Local and systemic thrombolytic therapy for acute deep venous thrombosis

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ABSTRACT

This article presents a review of the treatment of lower-extremity deep venous thrombosis (DVT) with systemic and catheter-directed thrombolysis (CDT) and percutaneous mechanical thrombectomy (PMT). Standard treatment including anticoagulation therapy and compression stockings may not be entirely adequate, because a significant proportion of patients eventually develop post-thrombotic syndrome (PTS). Thrombolytic agents might offer a potential advantage because they cause faster and more complete clot resolution, which may reduce or prevent residual vein stenosis and valve damage.

Thrombolytic therapy results in greater lysis, but also in higher complication rates than does anticoagulation alone. Major bleeding occurs in 11% of patients treated with thrombolytic therapy. The incidence of PTS tends to be lower in patients treated with thrombolytics. However, several methodological flaws limit the conclusions with respect to reduction in PTS.

No adequate randomised controlled trials have been performed comparing CDT or PMT with conventional therapy. Given the current data, thrombolytic treatment, CDT or PMT should not be applied except in extraordinary cases. First, the long-term effectiveness in terms of reducing PTS, although possible, remains uncertain. Second, the risks of thrombolytic therapy and PMT are higher. Third, current conventional therapy is relatively inexpensive, convenient and safe.

INTRODUCTION

Deep venous thrombosis (DVT) is an important disease with serious clinical sequelae. Its annual incidence is one per 1000 patients, but the incidence increases with age. The therapeutic goals for treating the patient with acute DVT include prevention of pulmonary embolism (PE), prevention of recurrent thrombosis and preservation of venous valve function. Success in the achievement of these clinical goals will minimise the morbidity and mortality of PE and will diminish the long-term sequelae of the post-thrombotic syndrome (PTS).

The current standard of care includes systemic anticoagulation with unfractionated heparin (UH) or low-molecular-weight heparin (LMWH) followed by oral anticoagulants. Such a regimen, however, does not promote lysis to reduce the thrombus load, nor does it contribute to restoration of venous valve function. Anticoagulation alone, therefore, might not sufficiently protect the limb from PTS. Catheter-directed thrombolysis (CDT) and percutaneous mechanical thrombectomy (PMT) have been proposed as a new treatment for patients with DVT. Application of these techniques could potentially result in a lowering of the PTS syndrome by preservation of the venous valve function.

This article provides a comprehensive review of the literature evaluating the efficacy and safety of systemic thrombolysis and CDT and PMT in patients with DVT, with the focus on PTS.

CLINICAL CONSEQUENCES OF DVT

In the acute phase, venous obstruction leads to impaired venous return and therefore most patients experience leg
Pathophysiology of PTS

PTS refers to a spectrum of post-thrombotic chronic venous diseases attributable to venous hypertension and stasis affecting a limb in which a DVT has previously occurred. The spectrum of PTS can encompass several combinations of symptoms in various degrees of severity. These include a chronic feeling of leg heaviness, leg aching and venous claudication, oedema, venous varicosities, and chronic trophic skin changes ranging from hyperpigmentation to frank nonhealing ulceration to fibrotic scarring.8,10

The pathophysiology is thought to be multifactorial, including venous obstruction and valvular incompetence; inflammatory damage caused by the thrombotic process and subsequent scarring is a likely mechanism. Valvular incompetence develops most frequently in segments affected by thrombosis and seldom develops in segments initially free of thrombus, with total thrombotic occlusions resulting in the highest risk for subsequent valve insufficiency.9,11 Unlike valvular incompetence, which can develop shortly after acute DVT, the onset of dermatological manifestations of PTS tends to be much more delayed, with symptoms usually occurring within two years after the initial DVT episode.9,15,16

