Early treatment of subarachnoid hemorrhage after preventing rerupture of an aneurysm

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Twelve patients with Hunt and Hess neurological Grades III to V underwent thrombosis of aneurysms using cellulose acetate polymer within 23 hours of aneurysm rupture. On computerized tomography (CT), nine of these patients had diffuse or localized thick subarachnoid blood clots, two had diffuse thin clots, and one had intraventricular clots. Immediately after thrombosis, all patients were administered tissue plasminogen activator (TPA) through spinal or ventricular catheters. The pressure of the lumbar cerebrospinal fluid was maintained at 100 to 150 mm H2O. The TPA was given as multiple injections of 2 mg on Day 0 and 1 to 2 mg on the following 1 to 2 days. In two patients the second injection of TPA was not given because of severe brain damage resulting from the initial subarachnoid hemorrhage. Ten patients showed complete clearance of the cisternal clot on CT within 72 hours after thrombosis. Seven partially thrombosed aneurysms and five multiple aneurysms were clipped during delayed surgery. Only one patient experienced mild vasospasm as shown on the follow-up angiogram. Eight patients improved clinically and had a good recovery, two had severe disability, and two died. Urgent thrombosis of a ruptured aneurysm followed by immediate postthrombotic administration of TPA may be a safe and reasonable means of preventing vasospasm and improving patient outcome.

KEY WORDS • cellulose acetate polymer • cerebral vasospasm • delayed aneurysm surgery • hypertensive hypervolemic therapy • cerebrospinal fluid drainage • tissue plasminogen activator

Aneurysm rerupture is a leading cause of death and disability in patients with subarachnoid hemorrhage (SAH) resulting from an aneurysm. The cumulative 2-week rebleeding rate ranges from 19% to 27.7% with the peak occurring in the first 24 hours, and the mortality rate ranges from 60% to 80%. The International Cooperative Study on the Timing of Aneurysm Surgery concluded that mortality from rebleeding accounts for nearly 26% of all deaths and that the postoperative risk after early surgery is equivalent to the risk of rebleeding and vasospasm in patients waiting for delayed surgery. Both vasospasm and rebleeding are potentially amenable to therapeutic intervention.

The investigators present here a method to effectively treat a ruptured aneurysm immediately after angiographic diagnosis using endovascular cellulose acetate polymer thrombosis and tissue plasminogen activator (TPA). This method eliminates the risk of early rebleeding and allows for aggressive medical treatment of vasospasm while avoiding the hydrocephalus associated with ruptured aneurysms.
Early treatment of SAH after prevention of rerupture

**TABLE 1**

<table>
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<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Aneurysm Location</th>
<th>SAH Grade†</th>
<th>Clinical Grade</th>
<th>Time (hrs) From SAH to Thrombosis</th>
<th>Result (%) of Thrombosis</th>
<th>TPA Dose (mg)</th>
<th>Duration of Spinal Drainage (Days)</th>
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* TPA = tissue plasminogen activator; SAH = subarachnoid hemorrhage; H & H = Hunt and Hess; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ACoA = anterior communicating artery; MCA = middle cerebral artery; T = thrombosis of aneurysm followed by clipping; U = unruptured aneurysms; BA = basilar artery; AChA = anterior choroidal artery; ICA = internal carotid artery; PCoA = posterior communicating artery; Op = ophthalmic artery; E = extravasating aneurysm; V = ventricle.

† SAH grade based on Fisher, et al.‡ Death caused by primary brain damage from SAH.

All 13 aneurysms were also clipped at delayed surgery. Seven thrombotic aneurysms were identified and was positioned in the deepest part of the aneurysm or in the dome of a potential rebleeding site. One patient (Case 10) had aneurysms of the AChA, and underwent thrombosis of both. In another patient (Case 12), the ICA–PCoA aneurysm extravasated contrast material during angiography. Thirteen of the 18 aneurysms were candidates for thrombus using cellulose acetate polymer. At delayed surgery, five unruptured aneurysms were clipped: two of the contralateral MCA (Cases 3 and 7), one of the contralateral AChA (Case 5), and one each of the ipsilateral MCA and the contralateral carotid–ophthalmic artery (Case 8). Seven thrombotic aneurysms were also clipped at delayed surgery.

