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2021-03

Qian , C , Huhtakangas , J , Juvela , S , Bode , M K , Tatlisumak , T , Savolainen , M , Numminen , H , Ollikainen , J , Luostarinen , L , Kupila , L & Tetri , S 2021 , ' Early vs. late enoxaparin for the prevention of venous thromboembolism in patients with ICH : A double blind placebo controlled multicenter study ' , Clinical Neurology and Neurosurgery , vol. 202 , 106534 . https://doi.org/10.1016/j.clineuro.2021.106534

http://hdl.handle.net/10138/330705
https://doi.org/10.1016/j.clineuro.2021.106534

Clinical Neurology and Neurosurgery 202 (2021) 106534

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Early vs. late enoxaparin for the prevention of venous thromboembolism in patients with ICH: A double blind placebo controlled multicenter study

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ARTICLE INFO

Keywords:
Intracerebral hemorrhage
Deep venous thrombosis
Thrombosis prophylaxis
Low molecular weight heparin
Safety

ABSTRACT

Backround: Venous thromboembolism (VTE) after primary intracerebral hemorrhage (ICH) worsens patient prognosis. Administering low-molecular weight heparins (LMWH) to prevent VTE early (24 h) may increase the risk of hematoma enlargement, whereas administering late (72 h) after onset may decrease its effect on VTE prevention. The authors investigated when it is safe and effective to start LMWH in ICH patients.
Methods: In the setting of double blinded, placebo controlled randomization, patients >18 years of age with paretic lower extremity, and admitted to the emergency room within 12 h of the onset of ICH, were randomized into two groups. Patients in the enoxaparin group received 20 mg twice a day 24 h (early) after the onset of ICH and in the placebo group 72 h (late) after onset respectively. Both groups immediately received intermittent pneumatic compression stockings at the ER. Patients were prospectively and routinely screened for VTE and hemorrhagic complications 1 day after entering the study and again before discharge.
Results: 139 patients were included for randomization in this study. Only 3 patients developed VTE, 2 in the early enoxaparin group and one in the late enoxaparin group. No patients developed PE. Thromboembolic events ($p = 0.901$), risk of hematoma enlargement ($p = 0.927$) and overall outcome ($P = 0.904$) did not differ significantly between the groups.
Conclusion: Administering 40 mg/d LMWH for prevention of VTE to a spontaneous ICH patient is safe regardless of whether it is started 24 h (early) or 72 h (late) after the hemorrhage. Risk of hemorrhage enlargement is not associated with early LMWH treatment. Administering LMWH late did not increase VTEs.

1. Introduction

Patients suffering a primary intracerebral hemorrhage (ICH) have a substantial risk of venous thromboembolism (VTE). Early studies showed that without prevention, deep venous thrombosis (DVT) occurs in about half of all stroke patients (47–53 %) and 3–16 % of them die of pulmonary embolism (PE) [1,2] In particular, those who have hemiparesis/hemiplegia run a very high risk of VTE (75 %) [3,4]. The development of VTE in a patient with ICH adds further detrimental complications to an already lethal disease, with an increase in the one-month case fatality rate from 35 % to 52 % [5].

Based on multiple RCTs [6,7] in both American (class 1 Evidence B) and European (strong recommendation) guidelines, intermittent pneumatic compression (ICP) is recommended together with long graduated

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https://doi.org/10.1016/j.clineuro.2021.106534
Received 10 August 2020; Received in revised form 15 January 2021; Accepted 24 January 2021
Available online 29 January 2021

compression/elastic stockings (ES) and low molecular weight heparins (LMWHs) as prevention of VTE in patients with acute ICH [8,9]. These guidelines are mostly based on trials employing a small sample size and heterogeneous approaches to stroke diagnosis, not limited to ICH. Still, the timing of medical prevention of VTE in the treatment of patients with ICH remains unclear.