Conventional Anticoagulant Therapy

Current conventional treatment of DVT consists of anticoagulation and the use of compression stockings. Anticoagulation therapy consists of subcutaneous LMWH or intravenous UH initially, followed by oral anticoagulants. LMWH is continued for at least five days and coumarin therapy for at least three months, the total duration varying according to underlying risk factors for recurrence. In general, this approach to treatment is effective and safe in most patients.4,17-20 Anticoagulation therapy has no direct thrombolytic effect, and thrombus recanalisation largely depends on the effectiveness of the endogenous fibrinolytic system and the initial thrombus load. The risk of major complications in large randomised trials of LMWH is low: fewer than 5% have recurrent venous thromboembolic events, fewer than 2% have clinically significant bleeding, and fewer than 2% have symptomatic PE.4,18,21,22

No major randomised trials of treatment in the initial phase have included PTS as a primary endpoint. Adjunctive treatments such as compression stockings have been shown to reduce the incidence of the PTS by 50%.23 However, a risk of moderate to severe PTS of about 10% is reported in patients who receive appropriate anticoagulation and compression therapy. Proponents of thrombolytic therapy argue that this rate is high enough to warrant interventional treatment strategies.24,25

Methods

Nonconventional thromboablative types of therapy in acute DVT include systemic thrombolytic therapy, catheter-directed regional thrombolytic therapy (CDT) and percutaneous mechanical thrombectomy (PMT).

A study using the electronic literature (PubMed) was performed using the keywords deep venous thrombosis, thrombolysis, catheter-directed thrombolysis and mechanical thrombectomy. Literature was reviewed up to January 2004. Eighteen controlled trials were identified comparing systemic thrombolytic therapy with standard treatment.46-48

Twelve studies compared streptokinase with heparin (468 patients), two trials compared urokinase with heparin (117 patients) and four trials compared tissue plasminogen activator with heparin (150 patients). There were eight trials reporting the incidence of PTS after thrombolysis. Only one trial compared catheter-related thrombolysis with standard anticoagulant treatment.49 There are no trials comparing PMT and conventional therapy. For this reason also non-randomised trials evaluating CDT and PMT are discussed.

Systemic Thrombolytic Therapy

The rationale for an aggressive thromboablative approach in acute DVT might be twofold. In the short term, it consists of preventing PE, achieving rapid reduction of pain and swelling of the involved leg, and, when applicable, preventing or allowing more effective management of phlegmasia cerulea dolens and venous gangrene. The long-term endpoint of treatment of an acute DVT episode relates mainly to the prevention of PTS. Rapid thrombus resolution may offer a potential for prevention of PTS based on the known favourable effect on the preservation of venous valvular function. It might also prevent the development of obstructive disease because it prevents organisation of an occlusive thrombus, which leads to downstream venous hypertension.

Tables 1 and 2 show a summary of the randomised controlled trials that have compared lytic therapy with standard heparin in the acute phase and in the long-term. It has to be noted that there are no trials comparing thrombolytic therapy with LMWH.
Short-term efficacy

The results of randomised controlled trials assessing the short-term efficacy of streptokinase, urokinase and rt-PA compared with heparin are summarised in Table 1.26-30,32,33,35-41,48

Most of these trials demonstrate that systemic thrombolytic therapy more often leads to complete or partial resolution than does heparin therapy. Complete lysis occurred in 26 to 67% and 0 to 22% of patients, respectively. Although at least some degree of lysis has been reported in 50 to 70% of patients treated with thrombolysis, no single study has had sufficient power to prove its efficacy in comparison with standard anticoagulation. Previous studies suggest that newer and nonocclusive thrombi are more likely to undergo successful lysis when compared with older and occlusive thrombi.49

Long-term efficacy

Eight studies (173 patients) were identified comparing lytic therapy with UH in which long-term efficacy was assessed.29,38,39,44-48,50 An additional study has been published in which patients were randomised to one of several thrombolytic regimens or UH (250 patients).39 Duration
of follow-up varied from two months to six years. Most of the studies invariably did not use a validated scoring system for assessment of PTS, but relied on clinical assessment. These assessments were performed at different intervals in each study and were not always blinded to the treatment allocation, and in some of the trials assessments were limited because of significant numbers of patients lost to follow-up.

