Impact of Anticoagulation Therapy on the Risk of Pulmonary Embolism and Bleeding Events in Patients with Isolated Distal Deep-Vein Thrombosis

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Summary
The efficacy of anticoagulation for isolated distal DVT (id-DVT) is still uncertain and controversial. The aim of this study was to elucidate the risk of pulmonary embolism (PE) from id-DVT and to investigate the need for anticoagulants.

We identified hospitalized patients with id-DVT diagnosed by lower-extremity ultrasonography (LEUS) from January 2013 to December 2013 in our institute. The exclusion criteria were the simultaneous detection of PE, a history of PE and/or DVT, and administration of anticoagulants before DVT detection. We retrospectively investigated the patient characteristics, treatments, occurrence of PE, and bleeding events between the groups with and without anticoagulation.

A total of 151 patients met the criteria. The median (IQR) age was 74 (67, 80) years old, and there were 60 (39.7%) men. The median (IQR) observation period was 571 (160, 721) days. Significant differences in patient characteristics were observed for hypertension, operation time, consultation with experts, and follow-up LEUS. During the observation period, only one patient in the no-anticoagulation group who had traumatic cerebral hemorrhaging and was bedridden developed PE (non-massive type). However, there was no statistically significant difference in the occurrence of PE between the groups (log-rank $P = 0.569$). Bleeding episodes were observed in 9 of 151 (6.0%) patients, and all patients with bleeding events were taking anticoagulants (log-rank $P < 0.001$).

The present retrospective single center study suggests that anticoagulation for id-DVT in inpatients with various backgrounds has a low efficacy to prevent the occurrence of PE and may increase bleeding events.

Key words: Anticoagulants

Deep-vein thrombosis (DVT) is a disease that can cause pulmonary embolism (PE). Generally, DVT can be divided into two categories: proximal (above-the-knee) or distal (below-the-knee) DVT. Isolated distal DVT (id-DVT) is a frequent event, with half of all patients with lower-limb DVT diagnosed on whole-leg compression ultrasonography.4

According to the American College of Chest Physicians (ACCP) guideline published in 2016,5 long-term (3 months) anticoagulant therapy is recommended in patients with proximal DVT. In contrast, the treatment of id-DVT is stratified by the symptoms or risk factors of the patients. However, these recommendations are generally weak and based on low-quality evidence.

The risk of PE from id-DVT and the need for anticoagulants and serial imaging of the deep veins remain unclear and controversial, and administering anticoagulants for id-DVT can be a fraught course of treatment, due to the risk of bleeding.

Some studies reported that the risk of PE was very low in patients with distal DVT.6,7 We hypothesized that id-DVT was very unlikely to induce PE and anticoagulants were not necessary. In the present study, we focused on id-DVT in order to clarify the risk of PE and to investigate the need for anticoagulants.

Methods

Patients: In our institution, from January 2013 to December 2013, 179 patients who were found to have id-DVT for the first time by lower-extremity ultrasonography (LEUS) were extracted from our database of LEUS. Among them, 12 were excluded because they had been diagnosed with PE by contrast-enhanced computed tomography (CECT) at the same time due to any symptoms. In addition, 16 were excluded because anticoagulants were already administered due to other diseases before DVT detection. Therefore, 151 patients were ultimately enrolled as the study participants. We divided these patients into two groups based on a retrospective review of medical re-
cords: an anticoagulation group of patients who were administered any anticoagulant regardless of period after id-DVT detection and a no-anticoagulation group of patients who were not given any anticoagulants. The anticoagulation group had 38 (25.2%) cases (Figure 1).

