IRB Proposal: Randomized controlled trial of IVC filters in patients with contraindications to anticoagulation

Venous thromboembolism (VTE) is a problem of large magnitude, affecting 100 patients per 100,000 population annually. Deep vein thrombosis (DVT) accounts for 2/3 of this [1]. It is well known that the formation of DVTs, lower extremity blood clots, predisposes patients to shearing of this clot and migration into the pulmonary arterial circuit causing pulmonary embolism (PE), a condition that can cause heart strain and carries significant mortality in the initial several days.

The established treatment for VTE is anticoagulation, but many patients cannot tolerate this treatment due to a narrow therapeutic index, numerous drug-drug and drug-diet interactions, and incidence of life-threatening bleeding associated with the treatment. Anticoagulation with standard oral medications is highly effective, resulting in 0.6 to 1.5 VTE events per 100 years on treatment. This comes at the expense of at least 0.9 and perhaps up to 4.6 major bleeding events per 100 patient years. [2,3]. Indeed, anticoagulation is contraindicated as treatment for patients with prior episodes of life threatening bleeding, those at risk for recurrent falls, poorly compliant patients, patients with recent surgery, and a number of other relative contraindications. For these patients, a relatively recent development is the design of mechanical devices placed in the inferior vena cava (IVC) designed to prevent embolization of lower extremity DVTs and thus prevent the feared complication of pulmonary embolism [an idea first advanced by Trousseau in the 1800s].

While IVC filters have attracted much attention and their use has expanded greatly in the last decade (particularly in these patients who cannot be anticoagulated), their precise efficacy is unknown as there have been no randomized clinical trials comparing their effect against placebo in this setting [1]. Indeed, there are reports of complications associated with filter placement, as well as suggestions that their clinical utility may only last transiently (during the first two weeks) due to a pro-clot forming propensity of the filter and formation of collateral veins that might carry emboli to the lungs around the filter [4].

The present proposal seeks to study patients with known contraindication to anticoagulation, asking the question whether placement of an IVC filter in these patients does indeed reduce the risk of pulmonary embolism. Secondary questions are whether mortality is affected and significant side effects or complications occur either with filter placement or close medical followup alone.

A randomized controlled trial is proposed that will enroll 320 patients total, 160 in the intervention arm and 160 in the close clinical followup arm. These subjects will be recruited in a multicenter fashion by seeking patients with diagnosed DVT in the radiology department and ascertaining if they are not candidates for anticoagulation. Once they are deemed candidates for the study, all subjects receive close medical followup with periodic physical exam and radiographic studies looking for DVT or PE. Once randomization is performed, half of the patients will be assigned to receive an IVC filter and half to close medical followup alone.

Analysis of radiographic and physical exam results will be conducted and the incidence of PE calculated in each group. Further analysis will be aimed at the incidence of complications in each treatment arm.

The trial will hopefully shed light on a heretofore understudied question: the efficacy of a IVC filters in the absence of anticoagulation.

Study purpose and rationale

Venous thromboembolism (VTE) is a problem of large magnitude, affecting 100 patients per 100,000 population annually. Deep vein thrombosis (DVT) accounts for 2/3 of this [1]. It is well known that the formation of DVTs, lower extremity blood clots, predisposes patients to shearing of this clot and migration into the pulmonary arterial circuit causing pulmonary embolism (PE), a condition that can cause heart strain and carries significant mortality in the initial several days.

VTE is effectively treated with anticoagulation, which reduces the incidence of subsequent embolism of known clot and formation of new DVT (stats). Anticoagulation with standard oral medications is highly effective, resulting in 0.6 to 1.5 VTE events per 100 years on treatment. This comes at the expense of at least 0.9 and perhaps up to 4.6 major bleeding events per 100 patient years. [2,3]. However, traditional methods of anticoagulation suffer from difficulty in monitoring anticoagulation goals, interaction of anticoagulants with diet and other medications, and unpredictable dose-effect response. Due to these problems, anticoagulation is associated with substantial complications, including life-threatening major bleeding. Indeed, anticoagulation is contraindicated as treatment for patients with prior episodes of life threatening bleeding, those at risk for recurrent falls, poorly compliant patients, patients with recent surgery, and many other relative contraindications [5].

