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Original Article

Deep Vein Thrombosis in Severe Motor and Intellectual Disabilities Patients and Its Treatment by Anticoagulants of Warfarin Versus Edoxaban

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Objective: Patients with severe motor and intellectual disabilities (SMID) often develop complications, including paralysis of the extremities due to abnormal muscular tonicity. Furthermore, the incidence of sudden death, which may be caused by pulmonary thromboembolism (PTE), is approximately 4.2%. Deep vein thrombosis (DVT) is attracting attention as an embolic source. In this study, DVT was confirmed in SMID patients by lower extremity venous ultrasound. The oral anticoagulant, warfarin, and novel oral anticoagulant, edoxaban tosilate hydrate, were administered, and their efficacies and safeties were evaluated.

Materials and Methods: DVT patients were randomly allocated to warfarin and edoxaban groups. The frequency of hemorrhagic events and incidence of adverse events were investigated to evaluate efficacy and safety.

Results: DVT was detected in 14 (8.4%) out of 167 patients. Four (0.067/person-month) hemorrhagic events occurred in the warfarin group from subcutaneous hemorrhage due to bruises caused by postural changes. Three (0.042/person-month) events occurred in the edoxaban group due to nasal hemorrhage caused by tracheal aspira-

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tion. There was no significant difference (p=0.5383) between groups.
Conclusion: No significant differences were observed in hemorrhagic events between SMID patients with DVT treated with warfarin and edoxaban.

Keywords: severe motor and intellectual disabilities, deep vein thrombosis, duplex ultrasonography, oral anticoagulants

Introduction

Sudden death accounts for approximately 4.2% of deaths in patients with severe motor intellectual disabilities (SMID). This may be partly due to venous thromboembolism (VTE).[1] One of the causes of this sudden death in SMID patients is pulmonary thromboembolism (PTE), and deep venous thrombosis (DVT) is attracting attention as an embolic source.[2–6]

Although the incidence of DVT is high in SMID patients,[3–6] current DVT-PTE guidelines[4] are targeted toward adults who can walk, not those with poor mobility who are often bedridden due to muscle tension abnormalities resulting from cerebral palsy and developmental movement disorders from early childhood.[1,3–6]

Although the DVT-PTE guidelines recommend administration of the oral anticoagulant warfarin, strict dose control, based on the international normalized ratio of the prothrombin time (PT-INR), is needed to ensure adequate efficacy and prevent bleeding complications.[4] Evaluations of time in the therapeutic range (TTR) have been proposed as an index to assess whether dose control is good or bad, which is important for maintaining TTR. However, difficulties are associated with controlling TTR within the PT-INR range specified in the guidelines and maintaining it appropriately. Furthermore, many SMID patients have paralysis of the extremities, which is accompanied by spinal deformities and joint contractures due to muscle tension abnormalities, resulting from cerebral palsy and developmental movement disorders. Therefore, blood sampling for PT-INR measurements is challenging, and managing DVT with warfarin is difficult.

Edoxaban tosilate hydrate, a non-vitamin K antagonist oral anticoagulant, has been approved for treating DVT but is not currently listed in the DVT-PTE guidelines. Dose regulations for edoxaban are less stringent than those for warfarin, and its efficacy and safety in treating DVT have been reported.[7–9]

We herein evaluated the efficacy and safety of anticoagulant therapy for DVT in SMID patients. The results will provide basic information for creating new DVT-PTE guidelines for preventing and treating DVT according to SMID patients' characteristics as well as developing new measures to prevent PTE in these patients.

Materials and Methods

This was a multicenter, open-label, randomized controlled trial that considered the DVT characteristics of SMID patients. The National Hospital Organization Central Research Ethics Committee approved the study, and the protocol was registered in the UMIN Clinical Trial Registry (UMIN000024736).[10] All patients provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects.

