Direct thrombolysis for cerebral venous sinus thrombosis

MARYAM RAHMAN, M.D., GREGORY J. VELAT, M.D., BRIAN L. HOH, M.D.,
AND J MOCCO, M.D., M.S.

Department of Neurosurgery, University of Florida, Gainesville, Florida

Cerebral venous sinus thrombosis (CVST) is an increasingly diagnosed disease with a wide range of symptoms, ranging from a mild headache to cerebral herniation. A potentially devastating syndrome, CVST has been associated with a mortality rate of 6–10%. In prospective studies, the overall rate of death and dependency from CVST ranges from 8.8 to 44.4%. Systemic anticoagulation remains the first-line treatment. However, a percentage of patients deteriorate despite medical therapy. These cases have resulted in the development of thrombolysis or endovascular treatment for CVST. Initial reports of the use of endovascular treatment of CVST have been promising. However, enthusiasm for the use of endovascular thrombolysis and thrombectomy should be tempered by an understanding of possible risks such as intracerebral hemorrhage and/or vessel dissection. The authors review the literature regarding endovascular treatment of CVST with a description of the chemical and mechanical thrombolytic techniques. (DOI: 10.3171/2009.7.FOCUS09146)

KEY WORDS • cerebral venous sinus thrombosis •
endovascular thrombolysis • mechanical thrombectomy

CEREBRAL venous sinus thrombosis manifests with a spectrum of signs and symptoms ranging from a mild headache to herniation from intracranial hypertension.^{16,18} Traditionally, CVST was considered an uncommon disorder.^{6,27} However, with improvements in imaging and increased awareness, CVST has been reported more often.^{4,34,89}

In contrast to previous thinking, CVST is not a benign diagnosis and is associated with a mortality rate of 6–10%.^{16,63} In prospective studies, the overall rate of death and dependency due to CVST ranges from 8.8 to 44.4%.^{32,34,76} The possibility of serious morbidity and mortality drives the need for timely diagnosis and treatment of CVST. Systemic anticoagulation is the first-line treatment. The majority of patients with CVST will respond to systemic anticoagulation. However, a percentage of patients either deteriorate despite medical therapy or present with dramatic symptoms that require emergent intervention. These cases have resulted in the development of thrombolysis^{24,36,60,65,88,91} or endovascular treatment for CVST.

With new endovascular techniques and devices, direct thrombolysis and thrombectomy without a craniotomy is becoming increasingly common.^{70,80} Endovascular treatment of CVST has the potential advantages of acute dissolution of clot, allowing normalization of blood flow, decreased ICP, and rapid improvement of severe symp-

toms. Conversely, these invasive procedures are also associated with risks such as hemorrhage, vessel dissection, and pulmonary embolism.^{24,91} We review the techniques and indications for endovascular treatment of CVST.

Methods

We searched the PubMed database for English-language literature published between 1950 and 2009 regarding CVST, thrombolysis, and endovascular treatment. The results of this search as well as relevant references from the publications reviewed were subsequently categorized as direct thrombolysis or mechanical thrombolysis/thrombectomy.

Results

The search revealed 71 original publications regarding endovascular treatment of CVST—51 with only direct chemical thrombolysis (Table 1) and 20 with chemical and/or mechanical thrombolysis (Table 2). These publications mostly consist of case reports beginning in 1988 until June 2009. A total of 161 patients underwent direct chemical thrombolysis and 34 patients underwent chemical and mechanical thrombolysis/thrombectomy. This literature is summarized below.

Discussion

The exact incidence of CVST remains unknown but has been reported to be as high as 9% in an autopsy

Abbreviations used in this paper: CVST = cerebral venous sinus thrombosis; GCS = Glasgow Coma Scale; ICH = intracranial hemorrhage; ICP = intracranial pressure; RCT = randomized controlled trial; tPA = tissue plasminogen activator.