These problems have led investigators to look for alternative methods of treating DVT and PE. The concept of vena caval interruption was first described by Armand Trousseau in 1865 [1]. Trousseau began to study the pathophysiology of venous thrombosis and the real risk of embolism into the circulation, leading him to suggest venous surgical ligation (either of the femoral vein, or later, of the IVC) in an attempt to form a barrier for clot migration. These techniques were limited by the development of embolism either proximal to the ligature or from the contralateral extremity; furthermore, nearly 50% of patients suffered consequences from reduced venous return in the IVC ligation procedures [6].

Investigators began to study a potential role for IVC filtration, rather than true IVC ligation, in preventing embolization of clot. Many filter designs have been created and marketed for use in the US. In general, these filters are metallic expandable objects, that can expand up to 30 mm in an ‘umbrella’ design. Although the data on recurrent PE with filter in place is limited due to small sample size and short term followup, the efficacy is felt to be slightly lower than anticoagulation [1]. As these methods have become more popular, IVC filter placement has arisen as an option for patients with known contraindication to anticoagulation (such as major bleeding events), or those who have evidence of PE despite effective anticoagulation.

While excitement for the use of this new technology has led to an explosion in the number of filters placed for DVT and PE, it is unclear whether they truly prevent embolization of known DVT. The filters are known to be thrombogenic, and genesis of clot proximal to the filter has been theorized to embolize in patients receiving IVC filters.

Collateral veins are known to form around the filter, bypassing its efficacy as a barrier for embolization. Furthermore, numerous complications have been reported in the literature from IVC filter placement. This includes failure of filter opening [7], improper placement of filter [8], and erosion of filter into the duodenum and vertebrae [9-11].

An observational study [12] sought to compare patients with VTE who received filters with patients with VTE who were discharged without IVC filters. Using a database of all California patients admitted for VTE, approximately 75000 patients were analyzed. Of these, roughly 4000 patients received filters and 71000 did not receive filters. Patients who received filters had significantly more comorbidities, including prior bleeding events, stroke, and presence of neoplasm. After adjusting for risk factors associated with recurrent venous thromboembolism, the study showed no difference in rate of rehospitalization for pulmonary embolism between filter treated and untreated groups. The filter group was also associated with a higher risk of rehospitalization for lower extremity venous thrombosis in patients initially admitted with pulmonary embolism (although not in patients admitted with lower extremity DVT alone). Thus in the 1 year followup provided by this study, IVC filter placement was not associated with reduced rates of hospitalization for PE or DVT; however, the study is clearly susceptible to bias and this should not be interpreted as a causal relationship. It is possible and probable that patients who ended up with IVC filters had an unaccounted for predisposition for rehospitalization for PE. A prospective study was needed to better determine causality (although the study was deemed hypothesis generating).

The only randomized controlled trial of IVC filters occurred in a patient population already receiving anticoagulation [13]. The trial randomized 400 patients to receive anticoagulation and IVC filter placement, versus anticoagulation alone. Patients were followed up with routine physical exams, plus timed V/Q scans (first between days 8 and 12, then at 3 months, and one year). Incidence of PE in this study was reduced in the filter+anticoagulation group at day 12, but this difference lost statistical significance at 3 months and one year. Furthermore, the incidence of DVT and lower extremity edema was increased in the IVC filter group. There was no difference in mortality between the two groups. However, this study did not address the group of patients most often instrumented with IVC filters – those with a contraindication to anticoagulation.

To date there has been no study of the traditional use of these filters (ie, patients with a known contraindication to anticoagulation, but with established DVT or PE). Such prospective data is needed for an intervention with questionable effect on outcome measures and substantial morbidity and mortality.

Study design and statistical analysis

The proposed study is a randomized controlled clinical trial of IVC filters in patients with a contraindication to anticoagulation.

Patients will be randomized to each group in strata of age, ensuring the same number of patients from each quartile of age between 18 and 85, and no crossover between study groups will occur.

The study will enroll 320 patients in total, 160 in an arm assigned to receive an IVC filter, and 160 in an arm assigned to receive close clinic followup alone. The analysis proposed is of proportions of a categorical variable using the chi-squared

distribution. The study is powered to detect a difference of 10% in rate of pulmonary embolism in 1 year (the natural history data, derived from surgical patients, suggests a rate of 15% pulmonary embolism, and prior studies of filters estimate a rate of 5% pulmonary emboli during variable followup). 157 patients in each group would be needed to demonstrate this effect with a power of 80% at a p-value of 0.05.