We conducted a multicenter double blind randomized controlled study to clarify timing on safety and efficacy of LMWH use for prevention of VTE in patients with paretic lower extremity after ICH. Enoxaparin 20 mg twice a day subcutaneously was started for paralyzed ICH patients either 24 or 72 h after the onset of the stroke. The ICP device was adopted at once when the patient was admitted to the emergency room. The safety and efficacy of both alternatives were analyzed.

2. Methods

2.1. Standard protocol approvals, registration, and patient consent

The ethical committees of all the hospital districts concerned approved the protocol. (Statement number 128/2007). Written concept informing the study protocol was obtained to all participants or their relatives and participants. Those willing to take a part to a study signed a proof. Any person taking part of this study cannot be recognized on the information published in this study. No changes to methods were made during the study after its commencement before starting this study; the study protocol was registered (Clinical Trials Gov Identifier/ NTC00699465 and Eudract 2007-006206-24).

2.2. Trial design

This multicenter study was carried out jointly at Oulu University Hospital, Helsinki University Central Hospital, Tampere University Hospital, and Lahti Central Hospital, Finland, as a national multicenter study. When a likely eligible patient arrived, investigators were alerted and one of the primary investigators checked the patient's eligibility. All eligible patients received an IPC device as soon as possible in the emergency room, and were then randomized into one of two groups.

2.3. Participants

All subjects with primary ICH admitted to the stroke units of the above-mentioned hospitals between 2008 and 2015 were screened by head CT or MR scan. Those aged at least 18 years were eligible if they were unable to walk unassisted due to motor impairment, with a score of $\geq$2 on the paretic lower extremity on the National Institutes of Health Stroke Scale (NIHSS), and if admitted to the emergency room within 12 h of the onset of ICH. Patients who had been receiving oral anticoagulants, SSRI drugs, clopidogrel, aspirin and other NSAIDs were included. These drugs were naturally discontinued at admission and the effect of warfarin was reversed immediately in the emergency room with Vitamin K and/or prothrombin complex concentrate. All eligible patients were asked to participate in the trial and informed consent was obtained. If the patient could not give informed consent a relative was approached.

A combination of CT, MRI, CTA and/or digital subtraction angiography was used to exclude patients with secondary ICH related to aneurysm, arteriovenous malformation, trauma or tumor. Patients who needed immediate hematoma evacuation or some other form of neurosurgical intervention were excluded. In addition, patients with previous VTE events were excluded. Patients who were comatose (Glasgow Coma Scale (GCS) <8), had no or only mild limb paresis (NIHSS < 2), or had been severely disabled prior to the stroke (Modified Rankin Scale (mRS) >2), or had the onset of the ICH related symptoms >12 h before admittance to hospital were excluded.

2.4. Interventions

Subcutaneous injections of enoxaparin or the placebo were started 24 h after the onset of ICH and repeated twice daily, i.e. at 12 h intervals. Each injection contained 20 mg (2000 IU) of enoxaparin, implying a daily dose of 40 mg. The placebo group received saline injections according to the same regime, and this was replaced with enoxaparin 72 h after the onset of the stroke. The enoxaparin treatment was stopped once the patient was able to walk independently, or if a severe recurrence of bleeding was observed. ICP devise was used until discharge to home or to another institute.

All the patients had a head CT scan on admission, a control CT scan 24 h after admittance, and a further CT scan before the patient was transferred to another hospital. In addition, a head CT was performed whenever a patient's condition deteriorated.

DVT duplex and compression ultrasonography (both proximal and distal) were performed directly if signs or symptoms of DVT appeared and for all patients before discharge from hospital.

All the recruited patients were followed up for three months from the onset of the ICH. A head CT was performed on all patients during a control visit to hospital.

2.5. Outcomes

The primary endpoint was the occurrence of a confirmed VTE, defined as the composite of symptomatic or asymptomatic DVT, or symptomatic or fatal PE (death related to VTE) occurring during the treatment period (up to 90 days after the onset of the ICH related symptoms).