TABLE 1: Direct thrombolysis for CVST*

Authors & Year	No. of Cases	Agent	Dose	Outcome	Age
Scott et al., 1988	1	uro	240,000 U/hr × 3 hrs, 60,000 U/hr × 8 hrs	neuro improve	adult
Higashida et al., 1989	1	uro	1000 U/hr × 2 hrs	normal development at 3 yrs old	child
Persson & Lilja, 1990	1	strepto	250,000 U/hr, 60,000 U/6 hrs, 30,000 U/17 hrs	neuro improve	adult
Barnwell et al., 1991	3	uro	58,000 U/hr × 4–10 days	clinical improve (1), no improve (1)	adult
Eskridge & Wess-becher, 1991	1	uro	4000 U/min × 2 hrs, 1000 U/min × 12 hrs (repeated × 1)	excellent	adult
Tsai et al., 1992	5	uro	200,000–600,000 U	complete neuro recovery in all	adult
Smith et al., 1994	7	uro	20,000–150,000 U/hr × 88–244 hrs	neuro improve (6), improve after tx of AVF (1)	adult
Griesemer et al., 1994	1	uro	470,000 U/75 min	excellent	ped
Kourtopoulos et al., 1994	1	tPA	5 mg/4 hrs × 2	neuro improve	adult
Barnwell et al., 1995	6	uro	100,000-U bolus, 40,000–80,000 U/hr up to 48 hrs	excellent (3), dead (2), blind (1)	both
Horowitz et al., 1995	12	uro	50,000–500,000-U bolus, 73,600 U/hr × 50 hrs	excellent/good (10), dead (1), lost to FU (1)	both
Kermode et al., 1995	1	uro/ strepto	uro: 20,000 U/hr, 100,000 U/4 hrs; strepto: 10,000 U/hr × 12 hrs	excellent	adult
Khoo et al., 1995	1	uro	400,000 U/100 min, 120,000 U/hr × 16 hrs	excellent	adult
Gebara et al., 1995	1	uro	25,000 U/10 min × 7	excellent	child
Evans et al., 1996	1	NR	NR	dead	adult
Aoki et al., 1997	1	tPA	1,600,000-U bolus	excellent	adult
Gerszten et al., 1997	1	uro	850,000 U/3 hrs	excellent	ped
Kim & Suh, 1997	9	tPA	10 mg/10 min, 50 mg/3 hrs, 5 mg/hr til dose of 100 mg/day or complete thrombolysis	excellent	adult
Rael et al., 1997	1	uro	250,000-U bolus × 2 hrs, 80,000 U/hr × 165 hrs	excellent	adult
Smith et al., 1997	2	uro	1,000,000 U/2 hrs	excellent	adult
Spearman et al., 1997	2	uro	600,000–850,000 U/3 hrs	neuro improve	both
Holder et al., 1997	1	uro	150,000-U bolus, 100,000 U/hr × 9 hrs (1st tx), 150,000-U bolus, 100,000 U/hr × 48 hrs	excellent	adult
Renowden et al., 1997	1	tPA	65-mg bolus	neuro improve	adult
Akai et al., 1997	1	uro	120,000-U bolus	neuro improve but died of meta-static melanoma	adult
D'Alise et al., 1998	1	uro	500,000-U bolus, 3,000,000 U/48 hrs	excellent	adult
Kasner et al., 1998	3	uro	60,000 U/hr × 36–84 hrs	excellent	adult
Kuether et al., 1998	1	uro	250,000-U bolus, 60,000–100,000 U/hr × 48 hrs	neuro improve	adult
Niwa et al., 1998	1	tPA	3,200,000 U	excellent	adult

(continued)

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TABLE 1: Direct thrombolysis for CVST* (continued)

Authors & Year	No. of Cases	Agent	Dose	Outcome	Age
Ekseth et al., 1998	3	tPA	8 mg/4 hrs (repeated in 2)	excellent (2), neuro improve (1)	adult
Frey et al., 1999	12	tPA	23–128 mg × 13–77 hrs	immediate recovery (7), long-term partial recovery (5)	adult
Philips et al., 1999	4	uro	200,000–1,000,000 U	all pts improved	both
Witham et al., 1999	1	uro	1,900,000 U	excellent	adult
Manzione et al., 2000	1	uro	400,000-U bolus, 120,000 U/hr × 3 days	excellent	adult
Ra et al., 2001	1	uro	900,000 U	excellent	adult
Wasay et al., 2001	20	uro	250,000-U bolus, 80,000 U/hr × 16–84 hrs	normal (16), neuro deficit: mild (3), mod (1)	both
Yamini et al., 2001	1	tPA	25-mg bolus, 1 mg/min × 19 hrs	complete neuro recovery	adult
Del-Rio Camacho et al., 2001	1	tPA	0.2-mg/kg bolus, 0.5 mg/kg/hr × 3 hrs	excellent	ped
Buccino et al., 2001	2	uro	150,000–200,000 U bolus, 50,000–60,000 U/24 hrs	good	adult
Dzialo & Black-Schaffer, 2001	1	uro	4,000,000 U/96 hrs	excellent	adult
Gebara & Everett, 2001	1	uro	125,000 U/80 min	excellent	ped
Kollar et al., 2001	1	uro	1st tx: 1,200,000-U bolus; 2nd tx: 1,400,000-U bolus, 50,000 U/hr × 24 hrs, 25,000 U/hr × 72 hrs	excellent	adult
Huh et al., 2002	1	uro	1,500,000-U bolus, 1,500,000 U/2 hrs	neuro improve	adult
Kao et al., 2002	1	uro	NR	neuro improve	ped
Ming et al., 2002	5	uro	200,000 U/15 min	excellent	adult
Soleau et al., 2003	10	uro (8)/tPA (2)	NR	clinical improve (6), deterior (1), dead (3) (hemorrhagic complications causing 3/4 poor outcomes)	adult
Weatherby et al., 2003	1	tPA	48 mg (2 separate tx)	excellent	adult (preg-nant)
Zerah et al., 2007	1	tPA	55-mg bolus, 3 mg/hr × 24 hrs	excellent	ped
Hocker et al., 2008	1	tPA	70 mg	excellent	adult
Sidani et al., 2008	1	tPA	NR	neuro improve	adult
Stam et al., 2008	20	uro	120,000–600,000-U bolus, 100,000 U/hr × 24 hrs	clinical recovery (12), handicapped (2), dead (6)	both
Sujith et al., 2008	3	uro	3,000,000–3,600,000/24–48 hrs	neuro improve	adult