Study procedure

Followup would proceed for 1 year. The studies to be performed (aside from routine clinical management) include

a) IVC filter placement, in patients randomized to this arm. This procedure involves venous access through a large caliber vein (usually femoral vein). After access, a guidewire is inserted, a filter advanced over the wire, and expanded in the IVC. The patient is provided light sedation through the procedure and discomfort during the procedure is minimal. The entire procedure takes on average 1 hour including time for premedication and insertion of the filter.
b) Followup V/Q scans. Patients are injected with a small amount of tagged radiotracer and a gamma camera is used to take snapshots of blood perfusion to each lobe of the lungs. Similarly, an inert gaseous radionuclide is inhaled by the patient and a camera used to take snapshots of ventilation. Mismatch between the two pictures are used in the diagnosis of pulmonary embolism. Although the procedure uses radioactive materials, the total amount of radiation exposure is extremely low. There is minimal discomfort to the patient aside from venous access for administration of contrast. The procedure can be performed in two phases over the course of one hour, in general.
c) Followup lower extremity venous ultrasound studies. An ultrasound machine is used to examine the deep venous structures in the lower extremities. Ultrasound is non-invasive, well-tolerated imaging modality. A probe is placed on the legs and compressibility of the veins is demonstrated. There is minimal discomfort during the procedure and it takes less than an hour to complete in entirety.

Purely for the purposes of the study, IVC filter placement would occur once, after randomization. V/Q scans would be completed at 3 month intervals during followup, as well as lower extremity ultrasounds at 3 month intervals. These studies would not be a part of usual clinical followup.

Patients would also undergo frequent clinical assessment with their primary care physician for history and physical exam, with close eye on signs and symptoms of DVT or pulmonary embolism. If in the treating physician's opinion there are such signs, a repeat V/Q scan or CT angiogram (per physician's preference) would be obtained, and if positive, at the physician's discretion, the patient might be removed from the trial and anticoagulation started (if benefits of this outweigh the initial risks). These assessments with the patient's PMD would occur every week during the first two weeks, then every two weeks for a month, every month for 3 months, and then every two months for the remainder of the followup period. These frequent assessments would be performed (more frequently than usual for these patients) due to the absence of protection from PE and the greater risk in these patients, in order to preserve patient safety.

Medical device

The IVC filters are the only medical device employed in this study; there are numerous models that are commercially available, safe and efficacious as highlighted above in the Study Purpose and Rationale section. These are widely used across the nation in routine clinical practice. The individual choice of type of IVC filter is left to the discretion of the performing physician (usually an interventional radiologist) at each institution.

Study subjects

Inclusion criteria involve patients aged 18 to 85 years of age, with known lower extremity DVT by lower extremity ultrasound and no history of prior PE. These patients should, in the estimation of the treating physician, have a contraindication to anticoagulation that precludes its use.

Baseline lab results would be drawn only to assess candidacy for IVC filter placement (these would include standard coagulation studies, platelet count, and estimation of renal function) – if these are outside normal limits, the patient may be excluded from the study or medications/blood products may be administered to allow safe placement of the filter.

No significant radiation exposure will be incurred during the study (aside from possibly a chest x-ray along with VQ scan). The radiation exposure incurred here is minimal and will be disclosed to subjects on consent form.

Recruitment

Recruitment would be performed by publicly disseminated information to housestaff and treating physicians at the participating institution via email, flyer, and postings at nursing stations. Patients would not be directly contacted. The treating physician must agree that the patient is suitable for the study and ascertain that the patient is willing to discuss the study with investigators.

All data would remain confidential and there are no conflict of interest involved in the study.

Location of study

The study would be conducted at CPMC and Cornell medical center to facilitate subject recruitment, and will be conducted at the hospital inpatient treatment centers.

Risks/benefits

The utility of IVC filters in patients not given anticoagulation is not presently known. The study thus potentially provides a great benefit to society in avoiding many unnecessary IVC filter placements. There is a risk that placement of IVC filter may promote DVT formation or that the patient may have a complication as result of filter placement. There is also a roughly 20-30% chance of symptomatic DVT or lower

extremity edema from filter placement over the first year. Similarly, since IVC filters are currently standard of care for patients with a contraindication to anticoagulation, if the patient is not randomized to filter placement, they may not receive the protective benefit of filter placement and experience PE. A conservative estimate of risk of PE over the first year may be up to 10% (compared with roughly 5% in filter patients). There may be significant post-thrombotic syndrome with skin changes and lower extremity edema in both treatment arms. However, these patients would be closely followed with periodic clinical assessment to ensure prompt treatment in the event of PE or symptomatic DVT.

Citations

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