Randomised Controlled Trial for Efficacy of Unfractionated Heparin (UFH) Versus Low Molecular Weight Heparin (LMWH) in Thrombo-Prophylaxis


Abstract

Objective: To study if low dose Unfractionated heparin (UFH) is as effective and safe as Low-molecular weight heparin (LMWH) and also economical as a prophylactic agent for venous thromboembolism in medically ill patients.

Methodology: A prospective double blind randomised controlled trial consisting of 92 patients fulfilling the inclusion criteria who were admitted to Bangalore Baptist Hospital, Bengaluru, between March 2008 and July 2009 were randomised to receive Unfractionated heparin (UFH) or Low-molecular weight heparin (LMWH).

Results: The result based on intention to treat (ITT) analysis with best outcome scenario: in the UFH arm there were 47 (97.9%) patients who had not developed DVT/PE as compared to 42 (95.5%) in the LMWH arm. The difference in proportion of patients who had not developed DVT/PE between UFH and LMWH was 2.4% (-5.0, 9.8). The results based on per protocol analysis: In the UFH arm there were 44 (97.8%) patients who had not developed DVT/PE as compared to 39 (95.1%) in the LMWH arm. The difference in proportion of patients who had not developed DVT/PE between the UFH and LMWH arm was 2.7% (-5.2, 10.5). Patients on UFH had higher major bleeding complications 4 (8.9%) as compared to 0 in LMWH arm. But with respect to other complications like thrombocytopenia (HIT) and mild or minimal bleeding both arms were comparable.

Conclusion: This study has demonstrated that low dose UFH is as effective as LMWH as a prophylactic agent for venous thromboembolism in medically ill patients and economical also.

Introduction

Venous thromboembolism is a frequent cause of preventable illness and death in hospitalised patients especially in intensive care units. About 25% of all cases of venous thromboembolism are associated with hospitalisation and 50 to 75% of cases of venous thromboembolism in hospitalised patients occur in those in the medical wards.

In prospective studies of hospitalised patients at high risk who were not receiving prophylaxis, deep-vein thrombosis was found by means of venography in 10.5% to 14.9% of patients and by means of venous doppler in 5.0% of patients. In these studies, pulmonary embolism occurred in 0.3 to 1.5% of cases, and proximal deep-vein thrombosis in 2.0 to 4.9% of cases. Thrombosis was asymptomatic in over 70% of cases.

Pulmonary embolism is thought to be associated with 5 to 10% of deaths of
hospitalised patients, but this diagnosis is not suspected clinically in the vast majority of cases. However, diagnosis and treatment alone are inadequate for hospitalised patients who are at high risk, in whom asymptomatic deep vein thrombosis is common and death from pulmonary embolism usually occurs rapidly, before the diagnosis is suspected. In such patients, primary prophylaxis with the use of a highly effective intervention that carries a low risk of adverse effects is the best approach.

The American College of Chest Physicians has published guidelines for the use of prophylaxis against thromboembolism in hospitalised patients. These guidelines strongly recommend the use of either unfractionated or low-molecular weight heparins in acutely ill hospitalised patients with heart failure, severe respiratory disease, acute stroke, immobility, or multiple risk factors. Mechanical methods of prophylaxis are recommended for patients at increased risk for bleeding.

Unfractionated heparin is less expensive but must be given at least twice daily, whereas low-molecular weight heparins and fondaparinux are more expensive but can be given once daily. All three agents have been shown to be effective in reducing the risk of venous thromboembolism in randomised trials.

This study was undertaken to establish whether unfractionated heparin is as effective and safe as low molecular weight heparin.

**Material and Methods**

All patients fulfilling the inclusion criteria, consisting of medically ill patients with high and higher risk for DVT/PE (as per the DVT/PE assessment score) in patients who required (1) at least 3 days of ICU stay or (2) same duration non-ambulatory condition in the wards among patients who were admitted to an intermediary care hospital in south India between March 2008 and July 2009 were considered for the study. Patients with moderate risk were not included in the study.

