Nonrandomized Comparison of Local Urokinase Thrombolysis Versus Systemic Heparin Anticoagulation for Superior Sagittal Sinus Thrombosis

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Background and Purpose—We sought to compare the safety and efficacy of direct urokinase thrombolysis with systemic heparin anticoagulation for superior sagittal sinus thrombosis (SSST).

Methods—At University at Buffalo (NY) and University of Texas (Dallas, Houston), we reviewed 40 consecutive patients with SSST, treated with local urokinase (thrombolysis group) or systemic heparin anticoagulation (heparin group). The thrombolysis group (n=20) received local urokinase into the SSS followed by systemic heparin anticoagulation. The heparin group (n=20) received systemic heparin anticoagulation only. Neurological dysfunction was rated as follows: 0, normal; 1, mild (but able to ambulate and communicate); 2, moderate (unable to ambulate, normal mentation); and 3, severe (unable to ambulate, altered mentation).

Results—Age (P=0.49), sex (P=0.20), baseline venous infarction (P=0.73), and predisposing illnesses (P=0.52) were similar between the thrombolysis and heparin groups. Pretreatment neurological function was worse in the thrombolysis group (normal, n=5; mild, n=8; moderate, n=4; severe, n=3) than in the heparin group (normal, n=8; mild, n=8; moderate, n=3; severe, n=1) (P=NS). Discharge neurological function was better in the thrombolysis group (normal, n=16; mild, n=3; moderate, n=1; severe, n=0) than in the heparin group (normal, n=9; mild, n=6; moderate, n=5; severe, n=0) (P=0.019, Mann-Whitney U test). Hemorrhagic complications were 10% (n=2) in the thrombolysis group (subdural hematoma, retroperitoneal hemorrhage) and none in the heparin group (P=0.49). Three of the heparin group patients developed complications of the underlying disease (status epilepticus, hydrocephalus, refractory papilledema). No deaths occurred. Length of hospital stay was similar between the groups (P=0.79).

Conclusions—Local thrombolysis with urokinase is fairly well tolerated and may be more effective than systemic heparin anticoagulation alone in treating SSST. A randomized, prospective study comparing these 2 treatments for SSST is warranted. **(*Stroke*. 2001;32:2310-2317.)**

Key Words: anticoagulants ■ cerebral thrombosis ■ heparin ■ thrombolysis ■ urokinase

Superior sagittal sinus thrombosis (SSST) is an uncommon cause of stroke. The clinical presentation, predisposing factors, neuroimaging findings, and outcome are extremely diverse.[1,2] Both systemic heparin anticoagulation and local thrombolysis have been used in the treatment of SSST.[2–35] Two controlled trials have shown that heparin is safe and effective for SSST, even in the presence of intracranial hemorrhage.[3,4] Since 1988, when Scott et al[5] reported the first case of local urokinase thrombolysis in SSST, >70 cases of local urokinase thrombolysis have been reported.[7–31,34,35] These studies are nonrandomized and uncontrolled but suggest that urokinase thrombolysis is safe and effective and is usually associated with favorable outcome even in hemorrhagic venous infarction. Systemic heparin anticoagulation is considered the standard therapy for SSST[6] because no data

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are available regarding the safety and efficacy of thrombolysis in comparison to systemic heparin anticoagulation. We reviewed our experience in treating SSST to compare the safety and efficacy of direct urokinase thrombolysis versus systemic heparin anticoagulation alone.

Subjects and Methods

Seventy consecutive patients with dural venous sinus thrombosis were retrospectively identified at 3 institutions (University at Buffalo–State University of New York; University of Texas Southwestern Medical Center, Dallas; University of Texas, Houston) during 1981–1997. Forty of these patients were included in the study because they had SSST and were treated with either local urokinase (thrombolysis group; n=20) or systemic heparin anticoagulation

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TABLE 1. Heparin- vs Urokinase-Treated Patients With SSST

	Heparin (n=20)	Urokinase (n=20)	*P*
Age, mean (range)	37 y (1 d–65 y)	34 y (4–61 y)	0.49
Sex	3 Male (15%)	8 Male (40%)	0.20
Venous infarction pretreatment on CT/MRI	7 (35%)	7 (35%)	
Nonhemorrhagic	3	4	0.73
Hemorrhagic	4	3	0.73
Hypercoaguable/comorbid state	9	12	0.52
Admission (pretreatment) neurological deficit			0.20
Normal	8	5	
Mild	8	8	
Moderate	3	4	
Severe	1	3	
Discharge (postreatment) neurological deficit			0.019
Normal	9	16	
Mild	6	3	
Moderate	5	1	
Severe	0	0	
Hemorrhagic complications	0	2 (10%)	0.49
Hospital stay, mean (range), d	13.5 (2–33)	12 (6–30)	0.79
Death	None	None	
Recurrence	3 (15%)	1 (5%)	0.61

