A Pilot Retrospective Comparison of Fondaparinux and Enoxaparin For the Prevention of Venous Thromboembolism (VTE) In Patients With Stroke

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Stroke is a leading cause of morbidity and mortality in the world, with an annual incidence of fifteen million cases each year, of which 5 million people die and 5 million are permanently disabled.[1] In addition to myriad neurologic deficits, people with stroke are susceptible to a variety of medical complications, including **venous thromboembolic disease (VTE)**. The analysis of pro-thrombotic factors in a small population of patients with stroke revealed elevated levels of biochemical markers of coagulation activity or fibrinolysis, in comparison to the levels of healthy control adults.[2] Clinical risk factors for VTE in patients with stroke include age, paralysis, immobility, and infections such as urinary tract infections and pneumonia.[3]

As a major source of morbidity and mortality after stroke, VTE has received a great deal of attention in terms of screening, prophylaxis, and treatment. In the absence of preventive measures, the incidence of **deep venous thrombosis (DVT)** after a stroke is 24 to 55%.[4-6] If the DVT is untreated, the mortality rate resulting from a **pulmonary embolus (PE)** is as high as 25%.[7,8] Even with treatment of a DVT, the mortality rate is still 6%.[9] Pulmonary embolus is the leading cause of mortality in the first 2-4 weeks after a stroke, based on autopsy studies.[10] Although the highest incidence of VTE diagnosis after a stroke is in the first four weeks, there is a significant continued risk of these events until the eighth week, and some patients at high risk will develop VTE more than three months after the stroke.[2]

In the setting of stroke rehabilitation units, the prevalence of DVT is almost 20%.[11] A recent cost-effectiveness study of routine Doppler ultrasound screening for DVT in patients with ischemic stroke was in favor of routine screening for only certain subgroups on admission for rehabilitation.[12]

Patients with stroke due to cardiac emboli are given warfarin for secondary stroke prevention, which reduces the risk of VTE. Warfarin is contraindicated for patients with intracranial hemorrhage, and they receive pneumatic compression sleeves to improve blood flow and reduce the risk of VTE.[2] Patients with ischemic strokes remain at high risk of VTE, in spite of treatment with anti-platelet agents such as aspirin and clopidogrel. All patients with acute neurologic conditions should receive prophylaxis for VTE, according to the **American College of Chest Physicians (ACCP)** consensus.[13]

A study of DVT prevention, in which 360 rehabilitation patients with stroke were randomized into four groups (heparin, intermittent pneumatic compression, functional electrical stimulation, or placebo), found no significant difference in the development of DVT.[14] In contrast, other studies of prophylaxis with **unfractionated heparin (UFH)** have

Table 1: Patient Demographics by Drug Group

	Fondaparinux	Enoxaparin
Mean Age ± SD	72.4 ±13.9	75.7±10.7
Gender n (%)		
Male	14 (46.7%)	12 (40.0%)
Female	16 (53.3%)	18 (60.0%)
Race n (%)		
White	23 (76.7%)	27 (90.0%)
Black	6 (20.0%)	1 (3.3%)
Hispanic	1(3.3%)	1(03.3%)
Asian	0 (00.0%)	1 (3.3%)
Mean Weight ± SD (kg)	74.7 ± 15.3	74.5 ±17.8
Mean LOS ± SD (days)	28.6 ± 3.1	30.0 ±13.2
Discharged n (%)		
Home	13 (43.3%)	15 (50.0%)
Nursing Home	11 (36.7%)	8 (26.7%)
Subacute Unit	4 (13.3%)	4 (13.3%)
Acute	2 (6.7%)	3 (10.0%)

shown effectiveness in reducing the rates of DVT/PE by about 60%.[4-5] In comparison with UFH, **low-molecular-weight heparin (LMWH)** appears more effective in preventing VTE among patients with stroke.[5,15] A Cochrane database analysis (2005) suggested that LMWH decreases the incidence of DVT, when compared to UFH, but there were insufficient data to comment on other outcomes including intracranial hemorrhage and death.[16]

