Technique and results of catheter-directed thrombolysis

Niels Bækgaard
Vascular Clinic, Rigshospitalet and Gentofte Hospital, University of Copenhagen

Background

Okrent introduced CDT in 1991 in the USA (1). The first review article by Grossman and Persson was published some years later presenting the results of catheter-directed thrombolysis (CDT) for iliofemoral venous thrombosis with almost 1 year of follow-up in 263 patients (2). The success rate to reopen the veins was 84 % and one death was observed. At the same time a multicenter study with CDT was published by Mewissen et al (3). This classical work including CDT of 303 lower limbs in 287 patients showed the same high patency rate of fully lysed vein segments including stent placement for iliofemoral segments. The stented group showed a higher degree of patency contra the non-stented group of patients. With involvement of the femoropopliteal segment the results were much less favourable. They reported 11 % of bleeding complications, 6 patients with pulmonary embolism (PE) and 2 deaths. These results, being better and safer compared to systemic thrombolysis (4) were the background for a new optimistic active attitude towards a disease with at least 40-50 % risk of postthrombotic syndrome (PTS) with venous claudication and dermal changes including venous ulceration as the most troublesome symptoms and signs (5, 6). Of those patients who will develop PTS, almost 80% will present signs already after 2 years. Severe symptoms at 1 month after the acute thrombus are shown to be a strong predictor for later serious problems shown by Kahn and colleagues (7)**.**

Patho-anatomy/physiology

A metaanalysis has demonstrated a relationship of clot burden reduction and less likelihood of recurrent thromboembolism (8). As shown by Johnson et al., the combination of reflux and obstruction correlates with the severity of the PTS, as opposed to reflux or obstruction alone (9). Another important issue is the May-Thurner Syndrome with left common iliac vein compression (Fig. 1), which requires mechanical restoration with a stent. This can be accomplished over a guide wire system as a minimally invasive procedure delivering a thrombolytic agent directly into the thrombus with the possibility to use the guide wire system for stenting. The fact, that almost 20 % of iliofemoral vein thromboses involve the inferior vena cava, raises consideration whether the procedure shall be protected with a caval filter (10), which can be inserted via another wire system.

Considerations of patients suitable for CDT

Which patients with DVT can possibly benefit from CDT? The treatment shall be used for those patients, who are at most risk of developing PTS and at the same time be feasible for the technique. The treatment has, until now, mostly been offered to patients with involvement of the iliofemoral segment, because these patients are technically easy to handle with puncture of the distal popliteal vein.

What about the duration of symptoms as inclusion criteria before treatment? Some papers have included patients with thrombus age of more than 2 weeks, which can influence the results negatively. It is well known from ultrasonographic findings, that thrombus material is becoming more solid after 2 weeks and may harm the venous endothelium and thereby the valves from this stage. This observation corresponds very well with the consensus statement that a DVT with duration of symptoms up to 14 days is judged acute DVT, 14-28 days subacute DVT and > 28 days is chronic (11).

What about DVT and cancer? An active cancer with no chance of survival for the patient will not fit into this new treatment modality even though release of pain is desirable. However, the risk of bleeding and rethrombosis may be troublesome, but patients with cured cancer can be candidates for CDT. Low or relatively high age as such is no limitation, meaning that teens and people in the seventies can tolerate the treatment..

The Copenhagen experience

With the above mentioned observations and considerations after years with systemic thrombolysis as well as venous thrombectomy we began with CDT in 1999. In Copenhagen, we have now performed almost 192 procedures with 196 limbs and published on the first 101 patients with 103 lower limbs (12). In the following, a brief summary with focus on the most important aspects will be given.

We have included patients from 15-60 years (for the first 150 patients) years with acute iliofemoral DVT according to the definition mentioned above. The most important contraindications were cancer, pregnancy, severe hypertension, cerebral hemorrhage, and surgical interventions including birth delivery within the last 7 days. Duplex ultrasound was used as a diagnostic tool and CT in special cases. The access site was in all limbs the popliteal vein.

Recombinant tissue plasminogen activator (rt-PA) was used as lytic agent (pulse-spray technique) with an average treatment time of 2½ days. As expected, most cases were left sided due to the iliac vein compression syndrome, which required stent placement in the majority of cases. A total of 56 % of the limbs has a stent inserted. After treatment, patients were started on anticoagulation therapy (AC) and short compression stockings class 2 for at least one year. Not surprisingly, more than half of the patients had thrombophilia.

According to a Kaplan-Meier plot the estimated percent of patent veins without reflux was 82 % after 6 years for 103 lower extremities. No PE or deaths occurred (13). New results (still unpublished) from the entire group will be presented at this meeting.