Values are number of patients unless indicated otherwise.

alone (heparin group; n=20) (Tables 1 and 2). One of these patients (thrombolysis group, patient 1; Table 2) was described in detail in a previous publication.[36] The remaining 30 patients were excluded because they did not receive either heparin or urokinase. All patients in the thrombolysis group were from Dallas (n=18) and Houston (n=2). The decision to treat patients with urokinase was based on physician preference and availability of thrombolytic treatment. All patients included from Buffalo were in the heparin group because the endovascular physicians had not established an approved protocol or previous experience with thrombolytic treatment for SSST. The diagnosis of SSST was confirmed by cerebral angiogram in all patients in the thrombolysis group and in 11 patients in the heparin group (Table 2). The diagnosis was based on MRI/MR venography (MRV) in all remaining patients in the heparin group (Table 2). There was a discrepancy between results of MRI and angiography in patients for whom both tests were performed. Angiography was more sensitive in the diagnosis of transverse sinus thrombosis (TST) and SSST than MRI/MRV (Table 2). With the use of the best available data from the diagnostic modalities that were used in each patient, the heparin group showed SSST alone in 7 patients, SSST+TST in 9 patients, and SSST+deep cerebral venous thrombosis (DCVT) or SSST+cortical venous thrombosis (COVT) in 4 patients. By comparison, the thrombolysis group had SSST alone in 3 patients, SSST+TST in 14 patients, or SSST+DVCT/COVT in 3 patients. Eleven angiograms performed in the heparin group showed SSST alone in 3 patients, SSST+TST in 4 patients, and SSST+DCVT/COVT in 4 patients. Cerebral angiograms in the thrombolysis group showed SSST alone in 3 patients, SSST+TST in 14 patients, and SSST+DCVT/COVT in 3 patients. While the thrombosis appears more extensive in the thrombolysis group (more patients had involvement of ≥2 sinuses than in the heparin group), this must be interpreted with caution because more patients had angiography in the thrombolysis group.

All patients in the thrombolysis group received local thrombolysis into the superior sagittal sinus (SSS). A 5F angiographic catheter and guidewire were placed in the internal jugular vein via femoral vein catheterization. A Tracker-18 microcatheter (Target Therapeutics) was advanced over the guidewire into the SSS. The catheter was advanced into thrombus as much as possible. Through this catheter, a urokinase bolus (250 000 U) was infused into the SSS, followed by continuous urokinase infusion (80,000 U/h). Only 1 patient (patient 18, aged 4 years) received a 50 000 U bolus followed by 10 000 U/h infusion (the dose was lowered for body weight). All other patients received the higher dose. The patients were then transferred to an intensive care unit with the catheter secured into the SSS with continuous infusion into SSS. A repeated angiogram was performed daily in each patient. The end point for urokinase infusion (patency of the SSS) was successfully achieved in all 20 patients. Thrombolysis of deep venous system and transverse sinus was achieved in some patients before the patency of the SSS was achieved, but the end point of infusion was patency of SSS. The infusion was discontinued after patency of SSS was identified on the repeated angiogram. In 3 patients (patients 3, 13, 18) patency of SSS was identified on first follow-up angiogram. The catheter was further advanced into the thrombus if possible after repeated angiograms. The duration of infusion was 16 to 84 hours (mean, 52 hours), as detailed for each patient in Table 2. This duration does not necessarily reflect time to achieve patency of SSS, but it represents the time between first angiogram (start of treatment) and last angiogram (when patency of SSS was first identified). While none of the patients received concomitant heparinization, the thrombolysis was always followed by intravenous heparin therapy, which was started within 24 hours of thrombolysis. The doses of heparin were adjusted to maintain a partial thromboplastin time (PTT) between 50 and 60 seconds. The heparin group received only systemic heparin to maintain a PTT between 50 and 60 seconds (Table 2). This level of anticoagulation was well maintained in the majority of patients with repeated adjustments in heparin doses. All patients in the thrombolysis group and 16 patients in the heparin group were subsequently started on long-term oral anticoagulation (warfarin therapy). The exact details about the duration of long-term oral anticoagulation were not available.

Clinical presentation, predisposing factors, neuroimaging findings, and outcome were determined by chart review (Tables 1 and 2).

