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Geriatrics Rotation

IRB Protocol:
Inferior Vena Cava (IVC) filters in patients who cannot tolerate anticoagulation

A. Study Purpose and Rationale

Deep vein thrombosis (DVT) and pulmonary embolus (PE), together called venous thromboembolism (VTE), occur frequently and cause a substantial amount of morbidity and mortality in the United States. The age-standardized incidence of a first VTE was 1.92 per 1000 person-years in one study.[1] Anticoagulation with medications such as vitamin K antagonist, unfractionated heparin, and low molecular weights heparin has been repeatedly shown to be effect for primary prophylaxis, secondary prophylaxis, and treatment of VTE. However, some patients are not eligible for anticoagulation due to co-morbidities. Some common relative or absolute contraindications are current bleeding, previous intracranial hemorrhage, recurrent gastrointestinal bleeding, high fall risk. In patients who are deemed poor candidates for anticoagulation, physicians often implant an umbrella-shaped piece of metal into the inferior vena cava (IVC), known as an IVC filter, which is intended to stop the migration of clots that form in the lower extremities to the pulmonary vascular bed. While theoretically grounded, little high quality evidence exists showing a clinical benefit of these devices.

A meta-analysis of IVC filters found that after placement of an IVC filter, 1.7 percent of patients had a PE in the short term (<30 days).[2] This study showed a likely short-term benefit, though there was no control group. Additionally, while many filters are retrievable, the same study found a retrieval rate of only 34

percent,[2] indicating how important the long-term effects of these devices are. One randomized controlled trial evaluating IVC filters in patients on anticoagulation found that while patients with IVC filters had 0.22 times the odds of a symptomatic or asymptomatic PE at day 12, there was no long term difference and, actually 1.87 times the odds of a recurrent DVT at two year follow up.[3] This study found no difference in mortality and, of note, half of the PEs found in the group without IVC filters were asymptomatic PEs. Thus, this study presents evidence that while there may be a short-term benefit of IVC filters, in the long-run this may benefit may not persist and may be replaced by harm.

Our study seeks to address whether there are short-term or long-term advantages of IVC filters in patients who are ineligible for anticoagulation. The focus will be on whether IVC filters reduce the rate of symptomatic PE or death from PE in patients without symptomatic PE at the start of the study. Given that implantation of an IVC filter is currently the standard of care, it seems appropriate begin the investigation of IVC filters in this lower risk population.

Symptomatic PE will be definite as dyspnea, SpO2 < 97%, pleuritic chest pain, or pulmonary hypertension attributed to PE. The assessment at the start of the study will be made by the treating physician as part of the recruitment process. Suspicion of PE during the study will be confirmed by a CT angiogram of the chest. Classification as a symptomatic PE will be determined by a single adjudication committee for all study participants regardless of study site. The adjudication committee will also make a determination as to whether the cause of death was the result of VTE for any subjects who die during the study period.

B. Study Design and Statistical Analysis

After recruitment, subjects will be randomized such that half of subjects receive IVC filters and the other half do not. Treating physicians, excluding the interventional radiologist, and patients will be blinded to study assignment. Subjects receiving an IVC filter will undergo the procedure within 48 hours of randomization. Subjects randomized to no IVC filter will undergo a sham procedure where they will be taken into an interventional radiology suite, given light sedation, and a superficial incision will be make in the groin so that an examining physician would not be able differentiate study subjects on exam.

All subjects will be interviewed and examined for evidence of PE at one month, six months, 12 months, and 24 months. During these visits, there medical records will also be examined for evidence of PE.

Assuming a type I error rate of five percent and a type II error rate of 20 percent, the study will be powered to detect a difference in the compound primary outcome of symptomatic PE or mortality from PE of five percent. Since the difference is assumed to be smallest at the two-year point, this will be used for the sample size calculation. At the one month time point, the only published estimate of PE for patient with known DVT and without anticoagulation or an IVC filter is 50 percent, [4] but this includes asymptomatic PE, so a 25 percent symptomatic PE rate at one month is a more reasonable estimate. As noted, PE is estimated to occur in 1.7 percent with IVC filter placement,[2] but this includes patients on anticoagulation, so a conservative to use 5 percent for patients not anticoagulated. There is likely an increase in the cumulative incidence before the two year end point. Given the

hypothesis that IVC filters could be a nidus for future clots, this rate of later PEs will likely be higher in patients with IVC filters, so the two year event rate for patients with IVC filters will be estimated at 25 percent, and for those without a filter will be estimated at 30 percent.

