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Direct Endovascular Thrombolytic Therapy for Dural Sinus Thrombosis: Infusion of Alteplase

Sun Yong Kim and Jung Ho Suh

PURPOSE: To evaluate the efficacy, safety, and results of direct thrombolytic therapy in intracranial dural sinus thrombosis by infusion of alteplase (recombinant tissue plasminogen activator). **METHODS**: Nine patients were treated during a 2-year period for intracranial dural sinus thrombosis. A microcatheter was placed directly into the thrombus in the dural sinus via the transfemoral route. Thrombolysis was initiated with a rapid injection of 10 mg of alteplase over 10 minutes, followed in 3 hours by a continuous infusion of 50 mg, then a continuous infusion at 5 mg per hour until complete thrombolysis or a total dose of 100 mg per day had been reached. Repeat thrombolysis was tried the following day if complete recanalization did not occur at 100 mg per day. **RESULTS**: Successful recanalization with improvement of symptoms was achieved in all cases. Time required for complete thrombolysis was between 8 and 43 hours. The total dose of alteplase ranged from 50 to 300 mg. Complications of a small intrapelvic hemorrhage and oozing at a femoral puncture site occurred in separate cases, but were not related to the amount of infused alteplase. MR venograms obtained 1 to 4 weeks after the procedure showed no evidence of reocclusion of the dural sinuses. **CONCLUSION**: Direct fibrinolytic therapy with alteplase is safe, fast, and effective in treating dural sinus thrombosis. However, to prevent hemorrhagic complications, further studies are required to determine its optimal dose and proper rate of administration.

Index terms: Thrombosis, dural sinus; Thrombolysis; Interventional materials

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Many causes and predisposing factors play a role in the development of dural sinus thrombosis (1). Because of the broad spectrum of nonspecific clinical findings, the early diagnosis is often missed, which results in a high rate of morbidity and mortality (2–4). Emergency intervention is inevitable in cases of dural sinus thrombosis, but methods of treatment still remain controversial.

Thrombolytic agents, such as heparin, streptokinase, or urokinase, are used frequently; however, significant risks of cerebral hemorrhage as well as systemic coagulopathy are encountered (2, 5). Recently, alteplase (recombinant tissue plasminogen activator), a fibrin-selective thrombolytic agent, has become available and has been used successfully in the treatment of thromboembolic disease of the peripheral vasculature (6, 7), heart (8, 9), and brain (10, 11). On the basis of these encouraging results and the recent development of advanced catheterization techniques relating to the dural sinus, this study was undertaken to evaluate the safety and efficacy of direct infusion of alteplase into the thrombosed dural sinuses.

Patients and Methods

Between August 1993 and September 1995, nine patients with intracranial dural sinus thrombosis were treated with direct infusion of alteplase into the thrombosed dural sinus. The study group consisted of six women and three men, ranging in age from 24 to 52 years (mean, 33 years). Patient information is summarized in the Table. The mean duration of symptomatic disease was 4.2 weeks (range, 1 to 16 weeks). Radiologic studies, including magnetic resonance (MR) imaging and computed tomography (CT), were obtained in all patients. A cerebral angiogram and

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Patients with dural sinus thrombosis and results of alteplase infusion

Patient	Age, y/Sex	Causes of Thrombosis	Signs and Symptoms	Duration, wk	Location of Thrombosis	Total dosage, mg	Time Required for Lysis, h	Complications
1	42/F	Acute mastoiditis	Headache, papilledema	3	R transverse sinus	50	9	None
2	29/F	Systemic lupus erythematosus	Lethargy, L hemiparesis	4	Superior sagittal sinus, R transverse sinus	150	8	Oozing at puncture site
3	44/M	Antiphospholipid antibody syndrome	Headache, seizure	16	Superior sagittal sinus, L transverse sinus	200	31	Intraperitoneal hematoma
4	52/F	· · ·	Headache, lethargy	4	L transverse sinus	100	12	None
5	37/M	Acute mastoiditis	Headache	1.5	R transverse sinus	130	22	None
6	24/F	Dehydration	Headache, seizure	2	Superior sagittal sinus, R transverse sinus Straight sinus, vein of Galen	100	13	None
7	27/F	Postpartum	Headache, seizure, palsy of fourth cranial nerve	1	L transverse sinus	75	8	None
8	42/M	· · ·	Headache, L hemiparesis	4	Superior sagittal sinus, R transverse sinus, jugular bulb	300	43	None
9	43/F	Catheter induced	Seizure	2	L transverse sinus, jugular vein	100	16	None

