Prospective study on the prevention of cerebral vasospasm by intrathecal fibrinolytic therapy with tissue-type plasminogen activator

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The authors have evaluated the efficacy of postoperative intrathecal injections of tissue-type plasminogen activator (tPA) in preventing cerebral vasospasm in patients with a diffuse thick subarachnoid hemorrhage (SAH). The present study examined 105 patients who underwent direct surgery within 48 hours of SAH and whose computerized tomography (CT) findings were classified as Fisher CT Group 3. Patients showing diffuse thick subarachnoid blood clots on CT with greater than 75 Hounsfield units (HU) were included in the tPA therapy group and those with below 75 HU comprised the control group. The surgical method was the same in both groups, and both groups had cisternal drainage instituted. On the day following the operation, the tPA group was given an intrathecal injection of tPA (2 mg), and this was continued for several days until all of the cisterns exhibited low density on CT scans. Follow-up angiography showed that 26 cases (87%) in the tPA group had no vasospasm, three (10%) had moderate vasospasm, and one (3%) had severe vasospasm. All four patients showing spasm on angiography were asymptomatic, and there were no cases of delayed ischemic neurological deficits (DIND). In contrast, there were 11 cases (15%) with DIND in the control group. In the tPA group, there was one case of SAH caused by drainage catheter removal, one with a small epidural hematoma, and one with subgaleal fluid accumulation; all of these were treated conservatively with favorable results. Overall, there were no infectious complications related to cisternal drainage and intrathecal injection of tPA. These results indicate that multiple intrathecal injections of small doses of tPA are effective and safe in preventing vasospasm. On the basis of this experience, the authors conclude that injection of 2 mg of tPA daily for 5 days (a total of 10 mg) is effective in preventing the development of vasospasm.

KEY WORDS: aneurysm · subarachnoid hemorrhage · vasospasm · fibrinolysis · tissue-type plasminogen activator

It is widely accepted that the evacuation of subarachnoid blood clots at an early stage is effective in preventing cerebral vasospasm. It is, however, not always technically possible to remove the entire hematoma. Consequently, various adjunct therapies have been devised to dissolve the hematoma at an early stage. In recent years, both experimental and clinical studies have demonstrated that intrathecal administration of tissue-type plasminogen activator (tPA) is effective in removing the remaining hematoma and preventing vasospasm. Debate has continued, however, with regard to the method of tPA administration and the optimum dosage. We have administered tPA in multiple injections to the basal cisterns and ventricles postoperatively in severe cases of subarachnoid hemorrhage (SAH) and have obtained satisfactory results in preventing vasospasm.

Clinical Material and Methods

Patient Population

Among the 142 consecutive cases of ruptured cerebral aneurysm admitted to our clinic between August, 1989, and March, 1991, there were a total of 105 patients who underwent direct operations within 48 hours of SAH and whose computerized tomography (CT) findings were classified as Fisher CT Group 3. The tPA group comprised patients in whom the subarachnoid hematoma gave mean CT scores of more than 75 Hounsfield units (HU); in these cases, tPA was administered intrathecally. The control group comprised patients with mean CT scores below 75 HU, and these underwent cisternal drainage only. The CT density of the hematomas was investigated in all patients by means of region-of-interest analysis. A total of six
Tissue-type plasminogen activator for vasospasm

![Image](https://example.com/image.png)

**Fig. 1.** Patient selection for intrathecal injection therapy of tissue-type plasminogen activator (tPA) was made according to the computerized tomography (CT) findings of a subarachnoid hemorrhage. *Underlined numerals* indicate the Hounsfield units of the hematoma in each region of interest. *Left:* Representative CT scans in the tPA group. *Right:* Representative CT scans in the control group.

regions of interest were placed in the suprasellar cistern, both sylvian cisterns, both insular cisterns, and the frontal interhemispheric fissure, as seen in the two CT slices through these areas (Fig. 1). The tPA group consisted of 30 patients, the control group of 75 patients. The age, sex, site of the aneurysm, preoperative Hunt and Kosnik grade, timing of the operation, and CT density of the hematoma of patients in both treatment groups are shown in Table 1. The CT scans from all of the patients in the tPA group are shown in Fig. 2.