**Aneurysm Thrombosis Using Cellulose Acetate Polymer**

All 13 aneurysms appropriate for the technique were completely or partially thrombosed using cellulose acetate polymer immediately after diagnostic angiography, within 23 hours after SAH. The mean time from initial hemorrhage (Day 0) to thrombosis was 6.8 hours (range 3 to 23 hours). Patients were chosen for this treatment according to five criteria: 1) they were poor surgical candidates because of secondary hemorrhage (Hunt and Hess Grade III, IV, or V); 2) they had diffuse or localized thick subarachnoid blood clots, diffuse thin clots, or intraventricular clots on CT (Fisher’s grade 2, 3, or 4); 3) the aneurysm extravasated contrast material during angiography; 4) the initial SAH was believed to have occurred within 24 hours before admission; and 5) the neck of the aneurysm made it a candidate for cellulose acetate polymer thrombosis.

Angiography was performed through the femoral artery under local anesthesia as soon as possible after admission. A Tracker-18 microcatheter was inserted into the angiographic catheter immediately after the ruptured aneurysm was identified and was positioned in the deepest part of the aneurysm or in the dome of a potential rebleeding site in multilobed aneurysms lying against the direction of blood flow in the parent artery. In patients with multiple aneurysms, the presumed source of bleeding was based on CT and angiographic findings and the patient’s neurological status.

The detailed technique and preliminary clinical experience of aneurysm thrombosis using cellulose acetate polymer have been described elsewhere.13–17 Using this procedure, four aneurysms were completely thrombosed and nine were intentionally partially thrombosed, including a bleb, to decrease the time needed to complete thrombosis and to reduce the difficulty of the complete thrombotic procedure. Introducing the catheter and infusing cellulose acetate polymer took approximately 10 minutes.

**Intrathecal Drainage, TPA Administration, and Pressure Control**

All patients underwent continuous lumbar drainage through a silicone tube inserted into the subarachnoid
Sterile lyophilized TPA powder (4.8 mg, Kowa Co., Tokyo, Japan) was reconstituted with 2 ml sterile water, and 2 mg TPA was administered through the catheters just after cellulose acetate polymer thrombosis. For the patient with ventricular drainage, TPA was injected into both the cistern and the ventricles. The catheter was clamped for 3 to 4 hours to prevent immediate expulsion of the TPA. In all patients, cerebrospinal fluid (CSF) pressure was set at 100 to 150 mm H2O, measured above the ear, and was maintained for 4 to 14 days until all the cisterns showed low density on CT scans and CSF obtained from the catheters was still bloody but diluted. We had planned to continue drainage for 14 days after SAH, but the tube was removed from patients when the CSF was almost clear and the lumbar spinal pressure returned to normal. Drainage tubes were removed early in two patients: one with brain death (Case 12) and one who refused aggressive therapy because of severe brain damage, age, and severe cardiac failure (Case 11). A dose of 2 mg TPA given on Day 0 and 1 to 2 mg given on each of the following 1 to 2 days was sufficient to clear the hemorrhage in the subarachnoid space. Prophylactic hypervolemic hypertensive therapy was used in four patients to prevent vasospasm (Cases 4, 6, 10, and 11). Calcium antagonists and antiplatelet agents were not used, but steroids, mannitol, and glycerol were administered to all patients.

Clot Clearance

After surgery, CT scans were obtained at 1- or 2-day intervals until the subarachnoid hematoma disappeared and no new low-density areas were visible. All but two patients (Cases 11 and 12) had almost complete resolution of cisternal blood clots on CT within 72 hours after TPA administration: one within 24, six within 48, and three within 72 hours.

One patient with intraventricular hemorrhage (Case 10) had complete resolution of the intraventricular clot within 48 hours and the cisternal clot resolved within 72 hours after direct injection, both ventricular and spinal, of TPA. A repeat CT scan was not obtained in two patients (Cases 11 and 12) who had early removal of drainage tubes.