Patients who met all inclusion criteria and no exclusion criteria registered for this study. The following inclusion and exclusion criteria were used: 1) Adult (aged 20 years or older) SMID patients with Oshima's classification[11] grades 1 to 4; 2) Patients with DVT evaluated by lower extremity venous ultrasonography: 3) Those who provided written informed consent through a legally acceptable representative. We excluded: 1) Patients who were considered by the principle investigator and sub-investigator to be ineligible for the study; 2) Patients whose creatinine clearance decreased to less than 15 mL/min; and 3) Patients taking agents contraindicated for coadministration with the study drug. Patients were randomized 1:1 to the warfarin and edoxaban tosilate hydrate groups by block randomization adjusted by the presence of either tracheostomy, gastric tube insertion, or urethral balloon insertion.

In the warfarin group, warfarin was orally administered after DVT was confirmed. If necessary, an appropriate initial treatment, such as heparin, was used in combination. Following the once daily oral administration of the initial dose of warfarin, the dose was adjusted to ensure that it was within the target therapeutic range using a blood coagulation test over a few weeks, and a maintenance dose was selected.

In the edoxaban group, edoxaban tosilate hydrate (Lixiana®) was orally administered after the DVT diagnosis. If necessary, an appropriate initial treatment, such as heparin, was administered. The normal daily dose was 60 mg (or 30 mg below 60 kg body weight) taken once orally. At one month of treatment, or depending on renal function and concomitant medication, the dose was adjusted to 30 mg orally once daily.

The primary endpoint was the incidence of hemorrhagic events (major bleeding and clinically important bleeding) in a 12-month follow-up.

Since there is currently no index for evaluating the degree of changes in DVT in the lower extremities, we created a composite of DVT changes as the secondary endpoint, including the size, location (proximal/distal), and number of DVT assessed by lower extremity venous ultrasonography. The maximum diameter × length of the thrombus was calculated for each thrombus, measured

with leg vein sonography, and the total score was obtained after adding weighted by the grade for thrombus formation sites. The extent of changes in the score from baseline after one year was assessed.

Grading: thrombus formation sites
1: Lower leg types (small saphenous vein, soleus and gastrocnemius veins, posterior tibial vein, anterior tibial vein, and fibular vein)
2: Femoral types (common femoral vein, femoral and great saphenous veins, and popliteal vein)
3: Iliac types (common iliac vein, internal iliac vein, and external iliac vein)

Sample size

The incidence of hemorrhagic events in SMID patients currently remains unclear. In 12 SMID patients from the National Hospital Organization Yanai Medical Center administered conventional warfarin, 50 bleeding events occurred in one year, which applies to the primary endpoint, including bleeding in routine care and management for SMID patients. Assuming that the number of hemorrhagic events per month follows a Poisson distribution, the baseline incidence of hemorrhagic events was estimated to be 0.35 per person-months. The hazard ratio of major hemorrhage with 60 mg edoxaban tosilate hydrate product against warfarin, targeted for middle- to high-risk atrial fibrillation, was 0.71 when body weight was 60 kg or lower.[12] Assuming the baseline incidence of hemorrhagic events is 0.35, and is 0.71-fold lower in the edoxaban group than in the warfarin group, 68 patients were needed for the treatment group with a significance level of 0.025 (one-tailed) with an 80% detection power. Based on an estimated 10% withdrawal from the study, 76 patients were included.

Statistical methods

We defined two analysis sets. The full analysis set included subjects who were enrolled, met the inclusion criteria, and had at least one measurement. The safety analysis set comprised subjects who were enrolled and started the study treatment. Regarding the primary endpoint, we calculated the incidence of hemorrhagic events for each group and compared between groups using the Poisson regression. Concerning the composite endpoints of DVT changes, including the size, location (proximal/distal), and number of DVT assessed by lower extremity venous ultrasonography, summary statistics of the score for the baseline, after one year, and changes were calculated for each group and compared using the Wilcoxon rank sum test. The significance level was 0.05 in a two-tailed test. These analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Interim analysis and monitoring

An interim analysis was not performed.

