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REVIEW ARTICLE

Determinants of Catheter-Directed Thrombolysis Success

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ABSTRACT:

BACKGROUND: Globally, deep vein thrombosis (DVT) is a serious health issue. Although the risk of pulmonary embolism after DVT is widely known, the long-term vascular consequences of DVT are frequently overlooked, expensive to treat, and can significantly impair quality of life. A minimally invasive endovascular procedure called catheter-directed thrombolysis (or CDT) is performed in conjunction with anticoagulation. By preventing valvular damage and lowering clot burden, CDT reduces the incidence of PTS. Under fluoroscopy, a catheter is inserted straight into the thrombosis site, and a relatively small dosage of thrombolytic drug is then slowly and continuously infused. Acute symptoms are relieved more quickly with CDT because it recovers venous patency more quickly than anticoagulation. Because they provide extra mechanical thrombectomy or ultrasound-enhanced thrombolysis at the moment of catheter placement, adjunctive CDT methods have grown in popularity among interventional radiologists. These pharmacomechanical CDT (PCDT) methods may shorten treatment durations and lower related medical expenses.

CONCLUSIONS: CDT may reduce the likelihood of PTS and/or lessen the intensity of PTS symptoms if they do occur, however it is most beneficial for patients with extended life expectancy and acute thrombosis affecting the iliac and proximal femoral veins (iliofemoral DVT). Additionally, CDT is crucial for patients with severe DVT symptoms or acute limb-threatening venous blockage.

KEYWORDS: Catheter; deep vein thrombosis; thrombolysis; catheter-directed thrombolysis; post-thrombotic syndrome.

INTRODUCTION:

A thrombus is made up of platelets and red blood cells that have been twisted together by fibrin strands. On top of an atherosclerotic plaque, thrombus formation most frequently occurs. In 1933, Tillett and Garner reported the lytic properties of streptokinase (SK), produced by group C β-hemolytic streptococci [1]. The first intravascular infusion of thrombolytic medications was documented by Tillett (1955); these medications were originally administered intravenously [2].

Since the 1980s, many thrombolytic medications have been administered to treat thromboembolic conditions, including peripheral venous and arterial occlusions, myocardial infarction, stroke, and pulmonary embolism. Catheter-directed thrombolysis, or CDT, was first used in the 1990s. The potential benefits of catheter-directed thrombolysis, which is believed to cause less intimal damage than surgical embolectomy, include the restoration of input and outflow for bypasses and patency for small arteries that are inaccessible. Additional benefits include lowering the extent of amputation and the need for major surgery right away. Only patients with viable or somewhat endangered limbs should undergo catheter-directed thrombolysis because these patients need to be able to maintain a prolonged duration of ischemia while the pharmacologic medication is being administered. Numerous endovascular therapeutic options are available to patients with acute limb ischemia. Catheter-directed thrombolysis can be administered as a medication alone or in

combination with a mechanical thrombectomy or thrombus aspiration device [3].

Thrombolytic medications start the fibrinolytic system by converting plasminogen into plasmin, which breaks down fibrin and disintegrates clots. All thrombolytic medications are plasminogen activators rather than direct fibrinolytics.

Initially, thrombolytic medications were not targeted to fibrin; instead, they increased the blood's plasminogen and caused it to attach itself to fibrin. The ability of more modern thrombolytic medications to distinguish between circulating and fibrin-bound plasminogen and avoid plasminemia is referred to as fibrin specificity [4].

Thrombolytic medications fall into many types. The source of the agent, its mechanism of action (enzymatic versus nonenzymatic), its ability to exhibit increased enzymatic activity on fibrin or cell surfaces, or its manufacture can all be used to create different classification schemes. The generational classification of thrombolytic medications is displayed in:

Streptokinase

The exogenous plasminogen activator known as streptokinase (SK) was first identified in 1933 and was isolated from βhemolytic streptococci. The body produces antibodies against streptokinase because of this antigenic material, which is not specific to fibrin.

SK has been associated with febrile reactions and inconsistent efficacy due to the formation of antigen antibodies.

Furthermore, compared to other medicines, SK can result in significant bleeding issues. As a result, SK is rarely used in contemporary practice [5].

