Intracisternal recombinant tissue plasminogen activator after aneurysmal subarachnoid hemorrhage

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Fifteen patients undergoing surgery within 48 hours of aneurysm rupture were administered recombinant tissue plasminogen activator (rt-PA) directly into the basal subarachnoid cisterns after minimal surgical clot removal and aneurysm clipping. Preoperatively, 13 patients had diffuse or localized thick subarachnoid blood clots on computerized tomography (CT), and two had diffuse thin clots. The rt-PA was given as a single intraoperative injection of 7.5 mg (one patient), 10 mg (nine patients), or 15 mg (five patients). Postoperative cisternal drainage was employed in three patients.

All patients except one demonstrated partial to complete cisternal clot clearance on CT scans within 24 hours after surgery. The patient who showed no clot reduction was the only patient in this series to develop symptomatic vasospasm and was the only fatality, dying 8 days after rupture. No vasospasm was seen on follow-up cerebral angiography in six of the 14 responding patients, and mild-to-moderate arterial narrowing was seen in at least one major cerebral artery in the remaining eight patients. Severe angiographic vasospasm was not seen, although the patient who died did not undergo repeat angiography. There was one major complication in the series which seemed clearly related to treatment, and that was a large extradural hematoma occurring within several hours of craniotomy. Intrathecal fibrinolytic treatment appears effective in clearing subarachnoid clot and reducing vasospasm, and may be associated with acceptable risks if given to patients with large-volume subarachnoid hemmorhages at high risk for severe vasospasm.

Key Words • aneurysm • subarachnoid hemorrhage • vasospasm • fibrinolytic therapy • thrombolytic therapy • tissue plasminogen activator

Experimental studies have shown that the fibrinolytic agent, recombinant tissue plasminogen activator (rt-PA), administered into the subarachnoid space, is able to lyse subarachnoid hematoma and prevent vasospasm. In primates, rt-PA given up to 72 hours after subarachnoid hematoma placement significantly reduced vasospasm compared to control preparations. This study was designed to assess the safety of intracisternal rt-PA in humans after aneurysmal subarachnoid hemorrhage (SAH), and to examine the effect of rt-PA on subarachnoid hematoma and vasospasm.

Clinical Material and Methods

Informed consent for this study was obtained from or for each of 15 patients suffering SAH from a ruptured saccular aneurysm. Table 1 lists the clinical aspects of each patient treated. None had a history of bleeding diathesis, and baseline coagulation screening and liver function tests in all patients were normal.

Surgery for aneurysm clipping was performed within 48 hours after aneurysm rupture in all patients. Although the dose of rt-PA administered ranged from 7.5 to 15 mg, the protocol for the last eight patients consisted of a single 10-mg bolus injection directly into the basal cisterns after aneurysm clipping. The dose range of rt-PA chosen for this study was based on the finding that 0.75 mg was the minimum dose of rt-PA required for consistent lysis of a 5-ml subarachnoid blood clot in monkeys. It was estimated that the volume of cisternal clot after aneurysm rupture in humans would be 10 to 20 times greater than the dose required for monkeys, and the rt-PA dose was multiplied accordingly. The rt-PA is supplied as a lyophilized powder* that, when reconstituted with sterile water, has a concentration of 1 mg rt-PA/ml, pH of 7.3, and osmolarity of 215 mOsm.

* Tissue-type plasminogen activator manufactured by Genentech, Inc., South San Francisco, California.
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### TABLE 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Aneurysm Location</th>
<th>Admission Grade†</th>
<th>Subarachnoid Blood on Admission CT</th>
<th>SAH to Surgery (hrs)</th>
<th>rt-PA Dose (mg)</th>
<th>24-Hr Clot Clearance on CT</th>
<th>Treatment Complications</th>
<th>Vasospasm</th>
<th>Outcome‡</th>
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<td>1</td>
<td>76</td>
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<td>24</td>
<td>15</td>
<td>+</td>
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<tr>
<td>2</td>
<td>23</td>
<td>M</td>
<td>ACoA</td>
<td>III</td>
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<td>10</td>
<td>+</td>
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<td>3</td>
<td>44</td>
<td>F</td>
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<td>diffuse, thick</td>
<td>48</td>
<td>15</td>
<td>-</td>
<td>+</td>
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<td>F</td>
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<td>III</td>
<td>diffuse, thick</td>
<td>18</td>
<td>15</td>
<td>+</td>
<td>-</td>
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<td>good</td>
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<tr>
<td>5</td>
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<td>M</td>
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<td>III</td>
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<td>15</td>
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<td>42</td>
<td>F</td>
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<td>III</td>
<td>localized, thick</td>
<td>13</td>
<td>10</td>
<td>+</td>
<td>-</td>
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<td>+</td>
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<td>-</td>
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<tr>
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<td>IVa</td>
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<td>41</td>
<td>10</td>
<td>+</td>
<td>-</td>
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</table>