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

Results

One hundred and seventy-one patients from 16 centers in Japan were enrolled and followed up between November

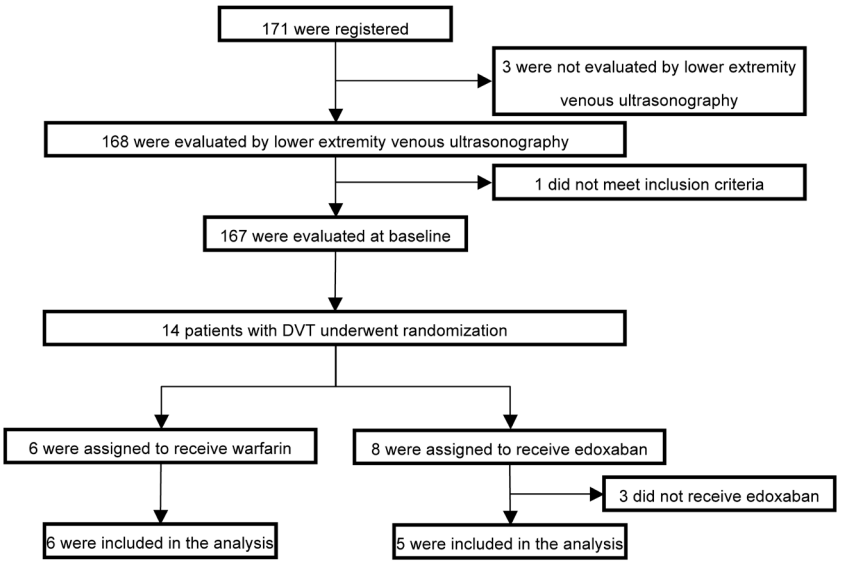

Fig. 1 Flowchart.
Flowchart for inclusion and exclusion of the study.
DVT: deep vein thrombosis