n (per group) = 8 [(0.3*0.7) + (0..25*0.75)]/(0.05^2) + 2/0.05 + 2

n = 1272 + 40 + 2

n = 1314

Thus, we will have a target accrual of 1314 participants in each arm of the study. Assume ten percent attrition, this requires 1460 patients per arm, for a total of 2920 participants. The outcome will be assessed at each time point using a Pearson's Chi-squared test of proportions. Given that this will result in four hypothesis tests, a Bonferroni correction will be applied, resulting in a p-value cutoff of 0.0125 for statistical significance.

C. Study Procedure

Insertion of an IVC filter, as above.

D. Study Drugs

There are no medications involved in this study.

E. Medical Device

Use of any FDA-approved IVC filter will be permitted to facilitate participation and to allow greater generalizability. Type of filter will be recorded and tracked for any higher incidence of adverse events with a particular filter model.

F. Study Questionaires

There will be no study questionnaire.

G. Study Subjects

In order to be eligible for the study, subjects must be age 18 or greater. The patient must have a DVT confirmed by ultrasonography. Subjects will be excluded if they have clinical evidence of PE (as above, this will be defined as dyspnea, SpO2 < 97%, pleuritic chest pain, or pulmonary hypertension attributed to PE by the treating physician) at the start of the study. Subjects with a glomerular filtration rate less than 60 will be excluded from the study; this will ensure than all participant can undergo CT angiography of the chest in the event that PE is suspected.

H. Recruitment of Subjects

Subjects will be recruited through multiple clinical centers. After publicizing the study, potentially eligible patients will be referred to the on call member of the research team, who will consent the patient. All patients will be recruited utilizing an informed consent protocol that explains the potential risks and benefits of the study.

I. Confidentiality of Study Data

All study data will be maintained on a secure, encrypted hard drive kept in a locked desk. All subjects will be tracked through a study identification number and will be de-identified in the dataset used for final analysis.

J. Potential Conflict of Interest

There are no potential conflicts of interest.

K. Location of the Study

The study will be a multicenter study in order to obtain an adequate sample size. Other study sites are yet to be determined, but the primary site will be Columbia University Medical Center.

L. Potential Risks

Patients randomized to placebo will have a potential risk from forgoing IVC filter placement, which is currently common practice, however, these patients will be saved the risk of procedural complications. Patients assigned to IVC filter placement will have a small risk of complications due to the procedure. The major complication rate is approximately 0.3 percent.[5] Complications of IVC filter placement include hematoma or DVT at the insertion site, filter migration or fragmentation and embolization, filter erosion through the IVC wall, clotting of the filter and occlusion of IVC.[6]

M. Potential Benefits

Patients may or may not participation in this study. Patients who receive IVC filter may or may not benefit from a decreased rate of PEs and an increased survival. Patients randomized to placebo have no clear short-term benefit from participation, but may have a long-term decreased risk for VTE.

N. Alternative Therapies

In patients deemed ineligible for anticoagulation, there is no current alternative therapy to IVC filters for patients with DVTs

O. Compensation to Subjects

Each subject will receive $50 compensation to cover the cost of transportation. This payment will be made in the form of a check at the first study visit. The payment will not be pro-rated if the subject does not complete the study as the additional administrative cost is likely to be greater than the savings from pro-rating the transportation stipend.

P. Costs to Subjects

There is no expectation of costs incurred by study subjects apart from transportation cost, as already discussed in the section on compensation.

Q. Minors as Research Subjects

There will be no minors recruited to the study.

R. Radiation or Radioactive Substances

There is no exposure to radioactive substances in this protocol. Participants randomized to IVC filter placement will be exposed to fluoroscopy as a part of filter placement. This would be concordant with the standard of care they would receive if not enrolled in the study. Subjects suspected to have a PE will undergo a CT angiogram of the chest, which is consistent with the standard of care and does not represent addition radiation exposure attributable to participating in the study.

References

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