Most recently, a randomized controlled trial of almost eighteen hundred patients with acute ischemic stroke found that daily enoxaparin reduced the risk of VTE by 43% in comparison with UFH (68 vs. 121 patients, P = 0.0001). The bleeding rates, a composite of major extra-cranial and clinically significant intracranial hemorrhage, were slightly higher in the enoxaparin group (11 vs. 6, P = 0.23).[17]

Fondaparinux (Arixtra), made by GlaxoSmith Kline, is the latest therapeutic option for DVT/PE prevention and treatment. This small, synthetic pentasaccharide is a potent inhibitor of Factor Xa, via its action on Antithrombin III. It does not significantly bind to plasma proteins or affect platelet function, and has a predictable pharmacokinetic profile that allows for daily dosing without routine monitoring of levels.[18-20]

Fondaparinux has been shown to be superior to enoxaparin, with comparable safety, in preventing VTE in patients after hip fracture, hip replacement, and knee replacement surgery.[21-23] Fondaparinux is also approved for the prevention of VTE in patients after abdominal surgery, who are at risk of VTE.[24] Finally, fondaparinux is approved for the treatment of VTE, in conjunction with warfarin; a comparative study with enoxaparin (for DVT) showed similar efficacy and safety.[25] Due to its efficacy and safety in comparison with current therapies, fondaparinux appeared to be a potentially valuable option for preventing VTE in patients with stroke. Therefore we compared it to enoxaparin.

Methods

After approval by the rehabilitation center's Research Oversight Committee, we conducted a retrospective chart review of adults with strokes admitted over three years who received enoxaparin (40 mg subcutaneously daily) or fondaparinux (2.5 mg subcutaneously daily) for VTE prevention. The first group included 30 consecutive admissions until 2005, when our rehabilitation center started using fondaparinux as the preferred agent for VTE prophylaxis. Thirty patients in the second group were also consecutive admissions. In effect, these patients were randomly assigned to the two drugs as there was no selection process. Both groups included only patients with non-hemorrhagic strokes, no active bleeding, and a calculated creatinine clearance of 30 ml/min or above, since both drugs are cleared by the kidneys. Patients received either drug until they consistently walked a total of 100-150 feet each day. All patients were assessed on a daily basis for DVT by examination of the legs and for PE by clinical signs such as chest pain and dyspnea; an ultrasound was obtained if indicated to diagnose a DVT.

Table 2: Clinical Characteristics by Drug Group

	Fondaparinux	Enoxaparin	
Location of Stroke			
Left	14 (46.7%)	19 (63.3%)	
Right	16 (53.3%)	11 (36.7%)	
Ultrasound	4 (13.3%)	4 (13.3%)	
Aspirin	18 (60.0%)	14 (46.7%)	
Clopidogrel	3 (10.0%)	1 (3.3%)	
Aspirin and Clopidogrel	4 (13.3%)	8 (26.7%)	
Aspirin and Dipyridamole	5 (16.7%)	4 (13.3%)	
Any Anti-platelet Agent	29 (96.7%)	26 (86.7%)	
Leg Edema	5 (16.7%)	3 (10.0%)	
Calf Tenderness	0 (0.0%)	0 (0.0%)	
Transfers (FIM)	2.7 ± 1.2	2.9 ± 2.5	
Ambulation (FIM)	1.7 ± 1.2	2.6 ± 0.3	T=2.7 P=0.01
Ambulation (Feet)	27.1 ± 49.4	23.2 ± 43.4	
Dorsiflexors	1.3 ± 1.6	2.2 ± 2.1	
Hip Flexors	1.8 ± 1.2	2.2 ± 1.3	
Knee Extensors	2.1 ± 1.5	2.6 ± 1.7	
Tone	-0.1 ± 0.7	0 ± 0.7	

*FIM scores, ambulation distance, strength, and tone are Mean ± SD. Other values are n (%).