Urokinase (UK)

The UK was initially identified and distinguished from human urine in 1951; in 1952, it was given a name. Urine was used to create the original formulations. In the early 1970s, tissue culture techniques were established as a viable manufacturing process in the United Kingdom. UK is not specific to fibrin; rather, it is an agent that directly activates plasminogen into plasmin. Because it frequently occurs in human plasma at low concentrations, UK is less antigenic than SK. When administered intravenously, UK has a half-life of 13 minutes and is primarily removed from the bloodstream by the liver. Despite having a poor affinity for fibrin and fibrinogen, naturally occurring UK is used as a therapeutic thrombolytic agent. Currently, it is manufactured in the United States under the Kinlytic brand (ImaRx Therapeutics, Inc., Tucson, AZ) [6].

The literature provides significant support for the use of UK for catheter-directed thrombolysis in cases of arterial and venous thromboembolic illness. Other types of UK-related medications are not yet on the market, despite having undergone clinical testing. Recombinant UK (r-UK) and recombinant prourokinase are two examples of these (r-pro-UK) [5].

Tissue Plasminogen Activator (Alteplase)

Among other bodily cells, vascular endothelial cells release human tissue plasminogen activator (t-PA), which is expected to maintain control over the thrombotic system. Altereplase, often known as recombinant t-PA (rt-PA), is the commercially available type of t-PA made via recombinant technology. t-PA functions as a weak plasminogen activator when fibrin is not present.

Recombinant t-PA has been widely used to treat acute myocardial infarction (AMI) since the UK withdrew, and it has more recently become the most often used lytic agent in the peripheral circulation. When given intravenously, the medication can now be used to treat a number of illnesses, such as stroke, pulmonary embolism, and AMI. Central venous catheters can also be used with it. Like all lytic drugs, rt-PA is considered off-label when used for catheter-directed lysis of arterial and venous thrombus [5].

The German company Boehringer Ingelheim and the American company Genentech worked together to develop alteplase, or rt-PA. Alteplase is a drug that is sold under the names Actilyse (Boehringer Ingelheim, Ingelheim, Germany) in Europe and Activase and Cathflo (Genentech, Inc., South San Francisco, CA) in the United States [6].

Reteplase

Recombinant plasminogen activator Compared to t-PA, (r-PA) has a longer half-life and a lower affinity for fibrin, is the result of altering the t-PA molecule. But it's still regarded as

specific to fibrin. It has been proposed that r-PA's decreased fibrin affinity accounts for its superior clot penetration than rtPA. While r-PA's comparatively low fibrin affinity enables it to penetrate deeper and expose more thrombus to the lytic agent, rt-PA's significant fibrin affinity or binding qualities are hypothesized to prevent this agent from reaching into the deeper layers of the thrombus [7].

As a result, it has been proposed that lysis happens more quickly with r-PA than rt-PA. It has not been determined how this variation affects the medication's catheter-directed delivery for peripheral thromboembolic diseases. As of right now, r-PA is only authorized for use in the intravenous treatment of AMI. It is not authorized to use the drug for peripheral lysis administered by catheter [5].

The company that first created retinplase, Boehringer Ingelheim, merged with Roche. Reteplase is sold under the brand name Rapilysin (Roche, Basel, Switzerland) overseas [6].

Tenecteplase

Tenecteplase (TNK-t-PA), a bioengineered triple point mutation of t-PA, has been shown to have better fibrin specificity and a longer half-life than rt-PA. There are currently limited reports and poorly monitored trials on the usage of this medicine in the peripheral system [5].

Determinants of catheter-directed thrombolysis success

The efficiency of catheter-directed thrombolysis is influenced by a number of patient-related parameters, including as the age of the thrombus, distal outflow, graft vs. native artery status, graft condition, and volume. Technique-related factors include whether to use a bolus approach or a simple infusion for the thrombus, whether to treat the underlying lesion to prevent re-thrombosis, and whether to provide the infusion directly into or near the thrombus [8].