TABLE 2. Clinical and Imaging Data in Heparin and Thrombolysis Groups

			Admission			Discharge							Long-Term Follow-Up	
Case No.	Age, y/Sex	Rx/PTT or Duration, h*	Symptoms	Exam	Neuro-score	Exam	Neuro-score	CT	MRI/MRV	Angiography	Etiology	Hospital Stay, d	Time, mo	Symptoms/ Exam
Heparin group														
1	27/F	H: 40–70	HA, DVT	WNL	0	WNL	0	N/P	SSST	N/P	Protein C	17	10	WNL
2	26/F	H: N/A	HA, SZ	HS	1	WNL	0	Parietal HVI	Multiple HVI, SSST	N/P	Bechet's	20	N/A	N/A
3	39/F	H: 38–100	HA, SZ, HP	HP, ENC	2	HP	2	Frontal HVI	Frontal HVI	SSST	Protein S	26	6	HP
4	33/F	H: 44–67	HA	WNL	0	WNL	0	N/P	SSST, TST	SSST	Idiopathic	7	N/A	N/A
5	38/F	H: 40–76	HA, HS	IICP	0	WNL	0	N/P	SSST	N/P	Idiopathic	10	4	WNL
6	30/F	H: 48–68	HA	WNL	0	WNL	0	WNL	TST	SSST, TST	Autoimmune hemolytic anemia	7	8	WNL
7	55/M	H: N/A	HA, HP	HP	2	HP	2	SSST, TST	SSST, TST	N/P	Idiopathic	12	10	Mild HP
8	42/F	H: 56–66	HA, HP	HP	1	HP	1	SSST, DCVT	SSST, TST	SSST	Idiopathic	10	1.5	HP
9	4 mo/M	H: N/A	Fever, ENC	HP	1	HP	2	Parietal NHVI	SSST, TST, DCVT	N/P	Idiopathic	29	6	HP
10	55/F	H: 44–60	HA, SZ	WNL	0	AP, HP	2	Temporal NHVI	SSST, temporal NHVI	N/P	Malignancy	13	7	HP
11	34/F	H: 33–100	HA, BV	AT	1	AT	2	N/P	SSST, TST	SSST, COVT	Lupus	15	3	Mild AT
12	1 d/M	H: N/A	SZ, HT	HP	3	HT	1	N/P	SSST	N/P	Protein C	33	12	WNL
13	42/F	H: 50–70	SZ, DY	DY, PP	2	HP	1	Bifrontal HVI	SSST, bifrontal HVI	N/P	Idiopathic	20	4	Mild HP
14	25/F	H: 45–60	HA	WNL	0	WNL	0	WNL	SSST, TST	N/P	Idiopathic	5	2	WNL
15	23/F	H: 50–66	HA	WNL	0	WNL	0	Temporal HVI	SSST, TST, temporal HVI	SSST, TST	Idiopathic	4	3	Mild AT
16	57/F	H: 62	HA	WNL	0	WNL	0	N/A	SSST	SSST, TST, DCVT	Idiopathic	6	3	WNL
17	39/F	H: 40–66	HA, HP	HP	1	HP	1	N/A	SSST	SSST, DCVT	Idiopathic	8	3	HP
18	65/F	H: 70	HA, DP	ENC, IICP	1	IICP	1	N/P	SSST	SSST, TST	Lupus	2	N/A	N/A
19	24/F	H: 36–54	HA, SZ	ENC	1	WNL	0	N/A	Bifrontal NHVI, SSST	SSST, TST, DCVT	Postpartum	5	7	WNL
20	53/F	H: 44–80	HA, SZ, ENC	ENC	1	HP	1	SSST	N/P	SSST, TST	Idiopathic	8	6	SZ
Thrombolysis group														
1	30/F	U: 70	HA, HP	HP IICP	1	WNL	0	SSST, DCVT	N/P	SSST, TST	DI-lithium[36]	9	3	WNL
2	53/F	U: 64	SZ, ENC, HP	HH, HP	2	HP	1	Parietal HVI	Biparietal HVI, SSST	SSST, TST	HC	30	2	HP
3	23/M	U: 18	HA	IICP, HS	1	WNL	0	WNL	White matter NHVI, SSST	SSST, TST	Lupus	6	7	WNL
4	38/M	U: 44	HA, DP	IICP, AT	2	WNL	0	N/P	SSST	SSST, TST	HC	8	3	SZ
5	36/M	U: 52	HA, DP	IICP	1	WNL	0	N/P	SSST	SSST, TST	PNH	12	10	WNL
6	32/F	U: 40	HA	WNL	0	WNL	0	WNL	SSST, TST	SSST, TST	Lupus	7	12	WNL
7	48/M	U: 66	HA, HS	HS	1	WNL	0	N/P	SSST, TST	SSST, TST	HC	8	1	WNL
8	28/F	U: 65	HA	IICP	1	WNL	0	WNL	SSST	SSST, TST	Idiopathic	7	N/A	N/A
9	23/F	U: 70	SZ, AP, HP	AP, HP	3	HP	1	TH-HVI	TH-HVI, SSST	SSST, DCVT	UC	11	6	Mild HP
10	27/F	U: 58	HA	WNL	0	WNL	0	DCVT	SSST	SSST, TST	Idiopathic	9	12	WNL
11	34/F	U: 50	HA, DP	ENC, IICP	2	WNL	0	DCVT	SSST, TST	SSST, TST	UC	7	3	WNL
12	35/M	U: 39	HA, SZ	WNL	0	WNL	0	N/A	Frontal NHVI	SSST, TST	Idiopathic	8	N/A	N/A
13	38/M	U: 19	HA, SZ, HP	HP	2	HP	1	BG-NHVI	BG-NHVI, SSST	SSST	Idiopathic	22	6	Mild HP
14	23/F	U: 70	HA, SZ	IICP	1	WNL	0	N/P	Parietal NHVI, SSST	SSST, TST	Idiopathic	17	1	WNL
15	61/F	U: 84	HA, BV	HP	1	WNL	0	TST	SSST, TST	SSST, TST	Idiopathic	10	10	WNL
16	32/F	U: 68	HA, dizzy	WNL	0	WNL	0	N/P	SSST	SSST	Postpartum	7	3	WNL
17	55/F	U: 38	HA, HP	AP, HP	3	WNL	0	WNL	SSST	SSST	Idiopathic	15	4	WNL
18	4/M	U: 16	HA, ENC	WNL	0	WNL	0	SSST	SSST, DCVT	SSST, DCVT	Nephrotic syndrome	10	N/A	N/A
19	29/M	U: 72	HA, SZ, HP	HP, ENC	3	HP	2	HVI	N/P	SSST, COVT	UC	29	15	HP
20	38/F	U: 48	HA, SZ	HP	1	WNL	0	WNL	SSST	SSST, TST	Idiopathic	12	1.5	WNL