sinus venogram were initially obtained to assess the extent of sinus thrombosis. Four patients (patients 1 through 4) were treated initially with systemic heparinization but each had continued symptoms with increasingly severe headaches, seizures, and lethargy. Direct thrombolysis was performed in four patients (patients 5 through 8) as an initial treatment because of its effectiveness in the first four patients. In three of the nine patients (patients 1, 4, and 7), brain parenchyma was normal on imaging studies. Five patients had minimal brain swelling and sulcal effacement but no signal change. Intracerebral hemorrhage was not seen except in one patient (patient 8; Fig 1), who had focal swelling in the right parietal lobe near the mid superior sagittal sinus, which was considered a recent venous infarction.

After confirming the presence of thrombus in the dural sinus and verifying its location and extent on the venous phase of carotid angiography, we introduced a 6F polyurethane guiding catheter into the internal jugular vein via the femoral vein. A 2.8F microcatheter (Target Therapeutics, San Jose, Calif) was advanced into the occluded dural sinus coaxially through the guiding catheter. The tip of the catheter was placed through and proximal to the thrombus as far as possible. When complete thrombosis of the dural sinus prevented optimal placement of the catheter tip, mechanical disruption of the thrombus was tried via manipulation of the guidewire and catheter (patient 6; Fig 2). When thrombi occluded the jugular vein, retrograde superselection was made along the contralateral jugular vein and transverse sinus (patient 9; Fig 3).

The alteplase (Actilyse, Boehringer; Ingelheim, Germany) solution was prepared by mixing 100 mg of lyophilized alteplase with 20 mL of distilled water, to which normal saline was added until the volume reached 200 mL (with an approximate final concentration of 0.5 mg/mL). The dosage and rate of alteplase administration modified as a treatment for myocardial infarction have been described previously (6). Thrombolytic therapy was initiated by bolus injection of alteplase, 10 mg over 10 minutes as a loading dose, within the initial thrombosed site in the sinus. Subsequent continuous infusion of 50 mg of alteplase was given over 3 hours via a rate-regulated infusion pump followed by a slower continuous infusion (5 mg/h) until complete thrombolysis or a dose of 100 mg per day had been reached. In four patients, who had residual thrombus in their partially recanalized dural sinuses, the same infusion regimen was used the following day. During the infusion therapy, digital dural sinus venography was performed every 30 minutes, and the catheter tip was advanced more proximally as thrombolysis progressed. Patients were kept in either the neurologic intensive care unit or the angiography suite throughout infusion so that vital signs and neurologic status could be assessed frequently.

All patients received heparin by means of continuous infusion via an introducer catheter to prevent pericatheter thrombus formation during thrombolysis (partial thromboplastin time at 1.5 times control). After the thrombolytic therapy, patients were converted to oral anticoagulant therapy (warfarin). Coagulation parameters (including prothrombin time, partial thromboplastin time, fibrinogen, and fibrin split products) and hematologic parameters (including hemoglobin and hematocrit) were determined just before initiation of therapy and at 4-hour intervals. Seven patients were treated with warfarin for 3 months after thrombolytic treatment. Patients were followed up closely with MR venography and clinical examination.

