Tranexamic Acid in Subarachnoid Hemorrhage.  
A Double-Blind Study  

MARKKU KASTE, M.D. AND MAGNUS RAMSAY, M.D.

SUMMARY The effects of intravenous tranexamic acid were compared with placebo in 64 patients with subarachnoid hemorrhage. A double-blind procedure was used. One gram of tranexamic acid was given intravenously every 4 hours up to the time of operation on an intracranial arterial aneurysm or for up to 21 days after the first bleeding if operative treatment was not feasible. There were no differences in re-bleeds, morbidity or mortality between the tranexamic and placebo-treated groups. No thromboembolic complications were noted in either group. Our results do not support the use of tranexamic acid in subarachnoid hemorrhage in daily doses of 6 g.

SUBARACHNOID HEMORRHAGE mainly affects adults in their most productive years. Re-bleeding is frequent and the mortality from re-bleeds remains high.1 Surgical treatment can protect against re-bleeding, but it is not always possible, and early surgery has, in fact, proven to be disastrous.2 8 Anti-fibrinolytic agents have been employed to reduce the risk of re-bleeding after subarachnoid hemorrhage.9-10 We have evaluated the effects of the antifibrinolytic agent tranexamic acid in patients with subarachnoid hemorrhage.

Patients and Methods

Sixty-four patients under age 61 were studied. All had a history of acute onset of severe headache accompanied by neck rigidity. A diagnosis of subarachnoid hemorrhage was made on the basis of hemorrhagic spinal fluid not due to lumbar puncture. Treatment either with tranexamic acid or placebo was started after diagnosis, the patients being allocated randomly to either group. We excluded patients with: unconsciousness, acute myocardial infarction within 6 months, overt renal failure, signs of disseminated intravascular coagulation, and pregnancy. Patients were also excluded if it was not possible to start the treatment within 72 hours of the onset of symptoms. All patients had detailed general and neurological assessment, cerebrospinal fluid examination, and routine hematological and urine analysis. Cerebral angiograms were done in 60 patients. Five of the eight patients who died were autopsied. Only one patient had neither angiography nor necropsy. Boterell’s classification11 was used in the neurological assessment. Patients were suspected of having a recurrent hemorrhage if they showed 2 or more of the following signs: 1) sudden deterioration in their level of consciousness, 2) increase in the degree of neck rigidity, 3) increase in severity of headache, 4) sudden appearance of new neurological deficits or further progression of existing ones.10 The lumbar puncture was not repeated in 12 patients whose clinical evidence of recurrent hemorrhage was convincing as the care of a seriously ill patient was the chief concern. In 3 of these, re-bleeding was confirmed by necropsy. For the purposes of this report, the remaining 9 patients who did not have a repeat lumbar puncture were presumed to have had recurrent bleeding. Five of them were allocated to the tranexamic acid group and 4 to the control group.

Tranexamic acid and placebo were prepared in identical phials bearing the patient’s number. The code identifying each substance was broken only after the final evaluation of all 64 patients. The active treatment was as follows: one g of tranexamic acid in 50 ml saline was given intravenously every 4 hours up to the time of operation on an intracranial arterial aneurysm or for up to 21 days if operative treatment was not possible. Fifty ml of 0.9% NaCl in place of tranexamic acid were given at exactly the same time to control group. Other drug treatments which were used if necessary consisted of analgetics, antiemetics, dexamethasone and laxatives. If necessary, intravenous fluids were also given. No antihypertensive medication was used. General medical care was the same for all patients.

Student’s t-test, the chi-square test with Yate’s correction and Fisher’s exact test were used for statistical comparisons.

Results

The tranexamic acid treated and placebo treated control patients were comparable in age and sex (table...
1), as well as in pretreatment neurological status graded according to Boterell's classification (table 2). All patients were in good medical condition. No one had infectious disorders or other conditions relating to fibrinolytic activity. There were no differences in blood pressure between the 2 groups. Treatment was initiated within the same time limits from the initial ictus in both groups (table 3). A ruptured intracranial arterial aneurysm was found in 25 patients in the tranexamic acid treatment group and in 24 patients in the control group. The localization of the ruptured intracranial aneurysm is shown in table 4. Multiple aneurysms were verified in 8 patients in the tranexamic acid treatment group and in 4 in the control group. On 2 occasions hemorrhage was caused by an arteriovenous malformation and both patients were in the control group. The ruptured aneurysm was treated surgically in the tranexamic acid group and in the control group in 15 patients each. One patient in each group refused operative treatment. In the tranexamic acid group the operation took place, on an average, 17 days (median 18 days) after the first bleeding and, on an average, 16 days (median 17 days) after initiation of treatment. The figures in the control group were 18 days (median 18 days) after the first bleeding and 17 days (median 17 days) after initiation of treatment.