**Surgical Procedures**

The surgical procedures were the same for both groups. After aneurysm clipping, the subarachnoid hematoma was aspirated as thoroughly as possible and, at the completion of the surgery, drainage catheters were usually placed in the bilateral sylvian cisterns and in the carotid cistern on the side of the craniotomy. The first 10 patients in the tPA group underwent bilateral craniotomy in order to facilitate aspiration of the hematoma, but most of the subsequent patients underwent unilateral craniotomies. In the case of unilateral craniotomy, drainage catheters were inserted into the carotid cistern, the distal portion of the ipsilateral sylvian cistern, and the proximal portion of the contralateral sylvian cistern. Ventricular drainage was instituted in patients with extremely high intracranial pressure. The majority of the operations were performed by one of the authors (K.M.), and there were no significant differences in the extent or degree of hematoma aspiration between the two groups.

**Protocol for tPA Treatment**

In the tPA group, a total of 2 mg of tPA* was administered via the catheters on the day following the operation. The catheters were clamped for 1 hour to prevent the immediate expulsion of the tPA, then they were released. In other words, in a case where a total of four catheters (three for cisternal drainage and one for ventricular drainage) were placed, 0.5 mg was injected in each. In order to adjust the tPA solution to a pH of about 7.0, 2 mg of tPA powder was dissolved in 10 ml of 10% arginine hydrochloride, and 0.3 ml of 8.4% sodium bicarbonate was added. Injection of tPA was continued until all of the cisterns exhibited low density on CT scans and, moreover, until the cerebrospinal fluid obtained from the drainage catheters was xanthochromic. The drainage catheters were usually not removed at the completion of tPA administration, but were left in place for a period of 2 weeks.

The tPA treatment protocol was based on the Japanese Ministry of Health guidelines and was accepted by the Clinical Research Board of the Kohnan Hospital. Informed consent for this protocol was obtained from all patients or their relatives. In the present series of patients, other medical treatments, including the intravenous administration of calcium antagonists and/or

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*Abbreviations: tPA = tissue-type plasminogen activator; ACoA = anterior communicating artery; ICA = internal carotid artery; MCA = middle cerebral artery; VBA = vertebrobasilar artery; CT = computerized tomography; HU = Hounsfield units; SD = standard deviation.

* Abbreviation: tPA = tissue-type plasminogen activator manufactured by Sumimoto Pharmaceutical, Inc., Tokyo, Japan.

**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>tPA Group</th>
<th>Control Group</th>
<th>Significance (p Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex (F:M)</td>
<td>14:16</td>
<td>49:26</td>
<td>0.0574</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>52:75</td>
<td>60:25</td>
<td>0.1741</td>
</tr>
<tr>
<td>mean aneurysm location</td>
<td></td>
<td></td>
<td>0.9851</td>
</tr>
<tr>
<td>ACoA</td>
<td>12</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>7</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>11</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>VBA</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>preoperative grade</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>12</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>11</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>timing of operation</td>
<td></td>
<td></td>
<td>0.0617</td>
</tr>
<tr>
<td>Day 0</td>
<td>12</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>16</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>2</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>CT density of clot (HU)</td>
<td>79.6 ± 6.4</td>
<td>66.8 ± 5.8</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Ranges shown as means ± SD.*
steroids, were not used. Prophylactic hypervolemic hypertensive therapy was also not employed. Mannitol and glycerol were administered to patients showing brain edema.

