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Treatment of High-risk Venous Thrombosis Patients Using Low-dose Intraclot Injections of Recombinant Tissue Plasminogen Activator and Regional Anticoagulation

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Abstract

Seven patients with venous thrombosis and contraindications to traditional thrombolytic therapy, consisting of recent intracranial surgery, recent pineal or retroperitoneal hemorrhage, active genitourinary or gastrointestinal bleeding, epidural procedures, and impending surgery, were successfully treated with a modified thrombolytic regimen. To improve safety, prolonged continuous infusions of tissue plasminogen activator (tPA) was eliminated in favor of once-daily low-dose intraclot injections of tPA to minimize the amount and duration of tPA in the systemic circulation, and low-therapeutic or regional anticoagulation was used to reduce anticoagulant risks. These modifications may allow thrombolytic treatment for selected patients with severe venous thrombosis who are deemed to be at high risk.

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Depending on the location or extent of involvement, venous thrombosis can cause severe morbidity and long-term impairment of quality of life if inadequately treated. Unfortunately, venous thrombosis often presents as a comorbid disorder with other conditions such as bleeding or recent or impending surgery that are contraindications to traditional forms of anticoagulation and thrombolytic therapy (1–3).

However, recent clinical and pharmacokinetic studies of thrombolytic therapy with low doses of recombinant tissue plasminogen activator (tPA) delivered once daily by catheter-directed intraclot injection without prolonged infusions of tPA have been shown to be effective, and appear to offer improved safety by reducing the amount and duration of circulating levels of tPA during thrombolytic therapy (4,5). In the present report, seven cases are presented in which this technique, combined with low-therapeutic or regional anticoagulation, was used successfully to treat severe cases of venous thrombosis in patients with contraindications to standard thrombolytic therapy.

Materials and Methods

Patient Presentations

Venous thrombosis developed in the seven patients described here while they were being treated for other disorders (Table 1) at the Clinical Center of the National Institutes of Health, which reviewed and approved publication of this retrospective review. These patients were treated at the request of their physicians because of the severity and potential disability from their thrombosis. The techniques used, and understanding of pharmacokinetics, are based on a recently published thrombolytic trial that used low-dose intraclot injections of tPA (4). Informed consent was obtained from each patient after the risks of bleeding complications of thrombolytic therapy and anticoagulation, and the proposed modifications to treatment to mitigate these risks, were explained. The contraindications to treatment were recent central nervous system surgery, recent pineal or retroperitoneal hemorrhage, active macroscopic urinary tract or gastrointestinal bleeding, and impending epidural or surgical procedures. One patient developed severe headache, nausea, and vomiting 5 days after a neurosurgical operation, and was found to have thrombosis of the straight sinus and left transverse cerebral venous sinus (case 1; Fig 1). The remaining six patients had symptomatic deep vein thrombosis (DVT) of the lower extremities.

Thrombolytic Regimens

The thrombolytic regimen used has been described previously (4–6). Briefly, tPA is administered once per day under fluoroscopic guidance in the radiology department in the time required to “lace” the entire clot by catheter-directed hand injections through pulse-spray catheters in large veins and end-hole catheters in smaller veins. On his ward, the patient continues infusion of anticoagulants, but no additional infusions of tPA.

Anticoagulation Regimens

In patients without known risk factors for bleeding, anticoagulation during thrombolytic therapy is provided by intravenous administration of unfractionated heparin to maintain systemic activated partial thromboplastin times (aPTTs) within 1.5–2.5 times the baseline levels or anti-factor Xa levels of 0.3–0.7 IU/mL (7–9). During thrombolytic therapy for lower-extremity DVT, we use 4-F catheters for intraclot injections of tPA and infuse heparin directly into the thrombosed veins through an ipsilateral 4–5 F retrograde femoral catheter placed after each thrombolytic session to provide continuous anticoagulation. The length of the retrograde femoral catheter is chosen to allow heparin infusion into or just below the

lowest end of the thrombus (eg, popliteal vein in case 6; calf veins in cases 2–5 and 7; Table 1).