* AVF = arteriovenous fistula; deterior = deterioration; FU = follow-up; improve = improvement; mod = moderate; neuro = neurological; NR = not reported; ped = pediatric; strepto = streptokinase; uro = urokinase.

series.⁸⁹ Risk factors for CVST are similar to risk factors for all venous thrombotic disorders and include oral contraceptive or hormone therapy, steroids, infection, malignancy, trauma, pregnancy, underlying hematological disorder, vasculitis, and mechanical precipitants (for example, lumbar puncture and neurosurgery).^{16,17,77} Although almost 25% of cases will have no clear cause even

after an extensive workup,² CVST is extremely variable in its clinical presentation. Headache is the most common clinical symptom, occurring in 75–95% of all cases.^{2,16,21} Other symptoms and signs include visual loss, papilledema, diplopia, stupor, motor deficits, seizures, coma, and death.^{21,34} Diagnosis is confirmed by angiography, CT venography, and/or MR imaging.⁵⁸

TABLE 2: Mechanical thrombolysis/thrombectomy for CVST*

Authors & Year	No. of Cases	Agent	Dose	Device	Outcome	Age
Gurley et al., 1996	2	uro	250,000 bolus, 4000 U/min $\times$ 2 hrs, 2000 U/min $\times$ 2 hrs	balloon angio (1)	clinical improve	adult
Dowd et al., 1999	1	uro	750,000-U bolus, 3,000,000 U/48 hrs	rheolytic catheter	significant neuro recovery	adult
Malek et al., 1999	1	NR	NR	balloon angio/stent	neurologically normal	ped
Chaloupka et al., 1999	1	uro	750,000 U	balloon angio	excellent	adult
Philips et al., 1999	2	uro	200,000–1,000,000 U	thrombectomy w/ wire microsnare	all improved	both
Gomez et al., 2000	1	uro	375,000-U bolus	rheolytic catheter	excellent	adult
Opatowsky et al., 1999	1	uro	450,000–750,000 U	rheolytic catheter	excellent	adult
Chow et al., 2000	2	uro (intra-arterial & directly in sinus)	100,000 U/hr $\times$ 4 hrs (arterial only), 400,000 U in 4 hrs (intraarterial & sinus)	rheolytic catheter	excellent (1), neuro recovery (1)	adult
Novak et al., 2000	1	uro	bolus, 125,000 U/hr $\times$ 4 hrs	balloon angio	excellent	adult
Baker et al., 2001	5	uro	NR	rheolytic catheter (all), balloon angio (3)	excellent/good (4), severe neuro deficits (1)	adult
Hunt et al., 2001	2	uro (1)	NR	balloon angio/stent	excellent	both
Kollar et al., 2001	1	uro	100,000–1,200,000-U bolus, then 10,000–50,000-U infusion/hr $\times$ 12 hrs	balloon angio	good	adult
Chaves et al., 2002	1	tPA	10–48 mg $\times$ mult tx/10 days	rheolytic catheter	neuro improve	adult
Chaharvi et al., 2004	2	uro		rheolytic catheter	neuro improve	adult
Curtin et al., 2004	1	tPA	0.3 mg/hr $\times$ 15 hrs (1st tx), 0.45 mg/hr $\times$ 22 hrs (2nd tx)	rheolytic catheter $\times$ 2 tx	excellent	adult
Prasad et al., 2006	1	tPA	2.75 mg	balloon angio	excellent	ped
Zhang et al., 2008	6	tPA	5–15 mg	rheolytic catheter	excellent/good (4), dead (2)	adult
Bishop et al., 2009	1	heparin	500 U/hr $\times$ 3 days	balloon angio	neuro improve	ped
Newman et al., 2009	1	retaplastase	1.5–2-U bolus	Merci clot retrieval device	excellent	adult
Summers, 2009	1	tPA	8 mg	thrombectomy	neuro improve	adult

* angio = angioplasty; mult = multiple.

