intracranial hemorrhage is further classified as one of the following:
- subdural
- epidural
- subarachnoidal
- intracerebral (including intracerebroventricular hemorrhage)
- hemorrhagic change in ischemic stroke
- unspecified

Clinically important bleeding does not fall under the criterion of major hemorrhage. However, it is defined as hemorrhage which requires treatment, unplanned communication to a doctor, or discontinuation of an anticoagulant, or hemorrhage that causes discomfort to a patient such as pain or impedes daily activities. All other forms of hemorrhage that affect the patient clinically are included (e.g. hemorrhage accompanying a routine medical examination, treatment etc. of a severely sick child).

Secondary endpoints:
- Composite endpoints of DVT changes including the size, location (proximal/distal) and number of DVT assessed by lower extremity venous ultrasound.

The maximum diameter x length of the thrombus is calculated for each thrombus measured with leg vein sonography, and the total score is obtained after adding the grading for the subsequent sites. The amount of change in the score from baseline after 1 year is assessed.

Grading: thrombus formation site
1: Leg types (small saphenous vein, soleus vein and gastrocnemius vein, posterior tibial vein, anterior tibial vein, and fibular vein)
2: Thigh types (common femoral vein, femoral vein and great saphenous vein, and popliteal vein)
3: Ilium types (common iliac vein, internal iliac vein, and external iliac vein)
- Coagulation marker tests, especially changes of D-dimer and fibrin degradation product

Exploratory endpoints:
- Frequency of PT-INR measurement (warfarin group only) as a dose adjustment indicator of warfarin
- Frequency of warfarin dosage adjustments (warfarin group only)

Safety endpoints:
- Bleeding in routine care and management for SMID patients
  - Bleeding from granulomas etc. at a tracheotomy site, bleeding with insertion of a tracheotomy tube or insertion of a gastric/urethral balloon, bleeding associated with tracheal aspiration, and subcutaneous bleeding etc. due to bruising associated with postural change.
- Incidences of adverse events

Sample Size

76 SMID patients with DVT

There are no reports on the incidence of hemorrhagic events in SMID patients. In 12 SMID patients from the National Hospital Organization Yanai Medical Center who used conventional warfarin, 50 bleeding events occurred in one year, with the primary endpoint including bleeding in routine care and management for SMID patients. Assuming that the number of hemorrhagic events per month follows the Poisson distribution, the baseline incidence of hemorrhagic events is estimated to be 0.35 per person-months. The hazard ratio of major hemorrhage with 60 mg edoxaban tosylate hydrate product against warfarin targeted for middle to high risk atrial fibrillation was 0.71 if the body weight was 60 kg or less [22]. Hence, based on this assumption that the baseline incidence of hemorrhagic events is 0.35 and that the incidence in the edoxaban
tosilate hydrate group would be 0.71 times lower than that in the warfarin group, 68 patients will be needed for the treatment group to achieve a significance level of 0.025 (one-tailed) with 80% detection power. Considering a withdrawal rate of about 10%, 76 patients will be included.

There are about 7,000 beds in 73 hospitals of the National Hospital Organization with SMID patient wards. If we include especially SMID patients with poor mobility with Oshima’s classification [19] grade 1 to 4 with a help of public or corporate SMID patient facilities, approximately 200 patients per year would be expected to register. Assuming a DVT incidence in 30 to 40% of these patients, it should be possible to accumulate an adequate number of DVT patients in 1 year.

Statistical analysis

Analysis set
Full analysis set: Subjects who were enrolled, met the enrollment criteria, and had at least one measurement
Safety analysis set: Subjects who were enrolled and started the study treatment

Statistical Methods
Analysis of the primary endpoint:
Calculate the incidence of hemorrhagic events for each group and compare groups using the Poisson regression.

Analysis of the secondary endpoints:
- For the composite endpoints of DVT changes including the size, location (proximal/distal) and number of DVT assessed by lower extremity venous ultrasound, summary statistics of the score for baseline, post-1 year, and change will be calculated for each group and compared using Wilcoxon’s rank sum test.
- Summary statistics of the changes in coagulation markers will be calculated for each group and compared using Wilcoxon’s rank sum test.
- Incidence of bleeding in routine care and management for SMID patients will be calculated for each group.
- Incidence of each adverse event will be calculated for each group.

Interim analysis and monitoring
Interim analysis will not be performed.
Central monitoring conducted based on data collected over the Internet will be used as a monitoring method. As a rule, site visit monitoring will not be carried out. As a result of monitoring, the site may be contacted regarding data confirmation, addition/entry of missing data if necessary. Regular monitoring will be performed once a year.

Study organization
Hiromitsu Ohmori is the coordinating investigator. Hiromitsu Ohmori, Takeshi Miyanomae, Hideo Kaneko, Yukihiro Koretsune are the steering committee. 16 institutions that belong to the Japanese National Hospital Organization will participate in the study.

DISCUSSION
Evaluation of the efficacy and safety of anticoagulation therapy in DVT treatment in SMID patients in a randomized controlled trial of warfarin and edoxaban tosilate hydrate will provide basic information for creating new guidelines for prevention and treatment of DVT according to the characteristics of SMID patients. This will also lead to development of prevention measures for PTE in SMID patients.

DECLARATION
Competing interests
MN has received remuneration from DAIICHI SANKYO COMPANY, LIMITED, Bayer Yakuhin, Ltd., Pfizer Japan Inc. and Bristol-Myers Squibb K.K. For the other authors, there are no conflicts of interest to declare.

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Not applicable.

Authors’ Contributions
HO made final approval of the protocol and summarized the entire study. MN, RS provided assistance in creating protocols. HO, TM, HK, YK devised and planned the present trial, and summarized the entire trial. AS is in charge of patient enrollment, data management, and central monitoring. AK is in charge of statistical analysis. HO, YS, TS, HF, AW, KM, AO, NT, HM, MI, HK, HT, MK, NS, SA, NT, SS, MK, TT, TM make adjustments at each site in order to conduct the study.

Ethics and dissemination
The study was approved by the National Hospital Organization Central Research Ethics Committee, and the protocol is registered in the UMIN CTR (UMIN000024736). The present study started to en-
roll participants from November 2016 and it is currently in progress. The results of this study are scheduled to be published within 2 years after the end of the study, by conference presentation or paper publication.

Data sharing
There is no data available.

REFERENCES