The same mortality was recorded in both groups. Three patients of each group (9.4%) died from re-bleeding. In the tranexamic acid treatment group one fatal re-bleeding occurred during the first week and 2 during the second. In the control group 2 fatal re-bleedings occurred during the first week and one during the second. One patient in the tranexamic acid group died when the aneurysm ruptured during surgery. One patient in the control group died after 12 days of progressive decline believed due to arterial spasm caused by the initial bleeding.

There were no significant differences in occurrence of re-bleeding between the 2 groups (table 5). Six of all re-bleedings in the active treatment group occurred during the first week and 5 during the second. Five of all re-bleedings in the control group occurred during the first and 3 during the second week. Eight of all re-bleedings in the tranexamic acid group occurred in patients with proven intracranial arterial aneurysm. Two of them were fatal. One of these fatal re-bleedings occurred in a patient with multiple aneurysms. Five of all re-bleedings in the control group occurred in patients with proven intracranial arterial aneurysm. One of them was fatal.

In the tranexamic acid treatment group cerebral vasospasm was seen in 23 and ventricular dilatation in 8 out of 29 patients in whom cerebral angiograms were obtained. These differences are not significant. Cerebral angiographies were comparable also in all other respects.

At the time of the study there were no computerized axial tomographies in Finland. Small intracerebral hematomas may have remained unvisualized.

One patient in the control group needed a ventriculo-atrial shunt. Six patients in the tranexamic acid treatment group and 2 in the control group complained of nausea and/or headache during infusion. Treatment had to be stopped on 2 occasions in the tranexamic acid treatment group (after 5 and 7 days respectively) and on one occasion in the control group (after 8 days).

Local thrombophlebitis developed in cannulated veins in 6 patients in the tranexamic acid group and in 2 in the control group. In one patient in the tranexamic acid treatment group the treatment was stopped because of thrombophlebitis occurring after 11 days treatment. None of the differences in the 2 groups reached significance. No re-bleedings were seen in any patients whose treatment was stopped because of the side effects. No severe thromboembolic complications were noted in either group. After the study period there were no significant differences in neurological status between the survivors of the 2 groups (table 2).

Discussion

Antifibrinolytic treatment has been advocated for conservative and preoperative treatment of sub-arachnoid hemorrhage. Some authors have reported favorable results using this treatment to reduce re-bleeding and mortality, while others have failed to find convincing efficacy of antifibrinolytic treatment. None of the previous studies was controlled or double-blind. Sengupta et al. reported good results with antifibrinolytic treatment on the re-bleeding rate in a controlled trial but they did not report the effect of the treatment on mortality and their control group comprised more severely ill patients than their active treatment group. In their active treatment group only 8 of 66 patients were not operated on, while in the control...
group, in 31 of 76 patients, there was reason to refrain from surgery making their groups non-comparable. Fodstad et al.\textsuperscript{13} had less re-bleedings in their tranexamic acid group than in the control group. There was, however, no difference in mortality between the groups. Girvin\textsuperscript{13} found no benefits from anti-fibrinolytic treatment in subarachnoid hemorrhage in a controlled trial.

Maurice-Williams\textsuperscript{14} has recently reported excellent results with prolonged anti-fibrinolytic treatment of patients with ruptured intracranial arterial aneurysm in a controlled trial. The re-bleeding mortality was 12\% in the active treatment group and 40\% in the control group. In our trial the re-bleeding mortality was 9.4\% both in the tranexamic acid treatment and control groups. Thirty (15 patients in each group) of our 64 patients had surgery. The surgery took place, on the average, 17 days after the first bleeding in the tranexamic acid treatment group and 18 days after the first bleeding in the control group. Early surgery is not carried out in Finland. Maurice-Williams used the same dosage and mode of administration of tranexamic acid for the first 7 days as we did for 21 days or until operation. Thereafter, his patients were given 1.5 g of tranexamic acid orally every 6 hours for 35 days or until operation. The selection of patients in Maurice-Williams' and in our trial was comparable. The discrepancy between the lack of effect of anti-fibrinolytic treatment reported here and the encouraging results reported by Maurice-Williams remains to be solved. If the encouraging results of Maurice-Williams could be repeated this certainly would be a great improvement; if the patient is in good condition 7 weeks after a hemorrhage from a single intracranial arterial aneurysm the outcome is good whether or not he is operated on.\textsuperscript{16} van Rossum et al.\textsuperscript{16} have reported the only double-blind study of the effects of tranexamic acid in subarachnoid hemorrhage. They found no favorable effects of this treatment, results which are similar to ours. In their study re-bleeding rates, morbidity and mortality were similar in the active treatment and control groups.\textsuperscript{16} Tovi\textsuperscript{8} showed that local fibrinolysis occurred in the cerebrospinal fluid on the third or fourth day after the initial bleed, and this observation has recently been verified by Maurice-Williams.\textsuperscript{14} If good results are to be expected from anti-fibrinolytic treatment, the medication must be started early after the initial bleeding. In the majority of patients we began the treatment during the first day. Patients were excluded if it was not possible to start the treatment within the first 3 days. Some earlier failures\textsuperscript{13, 14} may be due to inappropriate dosage of anti-fibrinolytic treatment. Tovi\textsuperscript{8} and Maurice-Williams\textsuperscript{14} have shown that one gram of tranexamic acid intravenously every 4 hours is enough to stop fibrinolysis in the cerebrospinal fluid which was the dose we used. There is little reason to assume that a higher dosage or a more frequent administration of tranexamic acid would produce different results which implies that factors other than fibrinolysis alone are responsible for re-bleeding after subarachnoid hemorrhage.

