Short-term Tranexamic Acid Treatment in Aneurysmal Subarachnoid Hemorrhage

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Antifibrinolytic treatment for 4 weeks after a subarachnoid hemorrhage has been shown to have no effect on outcome since a reduction in the rate of rebleeding was offset by an increase in ischemic events. To determine if a shorter course (4 days) of antifibrinolytic treatment before the expected onset of ischemic complications might reduce the rate of rebleeding yet avoid ischemic complications, we prospectively studied a series of 119 patients with subarachnoid hemorrhage; 479 patients with subarachnoid hemorrhage from our previous randomized double-blind study (238 treated with placebo, 241 with long-term tranexamic acid) served as historical control groups. At 3 months’ follow-up, the outcome of patients treated with short-term tranexamic acid was not different from that of patients treated with long-term tranexamic acid. The rate of rebleeding (24 of 119, 20%) was near that with placebo (56 of 238, 24%). In contrast, the rate of cerebral infarction (33 of 119, 28%) was almost identical to that after long-term tranexamic acid (59 of 241, 24%), although mortality from cerebral infarction was reduced. Compared with historical control groups, treatment with tranexamic acid for 4 days fails to reduce the incidence of rebleeding but still increases the rate of cerebral infarction. (Stroke 1989;20:1674–1679)

In a recent randomized controlled trial, we demonstrated that treating patients with aneurysmal subarachnoid hemorrhage (SAH) with tranexamic acid (TEA) significantly reduced the incidence of rebleeding. This benefit, however, was offset by an increase in the incidence of cerebral infarction. In this previous trial, the duration of treatment (4 weeks or until surgery or death) was based on studies showing raised levels of fibrin degradation products in the cerebrospinal fluid (CSF) for up to 5 weeks after SAH. However, we subsequently found reasons to doubt whether CSF levels of fibrin degradation products represent anything other than the permeability of the blood–brain barrier.

In the previous study, TEA was given during the period of maximum risk for cerebral infarction. The rate of cerebral infarction in the TEA-treated group started to diverge from that of the control group on Day 6 of treatment. This raised the possibility that a shorter period of treatment might avoid the concomitant increase in cerebral infarction and yet maintain the inhibition of rebleeding. In this study, we chose a treatment period of 4 days, with a maximum interval between SAH and initiation of treatment of 72 hours. Before considering a full-scale randomized trial, we prospectively studied the effect of short-term treatment with TEA on the rate of rebleeding and cerebral infarction in a series of 119 consecutive patients with SAH. We compared the results with those of two historical control groups from the previous randomized controlled trial.

Subjects and Methods

From January 1986 to May 1987, we prospectively studied 119 consecutive patients with SAH admitted ≤72 hours after the first clinical symptoms to one of three hospitals. The criteria for eligibility were symptoms and signs of SAH and computed tomographic (CT) evidence of aneurysmal hemorrhage in the basal cisterns or fissures. In three patients in whom CT scan showed no abnormality, lumbar puncture demonstrated blood, confirmed by blood pigments on spectrophotometry. As control
TABLE 1. Patient Characteristics at Entry Into Trials of TEA After Aneurysmal SAH