When the dose of heparin is adjusted to achieve full systemic anticoagulation (ie, aPTT of 1.5–2.5 times baseline), the anticoagulant level in the local infusion site is usually supratherapeutic because of the lesser dilution of the local blood flow compared with the cardiac output. Conversely, the dose of heparin infused locally can be reduced to maintain therapeutic anticoagulation locally while the systemic anticoagulant level is minimal or subtherapeutic, and this is the basis for regional anticoagulation that can be advantageous when using infusional anticoagulants. In the high-risk cases described here, anticoagulation was adjusted according to assessed risk (Table 2) to maintain systemic anticoagulation in the low therapeutic range (ie, 1.5–2 times baseline aPTT) or in the subtherapeutic range (1.0–1.5 times baseline aPTT or anti-factor Xa levels < 0.2 IU/mL) by using regional anticoagulation. If needed beyond the period of thrombolytic treatments, regional anticoagulation can be provided through 3-F retrograde femoral vein catheters (case 2; Fig 2).

Results

Case 1

A 34-year-old woman with von Hippel–Lindau disease developed severe headache and nausea and vomiting 5 days after surgical resection of a large right cerebellar hemangioblastoma (Fig 1a). Emergency unenhanced computed tomographic (CT) scan showed a ‘dense clot’ sign in the torcular herophili (Fig 1b), and magnetic resonance (MR) imaging confirmed thrombosis of the left transverse sinus and straight sinus (Fig 1e, 1f). After initiation of intravenous heparin anticoagulation, the patient was referred for thrombolytic therapy. At catheterization, only soft, flexible microcatheters (Renegade STC-18; Boston Scientific, Natick, Massachusetts) could be passed easily and safely from the jugular veins and sigmoid sinus to the transverse or straight sinus. By using shapeable 0.014-inch hydrophilic guide wires (Transend EX; Boston Scientific), the microcatheter was directed along multiple paths through the thrombus under fluoroscopic guidance, depositing a total of 6 mg of tPA in the course of 1 hour (Fig 1c). Although symptoms and venographic findings improved the next day (Fig 1d), evidence of residual thrombus prompted a second treatment with 3 mg of tPA, given in the same fashion. The patient's symptoms resolved completely. Oral anticoagulation with warfarin was continued for an additional 3 months, and follow-up MR imaging showed restoration of normal cerebral venous drainage (Fig 1g, 1h).

Case 2

A 57-year-old man with stage IV lymphoma developed DVT of the right leg 2 days before evaluation of severe orthostatic headaches, nausea, and vomiting following multiple intrathecal treatments with methotrexate. On admission, MR imaging examination revealed severe cerebrospinal fluid (CSF) hypovolemia as a result of CSF leakage at lumbar puncture sites, indicating an urgent need for an epidural blood patch to relieve symptoms and reduce risk of spontaneous subdural hemorrhage (Fig 1a–2c). The right leg was markedly swollen with severe pain, and there was cyanotic discoloration during ambulation, suggesting critical venous obstruction. An epidural blood patch was performed and, 1 day later, thrombolytic therapy (three treatments over 3 d with 6 mg, 6 mg, and 4 mg tPA) was begun, with anticoagulation provided by infusion of unfractionated heparin into the peroneal vein of the thrombosed right leg via an ipsilateral retrograde femoral vein catheter. To provide localized and regional anti-coagulation, the femoral—peroneal vein catheter was infused with unfractionated heparin at a rate of 700 U/h, and simultaneous anti-factor Xa measurements

showed a therapeutic level of 0.4 U/mL in the ipsilateral upper superficial femoral vein. A systemic blood sample showed an anti—factor Xa level of only 0.1 IU/mL (therapeutic range, 0.3–0.7 IU/mL). Regional anticoagulation provided through an 80-cm-long, 3-F catheter (Slip-Cath; Cook, Bloomington, Indiana) was maintained for 1 week to minimize risk of dissolution of the blood patch before conversion to systemic anticoagulation with enoxaparin (Fig 1e, 2f). Central nervous system and lower-extremity symptoms resolved, and the patient has been symptom-free for 7 months.