**Postoperative Studies**

Postoperatively, CT scans were obtained daily until Day 14 (Day 0 = day of SAH) and the disappearance of the subarachnoid hematoma and the absence of new...
low-density areas was confirmed. For measurement of regional cerebral blood flow (rCBF), single photon emission computerized tomography (SPECT) was performed at least twice prior to Day 14; SPECT was performed primarily on Days 4 and 8, but also when warranted by clinical evidence of neurological decline. The radionuclide used was $^{99m}$Tc-hexamethylpropyleneamine oxime, which has the advantage of possible emergency use. Cerebral angiography was carried out at least once before Day 14 in the tPA group. In the first 10 patients, angiographic studies were performed on Day 4 or 5 and between Days 7 and 10. However, in the last 20 cases, follow-up angiography was carried out primarily on Days 7 to 10 after SAH.

The control group underwent postoperative angiography on the basis of changes in SPECT imaging and neurological findings. The severity of the vasospasm on angiography was classified as follows: reduction in the luminal caliber by less than 25%, compared to baseline was classified as a mild spasm, 25% to 50% as a moderate spasm, and greater than 50% as a severe spasm. In a large number of cases, data from a simultaneous transcranial Doppler ultrasound study was not sufficiently reliable, and the results have not been included in the present report. Statistical analysis of the two groups was done using Student's t-test or the chi-squared test.

Results

Grading and Timing

In the tPA group, 23 (77%) of the 30 cases had preoperative Hunt and Kosnik grades of III or higher, in contrast to 25 (33%) of the 75 in the control group. This difference was statistically significant (p < 0.01). The mean CT density in the tPA group (± standard deviation) was 79.6 ± 6.4 HU, which was significantly higher than that of the control group (66.8 ± 5.8 HU) (p < 0.01). Most of the tPA-treated patients (28 of 30, or 93%) were operated on by Day 1, whereas 59 (79%) of the 75 patients in the control group underwent surgery within Day 1. Thus, there was a trend toward earlier operations in the tPA group, but this was not statistically significant (Table 1).

Angiographic Spasm and Delayed Ischemia

Angiographic studies were repeated in all cases in the tPA group, and 26 (87%) showed no evidence of vasospasm. Moderate spasm was found in three (10%) and severe spasm in one (3%). In none of these 30 cases (including the four cases with angiographic vasospasm), however, did SPECT indicate a decrease in rCBF, nor were there any cases of delayed ischemic neurological deficits (DIND) (Table 2), or low-density areas on CT scans.

In the control group, despite the fact that the severity of SAH was less severe than that in the tPA group, as judged from preoperative CT, 11 patients (15%) suffered DIND (Table 2). Among these 11 cases, five showed severe vasospasm and underwent transluminal balloon angioplasty immediately after the emergence of ischemic symptoms with favorable recoveries. Five other patients exhibited minimal symptoms, moderate angiographic vasospasm, and mild decrease in rCBF in SPECT studies. For these reasons, they were not treated.
with angioplasty, but underwent conservative therapy with induced hypertension. They also showed gradual recovery and favorable outcomes. The final patient in this group died. This 45-year-old woman, who underwent surgery for a small aneurysm in the right internal carotid artery 12 hours after the onset of SAH, showed DIND on Day 7. Angiography revealed severe spasm of the M1 and M2 segments of the middle cerebral artery (MCA) on the unoperated side, and angioplasty was performed immediately. The symptoms did not improve, however, and follow-up angiography on Day 9 demonstrated severe spasm of both anterior cerebral arteries and the distal segments of the left MCA (distal from the M1 segment). A CT scan showed diffuse brain swelling, and the patient died on Day 11.

Because repeat angiographic study was not performed routinely in control group patients, statistical comparison of the incidence of angiographic vasospasm between the two groups is not possible. There was, however, a significant effect of tPA in suppressing DIND compared to the control group (p < 0.01).

Clinical Outcome

The outcome 1 month postoperatively was evaluated according to the Glasgow Outcome Scale.\(^{15}\) In the tPA group, good recovery was obtained in 23 cases (77%) and moderate disability remained in seven (23%) (Table 2). All of the patients with moderate disability were preoperatively in Hunt and Kosnik Grade IV and had poor outcomes as a result of the primary brain damage caused by SAH.

