Low Molecular Weight Heparin Vs. Unfractionated Heparin In Pulmonary Embolism: Comparison Of Oxygenation And Perfusion Changes In The Immediate Post-Treatment Period

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A. Statement of study purpose and rationale

Pulmonary embolism is a common in-hospital diagnosis attributable to such clinical conditions as surgery or trauma, heart disease, and cancer. Primary or idiopathic PE accounts for approximately 40% of all cases with surgery or trauma accounting for 43%, heart disease for 12%, and neoplastic disease for 4%, of cases of PE.(1)

In randomized trials, low molecular weight heparin appears to be as safe and effective as intravenous unfractionated heparin in treating the spectrum of cases of venous thromboembolism including pulmonary embolisms(2). Advantages of subcutaneous low molecular weight heparin include the elimination of need for laboratory monitoring and the possibility of administering it in the outpatient setting.

While there have been randomized studies comparing the effects of thrombolysis vs. unfractionated heparin in PE on right ventricular function and pulmonary perfusion, there appear to be no such studies yet in low molecular weight vs. unfractionated heparin. Goldhaber et al. hypothesized from their study that the rapid improvement in right ventricular function and pulmonary perfusion in the patients receiving thrombolysis may translate to a lower rate of death and recurrent PE.(3) Blood gas analysis and perfusion lung scintigraphy are useful in quantifying the extent of recovery in acute PE.(4) It would be informative to compare the effects of low molecular weight heparin vs. unfractionated heparin on blood gas improvement and pulmonary perfusion in the immediate post-treatment period. And unlike the study recently published in the New England Journal where only a quarter of the 1021 subjects had pulmonary embolism, this study would focus on the effects of low molecular-weight heparin in treating pulmonary embolism, not all venous thromboembolic disease. Also unlike this previous study, this study will be a double-blind placebo controlled study.

B. Description of study design and statistical analysis

a. Study Design

The study will be a randomized, placebo-controlled double-blinded study, Subjects will be patients aged 18 years or older with the diagnosis of PE confirmed by high probability lung scan (defined as two or more segmental or greater perfusion defects in the presence of normal ventilation) and/or pulmonary anglography. After definitive diagnosis, the subjects will be consecutively randomized to either 1) subcutaneous low molecular weight heparin and a placebo normal saline infusion or 2) continuous intravenous unfractionated heparin dosed by weight and adjusted to achieve a target PTT of 1.5-2.5 times control paired with placebo subcutaneous injections. A computer program similar to the one used in the WARSS trial (Warfarin vs. Aspirin in Prevention of Recurrent Stroke Study) that will generate fake partial thromboplastin times for the subjects receiving placebo injections will allow investigators to remain blinded. Oral anticoagulation treatment in the form of coumadin with be started on the second or third day and continued for 6 months,

Exclusion criteria will include concurrent lung disease such as COPD, pulmonary hypertension, pulmonary edema, pulmonary embolism severe enough to require mechanical ventilation, hematocrit less than 30%, current anticoagulation therapy, patients who have received thrombolytic therapy,

gastrointestinal bleeding within the last 14 days, occult blood in stool, surgery requiring anesthesia within the last 3 days, stroke within last 10 days, platelet count less than 100,000, and documented pregnancy.

The mean Pa02 at 7 days between the two treatment groups will be analyzed with the hypothesis that the low-molecular weight heparin group will have better oxygenation by at least 10 min Hg. A difference less than 10 will be considered clinically unimportant.

b. Statistical Analysis

Based on previous blood gas analysis data in patients with pulmonary embolism as per the study by Donnamaria et al. published in Respiration 1993, a trial with 80% power and two-sided level of significance of .05 will require an estimated 60 subjects in each arm to detect a Pa02difference of 10 min Hg in the two groups at the 7 day point. This data will be analyzed by t-test.

The ventilation-perfusion scans will be compared by two radiologists and given a rating of either same/worse or better when the 24 hour scans and 7 day scans are each compared to the baseline scan. This data will be analyzed by chi-square testing.