Case 3

A 24-year-old man was admitted for evaluation of Cushing disease 2 months after treatment for pulmonary embolism. Inferior petrosal sinus sampling confirmed a pituitary source of excess adrenocorticotrophic hormone production, and the patient was scheduled for transsphenoidal surgery. Three days before surgery, the patient developed transient signs suggestive of Parinaud syndrome. At approximately this time, coagulation studies indicated that anticoagulation with enoxaparin had been excessive, with anti—factor Xa levels as high as 2.0 IU/mL (therapeutic range, 0.5–1.2 IU/mL) despite accurate weight-based dosing. The patient's ocular symptoms resolved quickly, and anticoagulation was discontinued for transsphenoidal surgery. Retrospective review of MR scans indicated that a hemorrhage had occurred in a pineal cyst that had been missed on initial evaluation. On postoperative day 15, the patient developed painful DVT of the left lower extremity. The patient underwent thrombolytic therapy (four treatments of 6 mg, 4 mg, 6 mg, and 6 mg tPA) with anticoagulation maintained in the low therapeutic range. The thrombus was cleared without complications, and the patient was able to resume ambulation.

Case 4

A 69-year-old man with metastatic and local invasive prostate cancer presented with abdominal pain, fever, gross hematuria, and pyuria 3 weeks following a cystoscopic procedure at another hospital. A CT scan showed air in the suprapubic soft tissue, raising the possibility of Fournier gangrene and prompting surgical exploration. On post-operative day 10, while undergoing bladder irrigations for gross hematuria, he developed severe pain in the left leg and could no longer ambulate. Fifteen years earlier, a Greenfield filter had been implanted for pulmonary embolism, and because of hematuria and the need for urologic procedures, anticoagulation had been discontinued in the year before the current presentation. Ultrasonography (US) and venography revealed thrombosis of the IVC, right iliac vein, and entire deep venous system of the left leg from the common iliac veins to the calf veins (Fig E1, available online at www.jvir.org).

This patient was treated once daily with intracut injections of tPA for 3 days (8 mg, 10 mg, and 9 mg), with regional anticoagulation via infusion of heparin through a retrograde femoral vein—to—infrapopliteal vein catheter in the left leg (infusing 500–700 U/h of unfractionated heparin) to maintain systemic aPTT levels between 40 and 60 seconds (preanticoagulation baseline aPTT, 39 s). Percutaneous bilateral nephrostomy tubes were placed the day after the last tPA treatment without interruption of regional anticoagulation to allow removal of the Foley catheter from the bladder and improve management of urinary incontinence. With clearance of the thrombus, hematuria also resolved (perhaps in part because of the relief of venous hypertension), and the anticoagulation level could be increased to systemic therapeutic levels. The patient was discharged with a prescription for subcutaneous enoxaparin with subsequent conversion to warfarin. There was no further evidence of venous thromboembolism before the patient's death as a result of metastatic prostate cancer 4 years later.

Case 5

A 45-year-old woman with 27-year history of ulcerative colitis developed DVT of the left leg and pulmonary embolism 17 days after a hemorrhoidectomy. Anticoagulation was instituted, but changed her bowel movements from blood-tinged to grossly bloody, along with a three-point decrease in hematocrit level. Anticoagulation was stopped, and a permanent IVC filter was placed. During the ensuing 9 days, swelling and pain increased and the skin became dusky, leading to readmission with a diagnosis of phlegmasia cerulea dolens. Thrombosis had progressed from the deep veins of the left calf to occlude the IVC around the IVC filter as well as down the right common iliac vein. The patient underwent 2 days of catheter-directed continuous infusion thrombolytic therapy with urokinase; there was initial progress, but thrombosis recurred the next day.

The patient was transferred to our hospital and underwent three treatments with low-dose intracut tPA injections (8 mg, 8 mg, and 4 mg) delivered into all thrombosed segments from the calf veins to the IVC and right iliac vein thrombus. Between thrombolytic treatments, the patient received regional anticoagulation via infusion of unfractionated heparin into a 4-F retrograde femoral vein-to-peroneal vein catheter to keep systemic aPTT between 40 and 55 seconds, or 1–1.5 times the baseline value. A prophylactic transfusion of 2 U of packed red blood cells was given, but there was no significant increase in colonic bleeding and no decrease in hematocrit level during thrombolytic therapy. After thrombolytic therapy, the patient was able to ambulate without pain, and the swelling and skin discoloration resolved. However, attempts to increase anticoagulation to systemic therapeutic levels again led to increased colonic bleeding, so the patient was transferred back to her referring hospital, while receiving regional anticoagulation, for a total colectomy. Subsequently, she was able to receive systemic anticoagulation and has remained symptom-free for 7 years.

