THROMBOLYTIC THERAPY FOR ARTERIAL DISEASE

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Pearls

1. Patient workup and evaluation is key to a successful intervention while limiting complications. In addition to physical exam and laboratory evaluation, review of prior imaging studies and surgical interventions is important to understanding the etiology of the occlusion and to guide therapy.
2. Use of arterial thrombolysis should be avoided in patients with evidence of irreversible limb or bowel ischemia.
3. Catheter directed thrombolysis for treatment of acute peripheral arterial occlusive disease compares favorably with surgical intervention with regards to technical success, patency rates and limb salvage.
4. Patients with duration of symptoms less than 14 days have lower amputation rates and shorter hospital stays with catheter directed thrombolysis.
5. Patients with embolic or thrombotic arterial occlusions without a source or evidence of ongoing thrombosis despite appropriate therapy should be worked up for hypercoagulable states.
6. Factors favoring successful thrombolysis include acute thrombus, short occlusion, intact runoff and absence of hypercoagulable state.
7. Despite its short half life and high affinity for bound plasminogen, t-PA has a second, latent half life of 1.3hrs and can cause a systemic lytic state through binding with fibrin degredation products.
8. Arterial access sites are the most common site of significant hemorrhagic complication during thrombolysis. Careful attention to initial arterial access with use of ultrasound guidance can minimize vessel trauma and decrease access site complications.
9. When using t-PA for thrombolysis, sub-therapeutic heparin dosing is most appropriate.
10. Use of standard order sets will improve patient care and ensure appropriate monitoring of the patient during thrombolysis.

Since its initial description, the use of catheter directed thrombolysis (CDT) has grown to include a wide variety of interventions. CDT and mechanical thrombolysis are used in acute and chronic peripheral arterial occlusive disease (PAOD), deep vein thrombosis (DVT), visceral and mesenteric interventions, as well as stroke. While the choice of agents available for thrombolysis, and their application to arterial intervention have evolved over time, there are basic principles of patient selection and techniques that promote a successful intervention. The following is a review of the available fibrinolytic agents, patient selection and workup, procedural techniques and post procedural care to maximize patient outcomes.

Clotting cascade

Through activation of both the intrinsic and extrinsic clotting pathway, the common result is conversion of prothrombin to thrombin. Thrombin converts soluble fibrinogen to fibrin which then binds with platelets and blood cells to form thrombus. During this process plasminogen is bound to the thrombus. It is the bound plasminogen that is the target of thrombolysis. Through activation of bound plasminogen to plasmin by thrombolytic agents, thrombus is broken down. While bound plasminogen is the target of thrombolytic agents, the activation of free circulating plasminogen can lead to a systemic lytic state.

Choice of Thrombolytic Agents

Tissue Plasminogen Activator (t-PA) – Most commonly used agent for arterial thrombolysis since withdrawl of urokinase from the United States market in 1998. In addition to its wide availability it is chemically identical to endogenous t-PA and is a fibrin specific agent that preferentially activates fibrin bound plasminogen. Although t-PA has a higher affinity for bound plasminogen then urokinase and r-PA, it can still cause systemic fibrinogen depletion when bound to fibrin degredation products. t-PA is cleared by the liver with a half life of 5 minutes, however there is a latent second half life of 1.3hrs which can result in plasminogen activation for significant durations after the procedure.

Urokinase (UK) – Urokinase directly activates plasminogen to plasmin but has low fibrin affinity and can cause a systemic lytic state. Urokinase has a half life of 15 minutes and is metabolized by the liver.

Retaplase (r-PA) - Reteplase is a mutant form of t-PA with a slightly longer half life of 13 minutes. It has a lower fibrin affinity with theoretical increased risk of hemorrhagic complications but has similar ability to activate circulating plasminogen through its affinity for fibrin degradation products.

Tenecteplase (TNK) – Genetically engineered variant of t-PA with a longer half life (20 minutes), increased fibrin specificity and decreased inhibition by PAI-1 (plasminogen activator inhibitor-1). TNK may preserve cirbulating fibrinogen, plasminogen and antiplasmin with resulting decreased risk of systemic lysis.

Pre-procedure evaluation of patient with acute ischemia

Initial Evaluation

The goal of arterial thrombolysis is to restore flow to a vascular territory in a timely fashion while minimizing complications either from the occlusion or the therapy used to treat it. When evaluating a patient with limb ischemia it is essential to determine the duration of symptoms and whether the limb is viable, threatened, or irreversibly ischemic. Threatened limbs are characterized by slow but intact capillary filling, mild muscle weakness and incomplete sensory loss whereas the presence of paralysis and total anesthesia is characteristic of irreversible ischemia. A thorough history and physical exam is key to patient selection, with special attention to possible contraindications to thrombolysis. Review of the patient's past surgical history and imaging studies will help to identify the etiology of the ischemia and elucidate anatomic issues which may affect the treatment plan.

