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Thrombolytic therapy in cerebral venous sinus thrombosis.

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Review Article

Thrombolytic therapy in Cerebral Venous Sinus Thrombosis

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Abstract

The use of thrombolytic agents to rapidly lyse the clot has emerged as a therapeutic modality, in concert with interventional neuroradiologic approaches to deliver the agent locally at the site of thrombosis.There are no randomized, double blind, placebo, controlled trials to support thrombolysis as a first line therapy in patients with cerebral venous sinus thrombosis compared to standard therapy using anticoagulation with weight based dose adjusted unfractionated Heparin. Numerous case reports and a single non randomized trial have shown that it is comparatively safe and may rescue patients who are deteriorating despite anticoagulation with unfractionated Heparin. Consideration must be given to the use of thrombolysis in this group. This is an approach that must be restricted to centers with considerable experience in neurointerventional therapy.

Introduction

Cerebral Venous Thrombosis (CVT) is a rare disorder with protean manifestations. It was associated with a mortality rate of 20% to 50% in older studies.[1] However, with the advent of MR venography, its wide range of manifestations, from relatively benign isolated pseudotumour like syndrome to coma with malignant uncontrollable ICP have begun to be recognized. It is now believed that the mortality rate for CVT ranges from 11% to 30%.[2] Thus the prognosis is not uniformly poor.

The widespread accepted treatment for CVT is systemic anticoagulation with Heparin or Heparinoid (LMWH).Anticoagulation is believed to be beneficial as it possibly prevents further venous clot propagation. It is not known, given the variability and unpredictable course of the disease, whether this mode of treatment will prevent progression in all patients.

Thrombolytic administration represents an alternate mode of therapy which may be used for patients with progression despite adequate anticoagulation, those with massive parenchymal haemorrhages to minimize the dose of systemic anticoagulation, those with poor prognostic factors on presentation, and finally those where the course is felt to be unpredictable with potentially dangerous deterioration.

Thrombolytics or fibrinolytics are agents which lyse the formed clot. The platelet - fibrin composition of a specific thrombus depends on the local development of fibrin, platelet activation, and regional blood flow. At arterial flow rates, thrombi are predominantly platelet rich, and at venous flow rates, more relevant to the pathology of CVT, coagulation seems to predominate. Thrombin (Factor II a) cleaves fibrinogen to form fibrin which is the scaffolding for the clot. Thrombus growth is limited by the endogenous fibrinolytic system. This system is composed of plasminogen, Plasminogen Activators (PA) and their inhibitors. Plasmin mediates the degradation of fibrin. All fibrinolytic agents are essentially obligate plasminogen activators that have variable electivity for clot bound fibrin. The two most common agents reportedly used in the setting of CVT are urokinase and recombinant tissue plasminogen activator (rTPA).

The first report of systemic thrombolytic administration for CVT is from 1971.[3] This idea is not novel. The development of neuroendovascular techniques has enabled the possibility of direct lytic administration into the affected sinus with mechanical or rheolytic aspiration of the clot. The clinical rationale for this approach is that the clot is removed and the occluded sinus is opened rapidly during the procedure. This rapid decanalization may potentially improve the clinical outcome and decrease the morbidity and secondary complications associated with CVT.

There are no randomized, double blind, prospective, placebo controlled trials evaluating this approach to standard systemic anticoagulation. Canhao et al have reviewed the literature until 2001, reporting 72 publications, involving 169 patients.[4] One third of these patients had some haemorrhage on their pretreatment CT or MRI scans, whereas 32% of these patients were in coma. These case series are non uniform and the treatment has been utilized in both deteriorating patients plus those who had a good neurologic status but a large clot burden on angiogram. Urokinase was the thrombolytic most frequently administered (76%). In the majority of cases the thrombolytic was locally infused in the occluded sinus (88%). At discharge, 11 cases (7%; 95% CI 3-12%) were dependent and 9 cases

Table 1. Thrombolytic Therapy for CVT.

Study	Therapy	Subjects	Venous Flow Restoration after therapy	Outcomes and Complication
Wasay, et al 2001[5]	Direct Urokinase vs. Systemic Heparin	N=40 Urokinase (n=20) Heparin (n=20) Retrospective Comparison		Urokinase group had better discharge neurologic function. No deaths were attributed to either Urokinase or Heparin.
Frey, et al 1999[7]	Direct TPA and I.V. heparin	N=12 Case Series Pretreatment ICH 3/12	Full in 6/12 partial in 3/12 Failed in 3/12 S/SX improved in full and partial flow	2/3 failed flow restoration had worsening ICH 1/3 tx stopped drop in fbrinogen
Kim & Suh 1997[8]	Direct TPA	N=9 Case series	Flow restored full 9/9	No haemorrhage or reocclusion
Horowitz, et al 1995[9]	Direct Urokinase	N=12 Case Series Pretreatment ICH 4/12	Flow restored full in 7/12 Partial in 4/12 Failed in 1/12	No haemorrhage or reocclusion
Spearman, et al 1997[10]	Direct Urokinase	N=2 Case report	Flow restored full in 2/2	No haemorrhage or reocclusion
Gartzen, et all 1997[11]	Direct Urokinase followed by I.V. heparin	N=1 Case report	Flow restored	No haemorrhage or reocclusion
Di rocco, et al 1981[12]	Urokinase and heparin	N=5 Case series	Flow restored in all	Full recovery in all