The diagnosis of CVST continues to be elusive given the wide spectrum of clinical signs and symptoms, subacute to chronic onset, imaging appearance, and outcome. However, given the possibility for serious morbidity and mortality, timely treatment is critical. First-line treatment is systemic anticoagulation with studies demonstrating improved neurological outcomes in patients who received systemic heparin compared with controls.^{22,28,40} Heparin has also been found to be safe in the treatment of CVST in the setting of ICH.^{22,28} After the acute period, patients are usually switched to oral anticoagulation for 3–12 months depending on the cause of CVST.^{33,62} Additionally, patients may require concomitant treatment for CVST complications including seizures and intracranial hypertension. However, even with these measures, some patients continue to decline or fail to improve. These cases have been shown to benefit from thrombolysis and thrombec-

tomy. Most reports of the use of thrombolysis for CVST have described direct infusion with a microcatheter, although some cases were treated with systemic delivery. In a systemic review published in 2003 comparing 118 patients who were treated with local thrombolysis with 15 patients treated with systemic thrombolysis, the groups did not differ in terms of the rates of death, dependency, hemorrhages, or other complications.¹¹ However, the systemic thrombolysis group was more likely to have only partial or no recanalization (OR 8.9, 95% CI 2.4–33.8).

Direct Thrombolysis

Systemic thrombolysis in the treatment of CVST was first described by Vines and Davis⁹¹ in 1971 with intravenous infusion of urokinase in 5 patients. Since the development of endovascular access to cerebrovascular disease,

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most reports of thrombolysis in the treatment of CVST involve direct infusion of thrombolytics. In the English-language literature, 70 publications have described direct infusion of various thrombolytics in the treatment of CVST. The early reports consist of case reports or small series that used urokinase in adults or children. These reports demonstrated excellent to good outcomes in 140 of 161 patients, even if direct thrombolysis was performed after prolonged treatment with systemic anticoagulation (up to 3 months).⁸² Additionally, thrombolytic infusion was found to be safe in the setting of preexisting ICH,⁴⁷ similar to treatment with systemic anticoagulation.^{22,28} Most of the publications described a transfemoral approach, although some clinicians accessed the venous sinuses via a fontanelle puncture, bur holes, or craniotomy.^{3,29,44,56,70,78} The dose of urokinase varied. Many regimens involved a bolus at the time of the intervention, followed by a continuous infusion by leaving the catheter in place.^{8,47,78,82} These patients underwent frequent venography to assess the status of the thrombosis. Other authors have described only a bolus⁹⁰ or a continuous infusion.^{7,44}

Two reports described treatment with streptokinase^{52,70} and 15 described treatment with tPA.^{3,19,23,35,45,67,72,75,79,83,87,93,95–97} Most of these patients received systemic and/or intrasinus heparin in addition to direct thrombolysis with thrombolytic therapy. Wasay et al.⁹² conducted a retrospective study to compare the efficacy of systemic heparin with that of direct chemical thrombolysis. The heparin group (20 patients) and thrombolysis group (20 patients) were at 2 different institutions, and the thrombolysis group did not receive heparin. The neurological function was worse in thrombolysis group before treatment, but it was better than the heparin group at the time of discharge ($p = 0.019$). Hemorrhagic complications were observed in 10% (2 patients) of the thrombolysis group compared with 0% of the heparin group. These results were promising for thrombolysis alone. However, further prospective trials have not been conducted, and most institutions continue to combine direct thrombolysis with systemic anticoagulation. Moreover, with the advent of sophisticated endovascular techniques, many have combined chemical thrombolysis and systemic anticoagulation with mechanical thrombectomy.