Aggregating the data from these studies, the long-term risk of developing PTS in the thrombolytic groups is 0 to 80%, whereas in the unfractionated heparin group it is 40 to 90%.

The largest study demonstrated relatively poor functional results (low reflux pathology) in heparin control patients, giving rise to more symptoms of PTS. They also observed that patients affected by thromboses in the pelvic region seemed to benefit less from lytic treatment, which is known due to early collateral formation. Lysis medication may, thereby, fail to reach thromboses in pelvic veins due to circulatory bypasses.

Complication rates
Potential complications of thrombolytic therapy include bleeding and PE. In a meta-analysis Lensing and Hirsh reported major bleeding events in 13.2% of patients treated with systemic streptokinase or recombinant tissue plasminogen activator (rt-PA) compared with 3.5% of patients treated with heparin. Systemic treatment with rt-PA resulted in one major haemorrhage for every 15 patients treated. Aggregating the data across studies in table 1 shows that 9% (range 0 to 38%) of patients receiving thrombolytic agents have a major bleed compared with only 5% (range 0 to 22%) of patients receiving UH. The wide range can be explained by more aggressive diagnostic and follow-up protocols in earlier studies and by the variable definitions of ‘major haemorrhage’. There was no significant difference in bleeding risk according to route of administration or dose. Haemorrhage following thrombolytic therapy most commonly occurs at vascular puncture sites, although spontaneous haemorrhage, especially gastrointestinal, retroperitoneal and intracranial, may also occur. Older age, a higher body mass index, and the performance of pulmonary angiography have been identified as significant predictors of bleeding.

Before initiating thrombolytic therapy, patients should undergo a thorough evaluation to elicit factors that increase the risk of major haemorrhage. A striking study is that of Markel et al, in which only 15 (7%) of 209 patients with DVT exhibited no contraindications for thrombolytic treatment.

Risk of PE while receiving the thrombolytic agent is a theoretical concern. Lensing and Hirsh demonstrated that in contrast to the haemorrhagic risk, the incidence of clinically significant PE was quite low. However,
Two groups of techniques have been developed.53 The most common agents used are urokinase and rt-PA. Complications.

**Failure of lytic therapy**
Reasons for lytic therapy to fail include extensive DVT in which the plasminogen activator does not contact the clot; old, organised thrombus; inadequate fibrinolytic response; and premature termination of lytic infusion.49 The success of lysis is related to the amount of fibrin bound to plasminogen within the thrombus and, therefore, correlates with the age of the thrombus. Treatment of patients whose thrombus is more than one week old is less likely to be successful. Unfortunately, clinicians cannot accurately determine the age of the clot but must rely on patient’s symptoms, which in many cases are not closely related. In most centres only patients with extensive venous thrombosis are treated with thrombolytic therapy. Because these patients frequently have iliofemoral venous thrombosis, they are likely to have the poorest long-term outcome. This patient selection process represents an inherent bias in evaluation of outcome based on therapy. In such patients, the venous system is frequently occluded by the thrombus and there is no blood flowing through the veins involved.

**Catheter-directed thrombolysis**
Local-regional thrombolytic therapy has emerged in the past decade as a possible superior approach, allowing delivery of the pharmacological thrombolytic agent directly into the venous thrombus. This technique has evolved to address the main limitations of systemic thrombolysis: namely, unpredictability of thromboablative effect, high risk for haemorrhagic complications and high rate of patient exclusion from therapy because of the need to adopt stringent selection criteria to avoid haemorrhagic complications. The most common agents used are urokinase and rt-PA. Two groups of techniques have been developed.31 The first is catheter-directed thrombolysis, which relies on administration of the thrombolytic agent directly into the clot with use of a variety of infusion catheters or wires and from various approaches. The second is flow-directed regional thrombolytic therapy, which is based on the direct regional infusion of concentrated thrombolytic agent from an ipsilateral dorsal foot vein into the deep venous system. Although the latter approach has the advantage of allowing regional thrombolysis of the crural veins, which are typically difficult to access with use of catheter-directed techniques, it is more time-consuming and requires larger doses of thrombolytic than catheter-directed protocols.53,54 Postprocedurally, all patients should be started on a long-term anticoagulation regimen with a target INR of 2.5 to 3.0 for three months unless contraindications exist.

