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Early Administration of Low Molecular Weight Heparin after Spontaneous Intracerebral Hemorrhage

A Safety Analysis

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Key Words
Intracerebral hemorrhage · Heparin · Hematoma growth

Abstract
Background: Venous thromboembolism (VTE) is a common complication after stroke. Application of low molecular weight heparins (LMWH) has been proven to be beneficial for the prevention of VTE in ischemic stroke patients. However, there is no consensus whether and how to administer LMWH for prevention of thrombotic complications after acute spontaneous intracerebral hemorrhage (sICH), the main concern being possible hematoma growth. The objective of this study was to assess the safety of early subcutaneous LMWH in patients with sICH with respect to hemorrhage enlargement. ***Methods:*** A total of 97 patients with sICH were analyzed. LMWH (either enoxaparin-natrium or dalteparin-natrium) were initiated within 36 h after admission in all patients without clinical evidence of hemorrhage enlargement or an absence of evidence of hematoma growth on CT. Hematoma growth (significant when >33%, moderate when >20%) was assessed on follow-up CT between days 5 and 11. ***Results:*** None of the patients showed a significant hemorrhage growth. Between days 2 and 10, 2 patients experienced a moderate hematoma enlargement of 22.4 and 20.9%. None of the included patients developed a fatal lung embolism. ***Conclusions:*** Early application of subcutaneous LMWH for prevention of venous thromboembolism seems to be safe, and probably does not increase the risk of hematoma growth in patients with sICH.

Introduction

Venous thromboembolism (VTE) is a common complication after hemorrhagic and ischemic stroke, and several risk factors such as age, adiposity, diabetes, immobility, hemiplegia and atrial fibrillation have been described [1]. The prevalence of objectively confirmed hospital-acquired deep vein thrombosis (DVT) in patients not receiving thromboprophylaxis is up to 20% in stroke and critical care patients, increasing the risk of pulmonary embolism (PE) [2–5]. After acute ischemic stroke, the ad-

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ministration of subcutaneous anticoagulants is recommended to prevent DVT among immobilized patients [1, 6, 7], the use of low molecular weight heparin (LMWH) being superior to unfractionated heparin [8].

In contrast to patients with ischemic stroke, in spontaneous intracerebral hemorrhage (sICH) there are: (1) less data on thromboembolic complications, and (2) up till now, no consentaneous guidelines on how to prevent VTE [9]. A comprehensive data analysis by Skaf et al. [10] identified 3.98% of thrombotic complications in 1,606,000 patients with ICH (PE in 0.68%, DVT in 1.37%, VTE in 1.93%). Maramattom et al. [11] reported 2 confirmed cases of PE in 144 ICH patients (1.4%), and Gregory and Kuhlemeier [12] diagnosed DVT in 1.9% of 1,926 ICH patients. In line with these studies, the prospective randomized trial on activated recombinant factor VII (rFVIIa; NOVO7) showed 2% of serious thromboembolic events in both the placebo and rFVIIa-treated group [13].

Nevertheless, there is no consensus on how to avoid thrombotic complications after ICH [9]. Anticoagulants, platelet antiaggregants, unfractionated and LMW heparins as well as the use of mechanical methods, such as intermittent pneumatic compression [14] and graduated compression stockings, are options with varying levels of evidence in preventing VTE [9]. Although 2 small prospective studies [15, 16] and 1 retrospective analysis [17] regarding the use of heparin in sICH have been published – none of them was associated with an increased risk of secondary bleeding – debate remains whether it is safe to administer unfractionated or LMW heparins to sICH patients. In particular, physicians continue to be concerned about possible hematoma growth in patients with sICH receiving heparins [18, 19], and the neurosurgical guidelines still discourage the use of heparin in intracranial hemorrhage [20].

The aim of the present study was to analyze the safety of early administered LMWH in sICH patients with regard to hematoma growth.