It is shown that intermittent pneumatic compression (IPC) improves the outcome of CDT in order to achieve complete lysis, and without an increased risk of PE (14). This has been mandatory to our patients during the treatment period.

We have included patients with DVT and caval atresia as well. In these patients there has been successful thrombus removal including subsequent opening of the collateral outflow system (15).

Another area worthwhile to mention is immediate postpartum DVT. These patients are kept on low molecular weight heparin (LMWH) in one week before starting CDT in order to prevent bleeding. In addition, 33 women completed 45 pregnancies only with one stent occlusion in week 23 using LMWH in a dosage adjusted to the individual risk (16).

A new published study from our group has demonstrated occurrence of PTS in 16.5 % among 109 patients treated with CDT with a median follow-up time of 71 months. The affected patients were associated with worse quality of life. The study showed that patients with patent veins without valve damage had higher quality of life scores compared to patients with venous insufficiency and occluded veins (17).

Biochemistry and safety

The patients have in all cases been treated in the clinical ward and not in the intensive care unit (ICU) as used in many other centers. The background for our attitude is a very precise monitoring of the biochemical parameters such as activated partial thromboplastin time (APTT), fibrinogen, anti thrombin, thrombin time, haemoglobin and D-dimer. Blood samples 3 times per 24 hours have contributed to adjust

the infusion of unfractionated heparin and rt-PA as well, and this has been done in close collaboration with a thrombosis centre. This concept has been used until patient no. 143. Due to logistic circumstances we have changed the treatment from unfractionated heparin to LMWH and adjusted dosage of this as well of rt-PA to the weight of the patient. After analysing the safety of this regime we are now able to take blood samples only once per 24 hours. Another important aspect of the treatment is to follow the D-dimer level. We have terminated rt-PA infusion when the venogram showed cleared vein segments and clearly decreased D-dimer. Major bleeding complications were seen in 2 % of the patients and minor bleeding episodes in 27 %. The vast majority of minor bleeding complications were from the puncture site, which could be managed with local compression (18).

Discussion

What about the evidence for CDT? There are few randomized controlled trials (RCT´s) and comparative studies in the area. Elsharawy and Elzayat published 9 years ago from a group of 35 patients with iliofemoral DVT treated with CDT contra AC. In the AC group, 7 patients (41%) had reflux contra 2 patients (11%) in CDT group after 6 months (p=0.04) (19). Comerota has compared a group of 68 patients treated with CDT to 30 patients treated with AC. There were significantly fewer with PTS symptoms in the CDT group (20). Finally, AbuRahma studied 33 patients treated with AC and compared them to a group of 18 patients treated with CDT and found the same significant difference concerning patency and a tendency towards fewer patients having C4-C6 in the CDT group (21). Furthermore, a relatively small number of other more or less small series have been published in the last 10 years.

A recent RCT trial from Oslo with 2 years of follow-up, including a group of 90 patients with iliofemoral DVT treated with CDT and AC contra 99 patients with iliofemoral DVT treated with AC, showed significantly fewer patients with PTS in the CDT group (P=0.047) (22). This result is promising, but still a little confusing. Some of the reasons for this are the inclusion criteria mentioned above: a lot of patients had only femoral involvement, even though the title was “iliofemoral” DVT. It is obvious, that especially opening of the iliac component is the most crucial in order to prevent PTS and it is necessary to stent the underlying obstructive lesion in contrast to only ballooning which also is used in this trial. We are looking forward to hear about QOL for these 2 groups of patients.

The future

The results of the ongoing RCT’s in the world are awaited. The American randomized ATTRACT trial is now recruiting patients for pharmacomechanical catheter-directed thrombolysis and comparing it to conventional anticoagulation therapy alone (23). The randomized Dutch CAVA study is now recruiting patients for either standard anticoagulation therapy or ultrasound accelerated catheter-directed thrombolysis (24).

Conclusion

CDT has showed promising results in selected cases with patients suffering from acute iliofemoral DVT. It is important, that focus still is concerned on the best outcome according to PTS and QOL and not favors a shorter time of treatment alone as an important issue. The results from the ongoing RCT´s will hopefully give us some answers.