Secondary endpoints included significantly increased ICH volume (>33 %) observed in a head CT or autopsy, including recurrent ICH, other severe bleeding complications, cardiovascular death or death due to any cause occurring within the treatment period. In the case of death from any cause while still in hospital an autopsy was performed. If death occurred later in the treatment period and outside hospital, an autopsy was recommended.

All the recruited patients were followed up for three months from the onset of the ICH. GOS and RANKIN scale examinations were performed during the follow-up in a control visit or in some cases by telephone to either the patient or a relative. Good or poor outcome was measured according to modified GOS: 1 = normal, 2 = minimal disability, 3 = moderate disability, 4 = severe disability, 5 = vegetative state, and 6 = dead. With this scale, 1−3 was considered as a good outcome and 4−6 as a poor outcome.

2.6. Sample size

The desired sample size was calculated on the basis on former publications [1,2]; of a thirty percent (35 %) expected incidence of the primary end point in the late enoxaparin group and a ten percent (10 %) incidence in the early enoxaparin group.

Approximately 138 patients (69 in each group) would be needed to detect these differences by a margin of twenty five percent (25 %) at a α level of 0.05 (two-tailed) and a β level of 0.2. After recruiting the first 80 patients, an independent safety committee analysed the observations. Non-significant difference was observed between the enoxaparin and placebo groups and the safety committee gave permission to continue patient recruitment.

2.7. Randomization

Subcutaneous injections were obtained from the hospital pharmacy. There were always 2–3 sets of injections ready for all eligible study patients i.e enoxaparin or placebo. All the injection sets looked the same whether they include enoxaparin or saline. The investigator randomly chose one of the injection sets and the code for the injection set was

placed in the sealed envelope together with the patient study number. The same information was sealed for the emergency envelope. One emergency envelope was opened during the study due to severe re-bleeding 36 h after the onset, and in that case, the patient had received the placebo. The patient study code and ID were sealed in another envelope, which was opened only after the study. This method of preparing the study medicine in the hospital pharmacy ensured that there would be no financial conflict of interest.

2.8. Blinding

The envelopes containing patient study code and the injection set code were opened during a witnessed meeting only after the end of the study. This method ensured that both the investigators and the doctors on duty were blinded as to the assignment of the patient to a particular group (treatment or placebo).

2.9. Radiological methods

The sites of the hematomas were divided into the following groups: subcortical, putaminal, thalamic, combined (extension of a putaminal hematoma into the thalamus and/or extensively into the subcortical white matter), caudate nucleus, cerebellar or pontine. Hematoma volumes were calculated from the CT scans using the following formula for an ellipsoid: volume ABC/2 (where A, B and C represent the radii in three dimensions) [10]. One of these radii was measured from the largest diameter on the CT image with the largest area of ICH and the two remaining radii were measured perpendicularly to the largest diameter. The degree of intraventricular hemorrhage (IVH) was classified as follows: grade 0, no IVH; grade 1, a small amount of blood in the occipital horns or in the third or fourth ventricle; grade 2, blood occupying most of one lateral ventricle with or without blood in the third or fourth ventricle; and grade 3, major IVH with blood filling all ventricles and frequently distending the ventricular system [11]. An increase in hematoma size >33 % was considered a significant enlargement and led to cessation of the placebo/ enoxaparin medication. All the CT scans were examined and the hematoma volumes measured by the same experienced neurosurgeon (SJ), who was blinded with respect to the patient records and modes of treatment.

Compression ultrasonography of both legs (proximal and distal) or, alternatively, bilateral contrast venography (<5 % of patients), was performed according to a standardized protocol. PE was confirmed by available methods, i.e., ventilation perfusion (VQ) or thoracic helical T scan, pulmonary angiography, or autopsy.

2.10. Statistical methods

Categorical variables were compared using the Fisher exact or two-tailed test. Continuous variables were compared between groups by using the Mann–Whitney *U* test or Student t-tests. A probability value less than 0.05 was considered significant.