In the control group, there were 56 cases (75%) with good recovery, 12 (16%) with moderate disability, three (4%) with severe disability, and four deaths (5%) (Table 2). One of the four deaths was due to the vasospasm described above; two patients were in Grade V preoperatively, and one suffered rerupture following incomplete aneurysm clipping. Although 15% of the control group suffered DIND, permanent neurological deficits were infrequent because most of the patients with severe vasospasm showed clinical improvement in the neurological condition following balloon angioplasty. Therefore, the outcomes in the two groups were not statistically different.

### TABLE 2

<table>
<thead>
<tr>
<th>Factor</th>
<th>tPA Group</th>
<th>Control Group</th>
<th>Significance (p Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>30</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Incidence of DIND</td>
<td>0</td>
<td>11</td>
<td>0.0026</td>
</tr>
<tr>
<td>Outcome†</td>
<td>0</td>
<td>15</td>
<td>0.6583</td>
</tr>
<tr>
<td>Good recovery</td>
<td>23</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Moderate disability</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Severe disability</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

* Abbreviations: DIND = delayed ischemic neurological deficits; tPA = tissue-type plasminogen activator.
† Glasgow Outcome Scale.\(^{15}\)

**Treatment With tPA**

The total dose of tPA was 2 to 7 mg in 13 cases, 8 to 14 mg in 11 cases, and 15 to 26 mg in six cases (mean dose 9.6 mg). The period over which tPA was injected was 1 to 3 days in 10 cases, 4 to 6 days in 14 cases, and 7 to 9 days in six cases (mean duration 4.7 days) (Fig. 3).

**Complications**

Complications related to the tPA treatment were seen in three cases: one patient had an SAH, one a small epidural hematoma, and one a subgaleal fluid accumulation (Fig. 4). Conservative therapy led to recovery in all cases. In the cases with SAH, tPA injection therapy was continued until Day 8 with no adverse effect, the catheter was removed on Day 9 and, on the following day, CT revealed the hematoma in the left sylvian cistern. However, the patient was unchanged neurologically following this complication. No infectious complications were noted in either the tPA group or the control group.

**Discussion**

**Intrathecal Fibrinolytic Therapy**

It is known that removal of the subarachnoid hematoma at an early stage is an effective means for preventing vasospasm following SAH, but it is not technically possible to remove all of the hematoma in the subarachnoid space. For this reason, various supplemental methods have been developed, such as cisternal drainage and cisternal irrigation.\(^{14,16,17,23,25,32}\) Cisternal irrigation using urokinase, a technique that was an early precursor of the intrathecal fibrinolytic therapy advocated by Yoshida, et al.,\(^{33}\) in 1985, is of particular note in Japan, where a policy of early surgery has been actively pursued. Subsequently, a variety of techniques have been tried and their effectiveness demonstrated.\(^{17}\)
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These methods have had practical drawbacks, however, demanding the efforts of a large medical staff.

In recent years, a new method for preventing vasospasm has attracted attention, based on the detailed experimental work of Findlay, et al., and Seifert, et al., in which tPA, a new fibrinolytic agent with high affinity for the fibrin clot, is injected instead of urokinase into the cerebral cisterns. Reports of its clinical effectiveness have continued to appear. We have previously reported that multiple intrathecal tPA injections are effective in preventing vasospasm, whereas Findlay, et al., and Ohman, et al., have described the effectiveness of a single-injection method in which tPA is administered only during the operation. It is thus evident that room for debate remains concerning the optimum dosage of tPA, the duration of tPA therapy, and the advantages of simultaneous cisternal drainage.