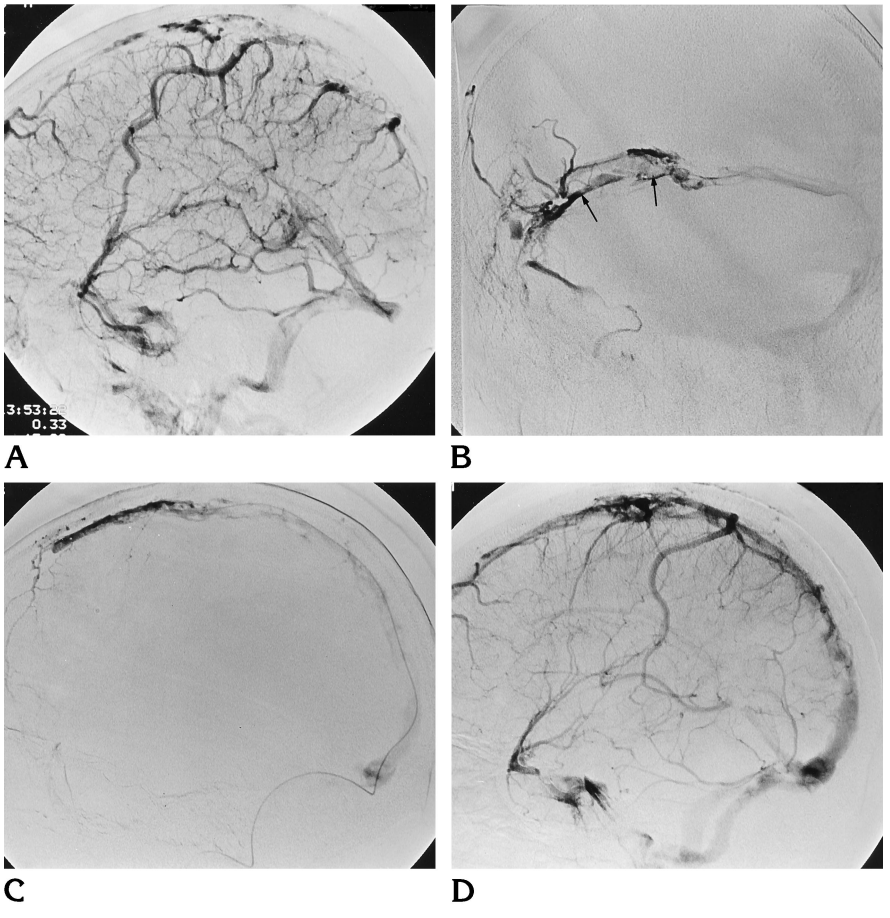

Fig 1. Patient 8.

A, Lateral, venous phase of carotid angiogram shows extensive filling defect due to thrombi throughout entire superior sagittal sinus.

B, Anteroposterior digital venogram, after placement of microcatheter into the right transverse sinus from the right jugular vein, shows extensive thrombus within the dural sinus (*arrows*).

C, Selective superior sagittal sinus venogram after partial thrombolysis of the mid and posterior thirds of the superior sagittal sinus. Microcatheter was advanced through the thrombus.

D, Venous phase of angiogram immediately after thrombolysis shows good opacification of the entire superior sagittal sinus.

Results

Results are summarized in the Table. Angiographic verification of thrombolysis and patency of the entire dural sinus system were achieved in all nine patients. Clinical signs and symptoms, including neurologic deficits, seizures, and headaches, were treated successfully in all patients during the 3-month follow-up period.

Two patients (patients 4 and 6), who initially had severe headaches, experienced a rapid reduction of symptoms during the procedure.

Although a small amount of retained thrombus was seen on the wall of the superior sagittal sinus and the adjacent cortical vein in one patient (patient 2), no additional thrombolytic treatment was performed owing to marked improvement of clinical symptoms and the patient's subsequent refusal of additional treatment. The mean time to complete the lysis was 20 hours (range, 8 to 43 hours). The mean total dose of alteplase was 135 mg (range, 50 to 300 mg).

During the catheterization of the thrombosed sinus, some patients complained of pain, presumably caused by friction on the wall of the dural sinus. The cause, extent of thrombosis, and intensity of symptoms did not correlate with the dosage of infused alteplase or with the time taken to achieve complete thrombolysis. In coagulation parameter profiles, no significant differences were observed in the prothrombin time and partial thromboplastin time at baseline and after alteplase treatment (except the intentional prolongation of partial thromboplastin time to 1.5 times normal). The level of fibrin degradation products in all but two patients was between 10 and 30 mg/mL, which was subnormal but of uncertain clinical significance. Complications were seen in only two patients. In one (patient 2), minor bleeding occurred at the femoral puncture site but did not require transfusion or interruption of lytic therapy. In the other (patient 3), a small intrapelvic hemorrhage developed the day after initial therapy. This patient received blood products (2 U of fresh frozen