in 5% they were associate with clinical deterioration. Extracranial haemorrhages occurred in 21%, but only 2% required blood transfusion. The mortality rate of 9% is comparable with that of the European trial with LMWH (9%) and compares favorably with the 7% in the heparin group of the trial.

A single retrospective non randomized trial compared the outcomes of CVT treated by local urokinase administration vs. dose adjusted heparin in 40 patients .The patients were well matched for baseline factors , pretreatment neurologic function was slightly worse in the thrombolysis group. There were no deaths in either group. At discharge, 16 / 20 patients who received urokinase were neurologically normal vs. 9 / 20 in those treated with heparin. The long term follow up is not reported. This group concluded that the treatment was at least safe and possibly effective.[5] The following table (Table 1) summarizes some of the case series that used thrombolysis for CVST, most show flow restoration and atleast no increase in mortality with the use of these agents.

Another adjunctive approach that should be discussed in this context is the use of mechanical disruption,

Table 2. Mechanical thrombus disruption after incomplete or failed thrombolysis.

Study	Therapy	Subjects	Venous Flow Restoration after therapy	Outcome and complication
Baker et al 2001[13]	Combined pharmalogical (Urokinase/ heparin) and one or mechanical (rheolytic and ballon catheters) clot disruption	N=5 Urokinase Treatment N=4/5 Mechanical disruption alone N=1/5	Immediate improvement on imaging studies N=5/5 Single intervention N=2/5 Two interventions N= 2/5 Multiple (5) interventions N=1/5	Complete recovery N=2/5 Residual neurologic deficit N=2/5 Significant neurologic deficit N= 1/5
Chow et al 2000[14]	Mechanical (angiolytic- rheolytic) thrombectomy with intra-artrial thrombolysis and failed heparin	N=2 Pretreatment ICH N=2/2	Flow restored full in 2/2	No reported haemorrhage or occlusion Good neurological outcome
Phillips et al 1995[15]	Peri-thrombus Urokinase infusion with mechanical wire microsnare maceration of thrombus	N=6 groups Urokinase N=4 Urokinase + mechanical Maceration N=2	Flow restored 6/6	No reported haemorrhage or occlusion Good neurological outcome

clot maceration and rheolytic suction to aspirate venous clot. The application of the AngioJet catheter to the treatment of dural sinus thrombosis has many potential benefits. First, the AngioJet catheter is one of the few available options when high doses of thrombolytic agents are contraindicated. Even locally delivered thrombolytic agents can require a substantial amount of time to completely lyse a massive clot; previous studies have documented thrombolytic infusions of 88 to 244 hours. Because the walls of the sinuses are thick dura mater, with a low risk of rupture, catheterization of all sinuses with the AngioJet catheter is relatively safe. This is not the case, however, for cerebral veins or the vein of Galen. The walls of these structures are thin and fragile and associated with an increased risk of rupture and cerebral haemorrhage. Therefore, thrombi in these locations should not be treated with the AngioJet and are ideally lysed with the direct infusion of thrombolytic agents such as urokinase. Table 2 Summarizes the data emerging from some of the studies employing a mechanical approach to lysis.

In terms of comparing anticoagulation with the use of an interventional approach, both the approaches have their value; the immediate administration of systemic anticoagulation is rapid, safe and does not require any special skills. The majority of patients will show benefit from this intervention. However, those who have poor prognostic factors[6] e.g. coma, refractory ICP, DVT associated with malignancy or infection, involvement of deep venous system , lack of venous collaterals may stand to benefit most from early intervention.

Inherent in the interventional approach are the unique complications of femoral puncture and cerebral angiography which must be factored in the calculation of risk/benefit decisions for these already sick patients. These include local haemorrhage, retroperitoneal haemorrhage, femoral pseudo aneurysm, stroke induced by angiography and local extension of cerebral ICH.

It seems that the use of thrombolytics is at least safe and in experienced centers, effective for those with a poor prognosis. A large international multicenter trial comparing the two treatments is warranted.

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