ACCSCIENCE PUBLISHING

INNOSC Theranostics and Pharmacological Sciences

SHORT COMMUNICATION

An observational study on the use of low-molecular-weight heparin for venous thromboembolism prophylaxis in acute stroke patients

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Abstract

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) are common complications post-stroke. The UK stroke guidelines recommend the early use of intermittent pneumatic compression devices (IPCDs). At our center, we noticed poor compliance with the use of these devices and sought to develop a pathway for early implementation of low-molecular-weight heparins (LMWH) instead. We retrospectively analyzed the data of 2351 patients in two separate groups and compared both groups to check the incidence of PEs and DVTs as stated on the discharge documentation. Group A consists of 1599 patients who used IPCDs as VTE prophylaxis, whereas Group B involved 752 patients who were placed on the new VTE prophylaxis protocol, which involved the early use of LMWH with enoxaparin delivered subcutaneously. It was observed that IPCDs were not well tolerated by patients, leading to poor compliance with VTE prophylaxis in Group A. VTE compliance was noted to be better in Group B in which the patients were given LMWH in the hospital. Furthermore, symptomatic DVT and PE were not found to be higher in Group B patients, but in fact, the incidence of these conditions was lower in this group. In conclusion, compared to IPCDs, LMWH appears to be well tolerated by patients during the admission period owing to acute stroke. It was observed that the incidence of VTE was reduced in patients who started on early LMWH in the post-stroke period. However, the long-term effects of LMWH prophylaxis, in terms of mortality and morbidity, need to be delineated. Therefore, an additional large trial on the early use of LMWH in comparison to IPCDs is warranted.

Keywords: Low-molecular-weight heparin; Venous thromboembolism; Deep vein thrombosis; Pulmonary embolism; Acute stroke; Blood clots; Intermittent pneumatic compression device

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1. Introduction

Venous thromboembolism (VTE), a term which encircles both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in stroke patients.[1] VTE is a considerable cause of morbidity, delayed hospital discharge, and potential increased health-care costs. It has been estimated to account for one-fourth of all deaths after stroke.[2] In the early post-stroke phase, the risk of VTE appears to be highest in

the initial few weeks.[3] Clinically, about 5% of hospitalized patients have definite DVT.[4] Similarly, about 1 – 2% of hospitalized stroke patients were clinically diagnosed with PEs, but in some studies, the incidence is about 10%.[5] Moreover, Warlow *et al.* revealed PE as an identifiable cause in about half of the patients dying after a stroke, based on data collected from a hospital where autopsies were more conventional.[6] Therefore, clinicians are expected to assess VTE risk among stroke patients and provide the most effective and safe prophylaxis.

Hemorrhagic transformation (HT) is another common complication in acute ischemic stroke, and its rate of occurrence can range from <1%.[7-9] The severity of hemorrhage may range from a few petechiae to a large hematoma with or without space-occupying effects. Based on the classification by the European Cooperative Acute Stroke Study, each HT category is divided into two subtypes, with each featuring distinctive characteristics (Table 1).[10]

HT does not usually have a significant impact on patient prognosis,[11] but massive parenchymal hematoma, albeit rare, is life-threatening.[12] The mechanism of HT formation during ischemic stroke is thought to be related to the early disruption of the blood–brain barrier (BBB).[13] The BBB is a physiological barrier between the brain parenchyma and brain circulation that nourishes brain tissue. It filters various substances from the brain to the blood and protects the brain.[14,15] The other factors that might influence HT are histological changes, vascular occlusion, collateral circulation, and infarct size.[16,17]

Post-stroke VTE prophylaxis can be achieved with non-pharmacological and pharmacological strategies. Non-pharmacological or physical methods consist of graduated compression stockings (GCSs) and intermittent pneumatic compression devices (IPCDs). The use of blood thinners such as low-molecular-weight heparin (LMWH) and unfractionated heparins (UFH) come under pharmacological interventions. HT should be taken into account when the timing for anticoagulation initiation in cardioembolic strokes has to be established.[18] The European Stroke Organization (ESO) guidelines recommend that prophylactic anticoagulation with UFH and LMWH should be considered in immobile patients with ischemic stroke in whom the benefits of reducing the risk of VTE are significant enough to offset the increased risk of intracranial and extracranial bleeding.[4] This was also suggested by Khan et al. following a systemic review of literature on deep vein thrombosis in acute stroke; LMWH was effective in reducing DVT and PE in patients with stroke at the cost of a slightly increased risk of intracerebral and extracranial bleeding.[19]