Rebleeding, Vasospasm, and Clinical Course

Follow-up angiography on Days 4 to 10 was performed to observe any vasospasm and the growth of any aneurysm. Angiography was also performed when warranted by clinical evidence of the patient’s neurological decline. If only partial thrombosis was performed, the patient’s condition was assessed continuously to monitor further change and to determine whether a repeat angiogram or surgery was necessary to completely obliterate the neck of the aneurysm. None of the 18 aneurysms (13 thrombotic and five multiple) rebled during clinical observation.

Figure 1 illustrates the course of the neurological condition of each patient as assessed using the Glasgow Coma Scale (G.C.S.) and Hunt and Hess (H&H) grading after subarachnoid hemorrhage (Day 0). The asterisks indicate the operative day.
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Fig. 2. Case 5. Left: Prethrombosis angiogram, anteroposterior view, showing the ruptured anterior communicating artery aneurysm. Right: Postthrombosis angiogram with compression of the right internal carotid artery showing complete thrombosis of the ruptured aneurysm.

scales were used to determine early small changes in motor deficits and the patient’s level of consciousness as a consequence of vasospasm. In one patient (Case 7), mild vasospasm appeared in the proximal segment of the middle and anterior cerebral arteries, associated with deteriorated consciousness. Angiographic evidence of vasospasm was not seen in nine patients undergoing repeated angiograms, except for two patients (Cases 11 and 12). In one (Case 11), angiographic and clinical vasospasm was unclear because the patient deteriorated as a result of renal, pulmonary, and cardiac failure and severe brain damage. The second patient (Case 12) was declared brain dead on Day 3 after SAH and died the next day. Four patients (Cases 1, 2, 5, and 6) showed marked improvement within 7 days after SAH, two (Cases 3 and 8) showed gradual recovery over 14 days, and two (Cases 4 and 7) gradually recovered within 30 days. The two remaining patients (Cases 9 and 10) reached Hunt and Hess Grades III and IV, respectively, in 30 days.

Surgical Clipping

Twelve aneurysms (in six patients), including five that were unruptured, were clipped using standard microsurgical technique at least 2 weeks after the patient experienced SAH. Surgery was performed 2 weeks after SAH in one of seven partially thrombosed aneurysms (Case 2), on Day 28 in one (Case 8), and more than 1 month later in five aneurysms (Cases 4, 6, 7, and 10).

Six patients with thrombotic aneurysms did not undergo surgery, either because of complete thrombosis (Cases 1, 5, and 9), increased thrombosis after the cellulose acetate polymer procedure (Case 3), or death from initial severe brain damage (Cases 11 and 12). An unruptured aneurysm of the contralateral MCA (Case 3) was surgically clipped 1 month after SAH.

Complications

One major complication caused by cellulose acetate polymer thrombosis occurred in a patient (Case 10) undergoing thrombosis of aneurysms in both the AChA and ICA–PCoA. A cerebral angiogram obtained after thrombosis showed that both aneurysms had been obliterated and the blood flow in the MCA was patent despite the impingement of cellulose acetate polymer. Three weeks later, the protrusion resulted in severe stenosis of the MCA, and the patient developed a persistent left-sided hemiparesis. The carotid artery angiogram had been misinterpreted as showing a complex aneurysm of the ICA–PCoA, and cellulose acetate polymer had been inadvertently overinfused into the dome of the aneurysm. The dose of TPA used in these patients did not cause systemic fibrinogenolysis, intracranial hematoma, or oozing from the operative incision, as has been reported in other studies.1,26,35 Ventricular enlargement after removal of the spinal catheter was observed on follow-up CT in four patients (Cases 2, 7, 8, and 10). Two of these patients showed symptoms of mildly elevated intracranial pressure and two developed normal pressure hydrocephalus. These four patients were treated using shunts.

Results

The long-term results of cellulose acetate polymer therapy were assessed 6 months after treatment. Of the original 12 patients, two died (Cases 11 and 12), two suffered severe disability because of the effects of occluding the MCA (Case 10) or the initial rupture (Case 9), and eight patients had good results.