2.11. CONSORT checklist

Finally the consort checklist was used for reporting this study [12].

2.12. Data availability statement

Authors state that anonymized data will be shared by request from any qualified investigator, please contact the corresponding author.

2.13. Disclosures

The funding sources did not have any involvement in design and conduct of the study; data collection, analysis, and interpretation; and preparation, review, writing, or approval of the manuscript; and decision to submit the manuscript for publication. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

3. Results

The participant flow diagram is shown in Fig. 1. 149 patients were enrolled for the study. In nine patients, the exact time of onset of stroke was uncertain and these patients were excluded. One patient refused to take a part in this study. After initial checking of the exclusion criteria, 139 consecutive patients were enrolled in the study. Complete follow up data existed for all 139 patients.

The baseline characteristics of the patients are shown in Table 1. There were 68 who had received early enoxaparin (24 h) and 71 who started enoxaparin later on (72 h). There were significantly more previous NSAID users (non-ASA) in the placebo group than in the enoxaparin group (9 vs. 0, $p < 0.005$).

The clinical characteristics and outcomes of the patients are shown in Tables 2 and 3. One patient in the placebo group (1 %) and 2 in the enoxaparin group (3 %) developed DVT, an overall rate of 2 %, but none developed PE. Accordingly, there was no significant difference between the two groups regarding the occurrence of VTE. Sixteen of the patients (12 %) had significant (>33 %) enlargement of the hematoma observable in repeated head CT scans, eight in both groups ($p = 0.927$).

No statistically significant difference in outcome was observed between the enoxaparin and placebo groups as 29 patients in the first and 31 patients in the latter group had a good outcome (GOS 1-3, $p = 0.904$). A non-significant difference in mortality rates was observed between the groups, as 12 patients (18 %) died within 3 months in the enoxaparin group compared to 11 patients (15 %) in the placebo group, $p = 0.733$. Only one patient was autopsied and no VTE nor PE was found.

Clinical data for the 3 patients who developed DVT can be seen in Table 4. All of them had been taking aspirin as a regular medication before the onset of the bleeding. None had been on anticoagulation before the ictus, and all three had a poor outcome (GOS 4-6).

4. Discussion

The aim of this work was to evaluate the safety and efficacy of early vs. late enoxaparin treatment for the prevention of VTE among patients with ICH. In the treatment group, enoxaparin (an LMWH drug) was administered at a dose of 20 mg twice a day starting 24 h after the onset of ICH and compared with a placebo for the first three days. Thereafter, i.e. from the 4th day onwards, all the patients received enoxaparin subcutaneously until they were able to walk or were moved to another hospital. We found that the early treatment was as effective and safe as the treatment started 72 h after the onset of ICH. Those who received early enoxaparin showed neither enlargement of the hematoma, increased amount of poor outcome or increased death rate compared to those who received enoxaparin later (placebo group).

There are only three published prospective randomized studies regarding prophylactic use of LMWH for the prevention of VTE in ICH patients [13–16]. In the early study by Dickmann et al., 46 patients were randomized into two groups [13]. The first group (n = 23) received heparin (3 × 5000 units/day) 4 days after ICH and the second group (n = 23) 10 days after the onset of ICH. Eighteen patients had evidence of VTE, and 14 patients had PE. No significant differences were found between the groups and heparin did not increase the risk of re-bleeding. Orken prospectively randomized 75 ICH patients into two groups, one of which (n = 39) received LMWH (enoxaparin 40 mg/d s.c.) 48 h after the onset of ICH while the other group (n = 36) received only long compression stockings [14]. Four symptomatic DVTs were observed, 3 of them (4%) in the LMWH group. No hematoma growth was observed in either group, and the authors concluded that LMVH should be used in patients with ICH. Boeer randomized 68 ICH patients into three groups, receiving low-dose heparins (3 × 5000 units/day s.c.) 2 (n = 22), 4 (n =