Methods

Patient Selection

The source of this retrospective and observational study was a prospectively organized database of our department, in which clinical and neuroradiological data of consecutive patients with sICH and who were treated in our stroke and neurocritical care unit between February 2006 and December 2007 had been entered. To be enrolled into the present analysis on the safety of LMWH with regard to hematoma growth, patients had to fulfill the following criteria: (1) brain imaging at 3 time points, i.e. presence of baseline imaging (CT or MRI), follow-up imaging 24 ± 6 h after baseline, and control CT, between days 5 and 11, and (2) administration of LMWH started after the 24-h control CT without evidence of hematoma growth. Ninety-seven patients fulfilled these criteria. We did not enroll patients with evidence of subdural, epidural or subarachnoid hemorrhages, or hemorrhage related to trauma, tumor, thrombolysis, arteriovenous malformations or oral anticoagulant treatment. Furthermore, patients were not analyzed if they: (1) underwent surgery for hematoma evacuation; (2) received a 'do not resuscitate' or 'do not treat' order initially or within 24 h because of a combination of age, hemorrhage volume, severe co-morbidity and absent consent of relatives for neurocritical care; (3) who showed evidence of moderate or significant hemorrhage growth (for definition, see 'Hemorrhage Growth') on the follow-up CT 24 h after admission; (4) did not receive follow-up imaging according to the above-mentioned criteria, and received other medication or treatment than LMWH for prophylaxis of VTE.

Clinical Management and Application of LMWH

Patients with sICH were treated according to the EUSI recommendations [21]. An external ventricular drain was inserted in all patients with evidence of occlusive hydrocephalus. Within 36 h after admission all 97 patients received subcutaneous LMWH once a day. From February 2006 until January 2007, 4,000 IU enoxaparin-natrium was given, and from February 2007 to December 2007 patients received 2,500 IU dalteparin-natrium, according to the manufacturers' recommendations. The switching to dalteparin-natrium was based on an institutional protocol of our hospital pharmacy department regarding the prophylactic use of LMWH for prevention of VTE.

Imaging

ICH was diagnosed immediately after hospital admission by CT or MRI. In cases of lobar and posterior fossa bleeding, patients underwent either CT, MR angiography or digital subtraction angiography to rule out an underlying cause of the hemorrhage (e.g. arteriovenous malformation). The hematoma site was categorized into deep (basal ganglia and thalamic hemorrhages), lobar, cerebellar and brainstem hematoma. ICH volume was calculated using the formula for ellipsoids (ABC/2) [22, 23]. Regarding the low reliability and feasibility of quantitative volumetry in ventricular hemorrhages [24], the intraventricular blood portion was not considered for hematoma volume measurement.

Hemorrhage Growth

Significant hemorrhage growth was defined as an increase in the volume of the parenchymal hematoma of >33%, as measured by image analyses of follow-up CT compared to the baseline scan [25]. Moderate hemorrhage growth was defined as an increase in hematoma volume of >20%.

Statistical Analysis

Statistical analyses were performed using the SPSS software package version 13.0 (SPSS, Chicago, Ill. USA). The Shapiro-Wilk test was used to determine the distribution of the data. Normally distributed data are expressed as means ± SD, other data are expressed as medians and ranges.

Table 1. Clinical and radiological parameters of the 97 patients included

Patient characteristics	
Age (median), years	68 (35–95)
Males/females, n	57/40
GCS on admission (median)	10 (3–15)
Imaging findings	
Volume, cm^3	33.47 ± 20.70
Location, n	
Deep (ganglionic and thalamic)	54 (56)
Lobar	27 (27)
Cerebellar	5 (5)
Brainstem	11 (12)
Intraventricular hemorrhage, n	60 (63)
External ventricular drain, n	33 (36)

Figures in parentheses are ranges or percentages.
GCS = Glasgow Coma Scale.

Table 2. Patient characteristics, clinical data and imaging findings of the 2 patients with moderate hematoma growth

	Patient 1	Patient 2
Age, years	84	91
Gender	male	female
GCS score (on admission)	13	14
NIHSS score (on admission)	6	17
Anticoagulant received	enoxaparin	dalteparin
Volume, cm^3		
Baseline	59.2	27.1
24-h follow-up	60.8	29.2
Day 7 (patient 1)/day 9 (patient 2)	73.6	35.8
Hematoma growth, %		
(between 24-h scan and days 7–9)	20.9	22.4
Ventricular involvement	no	yes
External ventricular drain	no	no
Clinical worsening	day 7	unapparent
Location	lobar	basal ganglia
GCS score (discharge)	13	13
NIHSS score (discharge)	9	17

GCS = Glasgow Coma Scale; NIHSS = National Institutes of Health Stroke Scale.

Results

For patient characteristics, clinical data and imaging findings of the 97 patients included, please refer to table 1. The median National Institutes of Health Stroke Scale score on admission was 14 (1–31). Forty-one patients (42%) received enoxaparin-natrium and 56 patients (58%) dalteparin-natrium. After initiation of subcutaneous LMWH on day 2, none of the patients developed a significant hemorrhage growth >33%. Figure 1 shows the mean hematoma volumes of all patients during the course of treatment.