Only one randomised controlled study comparing CDT vs conventional therapy has been performed.49 This trial is not reliable, since only 35 of 207 patients were included in the study. For this reason also the nonrandomised trials are being discussed (table 3).55-69 Several small series have demonstrated a high efficacy rate, with reported complete or substantial recanalisation rates of 60 to 83%.61-63,66,68,69 The success rate of CDT appeared to be increased by adjunctive procedures such as angioplasty, stent placement and mechanical thrombectomy. So far, the largest published experience with this approach in lower-extremity DVT has been from the Venous Thrombolysis Registry, which reported a collective multicentre experience with 287 patients (903 limbs) in whom one-year follow-up was available.60,70 The location of DVT was in the iliofemoral segment in 71% of patients with involvement of the inferior vena cava (ICV) in 21%. Complete thrombolysis was achieved in 31% of cases, whereas partial (>50%) thrombolysis with restoration of forward flow was achieved in 52% of patients. Complications included an 11% incidence of major bleeding that required transfusion of blood products and a 16% incidence of minor bleeding. The risks of intracranial haemorrhage and death were 0.2 and 0.4% respectively. Although the overall rate of valvular reflux on follow-up was 58%, valvular reflux occurred in only 28% of patients in whom complete thrombolysis was achieved. Comerota et al demonstrated that patients treated with CDT had better functioning and well-being, compared with patients treated with anticoagulation alone.71 Despite the possible promise of the data, the Venous Registry was not a randomised trial and lacked a control group treated with standard anticoagulation. Therefore the data cannot be used to establish a new standard of care for the treatment of acute DVT.

The most common complication during CDT is bleeding, either local from the access site or remote from onset of a systemic thrombolytic state. Reported rates of major bleeding requiring transfusion vary widely (0 to 25%), depending on the dosing regimen, duration of infusion, extent of concomitant anticoagulation and the specific

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Schweitzer’s data suggest that there is an increased risk as 4.5% of patients suffered a PE while on lytic therapy.59 Furthermore the prolonged infusion times (two to three days) typically required to treat iliofemoral DVT can be difficult to tolerate for some patients, and complications may become more frequent with longer infusion durations. Also the cost of thrombolytic infusion, multiple venograms, repeat laboratory studies and the intensive care unit monitoring required for thrombolytic therapy in many centres is substantial.

Table 3: Comparison of systemic and regional thrombolysis.

Catheter-directed thrombolysis has evolved to allow regional thrombolysis of the crural veins, which are typically difficult to access with use of catheter-directed techniques. It is more time-consuming and requires larger doses of thrombolytic than catheter-directed protocols.53,54 Postprocedurally, all patients should be started on a long-term anticoagulation regimen with a target INR of 2.5 to 3.0 for three months unless contraindications exist.

Janssens, et al. Local and systemic thrombolytic therapy.
thrombolytic agent used. It has been shown that prolonged infusions are associated with increased frequency of haemorrhagic complications, with intracranial bleeding occurring in as many as 3% of patients receiving systemic treatment.72,73 Other complications include PE, infections and sepsis. The need for ICV filtration during endovascular management of extensive DVT has been debated. Furthermore, although the medical literature indicates that CDT of proximal venous thrombosis is quite successful on a short-term basis, it does not address the long-term issue PTS prevention.