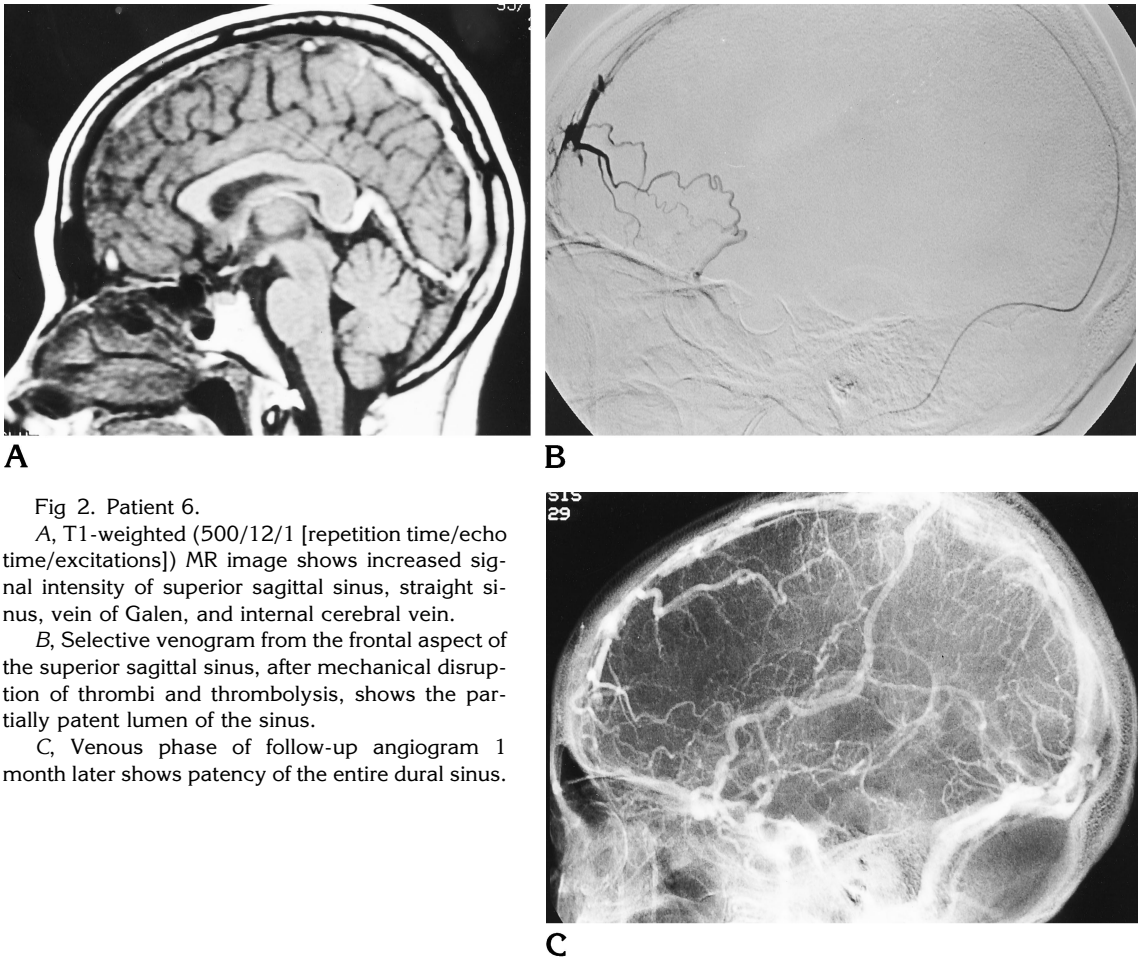

Fig 2. Patient 6.

A, T1-weighted (500/12/1 [repetition time/echo time/excitations]) MR image shows increased signal intensity of superior sagittal sinus, straight sinus, vein of Galen, and internal cerebral vein.

B, Selective venogram from the frontal aspect of the superior sagittal sinus, after mechanical disruption of thrombi and thrombolysis, shows the partially patent lumen of the sinus.

C, Venous phase of follow-up angiogram 1 month later shows patency of the entire dural sinus.

plasma) for the management of a precipitous decline in fibrinogen (baseline was 302 mg/dL; 18 hours after the procedure, it was 58 mg/dL). The fibrinogen level subsequently returned to normal.

Discussion

The clinical manifestations of dural sinus thrombosis are variable and the radiologic findings have been well documented (3, 4, 12). Symptoms depend on the specific sinuses involved, the rate of evolution of thrombosis, the involvement of cerebral veins, and the formation of collateral veins. Therefore, outcomes are unpredictable. This variability makes different treatment regimens difficult to compare.

Three different types of thrombus occur in the dural sinus, including a poorly organized red thrombus, a platelet-rich white thrombus, and an organized collagen-rich thrombus; all three have a similar appearance at MR imaging. The age of a thrombus is not clearly related to the response to therapy. Moreover, a chronic clot that contains different stages of thrombi and that may have existed for years may be lysed by fibrinolytics (13).

