The changing role of thrombolytic therapy in the management of acute deep vein thrombosis

Mahmood K Razavi[†] *& Charles P Semba*

[†]*Author for correspondence*
Cardiovascular-Interventional Radiology, Stanford Medical Center, H-3600, 300 Pasteur Drive Stanford, CA 94305, USA
Tel.: +1 650 725 5202
Fax: +1 650 725 0533
mrazavi@stanford.edu

Endovascular therapy for lower extremity venous obstruction is emerging as a viable adjunct to anticoagulation in selected patients with acute and chronic deep vein thrombosis. While the standard of care for deep vein thrombosis remains centered upon heparinoids and warfarin therapy, there is growing evidence to support early intervention with thrombolysis to preserve valve function and restore patency of the vein. The focus of this review is to provide an overview of endovascular techniques for the treatment of acute lower extremity deep vein thrombosis as an adjunct to routine anticoagulation.

Deep vein thrombosis – problems with current management strategies

Deep vein thrombosis (DVT) remains a common cause of morbidity with an estimated incidence of approximately 117 per 100,000 per year [1]. In the USA approximately 300,000 new cases are diagnosed annually [2]. The standard of care has not changed over the past few decades and remains anticoagulation with supportive measures including leg elevation, compression stockings and bed rest. Systemic anticoagulation has traditionally involved unfractionated intravenous heparin therapy until the patient is therapeutically anticoagulated using oral warfarin which required several days of hospitalization. The introduction of subcutaneously administered low-molecular-weight heparin (LMWH) compounds offer significant pharmacoeconomic advantages over unfractionated heparin since there is no need for hospitalization and no laboratory values to measure [3]. Despite the availability of LMWH, the overall goals towards approaching DVT have not changed – the purpose of systemic anticoagulation is to prevent thrombus propagation, reduce the risk of recurrent DVT and decrease the risk of pulmonary emboli. Three major problems exist with current management strategies:

- Anticoagulation is ineffective in actively removing acute thrombus
- Treatment algorithms are based solely on the presence or absence of thrombus without consideration to the extent and length of the involved venous segment
- Treatment of an underlying anatomic problem within the vein is underappreciated

Anticoagulation is ineffective in removing acute thrombus

While anticoagulation remains the cornerstone of DVT therapy, neither unfractionated heparin, LMWHs, or sodium warfarin enzymatically breakdown thrombus. Restoration of patency of the occluded vessel is dependent solely on the endogenous fibrinolytic capacity of the involved venous segment. Based upon our 15-year clinical experience in treating patients with DVT, spontaneous complete recanalization of large diameter veins (iliofemoral segments) seldom, if ever, occurs when treated with anticoagulants alone. If the vein does spontaneously recanalize, the venous lumen is often partially obstructed by synechiae and fibrous tissue and probably contributes to the increased risk of recurrent DVT in these patients. The rate of venous recanalization is dependent on the extent and level of involvement. Patients with DVT confined to one or two veins below the knee will do well on anticoagulation alone, while most with a clot in the femoral and iliac veins will develop problems related to DVT later in life. Of all comers, only 10% of patients will have spontaneous lysis of their DVT within 10 days of heparin therapy and up to 40% of patients will continue to have propagation of thrombus despite anticoagulation [4,5].

All DVT are treated the same despite differences in long-term outcome

The decision to treat DVT with anticoagulants is based primarily upon sonographic detection of thrombus in the deep veins and the work-up is essentially a binary process – patients with documented DVT receive anticoagulation; those with a negative serial ultrasound study are

Keywords: deep vein thrombosis, endovascular therapy, low-molecular-weight heparin, thrombolytic therapy

Future Drugs Ltd

evaluated for other causes of leg pain and swelling. The problem with this binary methodology is that no distinctions are made in treating patients with small thrombus volumes and relatively good clinical outcomes, for example, isolated infrapopliteal DVT versus patients with proximal thrombosis (iliofemoral thrombosis) who are at high risk of long-term morbidity. There are several studies demonstrating that iliofemoral DVT in particular is associated with the highest risk in the development of post-thrombotic syndrome (PTS). PTS is a constellation of clinical findings including chronic leg swelling, pain, skin discoloration, venous claudication and in advanced cases, venous stasis ulcers. PTS is caused by chronic ambulatory venous hypertension brought by venous outflow obstruction, valvular incompetence, or both [6]. Long-term studies over 5- and 10-year periods have shown that despite adequate long-term anticoagulation, 50% of patients with iliofemoral DVT developed venous claudication and significant occupational disability from their venous disease, 95% lost valvular competency, and all patients had chronic leg edema [7,8]. While it may initially appear that the use of LMWH agents are more cost effective in the treatment of DVT, what is often neglected is the long-term socioeconomic consequences of managing the late sequelae of extensive lower extremity DVT.