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Current study</th>
<th>Previous trial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short-term TEA</td>
<td>Long-term TEA</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n=119)</td>
<td>(n=241)</td>
<td>(n=238)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45</td>
<td>95</td>
<td>94</td>
</tr>
<tr>
<td>Female</td>
<td>74</td>
<td>146</td>
<td>144</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>52.9</td>
<td>50.3</td>
<td>50.2</td>
</tr>
<tr>
<td>Interval from SAH to entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24 hr</td>
<td>78</td>
<td>95</td>
<td>91</td>
</tr>
<tr>
<td>25–48 hr</td>
<td>23</td>
<td>86</td>
<td>75</td>
</tr>
<tr>
<td>49–72 hr</td>
<td>18</td>
<td>60</td>
<td>72</td>
</tr>
<tr>
<td>Loss of consciousness at ictus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60</td>
<td>130</td>
<td>111</td>
</tr>
<tr>
<td>No</td>
<td>59</td>
<td>131</td>
<td>127</td>
</tr>
<tr>
<td>Glasgow Coma Scale score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>33</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td>12 or 13</td>
<td>27</td>
<td>63</td>
<td>70</td>
</tr>
<tr>
<td>14</td>
<td>59</td>
<td>128</td>
<td>122</td>
</tr>
<tr>
<td>Clinical grade on Hunt and Hess Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>II</td>
<td>52</td>
<td>93</td>
<td>87</td>
</tr>
<tr>
<td>III</td>
<td>30</td>
<td>61</td>
<td>71</td>
</tr>
<tr>
<td>IV or V</td>
<td>27</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>Aneurysm confirmed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>68</td>
<td>130</td>
<td>155</td>
</tr>
<tr>
<td>No</td>
<td>9</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Angiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autopsy</td>
<td>9</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Normal angiogram</td>
<td>19</td>
<td>51</td>
<td>34</td>
</tr>
<tr>
<td>Angiography nor autopsy performed</td>
<td>23</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>Site of ruptured aneurysm (if present)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>21</td>
<td>64</td>
<td>70</td>
</tr>
<tr>
<td>Carotid artery</td>
<td>23</td>
<td>48</td>
<td>53</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>18</td>
<td>26</td>
<td>34</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>6</td>
<td>14</td>
<td>17</td>
</tr>
</tbody>
</table>

TEA, tranexamic acid; SAH, subarachnoid hemorrhage. % of total for characteristic.

We considered 238 patients treated with placebo and 241 patients treated with long-term TEA.

Treatment with TEA commenced ≤72 hours after the presenting SAH; 6 g/day were given for a maximum of 96 hours. TEA was administered by intravenous bolus in six doses. Treatment was discontinued at surgery, if a diagnosis other than aneurysm was established, if the angiogram was negative, or if venous thrombosis or pulmonary infarction developed. Exclusion criteria were the presence or history of recent deep-vein thrombosis, coagulation disorders, renal insufficiency, pregnancy, or negative angiography carried out before the start of treatment. If death appeared imminent, entry into the current study was delayed.

In addition, patients were randomized to receive fludrocortisone, and fluid and sodium balances and plasma volumes were compared in patients with and without this treatment; these results have been reported in a separate paper. During the study period all patients had a fluid intake of at least 3,000 ml/day. If a patient was on antihypertensive treatment before the SAH, the same dosage was continued. Hypertension developing in a patient without a history of hypertension was not treated.

CT was carried out on admission and after clinical deterioration. Four-vessel angiography was performed at the clinician's discretion. The amount of subarachnoid blood on CT scan was graded from 0 (no blood) to 3 (completely filled with blood) for the frontal interhemispheric fissure, the quadrigeminal cisterns, each suprasellar cistern, each ambient cistern, each basal sylvian fissure, and each lateral fissure; therefore, the maximum score was 30. Similarly, the amount of intraventricular blood on the
Stroke Vol 20, No 12, December 1989

TABLE 2. Outcome at 3 Months in Trials of TEA After Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Current study</th>
<th>Previous trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short-term TEA</td>
<td>Long-term TEA</td>
</tr>
<tr>
<td></td>
<td>(n=119)</td>
<td>(n=241)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>45</td>
<td>84</td>
</tr>
<tr>
<td>%</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>%</td>
<td>42</td>
<td>23</td>
</tr>
<tr>
<td>Delayed cerebral ischemia</td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td>%</td>
<td>22</td>
<td>45</td>
</tr>
<tr>
<td>Other causes</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>%</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>Severely disabled</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>%</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Good recovery or moderately disabled</td>
<td>65</td>
<td>127</td>
</tr>
<tr>
<td>%</td>
<td>54</td>
<td>53</td>
</tr>
</tbody>
</table>

TEA, tranexamic acid.

admission CT scan was graded for each ventricle, with a maximum score of 30.

In the current study (short-term TEA group) 113 (95%) and in the previous trial (long-term TEA or placebo groups) 352 (73%) of the admission CT scans were available for review.

