

Central venous catheter associated thrombosis of major veins: thrombolytic treatment with recombinant tissue plasminogen activator

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Abstract

Objective—Major thromboses can occur in the venous system in association with central venous catheters. This usually necessitates removal of the catheter.

Methods—The effectiveness of low dose recombinant tissue type plasminogen activator (rt-PA) in combination with heparin was assessed in patients with central venous catheter associated thrombosis.

Results—In five patients, all suffering from cancer, a 5-7 day continuous infusion resulted in complete lysis of the thrombus without complications in three. In the other two patients moderately severe haemorrhage was observed with only partial lysis, of the thrombus.

Conclusions—The infusion of heparin and rt-PA is potentially effective in thrombosis related to use of central venous catheters, but the risk of haemorrhage is not inconsiderable.

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Central venous access catheters are frequently used to facilitate the administration of cytotoxic agents into large veins and are often indispensable in patients receiving chemotherapy. The main complications of central venous access catheters are bacterial infections and thrombotic events. A thrombus may develop near the tip of the catheter in most patients, as suggested in a series of necropsies, but these are usually of little clinical significance. In a few cases, however, major thrombosis occurs in the veins along which the catheter is inserted, leading to a superior vena caval syndrome or to obstruction of the subclavian or brachiocephalic veins.¹ The usual management of such a condition includes removal of the catheter while heparin is administered to prevent embolisation.² Thrombolytic therapy with streptokinase or urokinase is of value when used early in the thrombotic process.^{3,4}

The use of high doses of thrombolytic agents is, however, unattractive in cancer patients, particularly in those receiving chemotherapy which causes thrombocytopenia. In addition, the removal of a central venous access catheter often requires prompt insertion of a new one, which must then be done during anticoagulant therapy. In theory at least recombinant tissue type plasminogen activator (rt-PA) could have advantages over streptokinase and urokinase, since it is the naturally occurring physiological agent that initiates fibrinolysis and has been shown to

lead to less degradation of fibrinogen than streptokinase.⁵ As a pilot study, we treated five consecutive patients who presented with catheter related thrombosis with a low dose continuous infusion of rt-PA in combination with heparin, while the catheter was left in situ.

Methods

All patients had either clinical symptoms or radiographic signs of thrombotic obstruction of a major vein draining the upper half of the body which was thought to have been precipitated by the presence of a central venous catheter. Venography to document the extent of the clot was performed when technically possible. Patients with known coagulation abnormalities, those who had undergone surgery within the past 14 days, or who had a recent history of peptic ulcer disease were not eligible. Informed consent was obtained from all patients or their legal representatives, and the study was approved by the Medical Ethical Committee of our institution.

The rt-PA was obtained as a gift from Boehringer Ingelheim. It was dissolved in sterile water according to the recommendations of the manufacturer and diluted in normal saline for a continuous infusion at a level of 0.5 mg/kg body weight per 24 hours, preceded by a 5 mg bolus injection (in adult patients) or a 2 mg bolus injection (in the child). Simultaneously, heparin was started with a bolus injection, followed by a continuous infusion aiming at lengthening the partial thromboplastin time by a factor of 1-2.

The rt-PA infusion was continued until complete resolution of the clinical and radiographic signs of thrombosis, or for a maximum of seven days (whichever occurred first). Oral anticoagulation with acenocoumarol was subsequently begun and heparin was discontinued when adequate prothrombin time values had been obtained. Oral anticoagulation was continued at least until the catheter had been removed and, in the absence of contraindications, for three months after that time.

Results

Five patients were entered in this pilot study between 1 January 1989 and 1 July 1991. Pertinent patient characteristics are given in table 1. The continuous intravenous infusion of the combination of heparin and rt-PA was effective in resolving large vessel obstruction in three of the five patients (table 2).

In two patients the central venous access

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Table 1 Patient characteristics

Patient number	Sex/age	Platelets ($10^9/l$)	Fibrinogen (g/l)	FDP (mg/l)	Obstructed vein	Antithrombotic therapy before rt-PA	Time from first symptoms
1	M/33	267	4.6	>40	Left subclavian and superior caval (both partial)	Heparin during 24 hours	36 hours
2	M/3	102	2.6	20-40	Superior caval vein (partial) and tricuspid valve	Heparin and streptokinase for 48 hours	3 days
3	M/49	371	4.6	30	Right brachycephalic (complete)	None	6 hours
4	M/49	200	5.5	Negative	Left subclavian (complete)	None	24 hours
5	F/54	88	1.6	>40	Left subclavian (complete)	None	6 hours

FDP—fibrin degradation products.

catheters did not have to be removed and could continue to be used for the administration of anticancer agents without new thrombotic complications. No serious untoward effects were seen except in patient 5. Two patients showed brief and minor elevations of liver enzymes possibly related to rt-PA, but these values quickly returned to normal after discontinuation of thrombolytic therapy. A bleeding tendency was not observed in patients 1, 2, and 3, but was present in patients 4 and 5, both of whom had haematomas and minor bleeding at injection sites. This complication rate is comparable to the 25% subcutaneous haemorrhage rate reported by Gray *et al.*⁶ Patient 5 developed large soft tissue haematomas at the sites where bone marrow had been harvested from the iliac crest which required blood transfusions.

Discussion

The successful use of rt-PA to treat catheter induced subclavian vein thrombosis has been reported recently in two patients.^{7,8} In both cases relatively high doses of rt-PA were used within a few hours, with schedules similar to those employed in the treatment of pulmonary embolism. Recent studies in deep venous thrombosis,⁹ however, have used low dose regimens that do not induce a systemic fibrinolytic state. The administration schedule employed in our five patients was based on such a low dose regimen.

The response rate in our patients is comparable with that reported in the largest study to date of thrombolytic therapy in catheter related superior vena cava syndrome⁶ in which eight of 11 patients with vena cava

obstruction in the presence of a central venous catheter were lysed successfully with high doses of either urokinase or streptokinase.

The findings in our small series of patients suggest that treatment with low dose continuous infusion of rt-PA combined with heparin is effective in deep venous thrombosis associated with a central venous catheter, but that major hemorrhage can develop even when no systemic fibrinolytic state is present. Recent bone marrow harvesting should possibly be added to the list of contraindications against the use of rt-PA. Studies with larger numbers of patients, employing even lower doses of rt-PA, may be worthwhile.

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Table 2 Effect of continuous infusion of rt-PA and heparin in five patients with central venous catheter associated large vessel thrombosis.

Patient number	Duration of rt-PA infusion (hours)	Maximum FDP levels* (mg/l)	Fibrinogen nadir† (g/l)	Bleeding tendency	Outcome	Catheter
1	164	40-80	2.2	None	Complete lysis	Preserved
2	151	80-160	1.9	None	Complete lysis	Removed (day 8)
3	190	20-40	4.6	None	Complete lysis	Preserved
4	109	40-80	5.5	Skin	No improvement	Removed (day 7)
5	138	40-80	1.6	Skin Soft tissue	Partial lysis	Removed (day 9)

FDP—fibrin degradation products.

*Normal: <10 mg/l; †normal: 2.5-5.5 g/l.