C. Description of study procedures

Blood gas analysis from the radial artery will be taken at baseline, 2 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours and 7 days after initiation of therapy. The purpose of the multiple data points will be to document, analyze, and compare the trend in blood gas improvement in both treatment groups. All blood gases will be taken on room air and the patients receiving supplemental oxygen will be taken off this for at least 5 minutes before the arterial gas is obtained.

Follow-up ventilation/perfusion scans will be done at 24 hours and 7 days after therapy was started and will be coded to prevent the radiologists and investigators from identifying the subject and the treatment.

D. Study drugs

Patients randomly assigned to low-molecular-weight heparin will receive reviparin sodium administered subcutaneously in the following fixed doses: 6300 units twice daily for patients weighing more than 60 kg; 4200 units twice daily for patients weighing 46 to 60 kg; 3500 units twice day for patients weighing 35 to 45 kg.

Patients randomly assigned to unfractionated heparin will receive a weight adjusted bolus of 80 units per kg followed by a continuous infusion of 18 units per kg per hour. The rate of the heparin drip will be adjusted to an activated partialthromboplastin time of 60 to 85 seconds or a fixed ratio of 1.5 to 2.5 times a control value.

All patients will receive oral warfarin begun on the second or third day after therapy is initiated and prothrombin time adjusted to 2.0 to 3.0. The study drug will be discontinued after the prothrombin time is maintained above 2.0 for two consecutive days and the patient has received the study drug for at least five days.

E. Medical Devices

None.

F. Study Questionnaires

None.

G. Description of study subjects and method of recruitment

Subjects will be recruited from inpatients as well as patients from the emergency room or admitted directly from doctors'private offices who are suspected to have pulmonary embolism by clinical symptoms, i.e. tachypenia, hypoxemia, and tachycardia. The subjects will not be randomized to the treatment arms until the diagnosis of PE has been confirmed by a high probability perfusion/ventilation scan or by pulmonary angiography. Clinicians and hospital staff will be informed of this trial and strongly encouraged to contact a special beeper whenever there is a patient with a suspected clinical diagnosis of pulmonary embolus so that he/she can be efficiently evaluated for suitability to be in the study.

According to the CPMC department of radiology, there is an estimated total 75 high probability V/Q scans per year of which 60 of those are patients who are not intubated. There is also an average of one pulmonary angiography study per month most of which are positive. In light of these numbers, the estimated time needed to recruit 60 subjects per arm will be 2.5 to 3 years.

H. Confidentiality of the study

Information regarding participation and individual results of this study will be kept strictly confidential. Data will be reported in an anonymous manner only.

I. Location of study

All study subjects will be admitted at Columbia-Presbyterian Hospital and all diagnostic procedures will be performed by the staff here.

J. Risks and benefits

Risks include those of bleeding from the anti-coagulation therapy as well as from the arterial punctures necessary to obtain blood gases. There is also risk of pain, bruising, hematoma and rarely clot from radial artery puncture. As per the New England Journal study, the rate of recurrent thromboembolic disease is 4%, in each treatment group.

K. Alternative therapies

None.

L. Compensation and costs to subjects

There will be no monetary compensation for this study.

M. Minors and research subjects

No minors (persons under the age of 18) will be studied.

N. Radiation and radioactive substances

None.

O. References

1.   Giuntini C, Di Ricco G. Marini C, Melillo E, Palla A. Epidemiology. Chest 1995; 107:3S-9S.
2.   Butler HR et al. Low molecular-weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med 1997; 337: 657-62.

3.   Goldhaber SZ, Haire WD, Feldstein ML, Miller M, et al. Alteplase versus heparin in acute pulmonary embolism: randomized trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993; 341: 507-11.

4.   Donnamaria V, Palla A, Petruzzelli S. Carrozzi L, Pugliesi 0. Ginntini C. Early and late follow-up of pulmonary embolism. Respiration 1993; 60: 15-20.