Type of thrombus

Arterial or graft occlusion can be caused by either thrombus or plaque occlusion. A guidewire can easily pass through an occlusion that is thrombus-dominant, whereas an arteriogram cannot be passed through an occlusion that is plaque-dominant. (Guidewire traversal test). According to research, when a guidewire can pass through a blockage, When it works, catheter-directed thrombolysis is 90–100% effective; when it doesn't, it's just 10–16%. Therefore, whether the lytic agent is delivered into the thrombus depends on guidewire penetration [9].

Correction of underlying lesion

Although lysis of the thrombus is the immediate objective, long-term success necessitates treating the underlying lesion that created the obstruction. Patency rates following catheter-directed thrombolysis are low for patients whose underlying lesions were either overlooked or not treated (7–37% at 6–12 months), but they are high for those whose lesions were discovered and treated (80–86% at 6–12 months) [8].

Bolus technique versus simple infusion

The rate of issues increases with infusion duration, for instance, from 4% after 8 hours to 34% after 40 hours. The infusion period is decreased, for example, from 27 hours to 14 hours, when an agent is administered as a bolus injection instead of a conventional infusion.

Additionally, pulse-spray thrombolysis methods, which employ a similar bolus technique, offer a better rate of effective lysis at 24 hours (78%) than slow infusion alone, which yields a lysis rate of less than 50% [10].

Directed versus systemic therapy

It has been observed that while treating acute limb ischemia, intrathrombus lytic therapy has a lower risk of adverse effects than systemic therapy. By injecting the thrombolytic agent directly into an existing thrombus, CDT allows for the reduction of thrombolytic drug dosages and the avoidance of the hazards of systemic hemorrhage [8].

Evidence from randomized trials

The Rochester trial

Both surgery and catheter-directed urokinase infusion were used to treat acute limb ischemia in the Rochester trial. Between the two groups, there was no appreciable difference in limb salvage at one year. Urokinase caused more bleeding than surgery. Most significantly, when compared to surgery, urokinase significantly reduced mortality at one year. Surgical mortality brought on by cardiopulmonary issues during the procedure. It appears that a significant risk of fatal complications resulted from sending patients with severe limb ischemia directly to surgery without allowing them time to prepare [11].

TOPAS trial

Patients in the TOPAS (Thrombolysis or Peripheral Arterial Surgery) experiment were randomly assigned to have either surgery or recombinant urokinase; nevertheless, neither the amputation-free survival at six months nor a year nor the amputation rate at discharge differed. respectively. On the other hand, individuals randomly assigned to urokinase therapy experienced a marked rise in bleeding issues; yet, urokinase-treated patients needed fewer surgeries [12].

STILE trial:

In the STILE trial, thrombolysis and surgery were compared for lower extremity ischemia. In this trial, patients were randomly assigned to receive either surgery or thrombolysis with urokinase or rt-PA. The data were combined to compare thrombolysis and surgery in general because the clinical outcomes of the rt-PA and urokinase groups were similar. It was found that patients with acute ischemia (lasting between 0 and 14 days) Patients were divided into two groups based on the duration of symptoms (more or less than 14 days), and those who got thrombolysis had shorter hospital stays and better amputation-free survival. Surgical revascularization was proven to be a safer and more successful treatment option than thrombolysis for patients whose acute ischemia continued longer than 14 days [13].

Plate et al study

121 individuals suffering from acute limb ischemia were randomly assigned to receive either low-dose tPA infusion or high-dose recombinant tPA by pulse spray. Every patient was also given heparin. Negative events were comparable. It took less time to finish the high dose tPA regimen (18 vs. 25 hours). despite the fact that the total dose was larger (36 mg vs. 13 mg). Despite no change in total thrombolysis, the greater dose decreased the number of treatments needed at one month or one year and enhanced the chance of early reperfusion. The success rates matched the findings of the Rochester, TOPAS, and STILE trials, and there was no difference in the groups' mortality, amputation rates, or amputation-free survival [14].