Table 1. ECASS classification of hemorrhagic events

Category	Subtype and characteristic
Hemorrhagic infarction	HI-1: Small petechiae along the margins of the infarct. HI-2: Confluent petechiae within the infarcted area but no space-occupying effect.
Parenchymal hemorrhage	PH-1: Blood clots in 30% or less of the infarcted area with some slight space-occupying effect. PH-2: Blood clots in more than 30% of the infarcted area with substantial space-occupying effect.

ECASS: European Cooperative Acute Stroke Study, HT: Hemorrhagic transformation

The CLOTS 1 and 2 trials showed that GCSs were ineffective in preventing VTE or improving functional outcomes in stroke.[20] The CLOTS 3 trial showed that intermittent pneumatic compression (IPC) using sequential compression with venous refill technology in immobile patients in the first 30 days after stroke is an effective treatment for reducing proximal DVT and improves survival but not functional outcomes.[21]

It is challenging for patients with a high risk of VTE and low risk of bleeding to use anticoagulants in a selective manner after stroke because the factors that predict VTE and those predicting bleeding risk overlap.[22,23] According to Geeganage *et al.*, LMWH minimizes the risk of recurrent ischemic stroke, DVT, and PE; however, on the other hand, they increase the risk of symptomatic intracranial and extracranial hemorrhage.[24] In stroke, the benefits of LMWH are often offset by its harms; according to the data from randomized controlled trials of subcutaneous heparins, there was no noticeable effect of anticoagulants on death or disability measured several months after stroke.[25-27]

1.1. Study justification

Poor compliance with IPCDs among admitted patients with acute stroke was common at our unit. The poor compliance can be described as patients not tolerating the device, increased risk of falls, patients being ignorant that they attempt to stand without support with the IPCDs still on, and forgetfulness in reattaching IPCDs after care (*e.g.*, showering or hygiene) or therapy.

Thus, we reviewed the adherence to VTE prophylaxis plans formulated for our stroke unit by auditing compliance with IPCD use in 2021. The auditing process was completed in two parts:

(1) Audit 1: Review of compliance of VTE prophylaxis prescription using IPCDs in acute stroke patients within 72 h of admission
(2) Audit 2: Review of compliance of VTE prophylaxis prescription using IPCDs in acute stroke patients,

after the initial 72 h of admission, but within 1 month of stay.

In Audit 1, we found that generally, following admission to the acute stroke unit, stroke patients and staff demonstrated a high level of compliance in using IPCDs for VTE prophylaxis, with only 8% of patients not using their prescribed IPCD. However, Audit 2 showed that compliance with using IPCDs greatly reduced as patients continued with their stroke recovery in the rehabilitation unit, with 87% of patients found not to be wearing their prescribed IPCDs despite staff recommendations. There was a variety of reasons recorded in the notes, *e.g.*, patients reporting pain or discomfort while using IPCDs and patients reporting difficulty with transfers.

Following these two auditing processes, discussions on finding ways to improve compliance with IPCDs or considering alternative methods to deliver VTE prophylaxis in the stroke unit were held. After a series of discussions at governance meetings, we introduced a new protocol in July 2022, recommending the early use of LMWH prophylaxis in acute stroke patients as a VTE prophylaxis strategy. This was done using enoxaparin 20 – 40 mg (based on weight), delivered subcutaneously. Acute stroke patients were prescribed LMWH prophylaxis based on their stroke type (ischemic vs hemorrhagic) and stroke severity (mild: Lacunar stroke [LACS]; moderate: Partial anterior circulatory stroke [PACS]; severe: Total anterior circulatory stroke [TACS]) (Figure 1).