AP indicates aphasia; AT, ataxia of gait; BG, basal ganglia; BV, blurred vision; COVT, cortical venous thrombosis; DCVT, deep cerebral venous thrombosis; DH, dehydration; DI, diabetes insipidus; DP, diplopia; DVT, deep venous thrombosis of leg; DY, dysarthria; ENC, encephalopathy; H, heparin therapy alone: PTT range; HA, headache; HC, homocysteinuria; HH, homonymous hemianopsia; HP, hemiparesis; HS, hemisensory loss; HT, hypotonia; HVI, hemorrhagic venous infarct; IICP, increased intracranial pressure (eg, papilledema, sixth nerve paresis); N/A, not available; neuroscore, ordinal rating of neurological deficit (see Subjects and Methods); NHVI, nonhemorrhagic venous infarct; N/P, not performed; PP, paraparesis; Protein C, protein C deficiency; SZ, seizures; TH, thalamic; U, urokinase therapy: duration of infusion (h); UC, ulcerative colitis; and WNL, within normal limits.

*PTT for heparin group; duration of infusion for thrombolysis group.

The neurological dysfunction was rated at admission and discharge on a 4-point ordinal scale of neuroscores: 0, normal; 1, mild (able to ambulate and communicate); 2, moderate (unable to ambulate, normal mentation); and 3, severe (unable to ambulate, altered mentation) (Tables 1 and 2). Determination of neuroscores in the 3 pediatric patients (heparin group, n=2; thrombolysis group, n=1) was more subjective and was based on the level of consciousness and the presence of focal neurological deficits. Two reviewers separately scored the neurological deficits. The reviewers were blinded in regard to the patient's treatment. Ninety percent agreement of neuroscores was found between the 2 reviewers. In 10% of cases, a third reviewer resolved disagreements in neuroscores. Secondary outcome measures included mortality, length of hospital stay, complications, and recurrence of SSST (Tables 1 and 2). For recurrence, MRI/MRV evidence of recurrent or more extensive thrombosis was necessary to make a diagnosis. Many of the patients were lost to follow-up and, unfortunately, long-term follow-up was not available. The Mann-Whitney *U* test for nonparametric data or the Fisher's exact probability test for categorical data assessed group differences. $P<0.05$ was considered statistically significant.