Case 6

Two days after cryoablation of a renal cell cancer of the right kidney (Fig E2a, available online at www.jvir.org), an 82-year-old woman developed multiple pulmonary emboli. Within 24 hours of anticoagulation, the patient developed flank pain accompanied by a decrease in hemoglobin level from 9.6 to 6.6 g/dL as a result of a retroperitoneal and perinephric hemorrhage (Fig E2b, available online at www.jvir.org), prompting discontinuation of anticoagulation and placement of a removable IVC filter. A thrombus developed at the left common femoral vein site of a temporary 7-F triple-lumen catheter that had been used for the initial attempt to institute anticoagulation and for the subsequent replacement blood transfusions. Serial US examinations over a period of 13 days showed progression of occlusive thrombosis from the left common femoral vein down the superficial femoral vein to the popliteal vein before the patient was referred for thrombolytic therapy. To reduce bleeding risks, the patient was treated with low-dose thrombolytic therapy (two treatments of 6 mg and 4 mg tPA) and regional anticoagulation with unfractionated heparin infusion (at 700 U/h) through ipsilateral retrograde femoral catheters with their distal tips positioned just below the lowest clot in the popliteal vein, which achieved therapeutic anticoagulation (aPTT, 73.4 s; anti-factor Xa level, 0.4 IU/mL) in the left leg while keeping subtherapeutic anticoagulation levels (aPTT, 47.6 s; anti-factor Xa, 0.2 IU/mL systemically). After clearing the thrombus with thrombolytic treatment, regional anticoagulation was continued for IVC filter removal, before gradually increasing anticoagulation to therapeutic levels systemically (requiring 1,000–1100 U/h unfractionated heparin) and conversion to enoxaparin anticoagulation.

Case 7

In a 48-year-old man, left-leg DVT developed 1 week before admission for resection of a painful melanoma metastasis near his right scapula. His surgery was delayed so he could

receive three thrombolytic treatments over a period of 3 days (6 mg, 8 mg, and 4 mg tPA), with full systemic anticoagulation (approximately 1,500 U/h unfractionated heparin) to clear the thrombus. Anticoagulation was then reduced to regional anticoagulation with infusion of 500 U/h unfractionated heparin directly into the left leg (or one third of the systemic dose) during surgery and 12 hours postoperatively, before systemic anticoagulation was resumed. With regional anticoagulation, the surgery was completed uneventfully while preserving the venous patency achieved with thrombolytic therapy. The patient was discharged with a prescription for systemic anticoagulation with enoxaparin, and a repeat US examination 2 months later showed no evidence of residual thrombus.