2. Study objectives

The purpose of this work is to evaluate the incidence of DVTs or PEs in patients treated with a new protocol for early use of LMWH prophylaxis. The secondary objective of this study is to examine if the same patient group is vulnerable to a higher incidence of symptomatic HT of ischemic stroke.

3. Method

The data of 2351 stroke patients admitted between January 1, 2021, and July 31, 2023, were evaluated retrospectively. In our analysis, these patients were subdivided into two groups:

- Group A consists of 1599 patients admitted between January 1, 2021, and July 31, 2022 (19 months). The patients in this group used IPCDs as VTE prophylaxis during the admission period for acute stroke

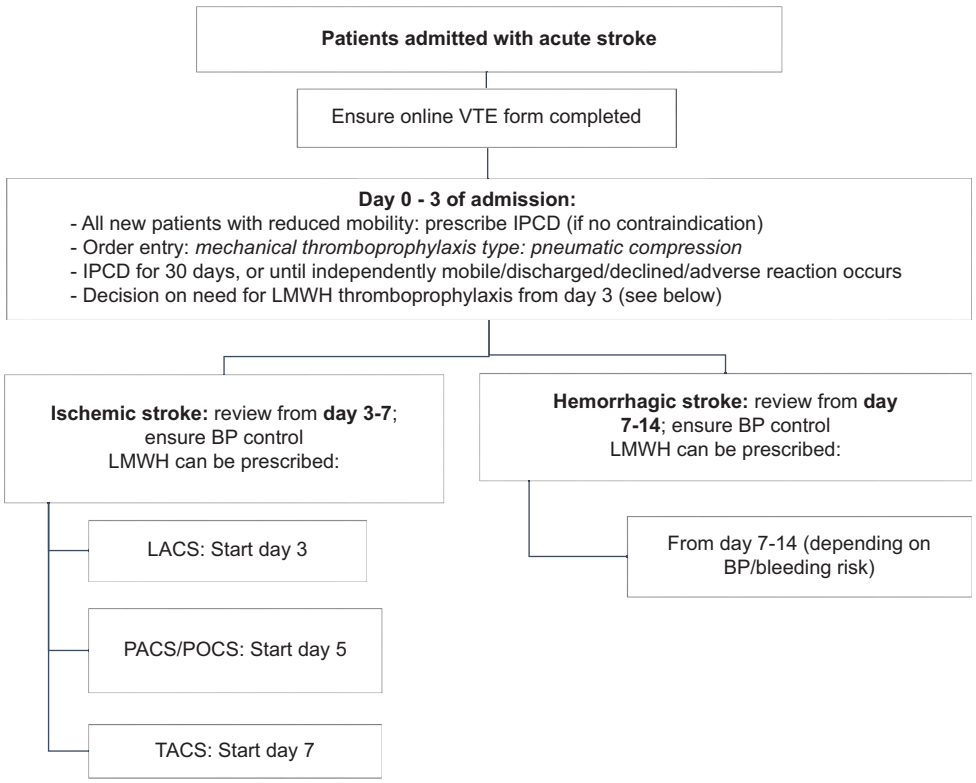


Figure 1. Flowchart for venous thromboembolism (VTE) prophylaxis with low-molecular-weight heparin (LMWH) therapy based on acute stroke presentation conducted in our hospital
Abbreviations: BP: Blood pressure; IPCD: Intermittent pneumatic compression device; LACS: Lacunar stroke; PACS: Partial anterior circulatory stroke; POCS: Posterior circulation stroke syndrome; TACS: Total anterior circulatory stroke.

- Group B consists of 752 patients admitted between August 1, 2022, and July 31, 2023 (12 months). The patients in this group used LMWH (enoxaparin 20 – 40 mg delivered subcutaneously, dose adjusted for weight) as VTE prophylaxis during the admission period for acute stroke.

In each of the groups, the patients who developed PE, DVT, or symptomatic HT within 3 months of their stroke were identified. They were investigated if they presented with clinical symptoms or were suspected of PE/DVT or symptomatic HT. The diagnosis of ischemic stroke, PE, DVT, and HT was confirmed by radiological means such as computed tomography (CT) of the head, CT pulmonary angiogram, and Doppler ultrasound.