* rt-PA = recombinant tissue plasminogen activator; CT = computerized tomography; SAH = subarachnoid hemorrhage; ACoA = anterior communicating artery; ICA = internal carotid artery; PCoA = posterior communicating artery; MCA = middle cerebral artery. + = positive; - = none.
† Classification according to the World Federation of Neurological Surgeons SAH scale.1
‡ Mild = 0% to 25% luminal narrowing; moderate = 25% to 50% luminal narrowing; focal = one major cerebral artery; diffuse = two or more major cerebral arteries.
§ Classification according to the Glasgow Outcome Scale.5

Only enough blood clot necessary for exposure and clipping of the aneurysm was removed surgically. In the last eight patients in this series, 15 minutes was allowed to pass after rt-PA administration, followed by vigorous irrigation of the subarachnoid space with 1 or 2 liters of warmed saline. Modification of the procedure allowed for dilution and dispersion of enzyme throughout the subarachnoid cisterns and served to reduce the concentration of nonfibrin-bound rt-PA from the wound prior to closure. After microscopic inspection of the operative site and pial banks for bleeding, the dura and wound were closed securely. Although a temporary cisternal drain was used early in the series, the last nine patients did not undergo postoperative cisternal drainage.

One patient (Case 11), who had a large intraventricular hemorrhage from rupture of an anterior communicating artery aneurysm, received additional intraventricular injections of 5 mg rt-PA via a ventricular catheter at 24 and 48 hours after aneurysm clipping. This was combined with extensive ventricular drainage in order to promote clearance of the intraventricular clot.

All patients had at least one computerized tomography (CT) scan performed within 24 hours of surgery, and scanning was repeated thereafter as necessary. Vasospasm was monitored clinically and with repeat cerebral angiography on or near Day 7 following SAH and, when possible, by daily transcranial Doppler ultrasound (TCD) examination (seven cases). All patients received nimodipine, 60 mg every 4 hours by mouth or through a nasogastric tube, for 14 to 21 days after surgery. Enough intravenous fluids were administered in each patient to maintain modest hypervolemia, and one patient (Case 3) was treated with induced hypertension.

Renal, hepatic, and coagulation testing was performed pre- and postoperatively in all patients. In addition, systemic fibrinogenolysis was monitored with one or two serum fibrinogen level assays during the first 2 postoperative days in the last six patients. Serum assays for D-dimer, a cross-linked fibrin degradation product, were performed pre- and postoperatively in seven of the last eight patients treated.

### Results

#### Patient Presentation

Table 1 provides demographic, clinical, and outcome data for each patient treated. There were six men and nine women, with ages ranging from 23 to 76 years (average age ± standard deviation 52.3 ± 16.4 years). Aneurysm location showed that seven patients had anterior communicating artery (ACoA) aneurysms, two had internal carotid artery (ICA) aneurysms, two had posterior communicating artery (PCoA) aneurysms, and four had middle cerebral artery (MCA) aneurysms. Thirteen patients had one aneurysm, one patient had...
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two aneurysms, and another had three aneurysms. The patient with two adjacent ICA aneurysms (Case 3) underwent repair of both prior to rt-PA administration. The patient with three aneurysms had a large left MCA aneurysm that was clearly the source of bleeding based upon CT and surgical findings. This aneurysm and a smaller proximal left MCA aneurysm were clipped prior to rt-PA administration, and a small contralateral MCA aneurysm was not repaired.

On admission, the patients were classified according to their SAH as follows: one Grade II, five Grade III, three Grade IVa, five Grade IVb, and one Grade V (World Federation of Neurological Surgeons Scale). Only one patient was alert preoperatively (Case 6). Admission CT scans classified subarachnoid blood as diffuse and thick in 11 cases, localized and thick in two, and diffuse and thin in two. Mean time to surgery was 22.5 ± 11.4 hours, with a range from 8 to 48 hours. There were no significant differences between sexes, time to surgery (<24 hours vs. ≥24 hours), or in aneurysm location.