Contraindications

Acute limb ischemia necessitating immediate surgical intervention, cerebral hemorrhage, protracted bleeding, Catheter-directed thrombolysis is absolutely contraindicated in cases of compartment syndrome. Recent gastrointestinal bleeding (10 days), an intracranial tumor, recent neurosurgery or ocular surgery within the last 3 months, intracranial trauma within the last 3 months, significant nonvascular surgery or trauma within the last 10 days, and a documented recent cerebrovascular incident are a few examples of relative contraindications. Analytical reports of absolute and relative contraindications are shown in Table 4. However, systemic thrombolysis research provides the majority of the evidence for these contraindications. Catheter-directed pharmacologic fibrinolysis has been shown to result in fewer bleeding events, therefore treatment decisions should always be based on the patient's risk-benefit analysis [15].

Absolute

Instant bleeding once hemostasis fails or uncontrollable, violent hemorrhage. Brain hemorrhage. The development or progression of compartment syndrome. Severe limb ischemia, where the treating physician determines that surgery is necessary right away.

Relative

A significant trauma or surgery within the last ten days. Diastolic or systolic blood pressure of 110 or 180 mmHg indicates uncontrolled hypertension; noncompressible vascular puncture.

A history of intracranial trauma within the last three months; an intracerebral tumor; recent eye surgery; surgery within the last three months; excessive contrast sensitivity or allergy; recent stomach bleeding (10 days); or a documented cerebrovascular incident (including any recent transient ischemic episodes).

Recent noncompressible or internal hemorrhage. Diabetic hemorrhagic retinopathy. Hepatic failure, particularly in the presence of coagulopathy. Pregnancy/postpartum conditions. Bacterial endocarditis.

Patient preparation

Preprocedural Laboratory Investigations

Acid-base equilibrium markers, platelets, renal function, partial thromboplastin time, clotting profile (prothrombin time and International Randomized Ratio, or INR), and baseline hemoglobin and hematocrit should all be measured in a laboratory [15].

Preprocedural Imaging

For patients with clinically confirmed acute lung injury (ALI), preoperative duplex ultrasonography is a rapid, radiation-free, and reasonably priced imaging method that can be employed as a first-line diagnostic tool. It gives details regarding the degree of ischemia and the volume of blood supplying the foot. Furthermore, Numerous essential pieces of information for creating a treatment plan can be obtained via CT angiography. The location of the occlusion, collateral flow, distant runoff paths, and the actual occluded length should all be assessed to determine whether a percutaneous intra-arterial thrombolysis is recommended [15].

Preprocedural medications

It has been demonstrated that administering unfractionated heparin intraperitoneally (IV) at therapeutic dosages can prevent thrombus formation and reduce ALI patients' morbidity and mortality rates [15].

Technique

Throughout the procedure, vital indicators such as the brachial blood pressure, oxygen saturation, heart and respiratory rates, and continuous electrocardiogram (ECG) should be tracked[15].

Vascular access: The results of any prior noninvasive arterial evaluation will be used to determine the best vascular access. An ultrasound-guided puncture would be beneficial for a patient who presents with a limb that has weak or nonexistent pulses. Depending on the patient's anatomy (body mass index, vascular features, and patency) and the site of the lesion, an antegrade, retrograde, or crossover arterial approach should be used. When treating ALI, most physicians prefer a contralateral approach. Ipsilateral femoral access increases the risk of hemorrhagic complications and wound infection if an open vascular procedure is necessary following thrombolysis. To lower the risk of problems from the puncture, it is recommended to employ a single-wall puncture. Once inside, a short 6 Fr sheath is presented. When the sheath is positioned, In order to see the run-off arteries, the blocked artery's outflow, and the shape and size of the lesion, vascular access is established and a high-quality diagnostic angiogram should be acquired. This diagnostic imaging is necessary for both the design of the percutaneous technique and the final bypass surgery following a failed effort at revascularization [6].

Guidewire Traversal Test: In this test, the guidewire passes through and over the lesion. This latter test, called the "guidewire traversal test," is based on the fundamental premise that a fresher, more current network should be easier to pass through than an older, more structured one. A positive guidewire traversal test is a reliable predictor of procedural technical success, according to published data. Soft Teflon-coated steel guide wires are perfect for thrombotic occlusion of sick arteries because they are less likely to break. If the blocked segment is easily penetrated by a soft guidewire, the clot is likely to respond favorably to thrombolysis [16].