**Implementation of LEUS, and definitions of DVT, PE, bleeding events, and recurrent venous thromboembolism:** LEUS was performed based on the judgement of each attending physician. A clinical technologist performed the LEUS and evaluated the findings before a second check to confirm by a cardiologist. DVT positivity on LEUS was defined as any hypoechoic filling defect, which was assisted by non-compression sign by ultrasonic probe. The definition of id-DVT was limited to the fibula, tibia, and sural/soleus vein, regardless of number. The definition of above was defined as a location in the popliteal or more proximal veins. When both above and distal DVT were detected, the patient was defined as having proximal DVT. A follow-up LEUS was conducted based on the judgment of the attending physician. PE was defined by a shadow-deficient image on CECT. Symptomatic PE was diagnosed by CECT performed at the discretion of each attending physician, depending on the patient’s symptoms, such as desaturation or dyspnea. If symptomatic PE was suspected, CT was always performed. In contrast, asymptomatic PE was defined as PE diagnosed incidentally without symptoms. Bleeding events were divided into major and minor bleeding events. The definition of a major bleeding event was based on the International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria. A bleeding event that was not major was defined as a minor bleeding event.

**Recurrent VTE:** Recurrent VTE was defined as any progression or new DVT detected by follow-up LEUS during the observation period.

**Administration of anticoagulants:** In the present study, the attending physicians basically decided on the administration of anticoagulants for id-DVT. The duration of anticoagulation therapy was also decided by the attending physician based on each patient’s risk. When one or more experts were consulted, their decision to administer anticoagulants or not was deemed final. The administration of anticoagulants for other diseases or prophylactic before id-DVT detection was left to the attending physician.

**Observation period:** We set the beginning point of observation as the time of id-DVT detection. The observation period...
period was calculated based on the final visit to our hospital or the date of death. The causes of death were categorized as death from PE, cardiac death, cancer, infection, others, and unknown. These were extracted from the medical records retrospectively.

**Study endpoints:** We set the primary study endpoint as the development of symptomatic or asymptomatic PE. In addition, the secondary study endpoints were the occurrence of bleeding events and recurrent VTE detected by follow-up LEUS. The types of anticoagulants were heparin, warfarin, direct oral anticoagulants (DOACs), and fondaparinux. Both endpoints were assessed from the patient’s medical record retrospectively.

**Statistical analyses:** The chi-squared and Fisher’ exact test were used for the between-group comparison of qualitative variables, and the Mann-Whitney U test was used for the comparison of quantitative variables. With regards to study endpoints, the Kaplan-Meier test and the log-rank test were used for cumulative incidences.

All statistical analyses were performed using an SPSS software program for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). A P-value < 0.05 was considered statistically significant.

**Ethics approval:** This study was approved by the ethics committee of Toranomon Hospital (protocol number; 2043) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived because the data were anonymized. The information disclosure document of the study has been published on our hospital webpage.

**Results**

**Patient characteristics:** The patient characteristics of the two groups are shown in Table I. The median (IQR) age was 74 (67, 80) years old, and there were 60 (39.7%) men. All patients were inpatients. Of the 151 patients, 40 (26.5%) had cancer, 62 (41.1%) underwent surgery, and 64 (42.4%) had symptoms of DVT. Regarding comorbidities, significant differences were observed between the two groups in hypertension. In addition, median operation time was significantly longer in the anticoagulation group than in the no-anticoagulation group. There were also significantly more cases of consultation with experts and follow-up LEUS in the anticoagulation group than in the no-anticoagulation group. The median (IQR) observation period was 571 (160, 721) days. Regarding anticoagulants, 24 patients (63.2%) were taking heparin, 12 (31.6%) were taking direct oral anticoagulants (DOACs), 28 (50%) were taking warfarin, and 3 patients (7.9%) were taking fondaparinux.

**Study endpoints:** Regarding the primary study endpoint, only 1 patient (0.7%) in the no-anticoagulation group developed PE among all patients, a non-significant difference (log-rank \( P = 0.569 \)) (Table II, Figure 2A). The patient who developed PE was a 79-year-old woman who had been hospitalized for traumatic subarachnoid hemorrhage. LEUS was performed for edema of the lower legs, and id-DVT was found only on the left side. Regarding comorbidities, she had operable breast cancer, hypertension, and dyslipidemia. Dyspnea and desaturation were observed 25 days after the first LEUS, and contrast-enhanced CT showed non-massive type PE. Follow-up LEUS was conducted the next day, which revealed progression of proximal DVT. There were no PE events regardless of whether symptomatic or asymptomatic DVT in the anticoagulation group.