Complications

There was one major complication that seemed clearly related to rt-PA treatment. This 45-year-old man (Case 6) underwent uneventful clipping of a large right PCoA aneurysm 16 hours postoperatively, after which 15 mg of rt-PA was instilled into the basal cisterns. The cisterns were not irrigated, but both ventricular and cisternal drains were inserted. Postoperatively, the patient did not awaken, and an immediate CT scan demonstrated a large right frontal extradural hematoma (Fig. 1). This was evacuated, and the following morning the patient underwent removal of residual right subdural and temporal hematoma. He had a prolonged convalescence and, although he eventually returned home and became partially independent, he remained with significant left hemiparesis and neglect. In another patient (Case 5), a thin asymptomatic epidural hematoma was noted beneath the cistriomy and was partially aspirated on the day following surgery.

Dosages of rt-PA used in this study did not result in systemic fibrinolysis. No patient had a prolongation in thrombin or partial thromboplastin time postoperatively. In the six patients in whom it was measured, the plasma fibrinogen level did not decrease postoperatively. D-dimers were detected in plasma preoperatively in two patients and postoperatively in six of eight patients tested (a positive D-dimer indicates a level > 1.0 μg/ml). The presence of fibrin degradation products in serum has previously been observed following SAH, and appears to be the result of subarachnoid fibrinolysis.

Clot Clearance

All patients except one (Case 3) demonstrated clot clearance on CT scans within 24 hours after surgery (Fig. 2). Two patients (Cases 13 and 13) underwent immediate postoperative CT scanning (under anesthe-

Fig. 1. Postoperative computerized tomography (CT) scans in Case 6. a: A large right frontotemporal extradural hematoma occurred within hours after craniotomy for clipping of a right posterior communicating artery aneurysm and administration of 15 mg of rt-PA into the basal cisterns. b: The hematoma was evacuated but the patient has remained moderately disabled due to an infarction in the right posterior cerebral artery distribution, seen on this CT scan obtained 3 days after subarachnoid hemorrhage.

sia), and neither study showed significant change in the amount of diffuse thick subarachnoid hematoma compared to their preoperative CT scans; however, scans from both patients 12 hours later showed almost complete resolution of cisternal blood clot. These results suggest that clot lysis mediated by intraoperative rt-PA is not immediate, but occurs over 24 hours. In Cases 1, 4, 7, and 9 to 15, the overnight reduction in cisternal blood clot was remarkable. One patient with hematoma (Case 11) had complete resolution of his intraventricular clot within several days after direct ventricular injections of rt-PA (Fig. 3).

Vasospasm

Clinical vasospasm was seen in a single patient (Case 3), who failed to demonstrate clot clearance. This patient deteriorated from renal, pulmonary, and cardiac failure and became comatose with evidence of severe brain swelling. Although repeat cerebral angiography was not obtained, TCD examinations revealed increased cerebral blood velocities in both MCA’s beginning on Day 3 after SAH, reaching values as high as 220 cm/sec (mean value in the left MCA) on Day 5. This patient was declared brain-dead on Day 7 following SAH and died the following day.

Thirteen patients underwent repeat cerebral angiography between 5 and 8 days post-SAH; 10 of these studies were carried out on Day 7 after hemorrhage. There was no evidence of angiographic vasospasm in five of these patients, mild vasospasm (≤25% reduction in luminal caliber compared to the preoperative caliber) was seen in five, and three had moderate vasospasm (25% to 50% reduction in luminal caliber) (Figs. 4 and 5). Severe angiographic vasospasm was not observed.

The two patients who did not undergo angiography
during the interval of peak vasospasm included the patient who died (Case 3) and the patient with a large postoperative extradural hemorrhage (Case 6). This latter patient underwent repeat angiography on Day 2 to check the aneurysm clipping, and further angiography was not performed; however, daily TCD studies did not demonstrate increased flow velocities indicative of vasospasm.
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**Fig. 3.** Computerized tomography scans in Case 11. Upper: Scans obtained at admission showing large intraventricular blood clots from rupture of an anterior communicating artery aneurysm. These were treated with two separate intraventricular injections of 5 mg rt-PA 24 and 48 hours after aneurysm clipping through a ventriculostomy catheter. Combined with ventricular drainage, this resulted in rapid and complete clot clearance. Center and Lower: Scans obtained on Days 4 and 12 after rupture showing resolution of the clots.

**Outcome**

The patients in this series have been followed for periods from 1 to 14 months. There has been one death (Case 3), one patient (Case 6) suffered moderate disability due to effects of a postoperative extradural hematoma, one patient (Case 12) had severe disability due to the initial effects of rupture from which she did not recover, and 12 patients had good results (Glasgow Outcome Scale).