Discussion

Historically, thrombolytic enzymes have been applied to the problem of vascular thrombosis through three treatment paradigms: (i) high-dose/prolonged infusion in early trials of systemic thrombolysis for DVT; (ii) high-dose/short infusions for arterial thrombosis encountered in acute myocardial infarction and ischemic stroke; and (iii) low-dose/prolonged (intraclot) infusion in catheter-directed continuous infusion thrombolysis for peripheral artery occlusion and DVT. However, all these regimens have been associated with bleeding complications that provided the basis for current contraindication guidelines for thrombolytic therapy (10–12). A fourth treatment paradigm, low-dose/short (intraclot) infusion or injection, became possible with the availability of recombinant tPA. The potential efficacy and safety of this approach can be understood from two key observations made by Agnelli et al (13,14) in the 1980s concerning the use of tPA as a thrombolytic agent: first, unlike urokinase, the thrombolytic effect of tPA continued long after completion of infusion; and second, when using tPA, bleeding risk was lower with shorter infusions. During the past 15 years, clinical trials and pharmacokinetic studies have been conducted that have verified and provided a basis for understanding these observations. Fundamentally, the ability of tPA to exert fibrinolytic action long after injection is completed is based on its ability to bind to fibrin clot, as opposed to other agents that must be continuously replenished as they begin to diffuse out of the thrombus as soon as they are injected. The period of tPA administration each day can be reduced to the time required to lase the targeted thrombus, and additional continuous infusion can be eliminated. This is important because, despite intraclot injection, much of the injected thrombolytic agent enters the systemic circulation to increase circulating levels of the thrombolytic agent as long as these infusions are maintained. In addition, elimination of prolonged continuous infusion allows exploitation of a second important property of tPA—the shortest half-life (approximately 5 min) of available plasminogen activators—to clear any tPA that entered the systemic circulation during injection, within 1 hour after cessation of tPA administration. By reducing dose and eliminating prolonged continuous infusions, pharmacokinetic studies indicate that the amount and duration of excess tPA in the systemic circulation can be reduced (4,5). Therefore, although the risk of thrombolytic therapy cannot be completely eliminated, the period of risk can be shortened to only a small portion of each day by changing the way tPA is administered.

Anticoagulation, which is required to prevent rethrombosis during thrombolytic therapy, must also be carefully managed whenever treating high-risk venous thrombosis because, unlike thrombolytic therapy, this risk cannot be confined to a fraction of a day. For patients who have active bleeding conditions or require surgery, regional anticoagulation can be used to preserve gains from thrombolytic therapy while reducing systemic anticoagulant effects to decrease bleeding risks from remote bleeding or surgical sites. Although this approach appears effective for clearing local thrombus, it must be remembered that only systemic levels of anticoagulation are documented to provide protection against pulmonary embolism. Regional anticoagulation might not provide protection against pulmonary embolism when

there are other sites of thrombosis—recognized or unrecognized—other than the area of treatment, and these additional sites of thrombosis could be a potential site for new pulmonary emboli. For this reason, the contralateral extremity is screened for DVT with US, and sequential compression devices are used on both extremities: to augment thrombolysis in the thrombosed side, and for prophylaxis on the unaffected side.

The cases described here suggest that, by making substantial reductions in dose and modifications of the way thrombolytic and anticoagulant therapy is administered, thrombolytic treatment can be made safer to allow treatment of some patients who are at high risk. Although a purely thrombolytic approach was used in this report, the implication is that some patients at high risk could also be treated with those pharmacomechanical approaches that adhere to the use of low tPA doses (< 10 mg/d) and carefully adjust anticoagulation levels commensurate with bleeding risks. However, until experience is obtained with many more patients, we do not advocate treatment of all patients with venous thrombosis deemed to be at high risk. Instead, each patient should be evaluated individually based on severity and potential morbidity of the thrombosis to have a sufficiently favorable risk/benefit ratio to warrant this more aggressive therapy. Within these limitations, we report these cases to outline a rational approach for thrombolytic treatment for other physicians who may be faced with the challenge of managing serious venous thrombosis in high-risk cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

aPTT	activated partial thromboplastin time
CSF	cerebrospinal fluid
DVT	deep vein thrombosis
tPA	tissue plasminogen activator

Figure 1.

Images from case 1. A 34-year-old woman with Von Hippel–Lindau syndrome developed dural sinus thrombosis 5 days after resection of right cerebellar hemangioblastoma. **(a)** MR scan shows right cerebellar hemangioblastoma (arrow) with adjacent edema that was successfully resected. **(b)** Noncontrast CT scan 5 days later shows dense clot sign (arrow) in torcular herophili. **(c)** Venogram through 3-F microcatheter shows acute thrombus filling and distending left transverse sinus (arrows). Six milligrams of tPA was injected into thrombus over a period of 1 hour. **(d)** Repeat venogram 1 day later shows improved flow and reduction in thrombus. Residual thrombus (arrows) was treated with a second dose (3 mg) of tPA. **(e–h)** Gadolinium-enhanced MR blood pool images before thrombolytic therapy **(e, f)** show absence of flow in straight and left transverse sinuses. **(g, h)** Images at 3-month follow-up show flow restored in left transverse and sigmoid sinus (arrows, **g**) and straight sinus (arrows, **h**).