Anatomic abnormalities of the iliac vein are a frequent contributor to DVT

Traditional concepts on the etiology of lower extremity DVT describe the pathogenesis of thrombus arising in the soleal sinuses and ascending into the popliteal and femoral veins. However, since the advent of catheter-directed (CD) thrombolysis, it has been our observation that iliofemoral DVT behaves differently and that the vast majority of patients have an underlying stenosis of the iliac vein and subsequent downward propagation of thrombus [9]. A frequent cause of iliac vein stenosis, which typically occurs in the left common iliac vein, is the 'May-Thurner' or 'iliac vein compression' syndrome. In this condition, the right iliac artery compresses the left common iliac vein as it crosses the pelvis. The high incidence of an iliac vein stenosis has been previously unappreciated since most patients have historically only received anticoagulation and no attempts have been made to lyse the thrombus and 'unmask' possible venous lesions [10].

Adjunctive thrombolytic therapy versus anticoagulation alone in acute DVT

There is abundant clinical evidence to demonstrate that systemic infusion of thrombolytic agents through a peripheral intravenous line in the antecubital vein has significant advantages over standard unfractionated heparin. A meta-analysis of 13 clinical trials involving over 600 patients comparing systemic streptokinase versus heparin demonstrated the clinical benefits of lytic therapy compared with heparin alone [11]. In lower extremity DVT, the streptokinase treatment group had a complete thrombolysis rate of 45 versus 4% for the heparin-only group. However, in long segment iliofemoral DVT, systemic lytic infusions tended to be ineffective presumably due to the inability of the drug to penetrate the thrombus in the occluded vein which is likely dispersed through collateral pathways instead [12]. Furthermore, the increased risk of bleeding is considerably higher for systemic thrombolysis compared with anticoagulation.

While systemic infusion of thrombolytic agents can improve the resolution of DVT better than standard heparin therapy, administration of the lytic agent through a peripheral arm vein is inefficient for complete clot resolution. CD thrombolysis has been the standard approach in treating a wide variety of arterial thrombotic and embolic ischemic occlusions for the past two decades. Delivering lytic agents directly into the thrombus using a catheter improves the efficiency of drug delivery, decreases the total quantity of drug required and provides venous access for adjunctive techniques such as angioplasty and stent placement. The goals of catheter-based therapy are to rapidly restore patency to the occluded vein, preserve valve function, and detect and treat underlying venous stenoses [13,14]. In the Venous Thrombosis Registry, which prospectively evaluated 473 patients with DVT who underwent CD thrombolysis with urokinase, significant clot lysis was observed in 82% of patients with follow up, confirming the better efficacy of CD thrombolysis as compared with either systemic lysis or anticoagulation alone [15].

The existing evidence is supportive of the notion that early removal of clot reduces the incidence of PTS and improves the quality of life. Elsharawy and colleagues, in a small, randomized study of anticoagulation alone versus CD thrombolysis plus anticoagulation observed that a dissolving clot significantly reduced valvular reflux and improved venous patency – the two main

pathophysiologic mechanisms of PTS [16]. In an assessment of patients with DVT, Comerota found significant improvements in the health-related quality of life in those who had been treated with adjunctive CD thrombolysis versus anticoagulation alone 16 months after treatment [17]. Results of multiple single-center, nonrandomized studies also confirm these findings [18–20]. The benefits of CD thrombolytic therapy, however, can only be realized if applied to acute – less than 14 days – clot. Technical and physiologic variables such as the route of drug administration, location and age of clot, and adjunctive use of stents can also affect the outcome of therapy [15].

Despite the evidence in favor of early aggressive treatment of patients with iliofemoral DVT, many medical specialists remain skeptical of the benefits of lytic therapy for DVT. This is mainly fueled by the potential for serious bleeding complications associated with thrombolysis. The Venous Thrombosis Registry reported an intracranial bleeding rate of 0.6%. Future randomized trials will hopefully illuminate more light on this controversy.