Table 1 Patient characteristics

	Group	
	Edoxaban[a] (n=5)	Warfarin[a] (n=6)
Gender		
Male	4 (80.0%)	4 (66.7%)
Age	63 (44–69)	47.5 (37–59)
Blood urea nitrogen (mg/dL)	9.0 (5.1–17.5)	11.4 (8.4–12.9)
Creatinine (mg/dL)	0.33 (0.26–0.49)	0.38 (0.31–0.54)
Activated partial thromboplastin time (sec)	29.2 (28.6–33.0)	30.6 (25.8–34.6)
D-dimer (g/mL)	0.72 (0.50–1.80)	0.70 (0.17–1.10)
PT-INR	1.08 (0.96–1.12)	1.00 (0.90–1.16)
Protein induced by vitamin K absence or antagonists II (mAU/mL)	49 (19–109)	48.5 (20–112)
Fibrin/fibrinogen degradation products (μg/mL)	2.0 (2.0–12.2)	2.0 (2.0–2.5)
AT (%)	84 (71–101)	105.5 (92–122)
Protein C (%)	86 (83–105)	93.5 (80–140)
Protein S (%)	81 (51–92)	64.5 (60–120)
White blood cell count (/μL)	4,700 (4,000–9,000)	6,700 (5,700–9,380)
WBC_Granulocyte (%)	46.2 (29.3–81.8)	43.15 (34.5–62.5)
WBC_Lymphocyte (%)	40.8 (14.4–58.9)	41.25 (26.5–59.6)
Red blood cell count (10^4/μL)	414 (396–433)	431 (406–484)
Hemoglobin (g/dL)	13.4 (12.1–15.5)	14.5 (13.0–15.0)
Haematocrit (%)	38.2 (36.3–42.8)	42.85 (38.7–44.8)
Mean corpuscular volume (fL)	92.3 (86.8–102.0)	95.5 (91.9–102.6)
Platelet (10^4/μL)	24.1 (8.8–30.5)	25.75 (17.6–30.9)
Reticulum (%)	1.50 (1.17–11.50)	1.10 (0.77–7.10)
TP (g/dL)	6.3 (6.1–7.0)	7.0 (6.5–8.0)
Albumin (g/dL)	3.5 (3.1–4.2)	3.75 (3.5–3.8)
Low-density lipoprotein cholesterol (mg/dL)	83 (73–128)	69 (35–85)
High-density lipoprotein cholesterol (mg/dL)	65.0 (36.4–76.0)	49.5 (38.0–67.0)
Triglyceride (mg/dL)	58 (52–121)	73.5 (43–102)
HbA1c (%)	5.2 (4.5–6.0)	4.85 (4.7–5.1)
Na (mEq/L)	131 (126–138)	139 (137–140)
K (mEq/L)	4.4 (3.9–4.9)	4.1 (3.9–4.8)
Cl (mEq/L)	96 (94–100)	104.5 (101–107)
Ca (mg/dL)	8.6 (8.1–9.2)	8.6 (8.4–9.1)
Inorganic phosphorus (mg/dL)	3.2 (2.3–4.3)	3.1 (2.9–3.7)
Creatine kinase (IU/L)	53 (32–72)	39 (25–72)
Uric acid (mg/dL)	2.2 (1.0–5.8)	3.65 (2.7–4.6)
Fe (μg/dL)	87 (28–112)	86.5 (58–146)
Ferritin (ng/mL)	27 (6–259)	26.55 (10–55)
Aspartate aminotransferase (IU/L)	20 (16–26)	25.5 (17–40)
Aalanine aminotransferase (IU/L)	16 (2–22)	27 (16–44)
Lactate dehydrogenase (IU/L)	144 (116–199)	216.5 (140–295)
eGFR (mL/min/1.73 m^2)	212.3 (112.8–285.9)	168.5 (99.8–223.6)
Creatinine clearance (mL/min)	135.6 (63.6–188.7)	108.1 (50.9–166.4)
Anti-phospholipid antibody		
—	4 (80.0%)	6 (100.0%)
None	1 (20.0%)	0 (0%)
Deformity of the spine		
—	1 (20.0%)	1 (16.7%)
+	4 (80.0%)	5 (83.3%)
Dislocation of the hip		
Right side	1 (20.0%)	0 (0%)
Left side	0 (0%)	1 (16.7%)
—	3 (60.0%)	3 (50.0%)
Bilateral	1 (20.0%)	2 (33.3%)
Thrombosis history		
No	4 (80.0%)	6 (100.0%)
Yes	1 (20.0%)	0 (0%)

[a] n (%) or median (min–max) were presented.

Table 2 Bleeding incidence

Group	N	Bleeding		Incidence (1 person-month)	Poisson model
		N	Event		
Edoxaban	5	1	4	0.066667	p=0.5383
Warfarin	6	1	3	0.041667	

2016 and August 2018. The study flowchart is shown in **Fig. 1**.

DVT was not evaluated in three patients. Furthermore, one patient evaluated for DVT was ineligible. DVT was observed in 14 patients, 8 and 6 of whom were randomly allocated to the edoxaban and warfarin groups, respectively. Three patients allocated to the edoxaban group did not receive edoxaban. Accordingly, the analysis set comprised five and six patients in the edoxaban and warfarin groups, respectively.

The registration period was extended from the initial plan to accumulate patients; however, the number of patients did not reach the target. Registration was completed because the state of hospitalization of SMID patients in Japan has mostly been clarified, and further increases were not expected.

Patient backgrounds are shown in **Table 1**. Four patients in each group were male, and median ages in the edoxaban and warfarin groups were 63.0 and 47.5 years, respectively. Regarding blood coagulation system markers, the median values of activated partial thromboplastin time, D-dimer, PT-INR, and antithrombin (AT) were 29.2 and 30.55 sec, 0.72 and 0.70 g/mL, 1.08 and 1.00, and 84.0 and 105.5% in the edoxaban and warfarin groups, respectively. Regarding other coagulation and fibrinolysis markers, the median values of protein C activity and protein S activity were 86.0 and 93.5%, and 81.0 and 64.5%, respectively. The median values of estimated glomerular filtration rate were 212.30 and 168.52 mL/min/1.73 m^2, respectively.

