Benefit of Catheter-directed Thrombolysis for Acute Iliofemoral DVT: Myth or Reality?

Anticoagulation, alone, does not reduce the overall thrombus burden following deep venous thrombosis (DVT). Accordingly, chemical, surgical and mechanical strategies have been developed for removing thrombus, rather than leaving it in situ. The history of thrombolysis dates back 40–50 years and several thrombolytic protocols have been developed as alternatives to surgical thrombectomy. Systemic thrombolysis was abandoned because of its limited success, with only 45% of acute DVT patients achieving significant or complete clearing of thrombus, compared with only 4% after anticoagulation (AC) alone. Regional intravenous thrombolysis has been utilized in combination with surgical thrombectomy in general anaesthesia. The most interesting, recent breakthrough in DVT treatment has been the introduction of intra-thrombus catheter-directed thrombolysis (CDT) for acute clot removal, followed by additional stenting if indicated. This technique was first described in 1991 and has primarily been used for the treatment of acute iliofemoral DVT. The rationale for delivering the thrombolytic agent directly into the thrombus is the protection of plasminogen activator from neutralization by circulating plasminogen activator inhibitors, and it also protects plasm in neutralization by alpha-2-antiplasmin.

Although most patients with acute DVT are still treated by AC alone, the search for new treatment strategies has been driven by awareness of the extremely troublesome and disabling symptoms associated with post-thrombotic syndrome (PTS). PTS can develop within 1 month of suffering an acute DVT and almost half of DVT patients will develop PTS within 2 years of the acute thrombosis. Perhaps, not surprisingly, proximally located thromboses are associated with poorer outcomes. The underlying pathophysiological mechanisms associated with PTS include outflow obstruction at the iliofemoral level and/or distal valvular incompetence, which can result in venous claudication, symptoms and signs of chronic venous insufficiency, and eventually venous ulceration. The alleged positive benefit of compression stockings for preventing PTS was challenged in a recently published RCT, once again emphasizing the need for a more targeted approach to treatment: namely, get rid of the thrombus before it can harm the vein.

Over the last decade, numerous case series, single center- and multicenter studies, comparative studies, and a few RCTs have evaluated the role of CDT. A recent meta-analysis, based on two RCTs and two comparative studies, compared CDT with AC for the treatment of iliofemoral DVT. Despite a relatively small number of patients and heterogeneous endpoints, CDT (compared with AC) significantly reduced the risk of residual obstruction (RR 0.38 [95% CI 0.18–0.73]) and PTS (RR 0.19 [95% CI 0.07–0.48]).

The long-term results of the Norwegian CaVenT trial (which randomized 209 patients to either CDT/AC or AC alone) were published in 2012. After 24 months, data on PTS were available for 189 DVT patients (90 treated with CDT/AC versus 99 treated by AC only). In the CDT/AC group, 37 patients (41.1%) presented with PTS, compared with 55 (55.6%) in the control group (p = .047), corresponding to an absolute risk reduction of 14.4% (95% CI 0.2–27.9). The border-line p value implies a somewhat moderate inter-group difference. This could, however, be explained by selection bias as only half of the randomized patients had a DVT involving the iliac segment. Patients with thrombus at the iliac level would, in all likelihood, benefit more from CDT with stenting of any iliac obstructive lesions, especially the left common iliac vein. Further subgroup analyses showed that CDT treatment appeared to be cost-effective, but quality of life (QOL) was not different between the two groups after 24 months. However, patients with PTS had a much poorer QOL than did patients without PTS (p < .001).

So what can be deduced from the Norwegian RCT? First of all, it is important to remember that the spontaneous natural history of DVT differs according to the involved venous segment(s). Partial or complete recanalization of the femoral segment is seen in almost 80% of patients after 6 months. The iliofemoral segment, on the other hand, will only recanalize in 20% of cases at 5 years. This emphasizes the importance of delivering CDT to that part of the venous system, which is considered to be the outflow tract for the entire limb. Furthermore, CDT is effective in reducing the incidence of PTS.

Results from Copenhagen underscore the potential long-term benefit of CDT. In a prospective study in 109 patients with iliofemoral DVT treated with CDT and additional stenting (where indicated), only 16% of patients developed PTS after a mean follow-up of 71 months. Patients with competent veins had significantly higher QOL than did patients with valvular incompetence.

The US multicenter registry study from 1999, which included 221 limbs with iliofemoral DVT treated by CDT and additional iliac vein stent placement in 99 (45%), showed that the 12-month patency of the lysed segment varied significantly between stented limbs (74%) and those that were not stented (53%) (p < .001). These data suggest that stenting the iliac vein should be considered in the majority of cases. In the CaVenT study, stenting of the...
iliac venous segment was performed in only 18% of cases. A further 26% underwent balloon angioplasty alone, which is most likely to fail in the venous system. In the Copenhagen series, almost 60% of cases were stented. Recently, new data with ultrasound accelerated thrombolysis have been presented, in which 83% were treated with iliac stenting.

CDT is an accessible and successful method of achieving thrombus removal in acute iliofemoral DVT, and stenting should be considered mandatory in more than 50% of cases. The results from the Norwegian CaVenT study should not bring CDT into disrepute. Centers with an interest in CDT should optimize inclusion criteria and technical aspects. Furthermore, the 2-year follow-up from the American ATTRACT trial and the 1-year data from the Dutch CAVA trial, both comparing CDT (with additional stenting) with anticoagulation alone are not yet available. In these two trials, limbs are stratified according to the involved venous segments, that is primarily to the iliofemoral level, but the ATTRACT Study will also stratify according to the femoropopliteal level. Additive mechanical devices for shortening treatment time are also being tested.

Hopefully, the results from these randomized trials (due in 3–4 years time) will provide greater clarity regarding the role of CDT, based on strict stratification of patients according to which venous segments are involved.

REFERENCES

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