**PERCUTANEOUS MECHANICAL THROMBECTOMY**

Since outcomes might be optimised with maximum clot removal, and because thrombolytic agents are less effective on subacute or chronic thrombus, PMT has emerged as a potentiator of pharmacological therapy. In addition, some patients with absolute contraindications to pharmacological thrombolysis may be candidates for mechanical lysis. Many devices have been developed recently, most using one of the following mechanisms to remove clot: rheolytic aspiration, mechanical aspiration or ultrasonic lysis. Some devices are designed to use both mechanical fragmentation and pharmacological lysis.74,75 The use of PMT might offer advantages in DVT. Flow can be established more rapidly, even though achieving complete or near-complete thrombus ablation often requires a combination of mechanical and pharmacological techniques. Furthermore it can be used primarily in situations in which rapid venous decompression and restoration of flow is crucial.76

### Technique

The extent of thrombus is determined by imaging with ultrasound and computed tomography. Cross-sectional images also reveal other pertinent anatomical factors such as May-Thurner syndrome, osteophytes, tumours or masses. Access is obtained peripheral to the thrombosed segment and an anterograde approach is used. A single wall puncture of the ipsilateral popliteal vein is made under ultrasound guidance. If the popliteal vein is thrombosed, the proximal posterior tibial vein may be cannulated. Venograms are performed to delineate the extent of thrombus. Combined mechanical thrombectomy and pharmacological lysis can take place.
There are no controlled studies comparing PMT and conventional anticoagulant treatment. Recent trials evaluating PMT are described in table 4.77 To 80. It has to be noted that these studies evaluated only a small selection of patients. Potentially significant complications with PMT are PE and valve damage.74,78,81,82 Because the goal of treatment is to improve quality of life by increasing the extent of lysis while minimising complications and cost, prospective randomised studies comparing PMT vs conventional treatment should be performed. Patients should be followed for at least two years to detect valve insufficiency and signs and symptoms of PTS.

**CONCLUSION**

It is difficult to draw definitive conclusions based on the published data on thrombolysis, since studies have included relatively small numbers of patients, a range of thrombolytic regimens, and varying durations of follow-up. Furthermore, outcomes, including the degree of clot lysis and the incidence of the PTS, have been assessed using a range of modalities.

When compared with anticoagulation, thrombolytic therapy for DVT leads to superior short-term venous patency and a higher risk of major haemorrhage but no difference in the rates of PE and mortality. It is not clear how many patients with DVT are actually candidates for thrombolytic therapy.

One study, for example, found that 194 out of 209 patients (93%) had a contraindication for thrombolysis, most often recent surgery. 54 Elshawary et al. also included only 35 out of 207 patients. 43

Based on this review, there is no advantage in using any thrombolytic agent over another, or using local vs systemic administration. There is a need to further evaluate CDT and PMT. CDT instils the thrombolytic agent directly into the thrombus and can be combined with mechanical removal of thrombus using a suction catheter or stenting of a residual clot. This type of therapy has been suggested as an alternative to standard therapy based on a better lysis rate of 60 to 80%. Unfortunately, because these rates are derived from case series and patient registry data, they are susceptible to selection or reporting bias and the true benefit may be lower. Furthermore, the bleeding rate with this therapy is considerably higher than rates with conventional therapy, even with this select population. It should be noted that, although CDT and PMT techniques offer advantages of allowing faster and more complete clot clearance, which translate into remarkably faster symptom resolution, to date there have been no randomised trials comparing this form of therapy with conventional anticoagulation in terms of prevention of PTS. Until such trials are conducted or more clinical experience suggests the superiority of these evolving treatment modalities in acute DVT, it is important to continue to restrict aggressive endovascular interventions to situations in which compelling indications exist (table 5).

With respect to the patient characteristics, we need to know which patients benefit most from aggressive therapy. Perhaps the younger, healthier patient, who will face many years of decreased productivity if severe PTS develops, is the main candidate. In addition, young, healthy patients possibly have a decreased risk of bleeding related to thrombolysis.

Future research using randomised controlled studies should focus on the following key questions:

- Does thromboablative therapy improve long-term outcomes of DVT with a favourable risk-to-benefit ratio and, if so, which patients are most likely to benefit in the long term?
- What is the precise role of CDT or PMT in the treatment of VTE, particularly the use of a low-dose thrombolytic agent in conjunction with mechanical clot disruption to minimise bleeding in patients with high risk?