Regarding the secondary study endpoints, total bleeding events were found in 9 patients (6.0%), including 2 (1.3%) with major bleeding and 7 (4.6%) with minor bleeding. All events were observed in the anticoagulation group, showing a significant difference between the groups (log-rank \( P < 0.001 \)) (Table II, Figure 2B). There were also significant differences between the 2 groups in the occurrence of major bleeding and minor bleeding events (Table II, Figure 2C, D, respectively). All patients had bleeding events while taking anticoagulants. Of the 9 patients, 2 with major bleeding events were also taking antiplatelet agents. Regarding the therapeutic range of anticoagulants, the international normalized ratio of prothrombin time (PT-INR) and activated partial thromboplastin time (APTT) were within the upper limit of the therapeutic range in all patients. The dose of DOACs was within the therapeutic range in patients with bleeding events. Six patients had used more than 2 anticoagulants or a combination of antiplatelet drugs (Supplemental Table).

Recurrent VTE was seen in 21.5% of the patients who underwent follow-up LEUS; the incidence in the 2 groups did not differ to a statistically significant extent (log-rank \( P = 0.936 \)) (Figure 2E).

**Discussion**

The main results of this study are as follows: The occurrence of PE from id-DVT in total was extremely low (0.7%), and there was no significant difference between the anticoagulant and no-anticoagulant groups (log-rank \( P = 0.569 \)). In contrast, 6.0% of all patients had bleeding events, which were observed only in the anticoagulant group (log-rank \( P < 0.001 \)). Recurrent VTE was seen in 21.5% of patients; the incidence in the two groups did not differ to a statistically significant extent (log-rank \( P = 0.936 \)).

Our study results are consistent with those of a previous randomized placebo-controlled study for low-risk patients. In that study, there was no significant difference in the extension of id-DVT to proximal veins and symptomatic PE between the anticoagulation and no-anticoagulation groups. In addition, a previous report showed that the risk of PE from id-DVT was very low (1.4%). Furthermore, Galanaud, *et al* reported that patients with id-DVT who discontinued anticoagulation therapy showed a low incidence of PE (0.9%) during 3 years of observation. However, some studies have obtained findings that conflicted with our own. According to a previous meta-analysis, the administration of anticoagulants for id-DVT significantly reduces the risk of developing PE and does not increase the incidence of major bleeding. Another report found that 6.1% of all trauma patients with id-DVT developed PE. In addition, another study found that pa-
patients with id-DVT and active cancers had a high risk of recurrent VTE and a high risk of death compared to those without active cancers. The others reported that use of anticoagulants was associated with significantly lower risk for developing VTE in patients with active cancer and about two-thirds of recurrent VTE occurred after anticoagulant treatment withdrawal, which suggested the prophylactic efficacy of anticoagulants for recurrent VTE.
We propose the following explanations for the low occurrence rate of PE in our study: First, our hospital focuses on DVT screening at admission using a questionnaire and recommends LEUS for high-risk cases, which might have led to the early and high rates of detection of id-DVT. Second, our hospital has enacted preventive measures for DVT (e.g. elastic stockings for bedridden patients) for all patients with a risk of DVT. These efforts probably contributed to the reduced occurrence rate of PE in our study.

In our study, the administration of anticoagulants significantly increased bleeding events. A previous randomized placebo-controlled trial found that the major or minor bleeding event rate in patients receiving Nadroparin was 4.1%, which was lower than that in our study (10.2%). This may be because of the differences in the patients’ backgrounds. The average age was much lower, and the observation period was much shorter in the previous study.

Figure 2. The cumulative probability of PE and bleeding events in the two groups. P-values were calculated using log rank tests. A: The occurrence of PE. B: The occurrence of all bleeding events. C: The occurrence of major bleeding events. D: The occurrence of minor bleeding events. E: The occurrence of recurrent VTE.
than in the present study (52 ± 17 versus 73 ± 11 years old, 42 versus 47 ± 293 days, respectively). In addition, the previous study excluded cases of active malignancy, which were reported to bleed more compared to those without, cases with a condition associated with a high risk of bleeding such as gastric ulcers, and the ongoing need for thromboprophylaxis. Based on these reasons, we believe our study population including cancer patients reflects the real-world population of patients who are more likely to present with DVT and bleeding in daily practice. The administration of anticoagulants should be decided based on the patient’s background and the extent of the DVT found on follow-up LEUS.