The data set included demographics (age, sex, race), length of stay, weight, location of stroke (right vs. left), admission **Functional Independence Measure (FIM)** scores for transfers and ambulation; distance of ambulation on admission; lower extremity strength (hip flexors, knee extensors, ankle dorsiflexors graded on a scale of 0 - 5); lower extremity tone; presence of leg edema and calf tenderness on admission; risk factors for DVT/PE based on the discharge summary and rehabilitation medicine evaluation; duration of enoxaparin or fondaparinux; concomitant use of anti-platelet agents including aspirin, clopidogrel, or aspirin/dipyridamole; calculated creatinine clearance; initial hemoglobin and platelets; hemoglobin and platelets obtained closest to the discharge date; presence of an ultrasound study to diagnose a DVT; and discharge disposition. Patients admitted with concomitant anti-platelet agents received them throughout the study. The outcome measures were occurrence of DVT and PE,

Table 3: Lab Characteristics by Drug Group

	Fondaparinux	Enoxaparin	
Initial Hemoglobin (gm/dl)	12.8±1.8	13.0±1.7	
Final Hemoglobin	12.3± 1.8	11.9± 2.9	
Mean Hemoglobin Change	-0.49± 0.8	-1.1± 2.8	
Initial Platelets (k/cumm)	232.5± 96.0	293.2± 111.9	T=2.3 P=0.03
Final Platelets	233.1± 63.6	258.2± 126.9	
Mean Change in Platelets	+0.5± 57.0	-35.1 ± 92.2	T=1.8, P=0.07
Creat. Clearance (ml/min)	71.8± 33.4	61.8± 51.0	

*All values are Mean ± SD.

Table 4: Presence of Risk Factors by Drug Group

	Fondaparinux	Enoxaparin
Age (n, %)	23 (76.7%)	27 (90.0%)
Weight	13 (43.3%)	9 (30.0%)
Infection	19 (63.3%)	24 (80.0%)
Paralysis	19 (63.3%)	15 (50.0%)
Edema	3 (10.0%)	3 (10.0%)
IBD	0 (00.0%)	1 (3.3%)
Cancer	0 (00.0%)	2 (6.7%)
History of DVT	0 (00.0%)	1 (3.3%)
Mean Total Risk Factors ± SD	2.6 ± 1.2	2.7 ± 0.8

*All values are n (%), except for the last variable.

as well as bleeding complications. All patients were closely monitored for bleeding complications. Bleeding was classified as either minor or major; the latter included bleeding that was fatal, in a critical organ, or with a bleeding index (decline in hemoglobin + units transfused) greater than 2.

The rationale for selecting these variables was as follows. In order for an unbiased comparison of the two drugs, we wished to ensure that the two groups were similar in terms of risk factors for VTE: age (over 60), obesity (weight > 120% of ideal body weight), paralysis (strength of = 1/5 at lower extremity muscles), immobility (FIM scores of 1 for transfers and ambulation, or initial ambulation < 5 feet), leg edema, and calf tenderness. In addition, other risk factors such as inflammatory bowel disease and hormone replacement therapy were noted, to obtain the total number of risk factors. The length of stay and discharge dispositions were indicators of stroke severity. Duration of enoxaparin or fondaparinux, creatinine clearance, initial platelet count, and the use of antiplatelet agents could all increase the risk of bleeding complications. Initial and final platelets and hemoglobin were laboratory indicators of bleeding complications, the outcome measure for safety.

Statistical analysis using cross tabulation was used to determine whether there was a significant difference in the frequency of PEs, DVTs, and bleeding complications between those patients taking fondaparinux versus those taking enoxaparin. Bivariate analysis, including difference of means test and Chi-square, was used to examine whether there were significant differences between groups that may affect the statistical significance of DVT/PE and bleeding complications after stroke.