Regarding the primary endpoint of hemorrhagic events (major bleeding and clinically important bleeding), four events occurred in one patient in the edoxaban group, at an incidence of 0.067/person-month. Three occurred in one patient in the warfarin group, at an incidence of 0.042/person-month, showing no significant difference between groups (p = 0.5383) (**Table 2**). Regarding hemorrhagic events (major bleeding and clinically important bleeding), there was no major bleeding event. Four events of subcutaneous hemorrhage due to bruises caused by postural changes, and three events of nasal hemorrhage due to tracheal occurred.

DVT was symptomatic throughout 0–12 months in 2 and 1 patient in the edoxaban and warfarin groups, respectively. DVT was bilateral in one patient in the warfarin group (**Table 3**). The number of thrombi was 1 in 5 patients in the edoxaban group, and 1, 2, and 3 in 4, 1, and one patient, respectively, in the warfarin group.

Table 3 Deep vein thrombosis (DVT) characteristics

	Group	
	Edoxaban	Warfarin
	N	N
Symptomatic DVT		
No	3	5
Yes	2	1
Bilateral		
No	5	5
Yes	0	1
Confluent distal to proximal		
No	5	6
Maximum width of thrombi (mm)		
Median (min–max)	2.0 (0.9–15.0)	4.0 (2.2–25.0)
Number of thrombi		
1	5	4
2	0	1
3	0	1

Regarding the number of DVTs by region, 2 and 3 DVTs were the crus and femoral types at the time of initiation and the number of the femoral type decreased to 2 after 12 months in the edoxaban group (**Table 4**). In the warfarin group, 1, 5, and 1 DVT were the crus, femoral, and iliac types, respectively, at the time of initiation, and the crus and femoral types decreased to 0 and 1, respectively, while the iliac type increased to 3 after 12 months. The median score calculated changed from 48.8 to 72.0 in the edoxaban group and from 74.49 to 0 in the warfarin group, with no significant intergroup difference (p = 1.000).

Regarding warfarin administration, the median number of dose changes in the 12-month period was 5 (min–max: 3–5), the median frequency of measurements for PT-INR was 0.90/month (min–max: 0.80–1.33/month), and the median TTR was 282 days (min–max: 214–385 days).

Discussion

Many SMID patients are quadriplegic, and lower limb muscles do not develop in early childhood due to cerebral palsy and dystonia caused by developmental motor disorders. We previously reported that the incidence of DVT was high in these patients.[10,13] In the present study,

Table 4 Deep vein thrombosis (DVT) scores

Group	Month	Site of DVT					Score		
		Crus type[a]		Femoral type[b]		Iliac type[c]			
		Soleal vein	Unknown	Common femoral vein	Femoral vein	External iliac vein	Median	Min	Max
		N	N	N	N	N			
Edoxaban	0	1	1	2	1	0	48.80	1.98	1,200.00
	3	1	0	1	1	0	36.80	0.00	152.00
	6	1	0	2	0	0	18.20	0.00	105.00
	9	1	0	1	1	0	18.20	0.00	96.00
	12	1	1	2	0	0	72.00	0.00	770.00
Warfarin	0	1	0	4	1	1	74.49	30.36	10,500.00
	3	1	0	1	0	2	6.30	0.00	4,837.00
	6	0	0	2	2	1	0.00	0.00	456.00
	9	0	0	0	0	3	0.00	0.00	1,950.00
	12	0	0	1	0	3	0.00	0.00	774.00

[a] Soleal vein, gastrocnemius vein, posterior tibial vein, anterior tibial vein, peroneal vein, unknown. [b] Common femoral vein, femoral vein, popliteal vein, unknown. [c] Common iliac vein, internal iliac vein, external iliac vein, unknown.

the frequency of DVT in SMID patients was investigated using lower extremity venous ultrasound. SMID patients with DVT, for whom no treatment method has been established, were administered an oral anticoagulant, warfarin, the standard treatment, or edoxaban tosilate hydrate (LIXIANA®), a non-vitamin K-inhibitory oral anticoagulant (NOAC) newly developed as a substitute for warfarin that is covered by national health insurance, and their efficacies and safeties were evaluated.