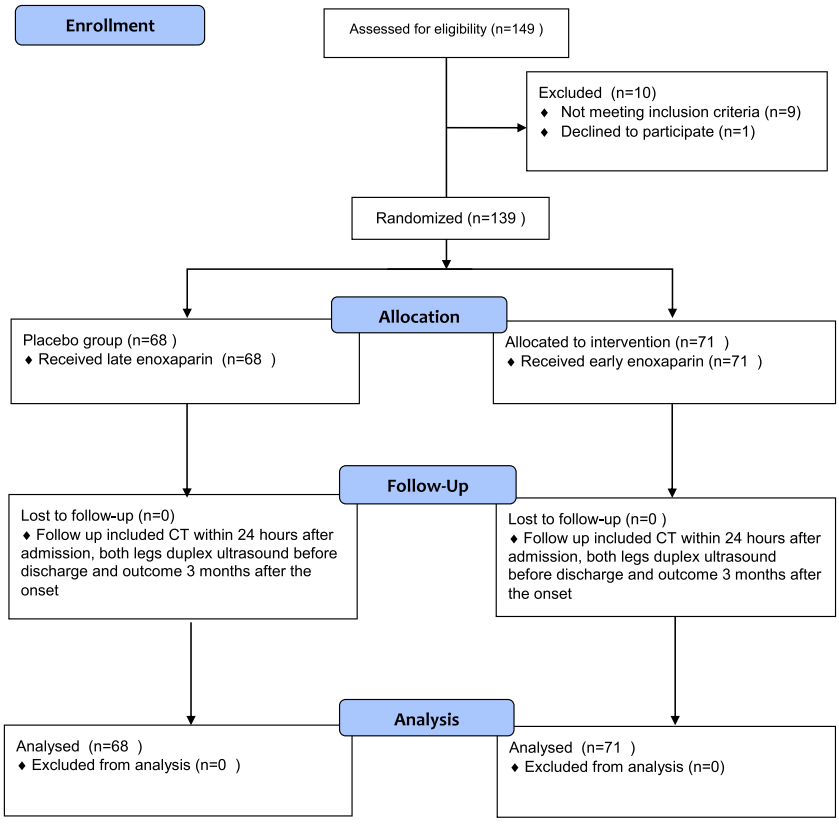

Fig. 1. Consort flow diagram of progress through phases of the trial.

Table 1
Baseline Characteristics of 139 patients with spontaneous ICH.

	Placebo n = 68	Enoxaparin n = 71	Total n = 139
Male n(%)	36 (53)	36 (51)	72 (52)
Mean age, y(±SD)	68 ± 6	66 ± 19	67 ± 11
Previous diseases n(%)			
Hypertension	54 (79)	52 (73)	106 (76)
Cardiac disease	18 (26)	14 (20)	32 (23)
Atrial Fibrillation	12 (18)	6 (8)	18 (13)
Diabetes	9 (13)	16 (23)	25 (18)
Cancer	2 (3)	5 (7)	7 (5)
Brain infarction/TIA	11 (16)	11 (15)	22 (16)
Epilepsy	2 (3)	2 (3)	4 (3)
Heavy drinking n(%)	4 (6)	2 (3)	6 (4)
VTE in history n(%)*	0 (0)	4 (6)	4 (3)
Previous medications n(%)			
anticoagulants	11 (16)	11 (15)	22 (16)
aspirin	19 (28)	29 (41)	48 (35)
clopidogrel	2 (3)	4 (6)	6 (4)
dipyridamol	1 (1)	3 (4)	4 (3)
SSRI	5 (7)	4 (6)	9 (6)
NSAID*	9 (13)	0 (0)	9 (6)

* $p < 0.005$.

23) or 10 (n = 23) days after ICH [15]. Again there were no differences in recurrent hemorrhage rates between the groups, but the early treatment group (2 days) showed significantly less PE (n = 1, 5 %) compared with the others (n = 5, 22 % and n = 9, 39 %). These other studies, however, had significantly smaller sample sizes than this study, which also employed more specific criteria for the prospective analysis of hematoma enlargement, and also started LMWH treatment earlier (only 24 h after onset).