Inserting the catheter: if a guide wire can be inserted into a runoff channel and through the obstruction, a multi-side hole It is recommended to insert an infusion catheter that extends the entire occlusion. The two most popular models are the Unifuse (Angiodynamics, Queensbury, NY) and the Cragg-McNamara (Irvine, CA: Micro Therapeutics Inc.). Both have many side holes

that the injected solution is forced to depart via by an end-hole occlusion mechanism [16].

Infusion techniques:

a. There are two types of regional intra-arterial infusion: selective infusion, in which nonselective infusion, in which the catheter is positioned proximal to the occlusion without entering the lesion, and the catheter tip is inside the proximal portion of the occlusion. These are the accepted local pharmacological thrombolysis medication delivery methods.

b. The procedure called "intrathrombus infusion" entails injecting the fibrinolytic chemical inside the obstruction by putting the catheter tip into the thrombus. This is the most commonly employed method, and it has been asserted that a full thrombolysis is accomplished and that higher benefit is typically observed following distribution into the thrombus.

c. Intrathrombus bolusing, often referred to as lacing, intends to introduce a concentrated thrombolytic agent into the thrombus for the first time in order to saturate the drug-occluded vascular region with the subsequent initiation of a continuous infusion.

d. Intrathrombus is typically administered by continuous infusion Continuous drug delivery can be accomplished by connecting a pump to the catheter.

a. Stepwise infusion is the method used to first infuse the fibrinolytic material near the thrombus's proximal region. The operator moves the catheter "step by step" toward the distal portion of the lesion as the thrombus starts to disintegrate.

f. Graded infusion is a time-dependent agent administration technique where a high dose of medication is given early in the process to increase procedure speed.

g. The pulse-spray technique, sometimes referred to as forced periodic infusion, is a vigorous intrathrombus medication infusion intended to increase the drug's distribution surface and cause thrombus laceration. Shorter procedure times should result from improved fibrinolytic drug penetration, enzymatic action, and concentration inside the blocked lesion. By beginning the catheter tip just above the distal end of the occlusion and leaving a small portion of the occlusion untreated, any potential distant microembolic episodes are avoided. Every 20 to 30 seconds, a syringe is used to manually inject the lytic agent with force. The least labor-intensive and most successful infusion strategy should be considered high-dose intrathrombus bolusing or lacing followed by low-dose continuous infusion [17].

Dosage:

Alteplase: continuous infusion at 0.5–1 mg/h (maximum total infusion); bolus at 2–5 mg.

Reteplase: continuous infusion between 0.25 and 0.5 U/h (20 units maximum); bolus between 2 and 5 U.

Tenecteplase: a continuous infusion of 0.125 to 0.25 mg/h after a bolus of 1 to 5 mg [16].

Adhesive bandages and skin sutures should be used to secure infusion catheters and sheaths. The patient may be admitted to an intensive care unit or an intermediate care unit following the placement of the catheter.

If it is safe to do so, periodic angiograms should be performed to check for lysis during the infusion, ideally every 10 to 12 hours. This will make it possible to repair any accidental catheter misplacement and modify the infusion rate according to the lytic process. The patient should always be constantly watched to identify any possible bleeding symptoms. It is important to compare regular hemoglobin and hematocrit measurements to baseline values. Through the sheath, heparin can be administered intravenously or intraarterially. It is not advised to administer a bolus at the beginning of thrombolysis. It is advised to increase PTT to only 1.25 to 1.5 of control using an infusion rate. Subtherapeutic dosages are used by the majority of practitioners, which range from 200 to 500 U per hour. Heparin and alteplase should not be mixed in the same syringe or catheter because this can cause precipitation. As long as alteplase is administered by a catheter placed into or close to the lesion and heparin is administered via a sheath placed proximally in the same artery, this does not exclude the administration of these two drugs concurrently [15].

End points:

Total lysis with flow restoration, total lysis of any susceptible thrombus with ongoing blockage from embolized plaque or organized thrombus, failure of thrombolysis

progression, and stopping thrombolysis for any reason—whether due to a serious side effect, exceeding the recommended time or dosage limitations, or progressing into irreversible (category III) ischemia—are one of the procedural outcomes of thrombolysis. The underlying lesions causing arterial or graft thrombosis are revealed by complete thrombolysis. To maximize the long-term effects of thrombolysis, these should be repaired by open or percutaneous surgical methods, according to the data that is now available. To get rid of any remaining thrombolysis-resistant material, a balloon embolome or aspiration thrombectomy might be required. Treatment should be stopped if a trial end-hole catheter infusion does not permit guide wire traversal at the site of occlusion [16].