**Discussion**

Although hypertensive hypervolemic therapy and the calcium antagonist nimodipine significantly ameliorate the ischemic consequences of vasospasm, individuals with large-volume SAH’s remain at substantial risk from severe diffuse vasospasm. Although operative clot removal at the time of aneurysm repair has been suggested to prevent vasospasm, an aggressive surgical effort to empty the subarachnoid spaces is both hazardous and frequently incomplete after extensive subarachnoid bleeding.

Experimentally, rt-PA was effective in clearing diffuse subarachnoid clot and preventing vasospasm in primates up until 72 hours after induction of SAH. In this study, the safety and efficacy of rt-PA were tested in patients after SAH from rupture of a saccular aneurysm. Thirteen of the 15 patients had thick SAH’s on CT scans.

The protocol developed in this series consisted of an intraoperative injection of 10 mg rt-PA (in 10 ml) directly into the basal cisterns following aneurysm clipping. After waiting 15 minutes, the subarachnoid space was irrigated with 1 or 2 liters of saline to dilute and disperse the enzyme throughout the basal cisterns and to partially remove nonfibrin-bound rt-PA. Cisternal drainage was used only in three patients early in the series, but ventricular drainage for acute hydrocephalus was employed in nine patients.

It is essential that the ruptured aneurysm be repaired prior to rt-PA administration. The one patient who had an unclipped contralateral aneurysm remaining at the time of treatment (Case 12) had unequivocal radiological and operative evidence that the ruptured aneurysm was indeed one of two aneurysms repaired before rt-PA was given.

This study demonstrates that intraoperative intracisternal administration of rt-PA promotes rapid clearance of clot from basal subarachnoid cisterns, including cisterns distant from the operative exposure. In a recent Canadian trial of nimodipine in poor-grade aneurysm patients, 42 patients with thick subarachnoid clot on admission CT underwent another scan between 5 and 10 days following SAH. Persistent subarachnoid clot was evident within this 5- to 10-day interval in 24 (57%) of these patients. In comparison, only one of the 15 patients treated with rt-PA in this series had subarachnoid clot persisting beyond 5 days. Large reductions in diffuse subarachnoid clot were generally apparent on CT obtained on the 1st postoperative day. In addition, postoperative intraventricular injections of rt-PA were effective in rapidly lysing biventricular hematomas resulting from rupture of an ACoA aneurysm.

Rapid clearance of subarachnoid hematoma appeared to be associated with a reduced incidence of
FIG. 4. Preoperative and follow-up cerebral angiograms in the first eight patients treated in the series, excluding Case 3 in which postoperative angio genesis was not performed. Areas of mild-to-moderate vasospasm (<50% luminal narrowing) are indicated by arrows. Day 0 (d0) = day of hemorrhage.
Fig. 5. Preoperative and follow-up cerebral angiograms in the last seven patients treated in the series. Areas of mild-to-moderate vasospasm (<50% luminal narrowing) are indicated by arrows. Day 0 (d0) = day of hemorrhage.
vasospasm in this series of patients. Among 101 patients with thick SAH’s in the Canadian trial of nimodipine in poor-grade patients, 77 underwent repeat cerebral angiography during the peak vasospastic interval 5 to 10 days following SAH. Imaging vasospasm was seen in 72 (94%) of these patients, and in 47 (61%) it was severe and diffuse. In the present series of 15 patients, 13 with thick SAH’s, mild or no vasospasm was seen in 11, and moderate vasospasm (25% to 50% luminal narrowing) was seen in three. The only patient with symptomatic vasospasm in this series did not have repeat angiography but, on the basis of TCD examination, likely had severe diffuse vasospasm. This was the only patient who had no evidence of clot lysis on postoperative CT, and the only incidence of a poor outcome (death) due to vasospasm.

The major risk of intracisternal rt-PA is postoperative bleeding; among the 15 patients presented here, one patient had a large extradural hematoma resulting in a poor outcome. The results of this preliminary investigation of rt-PA suggest that this risk may be acceptable if treatment is restricted to patients with large SAH’s at high risk for severe vasospasm. A randomized trial of intracisternal rt-PA in such patients would seem appropriate.

Addendum

Since this paper was submitted for publication, six additional patients with diffuse, thick SAH’s have been treated with 10 mg of intracisternal rt-PA. All have demonstrated overnight basal clot clearance without complication and only one patient developed angiographic vasospasm, which was localized, moderate in degree, and asymptomatic.

Acknowledgments

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References