Lower extremity venous ultrasound is a non-invasive examination for DVT. Although this examination has not yet extended to National Hospital Organization hospitals with a SMID ward, it was confirmed as an accurate evaluation in participant hospitals. Since lower extremity venous ultrasound may be performed at the bedside, an increase in clinical technologists skilled in vascular echo has resulted in lower extremity venous ultrasound being more frequently performed, which may facilitate close examinations of DVT. If the early discovery of DVT enables effective therapeutic interventions from an early stage, the incidence of sudden death may also decrease.

Four (0.067/person-month) and three (0.042/person-month) hemorrhagic events occurred in the edoxaban and warfarin groups, respectively, with no significant differences between groups, and this may have been due to the small number of patients. These hemorrhagic events comprised subcutaneous hemorrhage, due to bruises caused by postural changes, and nasal hemorrhage, due to tracheal aspiration, which are characteristic events observed in routine medical practice for patients with SMID.

The patient with subcutaneous hemorrhage in the edoxaban group was a 63-year-old female, and PT-INR increased from 1.04 to 1.78. The patient who developed nasal hemorrhage in the warfarin group was a 37-year-old female, and PT-INR increased from 1.14 to 3.02.

In a previous study on DVT in SMID patients, DVT was found in the femoral veins in most cases.[13] The most frequent site was the femoral vein in the present study. To evaluate reductions in multiple DVTs in the lower limbs by treatments, we prepared composite endpoints by changing the weight of scores by the region of thrombus formation, through which it was possible to summarize findings; however, precise evaluations were difficult because of the small number of patients. We intend to accumulate more patients and confirm this evaluation's validity.

Regarding warfarin administration, PT-INR needs to be periodically confirmed and doses changed; however, PT-INR measurements are difficult in SMID patients due to their physical characteristics. The median frequency of dose changes in the 12-month period was 5, the median frequency of measurements for PT-INR was 0.90/month, and median TTR was 282 days, based on which the state of warfarin administration was confirmed. Edoxaban does not require PT-INR measurements, which may reduce the burden on SMID patients.

We have three limitations. First, the planned number of patients was not reached. Second, the DVT evaluation was not centralized and was judged at each facility. We performed technical training for lower extremity venous ultrasound before initiating this study for a uniform evaluation. Third, this study was performed in Japan. Since SMID patients' environments differ from overseas, the present results need to be carefully interpreted. The development of DVT in SMID patients was confirmed. No significant difference was noted in hemorrhagic events in SMID patients with DVT between the warfarin and edox-

aban groups. Complexity accompanying warfarin administration, such as PT-INR measurements, was confirmed.

Long-term hospitalized patients were mainly investigated clinically in this study; however, we set a long-term objective to facilitate medical support for home care patients while establishing and preparing a comprehensive medical environment. Clarifying the state of SMID patients in this study may be significant. Since lower extremity venous ultrasound is a non-invasive approach to evaluate DVT and may be performed at the bedside, an increase in clinical technologists skilled in vascular echo may facilitate the close examination of DVT and proper therapeutic interventions.

Conclusion

The target of the current VTE treatment guidelines is adults after the acquisition of gait and does not include bedridden SMID patients with poor locomotive abilities due to cerebral palsy from early childhood. A close evaluation of VTE in SMID patients as complications of the circulatory and vascular systems and the preparation of new VTE treatment guidelines for SMID patients corresponding to their characteristic pathology is necessary.

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Disclosure Statement

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Author Contributions

Study conception: HO
Data collection: AMS
Analysis: AK
Investigation: MN, YS, TS, HF, AW, KM, AM, NT, HM, MI, HK, HT, NS, NT, MK, TT, YK, RS, TM
Writing: HO, AK
Critical review and revision: all authors
Final approval of the article: all authors
Accountability for all aspects of the work: all authors

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