

Thrombosis

Intravenous thrombolytic therapy in patients with *phlegmasia caerulea dolens*

In a prospective study, nine patients with *phlegmasia caerulea dolens* (PCD) related to iliac occlusive thrombosis were treated with intravenous thrombolysis. After thrombolysis, despite no significant improvement in the Marder score value, progression to venous gangrene, major hemorrhage or death was not observed and no amputation was needed. Intravenous thrombolysis should be seriously considered in patients with PCD.

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Phlegmasia caerulea dolens (PCD) is an uncommon, severe form of deep venous thrombosis. PCD represents a reversible phase of ischemic venous occlusion that may progress to venous gangrene in 40-60 per cent of cases.¹⁻² The development of venous gangrene has been associated with a significant rate of lower extremity amputation (up to 50% of cases) and mortality (up to 68% in patients undergoing above-knee amputation).³ Due to the very low frequency of PCD, its treatment has not yet been clearly established. Despite its theoretical benefits, the use of thrombolysis in PCD has been described in only a few case reports.^{2,4,5} In order to describe the efficacy and the safety of thrombolytic therapy in PCD, we performed a prospective cohort study on patients presenting with PCD treated with peripheral intravenous thrombolysis.

From August 1994 to July 2004, nine consecutive patients with PCD of a lower limb and with no major contraindication⁶ to thrombolytic therapy were included in this prospective study. During the entire study period, only one patient was not included because of intracranial hemorrhage. All patients suffered pain, and exhibited massive edema and cyanosis of the affected lower limb. All patients presented with at least occlusive iliac and femoral vein thrombosis. The main clinical characteristics of the patients are summarized in Table 1. All the patients were screened for antiphospholipid antibodies which were not detected in any case.

The mean interval between the first clinical signs of PCD and thrombolysis was 1.5 days (range: 1-3 days). Before thrombolysis, the mean Marder score of the affected lower limb was 23.1 (range: 10-40). Using V/Q scan, a high probability of pulmonary embolism was found in six patients (67%) while pulmonary embolism was symptomatic in only one case. Thrombolytic therapy for six patients consisted of streptokinase, as an initial bolus of at least 250,000 units followed by 100,000 units/h for 48 hours, and for three patients alteplase, 0.5 to 0.7 mg/kg for 4 hours. All patients were then treated with intravenous therapeutic doses of unfractionated heparin and an oral anticoagulant.

Following thrombolytic therapy, all patients experienced complete resolution of pain and cyanosis with a more limited reduction of limb swelling during the period in hospital. No patients subsequently developed signs of venous gangrene under heparin and oral anticoagulant therapy. Neither occurrence nor recurrence of clinical or radiological pulmonary embolism was observed. Finally,

Table 1. Patients' characteristics, including features of the *phlegmasia caerulea dolens*.

Patients' characteristics (n=9)	
Male gender	4 pts (44%)
Age, mean ± SD (min to max)	28 yrs±12 (19 to 50)
Predisposing factors*	9 pts (100%)
family history of venous thromboembolism	6
thrombophilia (factor V Leiden mutation, congenital deficit of antithrombin III or protein C)	4
hormonal therapy	4
personal history of venous thromboembolism	3
malignancy	2
Transient risk factors (surgery, immobilization)	2 pts (22%)

*Some patients had more than one condition.

Table 2. Evolution of the Marder score before and after thrombolysis.

Patient number	Total Marder score before thrombolysis	Total Marder score after thrombolysis	Evolution
1	31	17	↓↓↓
2	20	15	↓↓↓
3	21	17	↓↓↓
4*	17	16	↓
5	40	38	↓
6	14	14	→
7	40	40	→
8	10	13	→
9	15	40	↑↑
Mean score ± SD	23.1 ± 11.2	23.3 ± 12.1	

*The same evolution was observed in the other limb in this patient with bilateral PCD.

no major hemorrhage or death occurred and no amputation was necessary. On venograms, the mean Marder score after thrombolysis, blindly assessed by two radiologists, was similar to the scores recorded before thrombolysis (Table 2). Globally, a decrease in Marder score after thrombolysis was observed in five cases and a substantial lysis of iliofemoral clots (decrease of 4 points) was seen in only two cases. Three patients had no improvement in Marder score and one patient manifested large extension of the thrombus after thrombolysis. One patient suffering from disseminated pulmonary malignancy died after three months of follow-up. At six months, all eight surviving patients were receiving vitamin K antagonists and wearing elastic stockings. All eight patients had severe leg edema, which was associated with moderate pain in three cases. Using ultrasonography, a partial recanalization of the iliofemoral veins was recorded in three patients (37%) with a major obstruction still being present in five patients (63%), especially at the iliac level (four patients). At one year, a severe post-thrombotic syndrome was still observed in four of the seven patients being treated with oral anticoagulation and wearing elastic stockings.

In patients with deep vein thrombosis, a recent meta-analysis confirmed that thrombolysis is significantly superior to heparin in terms of clot lysis (OR=7.68 [4.39; 13.45]).⁷ In addition, this meta-analysis did not find any evidence that there is a difference in efficacy between thrombolytic agents or that local therapy differs from

systemic therapy. In our study, substantial lysis of the iliofemoral thrombus after thrombolysis was observed in only two of the nine patients (two of ten affected limbs). However, this poor venographic result was counterbalanced by a clinical success in terms of limb salvage in all patients. This clinical success is probably related to lysis of multiple microvascular peripheral thrombi which cannot be evaluated using venography but which are of major importance in the development of venous gangrene. Catheter-directed intravenous thrombolysis or intra-arterial thrombolysis has been reported in some patients with PCD.^{8,9} To date, it has not been clearly established that *local thrombolysis* is superior to systemic thrombolysis in terms of clot lysis, while the risk of a major bleeding complication could be increased.^{7,10} In one study, these major hemorrhages occurred at the venous insertion site in 39% of cases, and constituted retroperitoneal hematomas in 13% of cases.¹⁰

In conclusion, in view of its rapid positive effects in terms of limb salvage and mortality and despite its low impact on the Marder score, intravenous thrombolysis should be seriously considered in patients with PCD.

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