Illustrative Cases

Case 5. This 52-year-old woman came to medical attention with a severe headache and unconsciousness. Her neurological condition at the time of admission was classified as a Grade IV according to the Hunt and Hess scale. A cerebral angiogram showed a ruptured aneurysm of the ACoA (Fig. 2 left) measuring 4 × 7 mm. A Tracker-18 microcatheter was immediately inserted into the ruptured aneurysm and 0.04 ml cellulose acetate polymer was injected, using Matas’ procedure under fluoroscopy during angiographic evaluation. 5 hours after the initial hemorrhage (Fig. 2 right).30

Computerized tomography at the time of admission and immediately after thrombosis showed diffuse thick and dense SAH in the basal cisterns, the bilateral sylvian fissures, and predominantly in the interhemispheric fissure (Fig. 3 left). Cerebrospinal fluid was drained through the tip of a spinal catheter advanced to the upper thoracic level. The patient was initially given 2 mg of TPA through the catheter, 1 mg of TPA 24 hours later, and 1.5 mg 48
hours later. The CSF pressure at the tip of the drainage catheter was set at 100 mm H₂O, measured above the ear and maintained for 4 days. A CT scan obtained 72 hours after the hemorrhage showed complete lysis of the subarachnoid clots (Fig. 3 right). Within 4 days after SAH, the patient became alert, her headache disappeared, and her neurological state returned to normal. An unruptured aneurysm of the left AChA was successfully clipped on Day 30.

Case 7. This 68-year-old woman suddenly developed a severe headache with left-sided hemiparesis. Her neurological status was classified Grade IV according to Hunt and Hess. A right ICA angiogram showed a multilobed aneurysm at the trifurcation of the MCA (Fig. 4 upper left). During diagnostic angiography, a bleb considered to be at risk of rebleeding was thrombosed with 0.05 ml cellulose acetate polymer (Fig. 4 upper center). A CT scan showed thick and diffuse hemorrhage in the sylvian fissures and basal cisterns and an intracerebral hematoma in the right temporal lobe. Two milligrams TPA was administered through the spinal drainage catheter and supplemented by 2 mg TPA daily for the following 2 days. The patient’s consciousness level gradually improved after drainage.

A CT scan showed thick and diffuse hemorrhage in the sylvian fissures and basal cisterns and an intracerebral hematoma in the right temporal lobe. Two milligrams TPA was administered through the spinal drainage catheter and supplemented by 2 mg TPA daily for the following 2 days. The patient’s consciousness level gradually improved after drainage.

On the first day after the initial procedure, the patient became unresponsive to commands and CT showed evidence of brainstem compression (despite aggressive medical therapy) from an aneurysmal intracerebral hematoma. The patient underwent a pterional craniotomy, and the surgical approach was planned to evacuate only the hematoma without clipping the neck of the aneurysm. A CT scan obtained 72 hours after SAH showed complete lysis of the hemorrhage but a small intracerebral clot. The patient’s neurological status rapidly improved by Day 2 after SAH; however, her consciousness level deteriorated on Day 3. An angiogram showed mild vasospasm (<10% luminal caliber compared to the preoperative caliber) of the anterior and middle cerebral arteries, and 80 mg papaverine was selectively infused on Day 4. The narrowed arteries were successfully dilated and the normal luminal diameter restored. The patient’s level of consciousness rapidly improved, and the same amount of papaverine was repeated for fluctuations in her neurological status on Days 5 and 6. A ruptured aneurysm was clipped via a craniotomy on Day 38 (Fig. 4 upper right). After surgery, the patient had an uneventful recovery.