References

1. Okrent, Messersmith R, Buckman J. Transcatheter fibrinolytic therapy and angioplasty for left iliofemoral venous thrombosis. J Vasc Interv Radiol 1991; 2(2): 195-7.
2. Grossman C, McPerson S. safety and efficacy of catheter-directed thrombolysis for iliofemoral venous thrombosis. Am J Radiol 1999; 172: 667-72.
3. Mewissen MW, Seabrook GR, Meissner MH, et al. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. Radiology 1999; 211: 39-49.
4. Comerota AJ: Venous thromboembolism. In: Rutherford RB, ed. Vascular Surgery. USA: W.B. Saunders Company: 1995.
5. Delis KT, Bountouroglou D, Mansfield AO. Venous claudication in iliofemoral thrombosis. Ann Surg 2004; 239: 118-26.
6. Prandoni P, Kahn SR. Posttrombotic syndrome: prevalence, prognostication and need for progress. Br J Haematol 2009; 145: 286-95.
7. Kahn S, Shrier I, Julian JA et al. Determinants and time course of the posttrombotic syndrome after acute deep venous thrombosis. Ann Intern Med 2008; 149: 698-07.
8. Hull RD, Marder VJ, Mah AF, Biel RK, Brant RF. Quantitative assessment of thrombus burden predicts the outcome of treatment for venous thrombosis: a systemic review. Am J Med 2005; 118: 456-64.
9. Johnson BF, Manzo RA, Bergelin RO et al. Relationship between changes in the deep venous system and the development of the posttrombotic syndrome after acute episode of lower limb vein thrombosis: a one- to six-year follow-up. J Vasc Surg 1995; 21: 307-12.
10. Borst-Krafek B, Fink, AM, Lipp, C, Umek H, Köhn H, Steiner A. Proximal extent of pelvic veins thrombosis and its association with pulmonary embolism. J Vas Surg 2003; 37: 518-22.
11. Vedantham S, Thorpe PE, Cardella JF et al. Quality improvement guidelines for the teratment of lower extremity deep venous thrombosis with use of endovascular thrombus removal. J Vasc Interv Radiol 2006; 17: 435-47.
12. Baekgaard N, Broholm R, Just S et al. Long-term results using catheter-directed thrombolysis in 103 lower limbs with acute iliofemoral venous thrombosis. Eur J Vasc Endovasc Surg 2010; 39: 112-7.
13. Bækgaard N, Klitfod L, Broholm R. Safety and efficacy of catheter-directed thrombolysis. Phlebology 2012; 27 Suppl 1: 149-154.
14. Ogawa T, Hoshino S, Midorikawa H, Sato K. Intermittent pneumatic compression of the foot and calf improves the outcome of catheter-directed thrombolysis using low-doe urokinase in patients with acute proximal venous thrombosis of the leg. J Vasc Surg 2005; 42: 940-4.
15. Broholm R, Jørgensen M, Just S et al. Acute iliofemoral venous thrombosis in patients with atresia of the inferior vena cava can be treated successfully with catheter-directed thrombolysis. J Interv Radiol 2011; 22(6): 801-6.
16. Jørgensen M, Broholm R, Baekgaard N. Pregnany after catheter-directed thrombolysis for acute iliofemoral deep venpous thrombosis. Phlebology 2013; 28 Suppl 1: 34-38.
17. Broholm R, Sillesen H, Damsgaard MT et al. Postthrombotic syndrome and quality of life in patients with iliofemoral venous thrombosis treated with catheter-directed thrombolysis. J Vasc Surg 2011; 54 (6 Suppl): 18S-25S.
18. Baekgaard N, Klitfod L, Broholm R. Safety and efficacy of catheter-directed thrombolysis. Phlebology suppl. 1:149-154.
19. Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomized clinical trial. Eur J Vasc Endovasc Surg 202; 24: 209-14.
20. Comerota AJ, Throm RC, Mathias SD et al. Catheter-directed thrombolysis for ilofemoral deep venous thrombosis improves health-related quality of life. J Vasc Surg 2000; 32: 130-7.
21. AbuRahma AF, Perkins SE, Wulu JT et al. Iliofemoral deep vein thrombosis: conventional therapy versus lysis and percutaneous transluminal angioplasty and stenting. Ann Surg 2001; 233: 752-60.

22. Enden T, Haig Y, Kløw N-E et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVent study): a randomized controlled trial. Lancet 2012; 379: 31-38.
23. Vedantham S, Goldhaber S, Kearon C. Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis (ATTRACT). Available at: http://clinicaltrials.gov/ct2/show/study/NCT00790335) (accessed November 2012).
24. Dutch CAVA-trial: Catheter Versus Anticoagulation Alone for Acute Primary (Ilio)Femoral DVT. Available at: http://clinicaltrials.gov/ct2/show/study/NCT00970619) (accessed October 2012).

With the use of ultrasonography (US), the patients can be examined in order to define the age and the extension of the thrombus. Additionally, guidance for instrumentation at the puncture site can be performed. Ultrasonography must be used in the follow-up of the patients to determine patency of the veins and to examine venous valve function. If US is uncertain in the diagnostic phase a CT venography must be performed. This will often be the case in patients with suspicion of caval atresia.