Results

Baseline characteristics and outcome of the patients are shown in Tables 1 and 2. The 2 groups were well matched in terms of age, sex, the presence of venous infarction on pretreatment CT/MRI scans, underlying risk factors for SSST, and pretreatment comorbidity. The duration of symptoms ranged from 1 day to 6 months in the thrombolysis group and 1 day to 4 months in the heparin group. All patients with chronic symptoms had recent worsening or new neurological symptoms before presentation. Hemorrhagic venous infarcts were identified in 4 heparin group patients and in 3 thrombolysis group patients. Nonhemorrhagic venous infarcts were identified in 3 patients in the heparin group and 4 patients in the thrombolysis group. Hypercoagulable states were present in 12 (60%) of the thrombolysis group and in 9 (45%) of the heparin group. A comparison of all raw neuroscores on the 4-point scale showed that admission neurological function (neuroscore) was slightly worse in the thrombolysis group but not statistically significantly different than that of the heparin group (Table 1). A comparison of all raw neuroscores on the 4-point scale showed that discharge neurological function was better in the thrombolysis group than in the heparin group ($P=0.019$, Mann-Whitney *U* test). A post hoc analysis was also performed to further define the results. We categorized the discharge neuroscores into 2 categories, normal or mild versus moderate or severe, giving a nonsignificant Fisher's exact probability test ($P=0.18$) result between the 2 treatment groups.

Importantly, no worsening of hemorrhage or neurological deficit was seen in 3 patients with preexisting hemorrhagic infarcts in the thrombolysis group. Three patients in the heparin group had worsening of neurological function despite therapeutic anticoagulation (patients 9, 10, 11). One patient in the heparin group (patient 9) with hemorrhagic infarction showed worsening of the neurological deficit without any increase in size of the infarction or bleeding. Another patient in the heparin group (patient 10) presented with headache and seizures and then subsequently developed aphasia and hemiparesis. Initial CT scan showed a nonhemorrhagic infarct, but MRI showed SSST and a large temporal lobe infarct. It is likely that the neurological deterioration was related to extension of venous infarction or unwitnessed seizures and not due to the systemic malignancy. The patient was not considered a candidate for thrombolysis because of underlying malignancy.

Fifteen percent (n=3) in the heparin group developed complications of the underlying disease (hydrocephalus requiring ventricular shunt, refractory papilledema requiring optic nerve fenestration, prolonged status epilepticus requiring pentobarbital coma). There were no complications of the underlying disease in the thrombolysis group. No deaths occurred in either group. Recurrence rate of SSST was 5% (n=1) in the thrombolysis group and 15% (n=3) in the heparin group ($P=0.61$, Fisher's exact probability test). Recurrence was defined as clinical (new symptoms or recurrence of previous symptoms) and neuroimaging (MRI/MRV) evidence of recurrent or more extensive SSST. All 4 patients with recurrence presented within 3 months of discharge, and the diagnosis of SSST was established by MRI/MRV. One patient (thrombolysis group) had extensive SSST and underwent a repeated urokinase thrombolysis with recanalization of SSS. In all patients, recurrence was associated with subtherapeutic anticoagulation secondary to noncompliance with warfarin therapy. There was no significant difference between the 2 groups in recurrence rate and length of hospital stay (Table 1).

Two patients in the thrombolysis group developed hemorrhagic complications. One patient developed a subdural hematoma, which was successfully treated conservatively. The other patient, with paroxysmal nocturnal hemoglobinuria (PNH), developed retroperitoneal hemorrhage and was treated successfully with blood transfusions. We believe that retroperitoneal hemorrhage in the patient with PNH and SSST was due to a combination of coagulopathy associated with PNH and the use of thrombolytic therapy. Thus, the hemorrhagic complications were 10% (n=2) in the thrombolysis group and none in the heparin group ($P=0.49$, Fisher's exact probability test) (Table 1).

Discussion

This is the first study comparing the relative safety and efficacy of thrombolysis versus systemic heparin anticoagulation for SSST. In this review local urokinase was relatively well tolerated in all 20 patients. Recanalization was documented in all patients receiving urokinase. Multiple case reports and series have shown the safety and efficacy of urokinase thrombolysis in SSST.[7–31,34,35] A review of this literature, including the current cases, is provided in Table 3. Heparin has long been part of the standard therapy for SSST[2,6] and has been the subject of several large series,[2,4,5,32,33] as summarized in Table 4. The question of the safety and efficacy of thrombolytic therapy in comparison to heparin anticoagulation has been raised recently.[6] This study is an effort to address this important question.