Patients were assigned the DVT/PE assessment score for risk assessment as follows:

**A:** Each item represents 1 risk factor:
- Minor surgery
- Pregnancy or post partum
- Varicose veins
- Inflammatory bowel disease:
- Obesity (BMI > 20)
- Combined oral contraceptive/ HRT
- Age 40-60 yrs

**B:** Each item represents 2 risk factors:
- Age over 60 yrs
- Malignancy
- Immobilised plaster cast
- Medical or surgical patients with bed ridden > 72 hrs
- Central venous surgery

**C:** Each item represents 3 risk factors
- Myocardial infarction
- Congestive cardiac failure
- Severe sepsis/ infection
- History of DVT/PE
- Factor V Leiden mutation/activated protein c resistance
- Antithrombin III deficiency
- Dysfibrinogenemia
- Hyperhomocysteinaemia
- Lupus anticoagulant
- Antiphospholipid antibodies
- Myeloproliferative disorders
- Disorders of plasminogen and plasmin activation
- Heparin induced thrombocytopenia
- Hyperviscosity syndrome

**D:** Each item represents 5 risk factors:
- Stroke
- Acute spinal cord injury
- Multiple trauma
- Hip, pelvic or leg fracture
- Elective major lower extremity arthroplasty

Total Score = A + B + C + D

**Risk Category**

The risk categories are as follows -

Score 0 means No risk, 1 is Low risk, 2 is Moderate risk, 3−4 is High risk and a score of >5 means Highest risk for DVT/PE.

Simple randomisation scheme was developed using RALLOC software. All patients requiring thromboprophylaxis were randomly assigned to receive unfractionated heparin (UFH) or low-molecular weight heparins (LMWH), administered in a double blind fashion. Thrombo-prophylaxis administered in the form of

1. **UFH** – 5000 IU subcutaneously twice daily
2. **LMWH** – Enoxaparin 40 mg subcutaneously once daily

Thromboprophylaxis was continued till patient
became ambulant and ready for discharge. Coagulation parameters (PT-INR, PTT), platelet count and other lab investigations were done at admission and repeated as necessary. Platelet count was repeated every 4th day. Bilateral lower limb venous doppler was carried out at the end of thromboprophylaxis.

Among the complications, major bleeding was defined as that which required urgent blood transfusion or was fatal and Heparin induced thrombocytopenia as platelet count dropping to half or less than half of admission value after starting thromboprophylaxis.

If patient developed complications in the form of any bleeding manifestation (major or non major), then thromboprophylaxis was stopped temporarily and PT-INR and PTT, platelet count was repeated. If PT-INR was more than 2 or PTT was more than twice the normal value, platelet count had dropped to half or less than half of admission value then thromboprophylaxis was discontinued. Thromboprophylaxis was restarted if all lab parameters were in acceptable range and bleeding stopped. In patients where pharmacological thromboprophylaxis was not restarted mechanical thromboprophylaxis in the form of Graduated compression stockings were used, if required.

Any other supportive measures such as treatment of underlying condition, need for ventilatory support, need for fresh frozen plasma, blood, platelet, I.V. antibiotics and ulcer prophylaxis, inotropic supports were given as necessary. The study was approved by the Institute’s Research and Ethics Committee and informed consent was obtained from each patient.

### Statistical Analysis

Descriptive statistical analysis has been carried out to check for outliers and the distribution of the outcome. Our primary analysis was done on an intention to treat (ITT) basis. The primary outcome of the study is prevention of development of DVT/PE and the secondary outcome is associated accompanying complications. Non inferiority margin of 10% was taken as clinical significance. The baseline characteristics of the patients were obtained during the admission to the hospital. We calculated the difference of development of DVT/PE from UFH to LMWH.
Assessed for Eligibility (n=108)

Excluded (n=14):
Not Meeting the inclusion criteria (n=12)
Declined to participate (n=2)

Randomised (n=92)

Allocated to UFH: (n=48)

Allocated to LMWH: (n=44)

Lost to follow up (n=3)
Reason: Migration = 1
Expired = 2

Lost to follow up (n=3)
Reason: Migration = 3

Expected to be analysed for ITT = 48
Expected to be analysed for PP = 45

Expected to be analysed for ITT = 44
Expected to be analysed for PP = 41

Fig. 1 : Study Profile

LMWH arm and conclusions were made based on 95% confidence interval. We also performed per protocol analysis based on subjects who had completed follow up. We analysed data using STATA version 10.