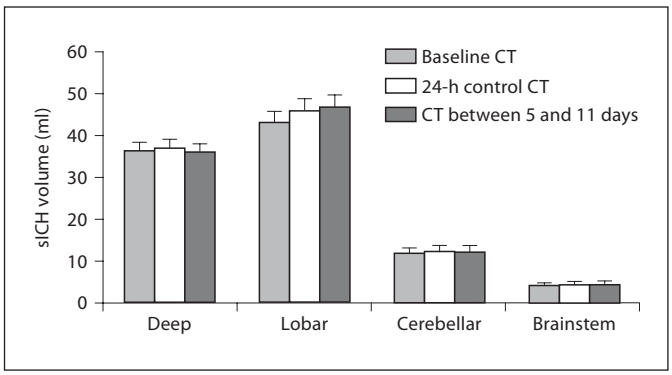

Fig. 1. Mean ± SEM hematoma volumes of the 97 patients included.

Two patients showed a moderate increase in hematoma volume of >20% (22.4 and 20.9%). Patient characteristics, clinical data and imaging findings of these patients are given in table 2.

It was beyond the scope of this study to investigate possible benefits of LMWH on the frequency of VTE, DVT and PE; however, at least it can be stated that in this series none of the patients died from PE, nor had clinical or electrocardiological evidence of severe PE. Two patients developed heparin-induced thrombocytopenia and anticoagulation was switched to hirudin.

Discussion

This study on the safety of LMWH in the acute stages of sICH is the first of its kind and contributes to the ongoing debate on how to best prevent possible VTE in hemorrhagic stroke patients. As the key finding, early administration of LMWH was not associated with an increased risk of parenchymal hematoma growth.

Two key points have emerged from our data. First, hematoma growth and rebleeding beyond the 24-h time window after the initial event are less frequent in sICH compared to other ICH populations, e.g. ICH related to oral anticoagulant treatment [18, 25–27] – Lim et al. [19] reported significant hematoma growth (>50%) in 0.9% of

sICH patients between days 2 and 7. Consistent with that study and similar findings reported previously [18], 2 out of the 97 patients analyzed here (i.e. 2.06%) showed moderate growth of >20%. A significant hemorrhage enlargement – according to the widely accepted definition by Brott et al. [25] – was not observed in our series. Hence, the frequency of hemorrhage enlargement was not different from these previous studies on incidence of rebleeding in ICH without application of LMWH [18, 19]. In line with earlier findings for unfractionated heparins [15, 16], LMWH do not seem to be associated with an elevated bleeding tendency in sICH, as long as given subcutaneously for thromboprophylaxis.

Second, the benefit of subcutaneous heparins, especially the easily applicable LMWH, for prevention of VTE and PE has previously been proven for a variety of diseases [4, 8, 28]. Although not investigated in a randomized and controlled design, LMWH are also likely to show positive effects in ICH patients in terms of VTE prevention. While severe thromboembolic complications occur in about 2% of ICH patients [10–13], physicians, however, still refrain from giving LMWH in sICH due to concern of possible rebleeding and hematoma growth, which led to class I guidelines (level of evidence B) recommending intermittent pneumatic compression for the prevention of embolic complications [9]. In the light of only a few existing studies addressing the issue of VTE prevention in sICH, our findings should contribute to a less anxious application of subcutaneously administered LMWH in sICH patients. A prospective randomized controlled analysis on the safety of LMWH, including efficacy aspects, appears warranted to expand the knowledge in this field.

Our study has certain shortcomings because of the nonrandomized and noncontrolled retrospective design. The lack of a priori determined time points for imaging controls results in only limited information regarding safety of LMWH in terms of hemorrhagic complications other than hematoma growth. In addition, we did not analyze the efficacy of LMWH with respect to frequency of VTE, PE and sonography-based diagnosis of DVT. Moreover, other factors possibly impacting the occurrence of hematoma growth, e.g. mean arterial pressure, were not investigated. Finally, in those patients who required an external ventricular drain, a possible hemorrhage enlargement within the ventricles was not analyzed.

In conclusion, our data suggest that subcutaneous administration of LMWH starting subsequently to a control CT 24 h after disease onset is probably not associated with an increased risk of hematoma growth in sICH patients. A prospective safety and efficacy study of LMWH for prevention of VTE in sICH patients seems indicated.

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