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Comparison of Enoxaparin vs. Placebo for the Prevention of Venous Thromboembolism in Nursing Home Patients

1. Study Purpose and Rationale

Venous thromboembolism (VTE) is a disease that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). It is a common and potentially fatal condition that represents a large medical burden to both hospitalized and non-hospitalized patients. The annual incidence of VTE has been estimated at 1 per 1000 people.[1] About 300,000 PE are diagnosed each year, of which 15-25% present with sudden death or result in death within 30 days.[2] It is estimated that 5-10% of all hospital deaths are attributable to PE prior to the advent of VTE prophylaxis.[3] The long-term complications of DVT/PE include post-thrombotic syndrome (occurring in about 30% of patients with a DVT)[4] and chronic thromboembolic pulmonary hypertension.

Due to the high disease burden that VTE carries, primary prophylaxis with anticoagulant medications has been extensively studied. Several large randomized clinical trials have shown that unfractionated heparin and low molecular weight heparin decrease the incidence of VTE in hospitalized patients and are associated with low rates of side effects (e.g. bleeding).[5,6,7] As such, the American College of Chest Physicians recommends that prophylaxis should be initiated in any acutely ill medical patient hospitalized with congestive heart failure or severe respiratory disease or patients confined to bed who have at least one additional risk factor for VTE, which include active cancer, previous VTE, sepsis, acute neurologic disease or inflammatory bowel disease.[8]

Studies of VTE prophylaxis have been confined to the hospital setting, which may omit a large segment of the population at risk for VTE. Nursing home residents are at higher risk for VTE than the general population given that many of them are non-ambulatory (i.e. confined to wheelchair or bed bound). Furthermore, the overwhelming majority of non-ambulatory nursing home residents are over the age of 75, which has been shown to be an additional risk factor for VTE.[9] A 2002 study found that about one-tenth of all VTE occurred in nursing home residents.[10] The purpose of this study is to explore the potential therapeutic benefit of VTE prophylaxis in nursing home patients by comparing the use of anticoagulation versus placebo in preventing VTE.

2. Study Design and Statistical Procedures

This will be a prospective, randomized, placebo-controlled clinical trial to evaluate the effectiveness of VTE prophylaxis with low molecular weight heparin (enoxaparin) in non-ambulatory nursing home residents. To be eligible for the study, patients will need to be permanent residents of nursing homes and completely non-

ambulatory at baseline. Patients with a known bleeding disorder or condition that predisposes to bleeding or renal failure with a creatinine clearance less than 30mg/dl are notable exclusion criteria (see below for full list of exclusion criteria). A baseline lower extremity duplex ultrasound will be performed in order to diagnose and exclude any patients with DVT at the outset of the study (these patients will then be treated as appropriate). Patients will be randomized to receive either a subcutaneous injection of 40mg of enoxaparin daily or a subcutaneous injection of isotonic saline daily for a period of 6 months. This dose of enoxaparin has been shown to effectively reduce VTE with an acceptable risk profile.[11] The concomitant use of aspirin, clopidogrel and non-steroidal anti-inflammatory drugs (NSAID) will be permitted though other forms of analgesia aside from NSAID will be encouraged. Any patients already receiving other forms of anticoagulation (including warfarin and all forms of heparin) will be excluded from the study and any patient deemed to have an indication for one of these medications during the study will be withdrawn from the study.

At 3 months and 6 months into the study period, bilateral duplex ultrasonography of the lower extremities will be performed to evaluate for DVT. Duplex ultrasonography will be performed earlier if there is any clinical suspicion for DVT by nursing home physicians or nurses. The ultrasounds will be interpreted by radiologists blinded to the clinical trial. Patients will be monitored daily as per nursing home protocols by nurses and other staff to evaluate for any signs or symptoms of bleeding. If any such event occurs or is suspected, enoxaparin will be stopped and the patient will be treated as medically appropriate. Blood tests for complete blood counts, coagulation studies and kidney function will be performed at baseline and at days 5 and 10 of the study and as necessary thereafter based on any clinical concern.