The history and physical exam have two primary aims: First, querying symptoms relating to the presence and severity of ischemia, and obtaining background information (such as a history of claudication, recent vascular intervention/surgery or cardiac arrhythmias) which may give clues as to the etiology of the occlusion. The presence of significant concurrent peripheral and cardiac disease is also important, as it can contribute to morbidity and mortality in these patients. The abruptness and time of onset of the pain, its location and intensity, as well as change in severity over time, should all be explored. The duration and

intensity of the pain and presence of motor or sensory changes are very important in clinical decision-making and urgency of revascularization. For example, thrombolysis may be less effective for extremity thrombosis of >2 weeks duration compared with more acute thrombosis.

Pre Procedure Imaging

While a thorough pulse examination will help establish the level of occlusion, non-invasive imaging to include CT, MR, PVR, segmental pressures and duplex can be used to determine the level of occlusion and help plan the intervention. The main disadvantage of CT in acute ischemia is the requirement of iodinated contrast in a patient who may require additional contrast during revascularization. The main disadvantage to MR is that it can be time consuming and may delay treatment.

Embolic ischemia

Acute non-traumatic arterial occlusion can be categorized as embolic or thrombotic. The majority of emboli originate in the heart due to atrial fibrillation, prosthetic valves, ventriculomegally or ventricular aneurysms. Non cardiac sources include aneurysms, ulcerated plaque, or sequlae of prior intervention. Excluding the carotid circulation, most emboli are seen in the lower extremities primarily in the ileofemoral distribution, with less than 25% involving the upper extremities, renal, or mesenteric arteries. In contrast to the lower extremities, upper extremity emboli are better tolerated owing to the collateral blood supply of the arm. In the upper extremities, tissue loss is usually seen only when there is distal embolization.

Thrombotic occlusion

Acute arterial thrombus usually occurs in significantly diseased vessels or in patients with surgical bypass grafts. The patient may report a long or progressive history of extremity/vascular symptoms with sudden exacerbation. Patients with acute ischemia secondary to thrombus who have no definite source, or have ongoing arterial thrombosis despite anticoagulation, should be worked up for a hypercoagulable state. Acute thrombosis in a patient with long standing ischemia may be better tolerated due to collateralization, and these patients may present remotely from the acute event.

Mesenteric/Visceral:

Acute mesenteric ischemia is a potentially devastating and life threatening emergency resulting from an acute decrease in mesenteric blood flow. A variety of manifestations exist but the most common is embolic occlusion of the SMA. Other etiologies include venous thrombosis and non-occlusive ischemia (i.e. low cardiac output). Acute occlusion is tolerated poorly due to lack of collateral circulation. The classic presentation is acute abdominal pain out of proportion to physical exam in a patient with vascular, thrombotic or cardiac risk factors. Nausea, vomiting, and bloody diarrhea may also be present. The development of peritoneal signs is an indication of bowel infarction and necessitates surgery. Therefore any intervention should be planned in consultation with a Vascular or General Surgeon. CT angiography is an excellent imaging modality to demonstrate the occlusion and may demonstrate other etiologies of the patient’s abdominal pain.

Thrombolytic Technique

Vascular Access:

Access site complications are the most common cause of hemorrhagic complications during thrombolysis. Therefore, ultrasound guided access of the common femoral artery is recommend to ensure single stick access within the target vessel, and to minimize arterial trauma. Typical access is in the right common femoral artery but consideration should be given for upper extremity access, i.e. in patients with upper extremity thrombus or with a history of aorto-bifemoral bypass.

A vascular sheath should be used to minimize trauma to the vessel from multiple catheter exchanges. Using a long vascular sheath should be considered if thrombolysis is performed over the bifurcation as this allows angiography to be performed through the sheath with the catheter in place. A baseline angiogram with runoff should be performed for comparison purposes.

Delivery of the Thrombolytic Agent

After initial angiography, the thrombus can be crossed with a wire which allows the operator to determine the likelihood of successful thrombolysis. If the guide wire passes easily, the clot is immature and will probably lyse. If the guide wire does not cross the lesion easily it is most likely mature clot and complete lysis may not be achieved.

There are many techniques described in the literature for delivery of thrombolytic agents; however, few comparison studies are available. The most common method for thrombolysis is continuous infusion. An infusion catheter, with multiple sideholes, is placed over the guide wire directly into the thrombus (along the entire course of the thrombus if possible). A bolus dose may or may not be given followed by infusion of the lytic directly into the clot for several hours. This method increases the surface area for enzymatic lysis, theoretically speeding the lysis process. Various catheter lengths can be used along with a variable number of side holes. If longer infusion lengths are necessary, coaxial catheters and infusion wires can be used. Another method, stepwise infusion, employs an end hole catheter placed at the proximal aspect of the clot which is gradually advanced as the clot dissolves. In addition, pulse spray technique can be used to lyse clot in a single intervention.