Findlay, et al., advocated a method in which a relatively large dose (10 mg) of tPA is administered in a single injection to the operative field immediately before completion of the surgery and in which cisternal drainage is not routinely placed. This simple method would be ideal if it sufficed to dissolve the subarachnoid clot completely. Unfortunately, it seems that it does not completely remove the periarterial hematoma in the cisterns that are not opened during surgery, such as the insular cistern and the distal sylvian fissure on the nonoperated side, and thus cannot prevent distal vasospasm. As a result of serial measurements of tPA levels after intrathecal injection, Zabramski, et al., have argued that multiple injections of small doses of tPA should maintain a higher level of tPA activity over a longer period than a single injection and therefore should be more effective in dissolving the hematoma.

In the present series, CT scans were obtained daily following hematoma aspiration, and it was found to be essential to give multiple injections of tPA for several days following the operation until all of the subarachnoid hematoma in the cerebral cisterns had disappeared, as determined by CT. For cases in which ventricular drainage was instituted, tPA was injected not only into the cisterns but also into the ventricles. Ventricular injection was also administered because the tPA could then flow to the cisterns of the posterior fossa and dissolve a clot located there. For the first 10 cases treated in this way, we gave two tPA injections per day and continued treatment for more than 1 week in most cases. Subsequently, however, we have reduced the dose and duration of tPA treatment, and have found that a dose of 2 mg once per day for 5 days (total dose of 10 mg) is sufficient for suppressing cerebral vasospasm.

**Vasospasm vs. Subarachnoid Clot**

It is generally accepted that there is a high correlation between the development of severe vasospasm and the amount and distribution of subarachnoid clot, but even within the cases classified as Fisher CT Group 3, there are large differences in the amount of the hematoma. We have previously reported that the CT density of a hematoma is useful as an index of the amount of the subarachnoid hematoma and of the risk of vasospasm. In the present study, we included in the tPA group patients with the largest hematomas among the Fisher CT Group 3 cases and therefore those with the highest risk of vasospasm. More precisely, the tPA treatment group consisted of those patients with diffuse thick SAH (with a mean CT density of the clot of more than 75 HU), whereas the control group consisted of those patients with less severe SAH and relatively small hematomas. Moreover, in this series, we did not use adjunct therapies such as calcium antagonist administration or prophylactic hypervolemia, and thus have been able to make an accurate evaluation of the effects of intrathecal administration of tPA.

**Complications**

In the present series, one patient demonstrated SAH following removal of the drainage catheter. It was apparent that the cause of the SAH was not the tPA treatment, but rather mechanical injury induced at the time of catheter removal. There was also one patient with an asymptomatic small epidural hematoma and one with subgaleal fluid collection; both occurred as a result of insufficient dural closure. Since there is a high possibility of epidural hematoma formation when intrathecally injected tPA leaks extradurally, it is essential...
that dural closure be completely watertight. We normally use silk sutures to close the dura mater, and then apply a large volume of fibrin glue over the stitches. However, since tPA can dissolve the fibrin glue if they make contact, it is critical that the stitching of the dura mater itself provide complete closure. In the present series, no patient suffered severe postoperative intracranial hemorrhage requiring craniotomy, as has been seen in other studies. We conclude that the injection of small doses of tPA is safe and effective for avoiding complications such as intracranial hemorrhage caused by intrathecal injection of a large dose of tPA.

Transluminal Balloon Angioplasty

Transluminal balloon angioplasty is a promising therapy that can offer marked improvement to patients with DIND by mechanically dilating the constricted vessels. Once dilated, those vessels will not again develop spasm. Since 1986, we have performed 30 cases of balloon angioplasty. In the present series, angioplasty was carried out in six patients in the control group, and five of the six had favorable outcomes. Thus far, angioplasty has not been required in any of the patients in the tPA group.

Conclusions

In light of the present results, we conclude that intrathecal injection of tPA is obviously effective in preventing cerebral vasospasm. The selection of patients treated with tPA was strictly limited to those with a high probability of developing severe vasospasm, as predicted by CT findings. We found that intrathecal administration of tPA should be given to all patients graded as Fisher CT Group 3.

References

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