Bibliography

1. Silverstein MD, Heit JA, Mohr DN, Peterson TM, O'Fallon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch. Intern. Med.* 158, 585–593 (1998).
2. Moser KM.Pulmonary thromboembolism In: *Harrison's Principles of Internal Medicine* Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci A, Kasper DL (Eds.), 18th Edition, McGraw-Hill, New York, NY, USA, 1214–1220 (1994).
3. Hull RD, Raskob GE, Pineo GF *et al.* Subcutaneous low-molecular weight heparin vs. warfarin for prophylaxis of deep venous thrombosis following hip or knee implantation. An economic perspective. *Arch. Int. Med*. 157, 298–303 (1997).
4. Sherry S. Thrombolytic therapy for deep venous thrombosis. *Sem. Intervent. Radiol.* 4, 331–337 (1985).
5. Krupski WC, Bass A, Dilley RB *et al.* Propagation of deep venous thrombosis identified by duplex ultrasonography. *J. Vasc. Surg.* 12, 467–475 (1990).
6. Johnson BF, Manzo RA, Bergelin RO, Strandness DE. Relationship between changes in the deep venous system and the development of the post-thrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one to six year follow-up. *J. Vasc. Surg.* 21, 307–312 (1995).
7. O'Donnell TF, Browse WL, Burnand KE, Thomas ML. Socioeconomic effects of an iliofemoral deep venous thrombosis. *J. Surg. Res.* 22, 483–488 (1977).
8. Akesson H, Brudin L, Dahlstrom JD *et al.* Venous function assessed during a five year period after acute iliofemoral venous thrombosis treated with anticoagulation. *Eur. J. Vasc. Surg.* 4, 43–48 (1990).
9. Hill SL, Holtzman GI, Martin D, Evans P, Toler W, Goad K. The origin of lower extremity deep vein thrombi in acute venous thrombosis. *Am. J. Surg.* 173, 485–490 (1997).
10. Kibbe MR, Ujiki M, Goodwin AL, Eskandari M, Yao J, Matsumura J. Iliac vein compression in an asymptomatic population. *J. Vasc. Surg.* 39, 937–943 (2004).
11. Comerota AJ, Aldridge S. Thrombolytic therapy for acute deep vein thrombosis. *Sem. Vasc. Surg.* 5, 76–81 (1992).
12. Hill SL, Martin D, Evans P. Massive vein thrombosis of the extremities. *Am. J. Surg.* 158, 131–136 (1989).
13. Semba CP, Dake MD. Iliofemoral deep vein thrombosis: aggressive therapy with catheter-directed thrombolysis. *Radiology* 191, 487–494 (1994).
14. Bjarnason H, Kruse JR, Asinger DA *et al.* Iliofemoral deep venous thrombosis: safety and efficacy outcome during 5 years of catheter-directed thrombolytic therapy. *J. Vasc. Intervent. Radiol.* 8, 405–418 (1997).
15. Mewissen MW, Seabrook GR, Meissner MH, Cynamon J, Labropoulos N, Haughton SH. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. *Radiology* 211, 39–49 (1999).
16. Elsharawy M, Elzayat E. Early results of thrombolysis versus anticoagulation in iliofemoral venous thrombosis. A randomized clinical trial. *Eur. J. Endovasc. Surg.* 24, 209–214 (2002).
17. Comerota AJ. Quality of life improvement using thrombolytic therapy for iliofemoral deep venous thrombosis. *Rev. Cardiovasc. Med.* 3(Suppl. 2), S61–S67 (2002).
18. Grunwald MR, Hofmann LV. Comparison of urokinase, alteplase and reteplase for catheter-directed thrombolysis of deep venous thrombosis. *J. Vasc. Intervent. Radiol.* 15, 347–352 (2004).
19. Ly B, Njaastad AM, Sandbaek G, Solstrand R, Rosales A, Slagsvold CE. Catheter-directed thrombolysis of iliofemoral venous thrombosis. *Tidsskr Nor Laegforen* 124, 478–480 (2004).
20. Baldwin ZK, Comerota AJ, Schwartz LB. Catheter-directed thrombolysis for deep venous thrombosis. *Vasc. Endovasc. Surg.* 38, 1–9 (2004).

Affiliations

Mahmood K Razavi, MD
Cardiovascular-Interventional Radiology
Stanford Medical Center, H-3600
300 Pasteur Drive
Stanford, CA 94305, USA
Tel.: +1 650 725 5202
Fax: +1 650 725 0533
mrazavi@stanford.edu

Charles P Semba, MD
Genentech, Inc., Department of Vascular Medicine and Neurology,
South San Francisco, CA, USA
cpsemba@gene.com