Monitoring of Patient During Thrombolysis

The patient should be admitted to the intensive care or a step down unit to allow for frequent monitoring of the patient. Standard order sets can be employed to improve patient care and appropriate monitoring during thrombolysis. The patient's nurse should be educated regarding the patient's clinical status, expected clinical course, thrombolytic used, and potential complications. The nursing staff should be aware of catheter locations, their respective infusion rates and that any adjustment in infusion or change in patients clinical status should be communicated to the physician immediately. The patient's access site and symptomatic extremity should be checked at least every hour to evaluate for bleeding and extent of revascularization. Due to the risk of intracranial hemorrhage, neurological checks are also prudent.

The patient may be placed on a clear liquid diet during infusion and made NPO 6 hours prior to the follow-up lysis check procedure. They should not receive intramuscular injections of medications and new arterial access should not be attempted while thrombolysis is ongoing.

Laboratory monitoring of thrombolysis is highly variable, however, one should consider monitoring a complete blood count and fibrinogen levels frequently. The infusion dose is usually halved if the fibrinogen drops < 150 and stopped if the fibrinogen drops < 100 due to the risk of spontaneous bleeding. Additionally, consider monitoring creatinine if large doses of iodinate contrast are used or the patient has renal insufficiency.

Endpoints

Thrombolysis is usually continued for 4-12 hours at which time the patient is scheduled for a lysis check. Thrombolysis may be continued until the extremity demonstrates signs and symptoms of improved flow (decreased pain, improved warmth, improved pulse) or to a max dose of tPA=40mg. Improvement in arterial circulation is readily assessed given that the vast majority of patients with acute limb ischemia present with no pedal Doppler signals, or with a severely depressed Ankle-Brachial-Index (ABI). Therefore, any improvement in these parameters during thrombolysis suggests successful intervention. Clinical evaluation of the patient during lysis can be complicated by transient worsening of limb pain which is seen as the thrombus is broken down and distal embolization occurs.

Thrombolytic therapy is terminated when there is evidence of recanalization. However, on repeat angiogram, lysis may only be 90-95% complete, and the residual disease may be treated with thrombectomy, angioplasty or stents depending on location and the underlying disease state of the vessel. Thrombolysis therapy should be terminated if there is no significant thrombolysis after a max tPA dose of 40mg.

All patients should be treated with heparin or lovenox in the immediate postoperative period. This should be followed by warfarin, usually for 3–6 months or longer. Patients with thromboembolism will need long-term anticoagulation, from years to life long. However, there are no clear guidelines regarding duration of therapy. The risk of recurrent limb ischemia is high during the follow-up interval; therefore, prolonged warfarin therapy is an appropriate strategy, despite the cumulative bleeding risk. It is important to seek the source of embolism after revascularization, whether cardiac or arterial, but in many cases no source is identified. Certainly, if long-term anticoagulation is contraindicated due to bleeding risk factors, platelet inhibition therapy should be considered.

Outcomes and Complications of Thrombolysis

Acute Limb Ischemia – Thrombolysis versus Surgery

In the STILE trial, patients with symptom duration of less than 14 days had lower amputation rates and shorter hospital stays with trends toward fewer perioperative complications. Amputation rate benefit of the thrombolysis cohort was sustained at 6 months. Patients with chronic ischemia had lower morbidity with surgical intervention. The TOPAS trial also evaluated thrombolysis with UK versus surgery in patients with acute arterial ischemia and found comparable outcomes for both arms, but patients who received thrombolysis had fewer subsequent surgical interventions.

Thrombolytic Therapy in SMA Occlusion

Treatment of acute embolic or thrombotic occlusions of the mesenteric vessels is an option if patients are diagnosed early and have no evidence of bowel necrosis or distal occlusion. Multiple case reports and small series have discussed the use of thrombolysis combined with adjuvant interventions such as suction embolectomy or angioplasty. Patients must be closely monitored for progression of symptoms with subsequent need for surgical embolectomy. The most recent review of the literature concluded that although no firm evidence that benefit from thrombolysis exists, it has the potential to quickly restore flow and obviate the need for surgery.

Comparison of thrombolytic agents

Direct comparison between the available thrombolytic agents is complicated by the varied delivery techniques and dosing regimens described in the literature. Within the thrombolysis arm of the STILE trial there was no difference in efficacy or bleeding complications between tPA and UK. In studies directly comparing the use of tPA to UK there is a trend towards faster lysis with tPA but overall no increase in overall clinical success. Bleeding complications are similar between tPA and UK despite increased affinity of tPA for bound plasminogen. Increasing the dose of thrombolytic may increase the speed of lysis, but overall efficacy is not increased and there are more bleeding complications.

Complication Rates with Thrombolysis

The most feared complication during thrombolysis is intracranial hemorrhage (ICH), which is reported to occur in approximately 1-2.5% of patients. The most common complications include arterial access site hematomas, symptoms of distal embolization which is often transient, and GI bleeding. Hematuria should prompt a workup for genitourinary tumors. Data regarding the use of heparin during thrombolysis is varied with some studies showing an increase in bleeding complications and others showing no correlation. Restricting the use of heparin during thrombolysis to sub-therapeutic doses is recommended to minimize bleeding complications. Bleeding complications at the arterial access site may be increased by underlying vascular disease, patient body habitus or inability to hold still.

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