Other studies on this issue have been retrospective ones and the

Table 2
Clinical Characteristics of 139 patients with spontaneous ICH.

	Placebo n = 68	Enoxaparin n = 71	Total n = 139
Hematoma volume, ml (±SD)	21 ± 23	28 ± 31	24 ± 27
Location of hematoma, n(%)			
Subcortex	10 (15)	21 (30)	31 (22)
Putamen	26 (38)	21 (30)	47 (34)
Thalamus	19 (28)	14 (20)	33 (24)
Basal ganglia	5 (7)	9 (13)	14 (10)
Combined	6 (9)	5 (7)	11 (8)
Other	2 (3)	1 (1)	3 (2)
Intraventricular haemorrhage, n(%)	45 (66)	53 (75)	98 (71)
Later hematoma evacuation, n(%)	2 (3)	3 (4)	5 (4)
Mean ICH Score, (±SD)	1.4 ± 1.0	1.4 ± 1.1	1.4 ± 1.0
Mean GCS score, (±SD)	14 ± 2	13 ± 3	13 ± 2

GCS = Glasgow Coma Scale. $p < 0.05$ none.

Table 3
Outcome of 139 patients with spontaneous ICH.

	Placebo n = 68	Enoxaparin n = 71	Total n = 139
Complications, n(%)			
hematoma enlargement 33 %	8 (12)	8 (11)	16 (12)
GI-bleeding	0 (0)	0 (0)	0 (0)
Seizure	4 (6)	3 (4)	7 (5)
DVT	1 (1)	2 (3)	3 (2)
PE	0 (0)	0 (0)	0 (0)
Outcome			
GOS 1-3 (good)	29 (42)	31 (44)	60 (43)
GOS 4-6 (poor)	39 (57)	40 (56)	79 (57)
Death within 3 mo	12 (18)	11 (15)	23 (17)

DVT = Deep venous thrombosis, PE = Pulmonary embolism, GI = gastrointestinal, GOS = Glasgow Outcome Scale. $p < 0.05$ none.

Table 4
Baseline, Clinical characteristics and outcome of 3 DVT patients.

	Patient 1	Patient 2	Patient 3
Age (yr.)	66	95	71
ICH volume, ml	49	50	45
ICH Score	1	1	1
GCS	11	14	15
Hematoma location	subcortical	putaminal	basal ganglia
Previous diseases			
Cardiac disease	no	yes	yes
Atrial fibrillation	no	yes	no
Diabetes	yes	no	yes
Previous medications			
Antigoaculants	no	no	no
ASA	yes	yes	yes
Complications			
Hematoma enlargement	no	no	no
Pneumonia	no	yes	no
Outcome			
NIHSS	22	21	8
GOS	6	5	4
Dead within 3 mo	yes	no	no

NIHSS=, GOS = Glascow Outcome Scale.

timing of the initiation of treatment varies widely. Tetri et al. [17] found in their series of 407 patients that the rate of clinical VT events in those who received enoxaparin 20 mg once a day was 3%. A slightly lower VTE rate occurred in the present study and the number of events did not increase if the LMWH drug was introduced later (on the 4th day). PE did not occur at all, but it should be remembered that the authors did not routinely perform embolic CT scans on asymptomatic patients. Elsewhere, Kleindienst et al. reported DVT and PE in 0.4 % of their patients [18]. That study, however, was retrospective in nature and included arteriovenous malformation, SAH and cerebral infarction patients, for whom only limited information was available as to whether they had hemiparesis/hemiplegia. All the present patients had lower limb paralysis and were unable to walk when enrolled for this study. In the case of these retrospective studies, no straightforward conclusions can be drawn as to whether it is safe to use anticoagulants for ICH patients, and if so, when it is safe to commence treatment and the most appropriate doses to utilize.