Intracranial hemorrhage is a feared and limiting complication of thrombolytic therapy. Three patients in our thrombolysis group had pretreatment hemorrhagic infarcts. No worsening of these hemorrhages or progressive neurological deficits were identified in these patients. Two patients in our thrombolysis group developed hemorrhagic complica-

TABLE 3. Studies of Thrombolysis for SSST

			Hemorrhage		Outcome				
Study	n	Agent	Pretreat	Worsen*	N/A	Good	Poor	Death	Major Complications
Horowitz[7]	13	Urokinase	4	0	1	11		1	Retroperitoneal bleed (n=1)
Frey[8]	12	tPA	7	2		9	3		None
Kim[9]	9	tPA	1	0		9			Retroperitoneal bleed (n=1)
Smith[10]	7	Urokinase	N/A			7			None
Tsai[11]	5	Urokinase	0			4	1		None
Kasner[12]	3	Urokinase	3	0		3			None
Barnwell[13]	3	Urokinase	N/A			3			None
Smith[14]	2	Urokinase	1	0		2			None
Rael[15]	1	Urokinase	1	0		1			None
Kermode[16]	1	Streptokinase	0			1			None
Renowdn[17]	1	tPA	0			1			None
Spearman[18]	2	Urokinase	1	1		2			None
Crawford[19]	1	Urokinase	N/A				1		N/A
Khoo[20]	1	Urokinase	0			1			None
Gerszten[21]	1	Urokinase	1	1		1			Brain hemorrhage (n=1)
Griesemer[22]	1	Urokinase	0			1			None
Eskridge[23]	1	Urokinase	0			1			Brain hemorrhage (n=1)
Manthous[24]	1	Urokinase	0			1			None
Takami[25]	1	Urokinase	0			1			None
D'Alise[26]	1	Urokinase	0			1			None
Niwa[27]	1	tPA	0			1			None
Kuether[28]	1	Urokinase	1	0		1			None
Smadja[29]	1	Urokinase	0			1			Hematuria (n=1)
Satake[30]	1	Urokinase	0	N/A		1			N/A
Manzione[31]	1	Urokinase	0	0		1			None
Chow[34]	2	Rheolysis+urokinase	2	1		2			
Gurley[35]	2	Urokinase	0	0		2			
Wasay (current report)	20	Urokinase	3	0		19	1	0	Retroperitoneal bleed (n=1) Subdural hemorrhage (n=1)
Total	96		25	5	1	88	6	1	7

N/A indicates not available.
*Exacerbation of hemorrhagic component.

tions (unrelated to the venous thrombosis). We reviewed 96 cases of SSST (including our series) treated with local thrombolysis (urokinase, n=72; tissue plasminogen activator, n=23; streptokinase, n=1), as summarized in Table 3. Eighty-eight of these patients (92%) had a good recovery, 1 patient died, and 5 patients had worsening of intracranial hemorrhage without a fatal outcome (Table 3). Seven patients developed new hemorrhages (retroperitoneal bleed, n=3; intracerebral hemorrhage, n=2; subdural hemorrhage, n=1; hematuria, n=1) (Table 3). Horowitz et al[7] described 13

TABLE 4. Large Studies of Heparin Treatment for SSST

			Hemorrhage		Outcome			
Author	n	Agent	Pretreat	Worsen*	Good	Poor	Death	Major Complications
Einhaupl[4]	77	Heparin	27	N/A	N/A	N/A	4	Intracranial bleed (n=8)
Brucker[32]	42	Heparin	22	0	39	2	1	N/A
de Bruijn[3]	30	LMWH	15	N/A	24	4	2	Gastric bleed (n=1)
Ameri[2]	82	Heparin	N/A	N/A	N/A	N/A	0	N/A
DeVeber[33]	22	Heparin/LMWH	6	N/A	N/A	N/A	0	N/A

N/A indicates not available.
*Exacerbation of hemorrhagic component.

patients, 4 of whom had pretreatment brain hemorrhages (Table 3). No worsening was seen after thrombolysis. Kim and Suh[9] described 9 patients, 1 of whom had pretreatment hemorrhage that remained stable (Table 3). Kasner and colleagues[12] described 3 patients with hemorrhages with no worsening after thrombolysis (Table 3). Frey et al[8] recently described 12 patients treated with recombinant tissue plasminogen activator (tPA), 7 of whom had pretreatment hemorrhages (Table 3). Two of these patients showed nonfatal worsening of hemorrhage after thrombolysis. A slightly increased risk of hemorrhage in the patients of Frey et al could be attributed to a more rapid and more potent effect of tPA and the concomitant use of heparinization during thrombolysis. Chow et al[34] described 2 patients treated with rheolytic thrombectomy and direct urokinase thrombolysis. Both patients had pretreatment intracranial hemorrhages. One patient showed worsening of preexisting hemorrhage and development of a new hemorrhagic infarction. Both of these patients had excellent recovery (Table 3).