Mechanical Thrombolysis/Thrombectomy

Twenty publications have described mechanical thrombolysis/thrombectomy in 34 patients. All but 3 of these studies used mechanical techniques in combination with thrombolytics.^{12,49,59} Two patients underwent craniotomy and direct dural sinus access of the catheter for endovascular thrombectomy.¹² Generally, the thrombolytics were given as a bolus during the procedure and in some cases, followed by continuous infusion. Many of the publications reported balloon angioplasty or use of a rheolytic catheter to break up the clot.^{5,9,12,13,15,19,25,43,68,72,97} Two reports described balloon angioplasty with stent placement.^{49,59} In 1 case, the patient initially underwent balloon angioplasty alone.⁵⁹ However, after initial improvement, the 13-year-old patient experienced worsening episodes of aphasia and underwent angiography, which revealed reocclusion. He subsequently underwent further balloon angioplasty and stent

placement in his occipital sinus. He was discharged home on a regimen of warfarin, ticlopidine, and aspirin, and he did not suffer any neurological deficits. The second report involved 2 patients who underwent balloon angioplasty of the transverse sinus with significant improvement in sinus venous pressure and the patients' vision.⁴⁹

The only prospective study of CVST endovascular treatment enrolled 20 patients with a mean age of 32 years.⁸⁵ Patients were selected for endovascular intervention if they had an altered mental status, straight sinus thrombosis, or large mass lesion. The study patients were mostly critically ill prior to treatment; 12 of the patients were comatose, 14 had hemorrhagic infarcts, and 11 had deep cerebral thrombosis. Fifteen patients underwent urokinase thrombolysis with thrombosuction using a rheolytic catheter, 4 underwent thrombolysis only, and 1 patient did not undergo any intervention because of difficulty in accessing the sinus. Nine patients recovered or had minimal symptoms, 3 had a minor handicap, and 2 had a moderate or severe handicap as measured using the Rankin scale. The 6 patients who died were more likely to have leukemia (3 of 6) and/or large hemorrhagic infarcts (4 of 6). Five patients had increased cerebral hemorrhage (3 minor and 2 major) after endovascular treatment, and 4 of these patients died. Although the authors noted that they believed that only 1 of these patients died of increase in ICH size, the other 4 patients were in critical condition prior to intervention.⁸⁵ This study demonstrated the significant morbidity and mortality that can be associated with CVST. Due to selection of a severely compromised patient population, the outcomes in this study were much worse than those in previous reports. However, despite the severe nature of the enrolled patients' CVSTs, many of the patients experienced a remarkable recovery, with 12 achieving almost complete recovery.

A large portion of the patients in the literature who were treated with thrombolytics were encephalopathic or comatose at the time of treatment, but they had excellent outcomes. Although promising, the results of direct thrombolysis and thrombectomy must be interpreted cautiously. The studies are mostly case reports, without standard reporting of treatment and outcome measures. Other therapy such as barbiturate coma or craniectomy may have also benefited the patients. Additionally, publication bias has most likely selected for publications with good outcomes. The authors of a review published in the Cochrane Database in 2004 concluded that the current evidence could not support the routine use of thrombolytics in the treatment of CVST. They discouraged further publications of case reports of this treatment and encouraged an RCT. An RCT analyzing vessel patency and/or complications after direct thrombolysis/thrombectomy would be useful in validating this treatment for CVST. On the other hand, an RCT measuring clinical efficacy would require a large sample size and multicenter collaboration, making it a more formidable undertaking. Based on our interpretation of the current literature, we have devised a treatment algorithm for our patients (Fig. 1). Patients who present with severe neurological deficits (GCS score ≤ 8) are strongly considered for direct thrombolysis/thrombectomy immediately. Patients with GCS scores between 9 and 12 may be considered for immediate endovascular treatment. For other patients (GCS

FIG. 1. Flow chart for the treatment of CVST.

score > 12), direct thrombolysis/thrombectomy would be considered only after a trial of systemic anticoagulation. Although useful, this algorithm can only be validated with a properly designed prospective study.

Conclusions

Cerebral venous sinus thrombosis is an increasingly recognized cause of neurological illness with a range of clinical symptoms. Standard treatment is systemic anticoagulation. However, in a subset of patients who decline despite adequate treatment or have a dramatic initial presentation, direct thrombolysis/thrombectomy may be performed. Small case series and prospective studies have demonstrated safety and good initial results with direct thrombolytic infusions, mechanical thrombectomy, and stenting. Well-designed prospective studies are necessary to further investigate endovascular treatment as standard of care for patients with CVST.

Disclosure

Dr. Hoh is a consultant for Micrus Endovascular and Codman Neurovascular. The authors report no other conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Address correspondence to: Maryam Rahman, M.D., Department of Neurosurgery, University of Florida, Box 10265, Gainesville, Florida 32610-0265. email: maryam.rahman@neurosurgery.ufl.edu.