The primary outcome is DVT as detected by duplex ultrasonography. The incidence of all-cause mortality, hemorrhage and other adverse events will also be recorded as outcomes. Hemorrhage will be divided into major and minor categories. Major hemorrhage is defined as overt bleeding associated with the need of at least a 2 unit packed red blood cell transfusion, decrease in hemoglobin concentration of at least 2 g/dl from baseline, or any retroperitoneal or intracranial bleed. Minor hemorrhage is classified as any covert bleeding that does not meet the criteria for a major hemorrhage.

In order to achieve 80% power with an alpha-error rate of 0.05, a sample size of 307 patients for each group was calculated using the Chi-square test, assuming a 7% prevalence of DVT detected by duplex ultrasonography in non-ambulatory nursing home residents over a 6 month period and a 2% prevalence of DVT in patients treated with enoxaparin. The analysis will be performed on an intention-to-treat basis.

3. Study Procedures

Duplex ultrasonography will be performed to evaluate for DVT in the lower extremities of each patient. This involves the use of a transducer that utilizes sound waves to form pictures that can then be read by a radiologist. There are no risks to this procedure.

4. Study Drugs or Devices

Enoxaparin is part of the class of medications known as the low molecular weight heparins. Its mechanism of action involves binding to antithrombin and potentiating its anticoagulant effect, resulting in systemic anticoagulation. It is a commonly used and well established drug for the prophylaxis of DVT, for which it is FDA approved. It is administered as a subcutaneous injection in the abdominal wall. As with all anticoagulation medications, the major side effect is bleeding, though this has been shown to occur in less than 2% of hospitalized patients across numerous studies. Injection side hematoma is the most common side effect. Other side effects are rare and include fever, bruising, abnormal liver tests and thrombocytopenia with thrombosis.

5. Study Questionnaires
N/A

6. Study Subjects

Inclusion Criteria:

- Permanent resident of a nursing home
- Non-ambulatory (confined to a wheelchair or bed bound)

Exclusion Criteria:

- Surgery within the last 3 months (or expected surgery during the study)
- Use of any heparin medication, warfarin, thrombin inhibitor or other anticoagulant excluding aspirin and clopidogrel
- Acute stroke within the last 3 months
- Known thrombophilia or coagulopathy
- Episode of major bleeding in the last 6 months
- Renal insufficiency with creatinine clearance less than 30 mg/dl
- Thrombocytopenia (platelet count less than 100,000 platelets/ul)
- Known hypersensitivity to heparin
- Hepatic insufficiency or active hepatitis
- Predicted life expectancy less than 1 month

7. Recruitment

Patients will be recruited by contacting the administrators and medical directors of New York City nursing homes for permission to perform the study in their patients. Patients will be eligible if it is clear by doctors' notes, nursing notes and discussions with the patient that the patient is non-ambulatory.

8. Confidentiality of Study Data

All patients will be de-identified. Study data will be kept strictly confidential and available only to study investigators on secure electronic health storage systems.

9. Potential Risks

The potential risk associated with this study lies largely in the side effects of enoxaparin. In a large study comparing the study dose of enoxaparin to placebo, there was a 1.7% risk of a major hemorrhage compared to a 1.1% risk in the placebo group.[12] Furthermore, there was a 1.4% risk of developing an injection site hematoma compared to 0% in the placebo group. There was no statistically significant difference in mortality at 110 days between the enoxaparin and placebo group.

10. Potential Benefits

The potential benefits of the intervention include preventing DVT, PE and subsequent post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension, and recurrent DVT and PE. Since PE is a fatal illness, reduction in mortality is a further potential benefit. As described earlier, DVT prophylaxis is an accepted practice across all hospitals as it has been shown to decrease the rate of VTE. While this study is only investigating DVT, it has been shown that 15-30% of DVT result in a PE.[13]

11. Alternatives

Alternatives to VTE prophylaxis with enoxaparin include other pharmacologic methods, including unfractionated heparin, and non-pharmacologic methods, namely lower extremity compression devices. Unfractionated heparin has been shown to be as effective as low molecular weight heparin (i.e. enoxaparin) but requires 3 daily injections as opposed to a single injection with enoxaparin. Compression devices are recommended only in patients with high bleeding risk and a contraindication to anticoagulation. They have not been shown to be effective in primary prophylaxis of VTE. Lastly, another alternative is to provide no prophylaxis. As mentioned earlier, this has been shown in selected hospitalized patients to carry a VTE risk of at least 10%.

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