The criteria by which patients are selected for treatment of dural sinus thrombosis with systemic thrombolysis are difficult to establish, because published results have been variable. High doses of a systemic standard thrombolytic agent (heparin, streptokinase, and urokinase) have often been used to lyse dural sinus thrombosis, but the results have not been satisfactory owing to slow rates of thrombolysis and hemorrhagic complications (14–16).

The impetus for our use of alteplase in the treatment of dural sinus thrombosis was based on the encouraging clinical results obtained in other sites of thromboembolic disease (4–9) and on the drug's mechanism of action and its pharmacophysiological characteristics. First, alteplase only catalyzes the conversion of fibrin-

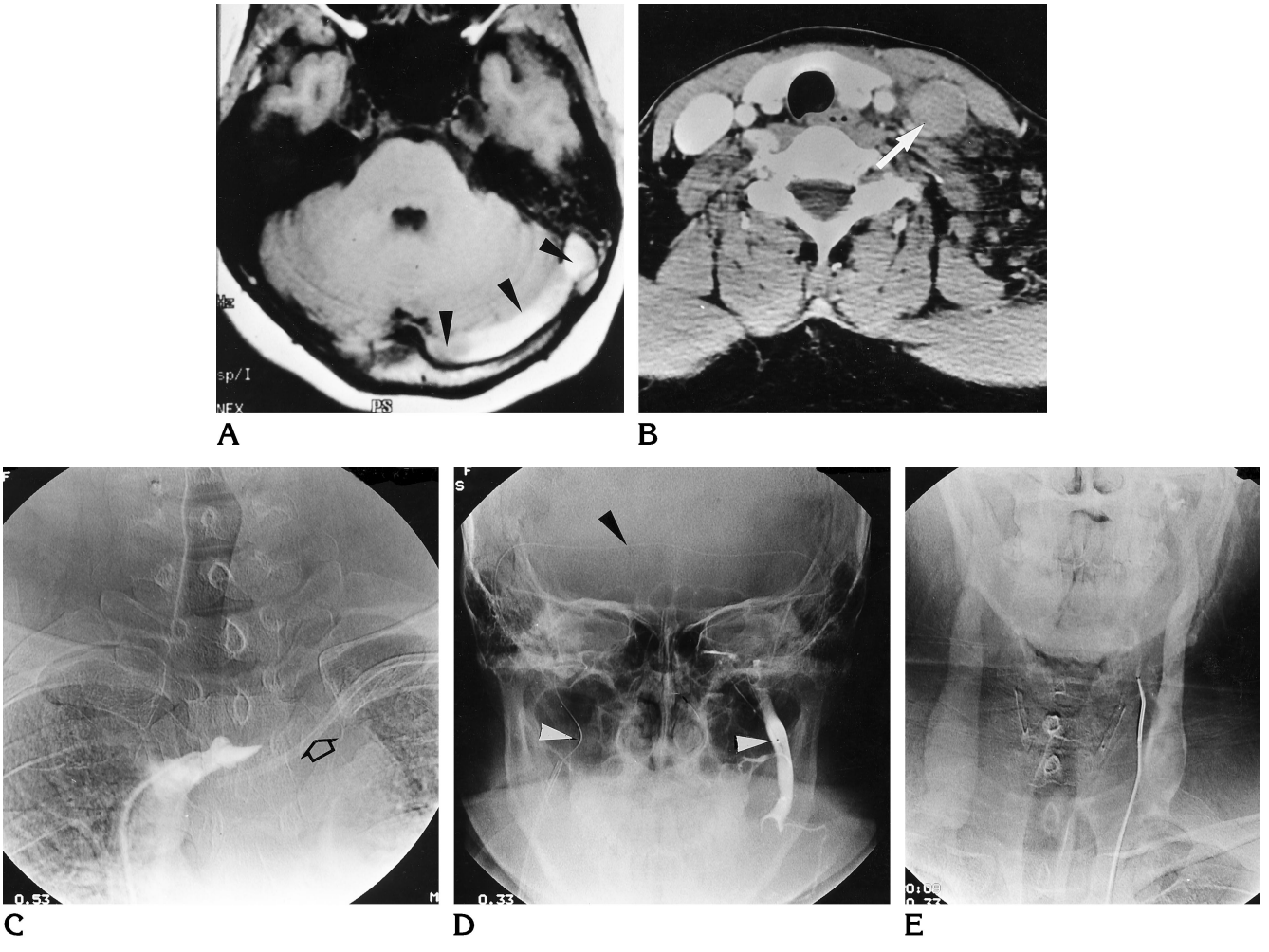

Fig 3. Patient 9.