The electronic VTE risk assessments (Appendix A1) and IPCD/LMWH prescriptions for patients were gathered from the hospital's electronic prescribing platform.

4. Results

The electronic VTE risk assessments of all the patients were completed at admission. This highlights that the admitting stroke team was aware of performing stroke VTE prophylaxis and the need to ensure the patients were adequately treated. We found that the early use of LMWH was associated with 100% compliance to VTE prophylaxis once the new protocol was implemented, as compared to 91.6% compliance during the admission period when the acute stroke patients were using IPCS (Figure 2).

In Group A, the incidence of PE and DVT is about 0.75% (12 patients) and 0.12% (Two patients), respectively. Among the 12 patients who developed PE, four cases were directly related to stroke, whereas the remaining eight cases were linked to other risk factors. In Group B, the incidence of PE is about 0.79% (six patients) and no case of DVT was identified. Among the six patients, only one patient was symptomatic, whereas the rest were found to have incidental PE based on the findings from other tests or investigations (Figures 2 and 3). None of the two groups have any reported cases admitted with symptomatic post-stroke HT in 3 months' time (Figure 3).

5. Discussion

Few studies have reported the use of early anticoagulation in acute stroke. Most studies have used LMWH as the anticoagulant agent and two of them used unfractionated heparin and a particular direct thrombin inhibitor, *i.e.*, argatroban.[28-30] The International Stroke Trial (IST) compared the administration of subcutaneous UFH versus aspirin within 48 h of onset of ischemic stroke symptoms. This randomized trial involved 19,435 patients from 467 hospitals in 36 different countries. The study revealed that

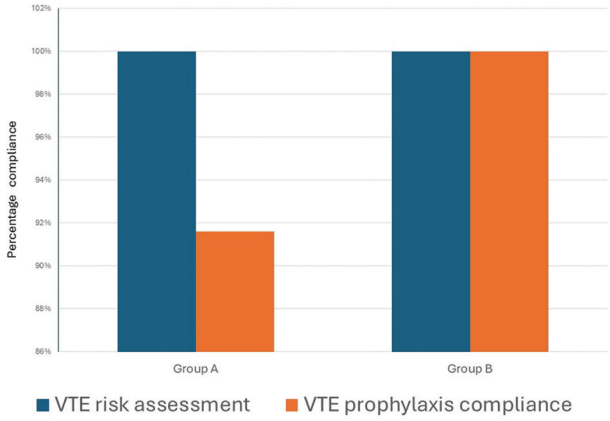


Figure 2. Venous thromboembolism risk assessment and prophylaxis compliance

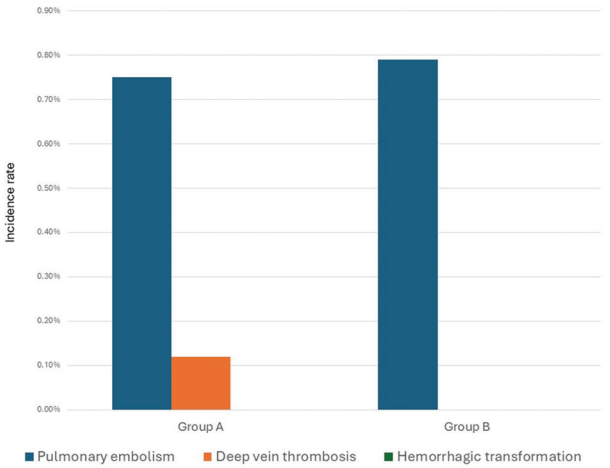


Figure 3. Incidence of pulmonary embolism, deep vein thrombosis, and hemorrhagic transformation. The incidence rate of hemorrhagic in Group A is 0, while the incidence rate of deep vein thrombosis and hemorrhagic transformation in Group B is 0

patients treated with heparin had a significantly lower recurrence of ischemic stroke within a 14-day period.[31] According to a FISS-tris trial involving patients with large-artery occlusive disease, nadroparin calcium was compared with aspirin. The therapy was initiated within 48 h of symptoms onset and patients were followed up until 6 months after the ischemic stroke. The results showed no significant benefit of nadroparin over aspirin in the patients assessed, and further investigation of anticoagulation in large-artery atherosclerosis patients was recommended.[32]