Results

In this randomised controlled trial the baseline characteristics of the study population was as follows:

108 patients were assessed for eligibility, of which 92 were found to be eligible and randomised. 48 patients were included in the UFH group and 44 in LMWH group (Figure 1). Average ± S.D age of the patients was 57.8 ±18.7 years in LMWH group and 50.9 ± 20.1 years in UFH group. Most of them were above 60 yrs age group (53.7%) in LMWH group while in UFH group patients were nearly equally distributed in 20-40, 40-60, > 60 age group(40%, 24.6%, 35.6% respectively). Samples were similar in gender. Patients were similar for underlying diagnosis in both groups. Patients were also similar in other baseline parameters like platelet count at admission, haemoglobin, serum creatinine, ECGs, in both the study groups (Table 1).

The result based on intention to treat (ITT) with best outcome scenario: in the UFH arm there were 47 (97.9%) patients who had not developed DVT/PE as compared to 42 (95.5%) in the LMWH arm. The difference in proportion of patients who had not developed DVT/PE between the UFH and LMWH arm was 2.4% (-5.0, 9.8). As the lower limit of the CI was within the non inferiority margin of 10% it was concluded that UFH would be as good as LMWH. The results based on per protocol analysis are also presented in Table 2. In the UFH arm there were 44 (97.9%) patients who had not developed DVT/PE as compared to 39 (95.1%) in the LMWH arm. The difference in proportion of patients who had not developed DVT/PE between the UFH and LMWH arm was 2.7% (-5.2, 10.5). As the lower limit of the CI was within the non inferiority margin of 10% it was concluded that UFH would be as good as LMWH.

Patients on UFH had higher major bleeding complications {4 (8.9%)} as compared to LMWH arm[0]. But with respect to other complications like thrombocytopenia (HIT) and mild or minimal bleeding both arms were comparable.

Discussion

There is evidence in literature that unfractionated heparin (UFH) is not inferior to low molecular weight heparin (LMWH) in preventing thromboembolism. However, bleeding manifestations and heparin induced thrombocytopenia (HIT) are more common with unfractionated heparin (UFH) than low molecular weight heparin (LMWH).

Most of the previous studies have been done with 5000 I.U. of unfractionated heparin (UFH) three times a day. A study by Clagett GP, Anderson Jr FA, Geerts W, et al shows Low dose unfractionated heparin (usually 5000 IU every 8 or 12 hours) started preoperatively reduces the risk of deep vein thrombosis by 31 to 39% compared with placebo or control in patients undergoing hip or knee arthroplasty, and it is not associated with an increased risk of major bleeding. Low dose unfractionated heparin is also effective in reducing the risk of deep vein thrombosis in patients undergoing surgery for hip fracture (44% risk drop off).

In our study low dose unfractionated heparin (5000 I.U. twice daily) was compared with low molecular weight heparin (Enoxaparin 40 mg once a day) for efficacy and safety in medically ill patients. Our result shows that low dose unfractionated heparin is as good as low molecular weight heparin in preventing thromboembolism.

Although occurrence of individual complications (thrombocytopenia, mild and major bleeding incidence) is not statistically significant in either group, overall complications (mild and major bleeding) were more in UFH Group.

The cost for daily thromboprophylaxis in UFH group is about 70-80Rs, whereas in LMWH group it is about 700-800Rs, which is 10 times more than UFH. Routine aPTT monitoring can be avoided with low dose unfractionated heparin.
The number of patients in each group was small in our study. Further studies are required with more patient numbers to assess the safety profile of unfractionated heparin versus Low Molecular Weight Heparin in thromboprophylaxis.

Conclusion

This study has demonstrated that low dose unfractionated heparin is as effective as low molecular weight heparin as a prophylactic agent for venous thromboembolism in medically ill patients, though however, adverse effects are slightly more with unfractionated heparin in preventing thromboembolism especially in resource constrained settings or developing countries. The effective cost for daily prophylaxis with unfractionated heparin is 10 times lower than low molecular weight heparin.

Disclosures

This study was partly funded by Sanofi-Aventis Pharma the manufacturers of Clexane (Enoxaparin, a low molecular weight heparin).

References