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Original Article

A non-randomized study of safety and efficacy of heparin for DVT prophylaxis in intracerebral haemorrhage

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Abstract

Objective: To evaluate the safety and efficacy of subcutaneous heparin for deep venous thrombosis (DVT) prophylaxis in patients with intracerebral haemorrhage (ICH) during acute phase in comparison to elastic stockings.

Methods: The diagnosis of ICH was based on imaging (CT or MRI) and DVT was based on Doppler ultrasound.

Results: A total of 458 patients were identified over a period of 5 years (1997-2001). Median age was 59 years (range:12-99 years). Two hundred (44%) patients received heparin (heparin group) in addition to elastic stockings and 258 (56%) patients were only given elastic stockings (stockings group). These two groups were not randomized. Heparin was administered subcutaneously (SQ) in doses of 2500-5000 international units twice daily. Two groups were matched for age (p=0.5), sex (p=0.28), presence of diabetes mellitus (p=0.14), cigarette smoking (p=0.045) and presence of hydrocephalus or midline shift on CT/MRI (p= 0.87). One patient developed DVT in control group while none developed DVT in heparin group (p=0.18). One patient had worsening of ICH on repeat CT scan in Heparin group. This worsening was non fatal. Systemic haemorrhagic complications (non fatal) were seen in 7 (14%) patients receiving heparin. Twenty five patients (12%) in heparin group and 52 (20%) in control group died (p=0.02).

Conclusion: Subcutaneous heparin in doses of 2500-5000 units twice daily during acute phase in patients with ICH may be safe for DVT prophylaxis. It was not superior to elastic stockings in a non-randomized comparison to prevent DVT (JPMA 58:362;2008).

Introduction

The frequency of clinical deep venous thrombosis (DVT) in patients with ischaemic stroke is 2-3%.[1-3] The absolute risk of fatal pulmonary embolism (PE) after ischaemic stroke within first month is 1-2%.[4-5] Exact incidence of clinical DVT and PE in patients with intracerebral haemorrhage (ICH) is not well known. It is suggested that it is probably in the range of 3-5%.[6]

Risk of rebleeding is the major limiting factor when considering these patients for DVT and PE prophylaxis with heparin or low molecular weight heparin. Studies have shown that risk of rebleed within first three months after ICH in patients receiving no aspirin or heparin is about 0.5%.[7] The only factor that predicted a higher recurrence rate was lobar location of haemorrhage.[8-9]

The data regarding risk of rebleeding in patients receiving heparin is scanty. One prospective study showed that one out of 45 patients receiving unfractionated heparin (UFH) 5000 units TID developed rebleed.[10] Another retrospective study showed that a subgroup of 22 patients with ICH receiving long term anticoagulation had a 2.7 times increased risk of rebleeding as compared to non-anticoagulated patients.[11] No cases of rebleeding were identified in another study of 68 patients with ICH that were treated with heparin.[12]

Our study represents a large cohort of patients with primary intracerebral haemorrhage. The patients were either treated with subcutaneous (SQ) heparin in addition to elastic stockings or elastic stockings alone. Pneumatic compression devices were not used in any patients. Patients were not randomized and decision to start SQ heparin was entirely based on physician preference. Despite being retrospective and non-randomized, the study provides useful information regarding natural history of rebleeding in untreated patients, incidence of DVT and risk of rebleeding in heparin treated patients.

Methods

Medical records of patients with diagnosis of primary intracerebral haemorrhage were retrospectively reviewed at the Aga Khan University Hospital, Karachi. The diagnosis of ICH was based on Brain computerized tomography (CT) or magnetic resonance imaging (MRI). Patients with ICH due to thrombolysis or anticoagulation or post traumatic ICH were excluded. Patients were divided

into two groups based on use of heparin. Thigh high elastic stockings were used in all patients while pneumatic or sequential compression devices were not used in any patient. The decision to start heparin and dosage of heparin was entirely based on physician preference (non-randomized). Heparin was administered subcutaneously in doses of 2500 international units (71 patients) and 5000 international units (129 patients) twice daily. Patients were daily examined for signs of clinical DVT (unilateral leg swelling, warmth and redness).Cases of clinical DVT were confirmed by Doppler ultrasound. Repeated scans were performed in patients with clinical neurological worsening to rule out expansion of haemorrhage.

Chi square test was used to compare both the groups for baseline characteristics and outcome.

Results

Four hundred and fifty eight consecutive patients were identified over a period of 5 years. Median age was 59 years (range: 12-99years). Two hundred (44%) patients received heparin (heparin group) and 258 (56%) patients did not receive heparin (stockings group). Heparin was started on day 1 in 44 patients; day 2 in 93 patients; day 3 in 25 patients; and day 4-7 in 38 patients. The duration of heparin treatment was less than 7 days in 12 patients; 7-14 days in 165 patients and more than 14 days in 23 patients.

Two groups were similar at baseline for age (p=0.5), sex (p=0.28), presence of diabetes mellitus (p=0.14) and presence of hydrocephalus or midline shift on CT/MRI (p= 0.87) and mean Glasgow Coma Score scale[13] (p= 0.19). One hundred and sixty nine (84%) patients in heparin group were hypertensive as compared to 184 (72%) in stockings group (p=0.01). One hundred and seventy (85%) in heparin group had basal ganglia haemorrhage as compared to 164 (75%) in stockings group. One hundred and eighty patients (90%) in heparin group and 201patients (78%) in stockings group had Rankin score >3 on admission (p<0.001).