Case 8. This 66-year-old woman developed severe headache and loss of consciousness. At the time of admission, her neurological status was rated Grade IV in the Hunt and Hess classification. A right ICA angiogram showed a ruptured aneurysm of the right ICA–PCoA and an unruptured aneurysm of the MCA (Fig. 4 lower left). Cellulose acetate polymer (0.05 ml) was immediately infused into the aneurysmal sac, leaving the neck of the
aneurysm intact (Fig. 4 lower center). Immediately after thrombosis, a CT scan showed thin and diffuse SAH and reflux into the lateral ventricle. The patient underwent CSF drainage through a spinal catheter and was then given 2 mg TPA through the catheter followed by 2 mg TPA 24 hours after SAH. A CT scan obtained 48 hours after SAH showed complete lysis of the hemorrhage but a small intraventricular clot. Because the patient developed normal pressure hydrocephalus after the CSF drain was removed, a ventricular peritoneal shunt was placed. Her neurological status gradually improved to normal by 14 days after SAH. Twenty-eight days after SAH, the right aneurysm was clipped (Fig. 4 lower right) and the cellulose acetate polymer remained within the aneurysmal sac. The MCA aneurysm was wrapped with a cottonoid sheet and fixed with a polymer. The patient’s postoperative course was uneventful.

Discussion

Thrombosis With Cellulose Acetate Polymer

Early obliteration of an aneurysm through intravascular thrombosis may be a useful way to prevent rebleeding, and the earlier thrombosis is performed, the lower the risk of rebleeding. Early thrombosis of a ruptured aneurysm combined with lumbar CSF drainage has been proposed as a means of improving the patient’s chances for recovery, not only by preventing rebleeding but also by promptly alleviating the early intracranial consequences of SAH.16,22,25

Since the reports concerning direct thrombosis using cellulose acetate polymer were first published,14,15 we have noted that even partial thrombosis including the bleb keeps the aneurysm from rebleeding for 2 to 3 months after the initial hemorrhage. Aneurysm rupture during angiography is an unusual but catastrophic event.1,34 Despite obliteration of the extravasating aneurysm in one of our patients (Case 12), however, severe primary brain damage occurred before thrombosis could be performed.

Continuous Lumbar Drainage

Early removal of subarachnoid clots and continuous postoperative drainage of CSF have been recommended to prevent vasospasm,18,22,25 and the drainage routes usually employed were from the cisterns or ventricles during the surgical procedure. We used conventional continuous spinal CSF drainage without surgical exposure in our 12 patients. In one patient (Case 10) who had intraventricular hemorrhage, ventricular drainage was combined with the spinal route to avoid mechanical obstruction of the CSF flow in the ventricular system or within the basal cistern.

Intracranial pressure must be controlled to keep intracranial hypertension from aggravating the insufficiency of the cerebral circulation.5,24 Nornes25 noted that 1 to 2 minutes after recurrent bleeding the intracranial pressure may be as high as, or higher than, the patient’s diastolic blood pressure and returns to near prerupture values within 15 minutes. However, the prerupture values were already elevated because the initial SAH had already occurred and continued for a period of a few days at high epidural pressure. Nornes also found an increased risk of rebleeding from intracranial aneurysms when the intracranial pressure normalized after SAH. Without respect to rebleeding, we found that all but the two patients who died could withstand continuous lumbar drainage immediately after thrombosis for 4 to 14 days to lower intracranial pressure, remove blood-contaminated CSF, and administer TPA.

Intrathecal Fibrinolytic Therapy

It is generally accepted that a high correlation exists between the development of vasospasm and the amount and distribution of subarachnoid blood. Consequently, it is believed that early and extensive removal of perivascular blood should effectively minimize the occurrence of vasospasm and delayed ischemic deficits.7,19,22,32

Recently, a new method for preventing vasospasm is to inject TPA, which is a fibrinolytic agent with a high affinity for clots, intracisternally.5,29 Findlay and colleagues3 and Öhman and coworkers56 described the effectiveness of a single-injection method of TPA administered only during surgery performed 24 to 48 hours after hemorrhage. Delaying treatment with TPA for 72 hours, however, did not prevent vasospasm.2 Serial measurements of TPA levels after intrathecal injection have proven that multiple injections of small doses of TPA maintain a higher level of TPA activity over a longer period than a single injection does and, therefore, should be more effective in dissolving the hematoma.21,35