After the sheath is removed, think about utilizing a vascular closure device or manual compression[15].

Definitions:

The most recent SIR Standard of Practice Committee Quality Improvement Guidelines, the TASC II Inter-Society Consensus for Peripheral Arterial Disease, and the SIR Reporting Standards for the Treatment of Acute Limb Ischemia are the primary sources of the following definitions and threshold values [15].

Technical success : the thrombus or embolus's complete or nearly complete (95% by volume) destruction to restore antegrade blood flow (70% threshold).

Clinical successes : reducing the need for amputation or additional surgical intervention, or alleviating the symptoms of ischemia that are present right away.

Overall clinical success : The patient should recover from the symptoms of ischemia and reach @ least one of his preocclusive clinical baseline values following the removal of the thrombus and the completion of supplemental operations.

Thrombolysis failure : is defined as the lack of clinical success [18].

Complications

1-Hemorrhagic

The most serious of the hemorrhagic effects is intracerebral hemorrhage (ICH). If treatment is delayed, additional severe bleeding, such as retroperitoneal or gastrointestinal hemorrhage, may occur and prove deadly. The site of the artery puncture is where the majority of the bleeding during CDT takes place. Pericatheter bleeding, which is typically not severe, can be managed by expanding the sheath or by providing direct pressure. Rarely, an arterial graft or suture may be necessary. Additionally, the thrombolytic infusion can be discontinued until the next planned angiography suite visit [16].

2-Antigenicity Related

Due to its bacterial composition, SK is the most allergic thrombolytic medication. While 1% to 10% of individuals experienced mild allergic reactions, less than 0.01% of cases had life-threatening allergic reactions. Recombinant tissue plasminogen activator (rt-PA) and UK are examples of other thrombolytic drugs that naturally arise in vivo and rarely result in allergy reactions [6].

3-Catheter Related

Catheter insertion for CDT carries the risks of any endovascular surgery, including arterial dissection, aneurysm after catheter removal, and thrombus dislodgment during wire or catheter manipulation with subsequent emboli [6].

4-Embolic

Distant emboli can occur when pieces of a lysed thrombus come loose. When the foot initially recovers clinically and a pulse or Doppler signal is recovered, this problem typically occurs after a period of sudden clinical deterioration brought on by embolism. It most commonly occurs in cases of acute limb ischemia. A quick (2–3 hour) increase in the thrombolytic medication dosage is often sufficient to treat this. If a more severe distal embolization does not go away in a few hours, re-imaging must be done immediately, and the catheter may occasionally need to be moved farther out of the way [6].

5-Reperfusion related

Severe limb edema and abrupt increases in compartmental pressures are two signs of damage to the target limb during reperfusion. Myoglobinuria and increased creatine kinase levels are common signs and symptoms, along with severe pain, hypothermia, and

limb weakness. The peroneal nerve function examination (motor function: dorsiflexion of the foot; sensory function: dorsum of the foot and first web space) should be carried out following the revascularization surgery since the anterior compartment of the leg is the most sensitive. Although the diagnosis can also be verified if the compartment pressure is greater than 30 mmHg, it is mainly based on the clinical indications. If compartment syndrome occurs, surgical fasciotomy is indicated to prevent irreversible soft-tissue and neurological damage [19].

Post procedural medications and follow up:

Aspirin (81 to 150 mg daily indefinitely), clopidogrel (75 mg daily for 6 weeks), or both antiplatelets and DOACs (rivaroxaban, 2.5 mg twice daily) are recommended as post-procedure prophylactics to avoid recurrent thromboses. Patients with embolic origins receive therapeutic heparin infusions until warfarin anticoagulation is no longer effective. Depending on how severe the situation is, treatment for arterial occlusion brought on by occlusive peripheral vascular disease should include yearly or less frequent clinic follow-ups [16].

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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