A, Axial T1-weighted MR image reveals thrombus in the entire left transverse sinus as bright signal intensity (*arrowheads*).

B Contrast-enhanced CT scan shows nonfilling of left jugular vein (*arrow*).

C, Venogram at left brachiocephalic vein shows complete occlusion of left jugular vein. A catheter for chemotherapy is positioned from the subclavian vein (*arrow*).

D, Selective venogram after thrombolysis of left transverse sinus and upper jugular vein. Microcatheter tip is positioned at occlusion site by way of the right jugular vein (*arrowheads*).

E, Venous phase of angiogram after thrombolysis shows complete recanalization of entire left jugular vein with smooth-margined vessel walls.

bound plasminogen. Excess plasmin is inactivated by alpha-2-antiplasmin found normally in the blood. Therefore, at appropriate doses, neither alpha-2-antiplasmin nor fibrinogen is depleted and fibrin degradation products do not accumulate (17, 18). Consequently, the concept of "fibrin-selective thrombolysis" is realistic. Second, recombinant DNA techniques allow the production of alteplase in adequate quantities for clinical and experimental use. Since it is a natural substance, it is not considered antigenic (19). Third, alteplase has a very short half-life (6 to 8 minutes) as compared with other thrombolytic agents (20).

The main concerns of this study were the dosage and rate of infusion of alteplase. Our selected dosage of alteplase, not adjusted for body weight, was based on alteplase delivered directly to the thrombus. This local therapy, which was not distributed throughout the intravascular compartment to produce a desirable pharmacologic response, precluded the need to adjust the dosage for either body size or weight. This type of treatment was based on previous reports stating that accelerated rapid intravenous administration of the agent in acute myocardial infarction was effective. Analysis of our dose rate showed that our patients received rel-

atively concentrated doses during the first few hours. As compared with the focal and small thrombi seen in coronary or peripheral arteries, the majority of thrombi in dural sinus thrombosis are large and extensive. This modified method was fairly effective. The time required for thrombolysis was relatively short (8 to 43 hours; mean, 20 hours) compared with the time required to obtain results with urokinase (88 to 238 hours) (14).

These advantages of alteplase seemed to contribute to the favorable and rapid improvement of clinical symptoms in patients with dural sinus thrombosis, as seen in our study. Reports in the literature have documented that thrombolysis can be accelerated by mechanical disruption of thrombus with transthrombus bolus infusion of fibrinolytic agents and with a pulse-spray technique via a side-hole catheter (21, 22). It was unfortunate that a side-hole catheter was not available on the market at the time of our study.

The age of the thrombus was not clearly related to the response to direct thrombolytic therapy. Although older organized thrombi are thought to lyse far more slowly than fresh ones, our experience showed that thrombolysis proceeds rapidly in most cases, suggesting that thrombolysis augmented by increasing the surface area between clot and thrombolytic agent through fragmentation with the catheter and guidewire is helpful. However, manipulation of a catheter in a thrombosed dural sinus should be performed with extreme care and without undue force, because vigorous contact with the sinus wall can be very painful and perforation of a dural sinus wall or a large cortical vein could be catastrophic.

In our series, minor hemorrhagic events in patients were not proportional to the dose of administered alteplase, even though total dosage greater than 0.9 mg/kg has been found to be related to intracranial hemorrhage when given intravenously for acute ischemic stroke (23). In one study (6), 0.7% of patients with myocardial infarction receiving 1.5 mg/kg of alteplase intravenously to a maximum of 100 mg over 90 minutes suffered hemorrhagic strokes. However, it is likely that undetermined and complex factors contribute to the development of hemorrhagic complications in patients receiving alteplase. It is also well known that diastolic hypertension (>100 mm Hg) is closely related to hemorrhagic complications in patients receiving fibrinolytics.

Although our preliminary results from a small number of cases do not allow us to propose a definitive treatment regimen for dural sinus thrombosis, alteplase nevertheless appears to be the first choice among various thrombolytic agents in terms of safety and efficacy. The rapid therapeutic response to alteplase in acutely deteriorating cases makes it especially appealing as an initial regimen. Further study is required to determine the optimal dosage and administration technique to prevent hemorrhagic complications and reocclusion.

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