In patients experiencing intraventricular hemorrhage, ventricular injection was also effective because TPA could flow to the cistern of the posterior fossa and to the basal cisterns to dissolve clots located there. In the acute stage of SAH, an accumulation of blood in the subarachnoid space, or an obstruction in the CSF pathway, prevents the egress of CSF from the basal cistern to the subarachnoid space over the cerebral hemispheres. Cerebrospinal fluid produced primarily by the choroid plexus continuously flows from the ventricles into the basal cistern.28 We infused TPA through the lumbar catheter into the subarachnoid space near the basal cistern. After TPA was administered, the spinal catheter was temporarily clamped to keep TPA from flowing out and to increase the lumbar CSF pressure to 200 mm H₂O. We expected that the CSF containing TPA would spread widely into the subarachnoid space with the help of the slightly increased pressure and facilitate lysis of the subarachnoid clots. Approximately 3 or 4 hours later, the drainage tube was unclamped. But it is unknown how the difference between CSF circulation patterns in intact arachnoid membranes, as in our study, and membranes cut during operative intervention affects the diffusion of TPA. Although mild vasospasm developed in one of our patients, our results indicate that multiple intrathecal injections of small doses of TPA effectively and safely prevent vasospasm. Rapid clearance of SAH on Days 0 to 3 appeared to be associated with a reduced incidence of vasospasm in our series. Based on this experience, we conclude that, if TPA is administered on Day 0, an injection of 2 mg TPA daily for 3 days (a total of 2 to 6 mg) effectively prevents vasospasm.
Timing of Aneurysm Surgery and Surgical Results

During the 6-month follow-up period, the International Cooperative Study on the Timing of Aneurysm Surgery evaluated surgical results and analyzed the causes of death and disability according to the time of surgery. In the early period after surgery, vasospasm was the major cause of morbidity and mortality. In addition, surgical complications were highest 4 to 6 and 7 to 10 days afterward. Overall, good recovery rates in patients who were drowsy, stuporous, or comatose preoperatively ranged from 49% to 62%, 27% to 33%, and 10% to 22%, respectively, 32 days after SAH; correspondingly, the mortality rate in the same groups ranged from 22% to 31%, 39% to 46%, and 32% to 79%, respectively. Among patients who were drowsy beforehand, surgery planned for Days 0 to 3 was not advantageous. The “tightness” of the brain during surgical exposure appears to be related to the interval between SAH and surgery. The brains of patients undergoing late surgery were softer than those of patients undergoing early surgery. The percentage of patients with “tightness” gradually decreased as survival times increased, and reached a minimum 1 month after SAH.

Obviously, the ideal time for surgical therapy is in the chronic stage of SAH, when aggressive treatment such as hypertensive hypervolemic therapy or fibrinolytic drug administration through the cisternal drainage can be performed without risk of rebleeding. We delayed surgery in poor-grade patients for approximately 1 month after SAH; these patients did not undergo surgery until they improved to a better grade than that at the time of admission.

Clinical Symptoms

The time-dependent reduction in the amount of blood seen on CT in the subarachnoid space and ventricles probably relates to the lysis and washing away of clot. Patients who had clots of long duration, however, were more likely to have vasospasm, and the incidence of angiographic vasospasm increased each day from Day 0 until Day 7.

Our results provide evidence that the capricious appearance of delayed ischemic dysfunction can be eliminated by the combined treatment presented here. Patients’ neurological status (both the level of consciousness and focal deficit) was poor when they were admitted after SAH, but tended to improve over a period of a few days. This tendency may reflect the improvement in neurological status that occurs naturally after aneurysmal SAH. In a series of patients with aneurysms operated on early, the sooner an attempt was made to remove the subarachnoid clot after the onset of SAH, the easier the clot was sucked from the subarachnoid space, and the less adherent the arachnoid membrane was to cerebral vessels. Alternatively, early administration of TPA (mean 6.8 hours after SAH) and wash-out of blood-contaminated CSF may result in rapid improvement of the patient’s neurological status and may be attributed to lysis of the subarachnoid clot and decreasing intracranial pressure.

At the 6-month follow-up evaluation, 67% of the patients in this study had a good outcome, 16% had severe disability, and 16% had died. These results compare favorably with those reported by Zabramski, et al., in which seven patients were admitted with Grade III lesions and three were admitted with Grade IV lesions. A randomized trial might justify this combined early treatment as appropriate for poor-grade patients with SAH.
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