### Table 4

**Percutaneous mechanical thrombectomy for DVT**

<table>
<thead>
<tr>
<th>AUTHOR (YEAR)</th>
<th>N</th>
<th>MEAN FOLLOW-UP (MONTHS)</th>
<th>DEVICE</th>
<th>THROMBOLYTIC</th>
<th>THROMBOLYTIC</th>
<th>PE</th>
<th>STENT</th>
<th>MAJOR BLEEDING</th>
<th>DEATH</th>
<th>PTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kasirajan (2001)</td>
<td>17</td>
<td>9</td>
<td>Angiojet</td>
<td>9</td>
<td>10 (59)</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>Delomez* (2001)</td>
<td>18</td>
<td>29.6</td>
<td>Amplatz/-</td>
<td>0</td>
<td>15 (83)</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vedantham (2002)</td>
<td>28</td>
<td>**</td>
<td>28 UK/ rt-PA</td>
<td>17 (62)</td>
<td>0</td>
<td>18</td>
<td>3 (14)</td>
<td>0</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Vedantham (2004)</td>
<td>23</td>
<td>19.8</td>
<td>Helix</td>
<td>23</td>
<td>19 (83)</td>
<td>0</td>
<td>23</td>
<td>1 (6)</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

PE = pulmonary embolism; PTS = post-thrombotic syndrome; UK = urokinase; rt-PA = recombinant plasminogen activator; ND = not determined;

*only mechanical treatment after failure of conventional heparin after 48 hours + cava filter, **different devices were used: Amplatz, Angiojet, Trerotola and Oasis.

According to the current data, thrombolytic treatment for DVT should not be applied except in extraordinary circumstances. First, the long-term effectiveness in terms of reducing PTS, although possible, remains uncertain. Second, the risks of thrombotic therapy are high. Third, current conventional therapy is relatively inexpensive, convenient and safe.

REFERENCES


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**BOEKAANKONDIGING**

**Richtlijn Behandeling van tabaksverslaving**

Met jaarlijks meer dan 20.000 doden door tabaksgebruik, is roken in Nederland een volksgezondheidsprobleem van de eerste orde. Dertig procent van de bevolking rookt nog. De winst van stoppen met roken is niet alleen voor de maatschappij als geheel, maar ook voor elke individuele roker, aanzienlijk. De meeste rokers blijken graag te willen stoppen. Velen hechten daarbij grote waarde aan advies van een medicus.

De richtlijn sluit aan op het principe van eenmalige en korte ondersteunende interventies en op het model van ‘stages of change’. De minimale-interventiestrategie (MIS) kent in ons land als toegepaste methode een zekere traditie waar het gaat om het bieden van ‘stoppen met roken’-adviezen: diverse beschikbare programma’s zijn hierop gebaseerd. In de richtlijn wordt de MIS echter als een methode gezien en wordt een andere indeling gehanteerd dan in de traditie van de MIS. Een belangrijk uitgangspunt in richtlijnen voor de medische praktijk is dat optimaal gebruik wordt gemaakt van beschikbare voorzieningen. In deze richtlijn is dat ook het geval waar het gaat om een consistente motiverende interventie bij rokers. Een bijzonder punt in deze richtlijn is echter het positioneren van gespecialiseerde voorzieningen. Deze, in het Verenigd Koninkrijk en de Verenigde Staten bekende, voorzieningen zijn in ons land op beperkte schaal voorhanden. Met het lanceren van deze richtlijn wordt bepleit dat zulke faciliteiten op grotere schaal beschikbaar komen. Daarmee zal het realiseren van de inspanning om via individuele interventies het tabaksgebruik terug te dringen, aan slagkracht winnen.

In de gezondheidszorg doen zich op grote schaal contacten met individuele rokers voor. In deze richtlijn worden die momenten als aanleiding beschouwd om stoppen met roken aan de orde te stellen. Voor de medische praktijk en de daarbij betrokken hulpverleners biedt deze richtlijn mogelijkheden om tabaksverslaving effectief te behandelen. Hoewel primaire preventie met name voor jongeren van groot belang is, komt in deze richtlijn alleen de behandeling van tabaksverslaving in de zorg aan de orde.

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