Figure 2.

Images from case 2. A 57-year-old man presented with right-leg DVT and a CSF leak that required epidural blood patch. (**a–c**) Development and resolution of CSF hypotension/hypovolemia is documented on axial CT images through the midthalamus obtained several months before diagnosis (**a**), at time of diagnosis (**b**), and 1 week after blood patch (**c**). Signs of CSF hypovolemia include subdural effusions, possibly with hemorrhage (arrows, **b**), decreased size of lateral ventricles (asterisk, **b**), and sulcal effacement (normal sulci indicated by arrows, **a** and **c**). (**d–f**) DVT thrombolysis and regional anticoagulation were performed. Right-leg DVT involved calf veins and the popliteal and femoral vein, stopping at the junction with deep femoral vein (arrow, **d**). (**e, f**) After thrombolytic therapy, regional anticoagulation was continued for 1 week via infusion of unfractionated heparin into a retrograde 3-F catheter (arrows, **e**) with its tip in the distal peroneal vein (arrow, **f**) at a rate of 700 U/h. Anti-factor Xa levels determined by a catheter inserted via jugular vein access show a therapeutic level (0.4 IU/mL) in the proximal superficial femoral vein (**e**), whereas systemic levels drawn from the right atrium were subtherapeutic (0.1 IU/mL). Note the chronic phlebitic changes revealed in peroneal veins (absence of valves and presence of narrow and irregular luminal changes) after thrombolysis.

Table 1

Demographic, Clinical, and Treatment Details

Case No./Age (y)/Sex	Primary Disorder	Site of Venous Thrombosis	Risk Factors	TPA Doses (mg)	Anticoagulation Regimen
1/34/F	VHL syndrome	Straight sinus, left transverse sinus	Large right cerebellar hemangioblastoma 5 d after resection	6/3	Low therapeutic
2/57/M	Lymphoma with CNS involvement	Right femoral to calf veins	Epidural blood patch for CSF leak	6/6/4	Regional
3/24/M	Cushing disease	Left femoral to calf veins	Pineal cyst hemorrhage, transsphenoidal surgery	6/4/6/6	Low therapeutic
4/69/M	Metastatic and invasive prostate cancer	IVC, bilateral iliac veins, left femoral to calf veins	Gross hematuria, open surgical debridement	8/10/9	Regional
5/45/F	Ulcerative colitis for 27 y	IVC, bilateral iliac veins, left femoral to calf veins, PCD	Chronic colonic bleeding	8/8/4	Regional
6/82/F	Renal cell cancer	Left common femoral to popliteal vein	Retropertitoneal bleeding after cryoablation, anticoagulation	6/4	Regional
7/48/M	Metastatic melanoma	Left femoral to calf veins	Surgical resection of soft tissue mass, right scapula	6/8/4	Regional during surgery

CNS = central nervous system, CSF = cerebrospinal fluid, IVC = inferior vena cava, PCD = phlegmasia cerulea dolens, VHL = Von Hippel-Lindau.

Table 2
Adjusting Anticoagulation Regimen to Risk Stratification

Risk Level	Description	Systemic aPTT Target (× Normal)	Systemic Anti-Factor Xa Target (IU/mL)	Local PTT in DVT Extremity (× Normal)	Local Anti-Xa in DVT Extremity
Low	No increased bleeding risks	1.5–2.5	0.3–0.7	> 2.5 [‡]	> 0.7 [‡]
Moderate	Can receive systemic anticoagulation, but not overanticoagulation	1.5–2.0 [*]	0.3–0.4 [*]	> 2.5 [‡]	> 0.7 [‡]
High	Systemic anticoagulation contraindicated	1.0–1.5 [*]	0.1–0.2 [‡]	1.5–2.0 [*]	0.3–0.4 [*]

Anti-Xa = anti-factor Xa, aPTT = activated partial thromboplastin time, DVT = deep vein thrombosis, PTT = partial thromboplastin time.

^{*} Low therapeutic level.

[‡] Subtherapeutic level.

[‡] Supratherapeutic level.