

Evidence-based practice for patients with severe venous thrombosis

In cases of extensive deep vein thrombosis, supplementary treatment with catheter-directed thrombolysis can reduce the number of cases of post-thrombotic chronic leg problems. We therefore believe that adults with acute thrombosis in the pelvis or upper thigh and with a low risk of bleeding should be considered for this type of treatment.

Post-thrombotic syndrome is a chronic condition that develops gradually after a deep vein thrombosis. The condition is characterised by swelling, a sense of discomfort and heaviness, skin discolouration and, in the most severe cases, the formation of venous ulcers. Even after adequately performed standard treatment with anticoagulation and compression stockings, at least one in four persons develops post-thrombotic syndrome after proximal deep vein thrombosis, i.e. deep vein thrombosis at the level of the popliteal vein and more proximally (1, 2).

first major randomised, controlled study with evaluation of the clinically relevant effect of supplementary treatment with catheter-based thrombolysis (7). After two years, the incidence of post-thrombotic syndrome was 56 % in those who received standard treatment only, compared with 41 % in those who received supplementary thrombolytic therapy. The study also provides support for what is called the «open vein hypothesis», in that venous rechanneling after six months occurred more frequently in the thrombolysis group and was

venous thrombolytic treatment cannot be expected to be as beneficial.

If symptoms last for over two weeks, there is an increased probability that the thrombotic masses are organised and less susceptible to thrombolytic medication, and the endogenous reactive inflammation may already have resulted in damage to the venous valves. Rapid evaluation is therefore called for when a high proximal deep vein thrombosis is detected. Transfer to a hospital that offers the procedure can then be planned, and in the meantime the patient can be treated with low-molecular or unfractionated heparin. As a general rule, proximal deep vein thrombosis has tended to involve short-term hospitalisation for the start of anticoagulation treatment and adjustment of compression stockings. Supplementary treatment with catheter-directed thrombolysis will entail longer hospitalisation with bed rest while infusion takes place, but the patients can be mobilised and transferred to a local hospital the day the treatment is completed.

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With deep vein thrombosis that extends up into the upper thigh or the pelvis, the risk of post-thrombotic syndrome is even higher (3).

There is no curative treatment, but accelerated lysis of the clot could probably prevent the development of venous dysfunction, and thereby post-thrombotic syndrome (4). Catheter-directed venous thrombolytic therapy in addition to the standard treatment is therefore being used in a number of institutions world-wide, despite a lack of documentation of its clinical effectiveness (5). Clinical experience and the results of a number of non-controlled studies indicate that the treatment is effective and entails a small risk of bleeding (6). There is no evidence of an increased risk of embolism or other complications. When a thrombolytic agent (alteplase) with a high affinity for fibrin is used, a primary local effect is achieved with a considerably lower dose than with systemic thrombolytic treatment (6).

In a major collaboration, the hospital trusts of the South-Eastern Norway Regional Health Authority conducted the

associated with a lower incidence of post-thrombotic syndrome after two years than in cases without recanalisation (7, 8). We hope that these results, together with those of two ongoing studies in the Netherlands and the USA, will result in better evidence-based practice for these patients (www.clinicaltrials.gov: NCT00970619, NCT00790335).

Who should be offered the treatment?

We believe that adults with acute venous thrombosis in the pelvis or upper thigh and who have a low risk of bleeding should be considered for this type of treatment. In elderly patients, the potential benefit and risk must be weighed against life expectancy and activity level. Treatment of patients with cancer is controversial, but in cases of not advanced cancer, catheter-directed thrombolytic treatment can be assessed with the same treatment goals if life expectancy is not reduced and there is no increased tendency to bleed. In cases with substantial post-thrombotic problems from previous deep vein thrombosis in the same leg,

Follow-up

Following thrombolytic treatment, patients must have anticoagulation treatment according to the currently applicable guidelines and should make daily use of knee-length compression stockings class II (30 mm Hg) for at least two years (4).

The practice for follow-up of venous thrombolytic treatment has varied, also within the Oslo hospitals. Some have monitored post-thrombotic venous function and morphology, usually by means of ultrasound-based methods. There is no documentation of the benefit of such follow-up, and we would emphasise that it is at least equally important for all patients with deep vein thrombosis, irrespective of the type of treatment, to be informed that they are at higher risk of a recurrent blood clot. If, after completing anticoagulation treatment, they develop new symptoms or suspect acute deep vein thrombosis, there should be a low threshold for contacting a doctor and being referred for diagnostic imaging. Patients with a recurrence of thrombosis or persistent pronounced post-thrombotic discomfort may require further endovascular treatment. However, it is unlikely that the indication for supplementary angioplasty or

re-intervention will be determined through randomised, controlled studies, as this would require very large trial populations.

The thrombolytic treatment requires close collaboration between clinicians (specialists in internal medicine and haematologists) and radiologists. The intervention radiologist establishes venous access, starts infusion of the thrombolytic agent and assesses the treatment effect by means of daily venography.

Several technical aspects of the catheter-directed procedure remain to be clarified, such as dosing of alteplase and supplementary mechanical thrombolysis. In the meantime, we believe that patients with deep vein thrombosis in the thigh or pelvis and a low risk of bleeding should be referred for assessment with a view to supplementary catheter-directed thrombolytic therapy. We also believe that the treatment should be administered primarily by clinicians with a special interest in this patient group and by intervention radiologists with experience of the method.

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References

1. Prandoni P, Lensing AW, Prins MH et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med* 2004; 141: 249–56.
2. Brandjes DP, Büller HR, Heijboer H et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997; 349: 759–62.
3. Kahn SR, Shrier I, Julian JA et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med* 2008; 149: 698–707.
4. Kearon C, Akl EA, Comerota AJ et al. Antithrombotic therapy for VTE disease: Antithrombotic Ther-

apy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141 (suppl): e419S–94S.

5. Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. *Eur J Vasc Endovasc Surg* 2002; 24: 209–14.
6. Vedantham S, Thorpe PE, Cardella JF et al. Quality improvement guidelines for the treatment of lower extremity deep vein thrombosis with use of endovascular thrombus removal. *J Vasc Interv Radiol* 2006; 17: 435–48.
7. Enden T, Haig Y, Kløw NE et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet* 2012; 379: 31–8.
8. Enden T, Kløw NE, Sandvik L et al. Catheter-directed thrombolysis vs. anticoagulant therapy alone in deep vein thrombosis: results of an open randomised, controlled trial reporting on short-term patency. *J Thromb Haemost* 2009; 7: 1268–75.

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