We observed the non-compliance of IPCD among stroke patients in 2021, despite that they were recommended to use the device. The reasons recorded include patients reporting pain or discomfort using IPCDs, staff and patients forgetting to effectively use the IPCDs after

therapy sessions, and patients reporting difficulty with transfers or positioning in bed. These situations were discussed in the local stroke governance meetings, and measures were taken to improve VTE compliance, *e.g.*, staff checking IPCD compliance during each nursing and medical ward round. At our institute, we followed the UK Stroke Guidelines 2016 (now replaced by the 2023 version, with the same document title). Accordingly, "patients with immobility after acute stroke should be offered IPC within 3 days of admission to hospital for the prevention of DVT. Treatment should be continuous for 30 days or until the patient is mobile or discharged, whichever is sooner."[33.p.60] However, despite staff checking, compliance was still found to be lacking with IPCD use.

Following discussions at governance meetings, we introduced a new protocol in July 2022, recommending the early use of LMWH prophylaxis in acute stroke patients as a VTE prophylaxis strategy. This was done using enoxaparin 20 – 40 mg (based on weight), delivered subcutaneously. Acute stroke patients were prescribed LMWH prophylaxis based on their stroke type (ischemic and hemorrhagic) and stroke severity (mild: LACS from day 3; moderate: PACS from day 5; severe: TACS from day 7) (Figure 2). Following this new protocol for VTE prophylaxis, we noted an improvement in VTE compliance among patients admitted to the stroke ward, probably due to regular monitoring done on the patients receiving VTEs prophylaxis and the LMWH being better tolerated by the patients. Furthermore, the incidence of DVT in stroke patients reduced, as no cases have been identified since the implementation of the new protocol. Both Groups A and B have more cases of asymptomatic incidental PE compared with DVTs. Relatively, the incidence of PE was slightly increased in Group B as compared to Group A, after taking into consideration their cohort size (Figure 3). This is probably due to the lower number of patients in Group B being analyzed (752 vs 1599 patients), which is a pitfall of this analysis. However, there was only a small proportion of patients with post-stroke PE in Group B who became symptomatic with shortness of breath or reduced blood oxygen saturation levels (Figure 4). Interestingly, one of the cases, who was admitted with a posterior circulatory stroke (POCS), showed no reduced mobility even if IPCD was prescribed. The patient later, on day 4 of admission, developed symptomatic PE.

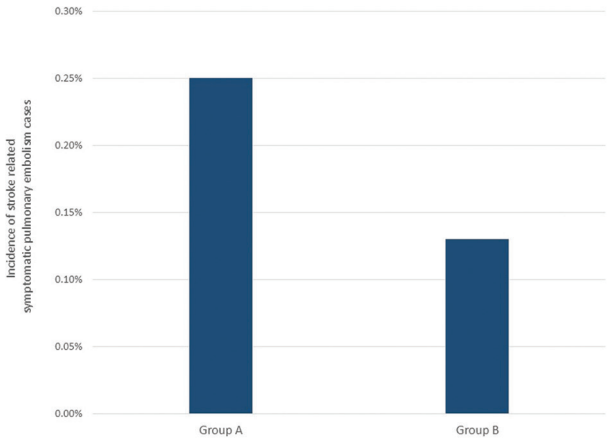


Figure 4. Incidence of stroke-related pulmonary embolism

In this study, we observed that being male with age around 71 – 80 years and/or having health issues such as diabetes mellitus, hypertension, and cardiac problems are

Table 2. Demographics of the patients from Groups A and B with pulmonary embolism and deep vein thrombosis

	Group A (*n*=14)	Group B (*n*=6)	N (number)	Percentage
Gender				
Male	8	5	13	65
Female	6	1	7	35
Age group				
51 – 60 years	2	1	3	15
61 – 70 years	3	2	5	25
71 – 80 years	5	2	7	35
81 – 90 years	4	1	5	25
Thromboembolism risk factors				
Hypertension	5	3	8	40
Diabetes mellitus	5	2	7	35
Ischemic heart disease or heart failure	3	1	4	20
Chronic illness or malignancy	5	1	6	30

the risk factors in both Groups A and B. Strangely, a small number of the population assessed tend to have cancer of various organs that may also contribute to VTE formation. Table 2 shows the patient demographics of all 20 patients from Groups A and B with DVTs and PEs.