In the recent AHA/ASA guideline and an ESO guideline it is concluded that the evidence for when to recommend LMWH for ICH patients is weak [19,20]. AHA/ASA recommends LMWH for ICH patients 1–4 days after onset, and states that current data suggests that administering LMWH does not seem to increase the incidence of recurrent hemorrhage. This is based on the two small-randomized studies mentioned above, namely Dickman 1988 (with 46 patients) and Boeer 1991 (with an additional 22 patients). Unfortunately, these series also included angiomas, aneurysms and embolic stroke patients (n = 12). Besides the small sample size, it is also unclear whether ES or IPC was applied. The ESO guideline does not make any recommendation in this matter due to the lack of a large RCT. In the absence of proper recommendations, clinicians are reluctant to administer LMWH to ICH patients for fear of hemorrhagic complications. It is significant that in the paper published by Prabhakaran et al., only 16.5 % of the ICH patients received any medical prevention of VTE during their hospital stay and 44.8 % out of these (16.5 %) began to receive it on day 2 [21]. It is clear that in the current situation a large number of ICH patients do not have proper thrombosis prophylaxis.

Three patients in the present series (2%) developed DVT, one in the placebo group and two in the enoxaparin group, when following the guidelines strictly in a prospective setting. However, no PE events occurred, even though routine pulmonary CT was not performed and only one patient who died during the follow-up period was autopsied, revealing neither PE nor DVT. The patients' outcomes did not differ between the two groups: 42 % in the placebo group and 44 % in the enoxaparin group had a good outcome (GOS 1-3) and 58 % and 56 %, respectively, a poorer outcome (GOS 4-6). It seems that if the guidelines are followed strictly and if LMWH treatment is actually started at an early stage after ICH, VTE events will become very rare even in patients having major risk factors for these.

This is the largest randomized double-blinded study to date that has evaluated the safety and efficacy of administering an anticoagulant to primary ICH patients. Our goal was to collect 138 patients (69 in each group), which was achieved. However, due to the strict inclusion criteria of lower extremities paresis and randomization within 12 h after onset, it took stipulated 10-year period, in spite of the national multicenter setting. After ending the study, the authors saw that additional recruitment of several hundred more patients for several additional years would be needed to even show a trend for association between lower VTE occurrences with earlier administration of enoxaparin. Thromboembolic events occurred notable less frequently than expected in the power calculation or even compared to some newer studies [22]. We suggest this is the result of strictly following the guideline and using ICP and compressive socks prevention of VTE as early as possible combined to medical prophylacsis. Nevertheless, the strict inclusion criteria and the double-blinded randomization procedure do mean that the results add valuable information to the previously limited data available in this field. In this study, bilateral ultrasound (both proximal and distal) was performed routinely on every patient in the hospital period. The limitations are that pulmonary CT was only carried out for symptomatic patients (not routinely) and only one of the deceased patients was autopsied to exclude VTE.

5. Conclusions

Thromboembolic complications are very rare in paralyzed ICH patients if IPC is used together with early LMWH. The data in this study suggests that administering an anticoagulant to a spontaneous ICH patient is safe regardless of whether it is started 24 h (early) or 72 h (late) after the hemorrhage. No risk of hematoma enlargement is associated with administering 20 mg of anticoagulant LMWH twice a day at an early stage, nor does late administration of LMWH entail an additional risk of VTE.

Funding

TT received academic grants for ICH research from Helsinki University Central Hospital, University of Gothenburg, Sahlgrenska University Hospital, and Sigrid Juselius Foundation.

ST received academic grants from Finnish Medical Foundations.

Registration

Trial Registration Number NTC00699465, EudraCT number 2007-006206-24

Author statement

The funding sources did not have any involvement in design and conduct of the study; data collection, analysis, and interpretation; and preparation, review, writing, or approval of the manuscript; and decision to submit the manuscript for publication. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2021.106534.

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