We believe that there is increased risk of hemorrhage in patients treated with urokinase, as shown in our series. Large studies on the use of heparin in SSST are summarized in Table 4. Einhaupl et al[4] reported a series of 102 patients, 77 of which were treated with heparin (dose-adjusted heparin, n=56; low-dose or intermittent heparin, n=21). Eight patients developed intracranial hemorrhage after the onset of anticoagulation therapy. In our series, 3 patients in the heparin group had worsening of their neurological deficit despite therapeutic anticoagulation. One of these patients had pretreatment intraparenchymal hemorrhage, which did not show any change by serial CT. Neurological worsening is common in patients with SSST and is usually attributed to clot progression, involvement of deep cerebral veins, hematoma formation, or the development of venous infarcts.[1,2] It has been proposed that patients with neurological worsening are the most appropriate candidates for local thrombolytic therapy.[6] The clinical outcome in our heparin group is comparable to previously reported series (Table 4). In our series, 55% of the heparin group had a neurological deficit at discharge. Two randomized trials reported the use of heparin or low-molecular-weight heparin (LMWH) in SSST. Among 30 patients treated with LMWH, 2 died, 24 had a good recovery, and 4 had a poor outcome (Table 4).[3] Three other nonrandomized series described 146 patients treated with heparin and LMWH (Table 4).[2,32,33] The data on neurological outcome are not well reported in these studies.

It has been suggested that extent of clot or thrombosis may be related to outcome. We did not perform a statistical analysis of the extent of clot in the 2 groups because of the limited sample size. Evaluation of the extent of thrombosis by cerebral angiogram was performed in only 11 patients in the heparin group compared with 20 patients in the thrombolysis group. Many patients in both groups had involvement of ≥2 sinuses or deep cerebral veins and thus seem comparable. The duration of symptoms in the thrombolysis group ranged from 1 day to 6 months, but all patients with chronic symptoms had recent worsening or developed new neurological symptoms or deficits. We believe that despite chronicity of symptoms in these patients, there was a component of new or worsening thrombosis that was probably responsible for their acute presentation. The fact that patency of the SSS was achieved in all patients after thrombolysis supports our hypothesis.

Complications in the thrombolysis group were directly related to treatment and are comparable to previous reports. The patient with retroperitoneal hemorrhage and PNH was treated with transfusions and corticosteroids (for PNH) and was started on warfarin before discharge. The other patient with a subdural hematoma was managed conservatively and ultimately received warfarin as an outpatient. Complications in the heparin group were manifestations of the underlying disease and were not directly related to heparin therapy. One patient in the heparin group had refractory papilledema requiring optic nerve fenestration. It is possible that thrombolytic therapy with recanalization of the SSS could have prevented these complications. Papilledema was present in 5 (25%) of the patients in the thrombolysis group, but none required optic nerve fenestration.

In contrast to previously reported series, 5 patients (25%) in our study underwent urokinase thrombolysis despite a normal neurological examination, although these patients had significant symptoms of SSST. It has been suggested that local thrombolysis should be used only for patients with moderate disability or a worsening neurological deficit despite effective systemic anticoagulation.[6] Another view is that the course of SSST is unpredictable and often relentless, and therefore thrombolytic therapy should be instituted as soon as the diagnosis is confirmed, even in patients with mild neurological deficits.[7] We believe that disability in this condition is often related to venous infarction and hemorrhage, as illustrated in our series. We believe that local urokinase thrombolysis should be instituted promptly, if available. Otherwise, patients with SSST should be treated with heparin anticoagulation. The decision to administer thrombolysis to these patients was based on our clinical experience that the clinical course of SSST is often unpredictable and early, aggressive treatment to recanalize the SSS is relatively well tolerated and promotes recovery. A prospective, randomized trial is warranted to compare safety and efficacy of these 2 treatments.

The matching of baseline characteristics between our 2 groups makes it unlikely that the differences were due to a selection bias. If anything, the thrombolysis group was disadvantaged by slightly worse pretreatment neurological deficit and possibly more extensive thrombosis. The diagnosis of SSST was confirmed by angiography or MRI/MRV in all patients. This study is limited by the retrospective approach with nonrandomized treatment groups and a relatively small number of patients. Neurological deficit was determined by chart review, and this may have introduced variability in outcome assessment. To overcome this limitation, we did not use a detailed standardized disability scale for evaluation of neurological deficit. Instead, we used a simple scale to grossly measure neurological deficit using information readily documented in charts. Baseline characteristics were matched in the 2 groups, but as a result of the multicenter and retrospective nature of the study, patients did not have similar evaluations for etiology. Because of the heterogeneous patient population and small sample size, the

chance of finding a statistically significant difference in baseline characteristics is small. An important problem with local thrombolysis therapy is limited availability. In comparison, heparin and LMWH are widely available and do not require a specially trained physician or angiography suite for institution of therapy. These factors are important in clinical decision making. Another limitation of our study is the unavailability of long-term follow-up. Our statistical analysis was done at discharge, which showed improved outcome in urokinase-treated patients. We do not know whether the heparin group achieved the same long-term neurological function as the thrombolysis group months or years later. Therefore, we cannot evaluate whether local thrombolysis only increases the rate of recovery rather than the magnitude of recovery. Properly designed, larger, randomized prospective studies with long-term follow-up will be necessary to confirm and extend our findings. The role of urokinase as a thrombolytic agent is uncertain because the drug was recently removed from the US and Canadian markets. The company is evaluating the possibility of bringing the drug back to the market. The use of tPA has been reported in recent literature with results comparable to those with urokinase in SSST.[8,9,17,27] However, there is less information on the use of tPA in SSST, and further experience is desirable for a complete evaluation of this therapy.