Results

There were no significant (NS) differences between the groups in almost all demographic characteristics (Table 1); clinical features, anti-platelet agents, and level of disability related to the stroke (Table 2); lab characteristics (Table 3); and risk factors for DVT/PE (Table 4). The mean duration of treatment was 21.1 ± 14.1 days with enoxaparin and 20.6 ± 15.0 days with fondaparinux. Significant differences occurred only with FIM scores and platelets. Mean FIM scores for ambulation were higher among the enoxaparin group (2.6 ± 0.3, 95% CI, 2.05 - 3.1) vs.1.7 ± 1.2 (95% CI, 1.2-2.1) with fondaparinux (T=2.7, P=0.01). The enoxaparin group had higher mean admission platelets than the fondaparinux patients (293.2 ± 111.9 k/cumm, 95% CI, 251.5 - 335.0) vs. 232.5 ± 96.0 k/cumm (95% CI, 196.7 - 268.4; P = 0.03). There was also a greater mean decline in the platelet count at discharge with enoxaparin (- 35.1, 95% CI, -69.5 to -0.6) vs. + 0.5 k/cumm (95% CI, -20.8 - 21.8; T = 1.8, P = 0.07, NS).

Among the fondaparinux patients, the greatest decline in platelets was from 622 to 371 k/cumm and with enoxaparin the worst decline was from 474 to 301 k/cumm. The major bleed with fondaparinux was a decline in hemoglobin that required transfusion, and the one with enoxaparin required transfer to the acute care hospital.

The number of patients on antiplatelet agents was higher in the

fondaparinux group (29, or 96.7% vs. 26, or 86.7%, P = 0.16), but the combination of aspirin and clopidogrel was higher in the enoxaparin group (8, or 26.7 % vs. 4, or 13.3 %, P = 0.16); neither of these findings was significant. The fondaparinux group had a decline in hemoglobin of 0.49 (from a mean of 12.8 gm/dl ± 1.8), but the enoxaparin patients had a decrease of 1.1 (from a mean of 13.0 gm/dl ± 1.7, P =0.28, NS).

More patients in the fondaparinux group had leg edema (5 vs. 3), but this was not a significant finding (P=0.58). The mean total number of risk factors for DVT/PE was higher in the enoxaparin patients (2.7 vs. 2.6), and this was also not significant (P=0.53).

There were no significant differences between the two drugs in the safety and efficacy outcomes (Table 5). Neither group had a PE. The incidence of DVTs was 3.3% (1) with enoxaparin and no patient on fondaparinux had a DVT (P= 0.31, NS). There were 3 (10%) minor and one major bleeding incidents 1 (3.3%) among the fondaparinux group, and 4 (13.3%) minor and 1 (3.3%) major bleeding incidents among the patients on enoxaparin. With the minor bleeding episodes, the fondaparinux group had two instances of hematuria and one of epistaxis. With enoxaparin, the patients had one subconjunctival hemorrhage, one knee effusion, and two instances of gastrointestinal bleeding.

Bivariate analysis of the impact of those traits that significantly differed by group showed no significant relationship to the outcome measures. For instance, the ambulation FIM did not change the statistical significance of the difference in DVT incidence.

Table 5: Outcomes by Drug Group

	Fondaparinux	Enoxaparin
PE (n, %)	0 (0%)	0 (0%)
DVT	0 (0%)	1 (10%)
Minor Bleeding	3 (10%)	4 (13.3%)
Major Bleeding	1 (3.3%)	1 (3.3%)
Mean Drug Duration (Days ± SD)	20.6 ± 15.0	21.1 ± 14.1

*All values are n (%), except for the last variable.

Discussion

There was no DVT in the fondaparinux group and one occurred in the enoxaparin group, but this difference was not statistically significant. The two groups were similar in terms of age, gender, race, weight and risk factors for VTE, except for the ambulation FIM score at admission, which was significantly lower in the fondaparinux group.

Safety assessment in both groups revealed no significant differences. Major bleeding in the fondaparinux group involved a patient who was on two medications that significantly increase the risk of gastrointestinal bleeding: aspirin and clopidogrel. The patient on enoxaparin with a major bleeding episode was on aspirin. Both the creatinine clearance and platelet count were normal in these two patients.