Tranexamic acid has been reported to cause cerebral vasospasm\textsuperscript{15} and transient dilatation of the third ventricle.\textsuperscript{17} Arterial spasm and ventricular dilatation are also often seen without anti-fibrinolytic treatment in patients with subarachnoid hemorrhage. There were no significant differences in our study in the occurrence of radiological vasospasm and ventricular dilatation between tranexamic acid treatment and control groups. This agrees with the similar neurological condition of the survivors in both groups after the study period. In the present study no severe thromboembolic complications were seen; these have occasionally been reported in connection with anti-fibrinolytic treatment.\textsuperscript{9, 8, 10, 18-20}

Our results do not support the use of tranexamic acid in subarachnoid hemorrhage.

**Acknowledgment**

This study was supported by the Paavo Nurmi Foundation, Finland. The tranexamic acid used (Cyklokapron) was supplied by courtesy of AB Kabi, Stockholm, Sweden.

**References**

8. Tovi D: Studies on fibrinolysis in the central nervous system with special references to intracranial haemorrhages and to the effect of antifibrinolytic drugs. Umeå University Medical

**Table 4** Site of Ruptured Intracranial Arterial Aneurysm

<table>
<thead>
<tr>
<th>Aneurysm Type</th>
<th>Anterior Communicating Artery</th>
<th>Middle Cerebral Artery</th>
<th>Internal Carotid Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active treatment</strong></td>
<td>8</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>9</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

**Table 5** Details of Deaths and Episodes of Re-bleeds

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>No. died</th>
<th>No. from re-bleed</th>
<th>No. re-bleed</th>
<th>No. re-bleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active treatment</strong></td>
<td>32</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>32</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>
Detrimental Effect of Prolonged Hypothermia in Cats and Monkeys With and Without Regional Cerebral Ischemia

Petter A. Steen, M.D., Edward H. Soule, M.D., and John D. Michenfelder, M.D.

SUMMARY In a previous study occlusion of a middle cerebral artery (MCA) followed by 48 h of hypothermia (29°C) was lethal in 5 of 5 monkeys as compared to only 3 of 9 normothermic animals. The present study extended these observations in monkeys and cats with or without MCA occlusion. In monkeys MCA occlusion plus 48 h of hypothermia was consistently lethal. Without MCA occlusion 2 of 3 monkeys survived, but were comatose the first 12 h post-hypothermia. In normothermic cats, MCA occlusion was lethal in only one of 5 animals whereas hypothermia was lethal in 20 of 21 cats with or without MCA occlusion. The detrimental effects of hypothermia were not favorably influenced either by hemodilution or by deliberate alterations in PaCO₂. The effect of 48 h of hypothermia and rewarming on cerebral blood flow (CBF) and cerebral metabolites was evaluated in 6 normal monkeys. CBF was reduced 60 to 70 percent at 29°C and returned to only a maximum of 50 percent of control with re-warming. Prior to re-warming distribution of CBF was in-homogeneous. Cerebral metabolites were borderline normal prior to re-warming but energy stores decreased while lactate increased with re-warming.

MANY MEASURES have been proposed as potentially efficacious in the treatment of acute regional cerebral ischemia; few of these have been found to favorably influence the outcome for patients suffering from acute stroke. The cerebral protective effect of hypothermia is well established, particularly as a technique for prolonging the brain’s tolerance to periods of complete cerebral ischemia. Rosomof also reported a beneficial effect of hypothermia in an acute canine stroke model produced by occlusion of a middle cerebral artery (MCA). A study from this laboratory did not confirm these findings in monkeys with MCA occlusion subjected to 48 h of hypothermia; a detrimental effect was observed instead. It was speculated that hypothermia might ultimately diminish oxygen delivery to the region of ischemia by an effect on blood viscosity with a resulting decrease in collateral flow. Decreased oxygen delivery could also result from a temperature effect on oxygen-hemoglobin dissociation resulting in decreased release of oxygen to the tissues. The present study was designed to examine these possibilities as well as the effect of hypothermia and rewarming on cerebral blood flow and cerebral metabolites.

Materials and Methods

Twelve Macaca fuscata or Macaca phillipina (3-5 kg) and 26 cats (2.5-5 kg) of both sexes, unmedicated and

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