Several limitations associated with the present study warrant mention. First, this was a single-center retrospective study, and the sample size was small. Second, the median (IQR) observation period was relatively short (571 [160, 721] days), so the long-term results are unclear. Third, the subjects were all inpatients at the time of detection of id-DVT, which was a bias in the patient background. In addition, a selection bias could not be avoided because some patients did not receive expert consultation. Fourth, the duration of anticoagulation therapy varied because it was decided by the attending physician based on the patient’s risk. Finally, the primary endpoint was judged by CECT performed due to a patient’s symptoms. Therefore, asymptomatic PE could not completely be detected. However, the strength of this study was its inclusion of all aspects of inpatients with id-DVT detected for the first time. Several previous studies focused only on patients without active cancers, active cancers or asymptomatic DVT, etc. As we mentioned above, our population reflects the real-world status of inpatients including patients at high risk of developing VTE. Further randomized controlled studies to explore the efficacy of anticoagulants for high risk patients with id-DVT in developing proximal DVT or PE are needed.

In conclusion, the present retrospective single center study suggests that anticoagulation for id-DVT in patients with various backgrounds including high-risk patients, has a low efficacy to prevent the occurrence of PE and may increase bleeding events.

Disclosure

Conflicts of interest: The authors declare that there are no conflicts of interest.

References

1. Galanaud JP, Bosson JL, Quere I. Risk factors and early outcomes of patients with symptomatic distal vs. proximal deep-vein thrombosis. Curr Opin Pulm Med 2011; 17: 387-91.
2. Kearon C, Akd EA, Ornellas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016; 149: 315-52.
3. Palareti G, Cosmi B, Lessiani G, et al. Evolution of untreated calf deep-vein thrombosis in high risk symptomatic outpatients: the blind, prospective CALTHRO study. Thromb Haemost 2010; 104: 1063-70.
4. Brateanu A, Patel K, Chagin K, et al. Probability of developing proximal deep-vein thrombosis and/or pulmonary embolism after distal deep-vein thrombosis. Thromb Haemost 2016; 115: 608-14.
5. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3: 692-4.
6. Righini M, Galanaud JP, Guenneguez H, et al. Anticoagulant therapy for symptomatic calf deep-vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial. Lancet Haematol 2016; 3: e556-62.
7. Nitta D, Mitani H, Ishimura R, et al. Deep vein thrombosis risk stratification. Int Heart J 2013; 54: 166-70.
8. Galanaud JP, Sevestre MA, Genty C, et al. Incidence and predictors of venous thromboembolism recurrence after a first isolated distal deep vein thrombosis. J Thromb Haemost 2014; 12: 436-43.
9. Franco L, Giustozzi M, Agnelli G, Becattini C. Anticoagulation in patients with isolated distal deep vein thrombosis: a meta-analysis. J Thromb Haemost 2017; 15: 1142-54.
10. Olson EJ, Zander AL, Van Gent JM, et al. Below-knee deep vein thrombosis: an opportunity to prevent pulmonary embolism? J Trauma Acute Care Surg 2014; 77: 459-63.
11. Galanaud JP, Sevestre MA, Pernod G, et al. Long-term outcomes of cancer-related isolated distal deep vein thrombosis: the OPTIMEV study. J Thromb Haemost 2017; 15: 907-16.
12. Yamashita Y, Shioni H, Morimoto T, et al. Asymptomatic Lower Extremity Deep Vein Thrombosis: Clinical Characteristics, Management Strategies, and Long-Term Outcomes. Circ J 2017; 81: 1936-44.
13. Dentali F, Pegoraro S, Barco S, et al. Clinical course of isolated distal deep vein thrombosis in patients with active cancer: a multicenter cohort study. J Thromb Haemost 2017; 15: 1757-63.

Supplemental Files

Supplemental Table
Please see supplemental files; https://doi.org/10.1536/ihj.20-726