Platelets declined among the enoxaparin group by a mean of 35.1 k/cumm, a difference that approached significance (P = .07, NS). This finding may be consistent with the pharmacology of these two drugs in relation to **heparin-induced thrombocytopenia (HIT)**. An in vitro study (platelet aggregation test) of 25 patients with HIT showed that 19 (76%) samples of serum cross-reacted with enoxaparin, but none interacted with fondaparinux.[26]

A randomized controlled trial of enoxaparin and heparin in 212 patients revealed that VTE, major bleeding, and death within three months of stroke occurred in 37.7 % of patients on daily enoxaparin and 49.1 % of patients on thrice daily heparin (P = 0.127).[15] A larger study of almost 1,800 patients showed a 10.2 % incidence of VTE with enoxaparin and 18.1 % for those given heparin (P = 0.0001), although bleeding occurred more often with enoxaparin. [17] Enoxaparin seems to be superior to heparin for VTE prevention in the stroke population.

The ACCP guidelines for VTE prevention were updated in 2008. Unfractionated heparin, low molecular weight heparin, and fondaparinux all received the highest recommendation of Grade 1A for acutely ill medical patients who are confined to bed and have an acute neurological disease.[27]

Limitations of our study include the small sample size and lack of randomization. In addition, mandatory venography was not performed (as was done for the orthopedic studies comparing the two drugs), so there was the possibility of undiagnosed DVTs.

Conclusion

Based on this retrospective chart review, fondaparinux appears as effective and safe as enoxaparin in preventing DVTs and PEs in patients with stroke. There were no DVTs with fondaparinux, but one occurred in the enoxaparin, and minor bleeding was slightly higher with enoxaparin. These differences in efficacy and safety were not significant. A randomized controlled trial with a sufficient number of patients is needed to determine if one of these medications is superior.

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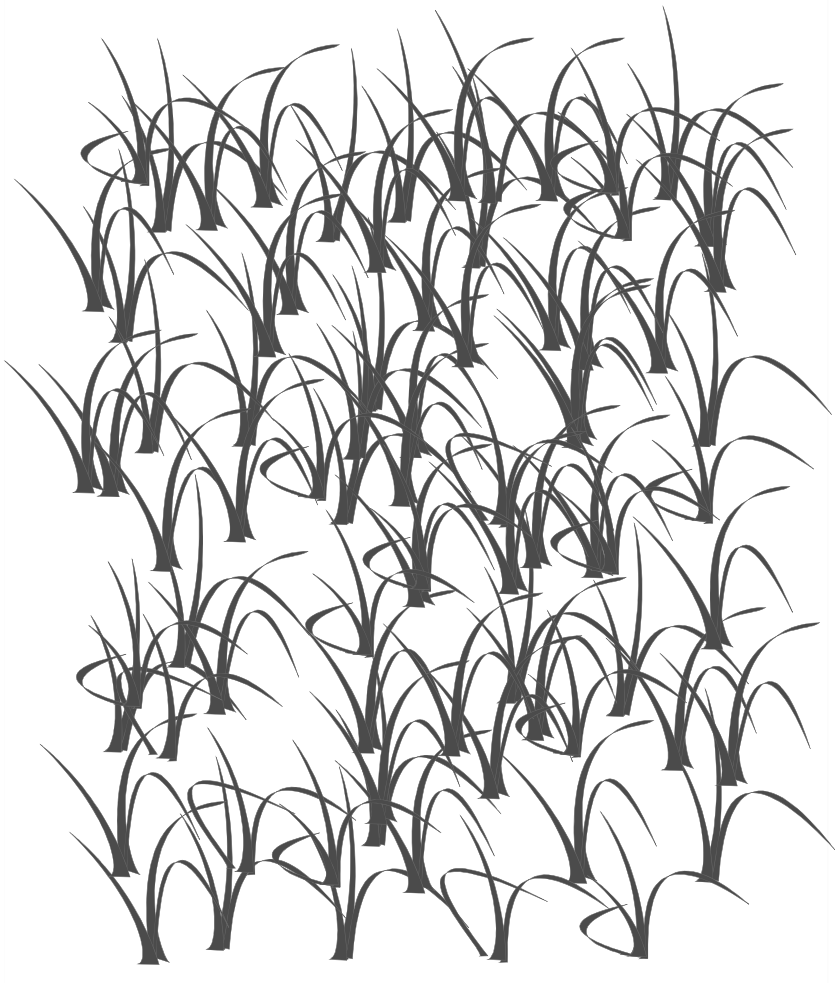

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