The current study had several limitations. One apparent shortcoming of this analysis is that potential risk factors, including obesity, dehydration, and family history of thromboembolism, were not covered in this study. Another pitfall is that Group B consisted of a small number of subjects (only 752 patients), who were recruited over a shorter period of time (12 months versus 19 months in Group A), preventing us from exploring the long-term significance of LMWH in reducing mortality and morbidity. Finally, although no definite cases of symptomatic HT were detected in either Groups A or B, this observational study was not statistically powered enough to ascertain the significance of the findings.

6. Conclusion

There are numerous controversies over the utilization of VTE prophylaxis in the management of acute ischemic stroke. According to our analysis, early use of LMWHs was better tolerated as a form of VTE prophylaxis. However, given the short-term nature of this project, we cannot establish the long-term significance of LMWH in reducing death and disability rates, and thus, additional large trials are warranted to validate the efficacy of earlier use of LMWH.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Revin Thomas
Formal analysis: All authors
Investigation: Faizan A. Sandhu
Methodology: All authors
Writing – original draft: Faizan A. Sandhu
Writing – review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Data are available from the corresponding author upon reasonable request.

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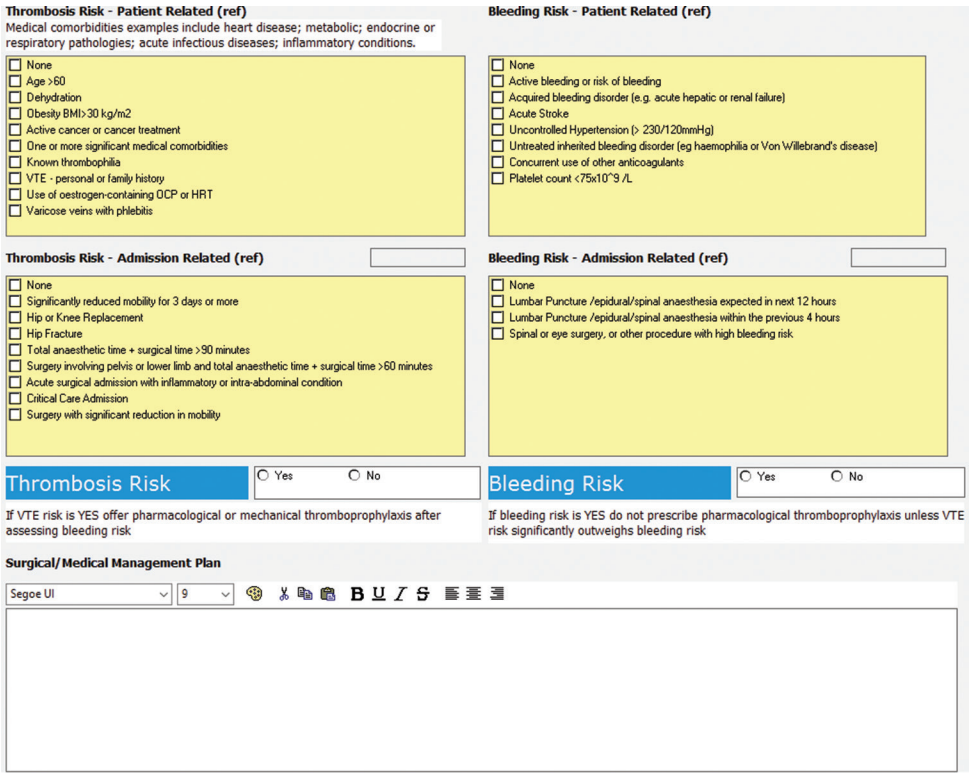
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Appendix



Appendix A1. Venous thromboembolism risks assessment form used at our hospital