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Editorial Comment

Cerebral Venous Thrombosis and Thrombolysis

Cerebral venous thrombosis is an uncommon disorder. It can manifest as isolated raised intracranial pressure presenting with headache and papilledema associated with a relatively benign course. Alternatively, it can present as a fulminating and rarely fatal stroke syndrome, with severe headache, seizures, and focal neurological signs developing within hours to days.

Heparin, first suggested by Stansfield,[1] has been the mainstay of treatment. Patients improve within hours of commencing treatment and well before recanalization of thrombosed sinuses occurs. Recovery can be excellent even in the absence of recanalization. Two randomized trials of anticoagulation have given conflicting results. The first[2] demonstrated a benefit of intravenous heparin, the second[3] failed to show a benefit with low molecular weight heparin. However, in the latter study, the 2 groups were not evenly matched: there were more patients with isolated raised intracranial pressure in the placebo group. Despite this, most authorities would recommend treatment with intravenous heparin followed by a 3- to 6-month course of anticoagulation with warfarin.[4]. These studies also showed that some patients do well even without treatment.

Thrombolysis was first suggested by Scott et al,[5] and since then a number of reports have established the relative safety of thrombolysis even in the presence of hemorrhagic infarction or frank parenchymal hematoma. These studies have also demonstrated that thrombolysis can rapidly restore the patency of the thrombosed venous sinuses.[2,3]

In their article, Wasay and colleagues report the results of a comparison of thrombolysis versus anticoagulation. The study compared patients treated with intravenous heparin alone to those treated with intravenous thrombolysis (use of urokinase directly into the occluded venous sinus followed by intravenous heparin). Their study confirms previous observations that thrombolysis is very effective in recanalizing occluded venous sinuses and relatively safe. The authors argue that the thrombolytic group had more extensive thrombosis and were more severely affected before treatment and had a greater rate of recanalization and a better outcome after treatment compared with the heparin group. However, the study was nonrandomized and retrospectively assigned a severity of neurological deficit using a nonstandardized scale. Although the extent of venous thrombosis was greater in the thrombolytic group, this may relate to the greater use of formal angiography in the thrombolytic group. Formal angiography is, as the authors admit, more sensitive than MRI in detection of transverse and superior sagittal sinus thrombosis. Although there was a greater rate of recanalization, this has yet to be shown to relate to clinical outcome. An increased risk of hemorrhage with thrombolytic therapy is recognized[6] and was also seen in this study, in which there was a 10% incidence of hemorrhagic complications with thrombolytic therapy, whereas with heparin therapy there were no hemorrhagic complications.

Although the recurrence rate was higher in the group treated with heparin, the authors admit that this was related to inadequate anticoagulation. This study, however, fails to convincingly demonstrate that thrombolysis improves outcome compared with heparin. Thrombolysis is more expensive and would be available only in major centers, whereas heparin is cheaper and can be administered in any hospital. Patients treated with heparin usually make an excellent recovery, with improvement occurring before recanalization occurs. A good outcome can occur in the absence of complete recanalization.

On the other hand, as the authors conclude, it is now time for those who propose thrombolysis to conduct a multicenter, randomized, controlled trial to prove that thrombolysis with either urokinase or recombinant tissue plasminogen activator directly into the occluded venous sinus is more effective than treatment with intravenous heparin. The patients should be stratified into 2 groups: those with isolated intracranial hypertension and those presenting with stroke syndrome. Strict criteria need to be established, with full anticoagulation using heparin followed by 6 months of warfarin versus a standardized bolus dose of a thrombolytic agent with clearly defined bolus doses, rates of administration, and duration of thrombolysis. The definition of efficacy should not be recanalization; rather, it should be a standardized stroke outcome scale and, in addition, neuropsychological assessment of cognitive function. Until such a study is undertaken, these authors will continue to use intravenous heparin as the treatment of first choice. In our experience, a poor outcome relates more to a delay in diagnosis.

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Nonrandomized Comparison of Local Urokinase Thrombolysis Versus Systemic Heparin Anticoagulation for Superior Sagittal Sinus Thrombosis

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