DVT was suspected clinically in seven patients (stockings group=5, heparin group=2). Doppler evaluation showed that only one patient developed DVT in stockings group while none developed DVT in heparin group (p=0.18). Repeat CT scans were performed in 45 patients due to neurological worsening to rule out expansion of haemorrhage (33 in heparin group and 12 in no-heparin group). Follow up scans were done on day 2 (7 patients), day 3(16 patients), day 4(8 patients), day 5 (6 patients) and after day 6(8 patients). One patient had worsening of ICH (20% increase in haematoma volume) on repeat CT scan in heparin group. The location of this patient's haemorrhage was parietal lobe and she was receiving 5000 units SQ Heparin twice a day. This worsening was non fatal. No patient in stockings group had worsening of ICH on repeat CT scan. Heparin was discontinued in seven patients due to systemic haemorrhagic complications including haematuria, superficial haematoma and excessive gum bleeding. Twenty five patients (12%) in heparin group and 52 patients (20%) in stockings group died (p=0.02). According to death records none of these patients had PE or suspected PE as cause of death.

Table. Comparison of Heparin and stockings groups (baseline characteristics and outcome).

variables	Heparin group (n=200)	stockings group (n=258)	p- value
Mean age (years) + SD	59 ±33	57±29	0.5
Sex			0.28
Male	108 (54%)	150 (58%)	
Female	92 (46%)	108 (42%)	
Diabetes	57 (28%)	58 (22%)	0.14
Cigarette Smoking	26 (13%)	19 (8%)	0.045
Hypertension	169 (85%)	186 (72%)	0.01
Modified Rankin score >3	180 (90%)	201 (78%)	0.01
Basal ganglia haemorrhage	170 (85%)	164 (75%)	0.05
Mean GCS (Glasgow coma scale)	7	6	0.19
Hydrocephalus or midline shift on imaging	56 (28%)	74 (29%)	0.87
DVT	0	1	
Worsening of ICH	1	0	
Died	25 (12%)	52 (20%)	0.02

Discussion

The efficacy of heparin for DVT prophylaxis is well established.[14] There are no well-designed, large, prospective studies supporting use of heparin for DVT prophylaxis in patients with ICH. Our study presents one of the largest cohorts of these patients that were treated with heparin.

We identified three patterns of practice among our physicians for DVT prophylaxis in ICH patients. These patterns were not based on evidence but physician preferences. Fifty six percent patients did not receive heparin for DVT prophylaxis, 30% received SQ heparin 5000 units twice a day and 14% received SQ heparin 2500 units twice a day.

The incidence of clinical DVT confirmed by Doppler was extremely low in all groups (0.22%). We were unable to identify factors contributing to low frequency of clinical DVT in our patients with ICH as compared to western studies (2-3%).[6] No patient in Heparin group developed DVT as compared to only one patient in stockings group.Based on this information we cannot comment on efficacy of heparin for DVT prophylaxis as compared to stockings use. It is likely that conventional

measures for DVT prophylaxis including early mobilization, limb passive physiotherapy and compression stockings are as good as heparin as there was no statistical difference in the incidence of DVT in our patients.

The frequency of haematoma expansion due to rebleed was very low (0.23%) when compared to reported frequency by western literature (0.5%).[7] The reason for this low numbers is probably related to timings of initiation of Heparin treatment. Increase in haematoma volume usually occurs within first 24 hours. More than 75% patients in our study were started on heparin after 24 hours. Repeat Head CT scan was done more frequently in patients receiving heparin. This may be the result of more cautious approach of physicians when they were using heparin. Haemorrhagic complications were seen more frequently in patients receiving heparin than no-heparin group. One patient with parietal haemorrhage in Heparin group developed worsening of ICH on CT scan. Studies have shown that the only factor that predicted higher rate of rebleed was lobar location of hemorrhage.[8] We do not know that worsening of haemorrhage or rebleed in this patient was due to Heparin or lobar location. Further studies may be able to guide that patients with lobar haemorrhage on Heparin are at increased risk of rebleed as compared to basal ganglia haemorrhage on Heparin.

The study is limited by its retrospective nature. The higher mortality in stockings group was difficult to explain as the baseline modified Rankin score, and prior history of hypertension both were more common in the heparin group. These two factors have a prognostic implication. Our study did not look at the volume of haemorrhage or severity of neurological status on standardized scale (NIH stroke scale), which is one of the limitations of our study. Major limitations of study include non availability of Follow up or repeat CT scan in majority of patients and reliance on clinical examination for identification of DVT cases.

Although we believe that SQ heparin is safe for DVT prophylaxis in patients with acute ICH but it was not superior to conventional measures when compared to stockings group. Recent studies have suggested that intermittent pneumatic compression devices may be useful in prevention of asymptomatic DVT.[15,16] There are no trials comparing efficacy of heparin versus pneumatic compression devices for DVT prophylaxis. We are of the opinion that value of DVT prophylaxis is highly dependent upon the in-bed early mobilization of patient and heparin therapy which can be considered a "replacement therapy".

Systematic review of previously published studies do not support reliable conclusions related to safety or efficacy of heparin in patients with intracerebral haemorrhage. Our study adds to the current pool of information. A large, prospective, randomized trial is warranted to further address this question which is faced by practicing physicians routinely.

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