All patients remained under continuous observation in an intensive care or high-dependency unit for 4 weeks or until the patient underwent surgery or died. Any deterioration in the level of consciousness or the development of focal signs was reported, in which case the patient was reexamined. Whenever possible these events were investigated with CT. Intracranial complications were recorded as rebleeding, infarction, hydrocephalus, local edema from a hematoma, epilepsy, or other. Definite rebleeding was defined as sudden deterioration, with increased hemorrhage on CT scan or at autopsy compared with a previous CT scan; probable rebleeding was defined as sudden deterioration and death, without the possibility of confirmation by CT and when autopsy was refused; definite infarction was defined as gradual development of focal signs, with or without deterioration in consciousness level and with CT or autopsy confirmation; probable infarction was defined as gradual development of focal signs, with or without deterioration in consciousness level, without confirmation by CT or autopsy, but with exclusion of other causes that could explain the deterioration; and extracranial events were recorded as cardiorespiratory, metabolic, gastrointestinal bleeding, or other.

Outcome was assessed at 3 months according to the five-point Glasgow Outcome Scale,9 and the presence of a limb or speech deficit was noted. If a patient died ≤3 months after the SAH, the cause of death was recorded.

Results

Of the 119 patients with SAH enrolled in the current study, 57 (48%) were from Rotterdam, 36 (30%) were from London, and 26 (22%) were from Utrecht. Table 1 compares patient characteristics at entry in the current study and in the previous randomized trial. Only the distribution of interval from SAH to entry differed significantly. This difference resulted from the large contribution of neurologic centers with primary referral to the current study; neurosurgical centers contributed more heavily to the previous trial. Differences in the interval from SAH to entry did not prove to be an important prognostic factor, at least not within the first 3 days.10 The incidence of near-maximal subarachnoid blood scores (21–30) was slightly higher in the current study, but the difference did not reach significance (32 of 113, 28% vs. 66 of 352, 19%). Frank intraventricular hemorrhage (score >2) was distributed similarly (21% vs. 23%). Other characteristics were closely similar, and no difference reached significance.

In the current study, angiography was carried out in 87 patients (73%). An aneurysm was demonstrated in 77 patients (65%) on angiography or at autopsy. More than one aneurysm was demon-

TABLE 3. Rate of Events in Trials of TEA After Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Event</th>
<th>Current study</th>
<th>Previous trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short-term TEA</td>
<td>Long-term TEA</td>
</tr>
<tr>
<td></td>
<td>(n=119)</td>
<td>(n=241)</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>% 95% CI</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Delayed cerebral ischemia</td>
<td>33</td>
<td>59</td>
</tr>
<tr>
<td>% 95% CI</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>Hydrocephalus requiring shunt</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>% 95% CI</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>% 95% CI</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>% 95% CI</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

TEA, tranexamic acid; CI, confidence interval. % of n.
strated in 16 patients (13%) in the current study. Fifty-one patients (43%) underwent surgical clipping of the aneurysm.

In the current study, short-term TEA treatment lasted 96 hours in 100 patients (83%). Treatment was discontinued earlier in two patients who had surgery, in four who died, in four who had a negative angiogram, in two in whom a cause for the SAH other than an aneurysm was identified, and in four for a variety of other reasons. In no patient did side effects make it necessary to stop treatment. Because the current study was designed to look at patients with signs and symptoms of SAH on an intention-to-treat basis, all 119 patients were included in the final analysis.

Short-term treatment with TEA did not result in a better outcome than long-term treatment with TEA or treatment with placebo (Table 2). Of the patients who died, almost half died of rebleeding. Mortality from delayed cerebral ischemia was less in the current study after short-term TEA than in the previous trial after long-term TEA. Other causes of death included ventriculitis following shunting in three patients, the direct effect of the initial SAH in one patient, and operative complications in three patients. Restricting analysis of outcome to the 68 patients in the current study with an aneurysm demonstrated on angiography did not alter these findings; 19 patients (28%) died, five (7%) became severely disabled, and 44 (65%) had a good recovery or remained moderately disabled.

Short-term treatment with TEA in the current study did not reduce the rate of rebleeding compared with treatment with placebo in the previous trial (Table 3), although marked differences occurred among the three centers; in Rotterdam 11 of 57 patients (19%), in London two of 36 (6%), and in Utrecht 11 of 26 (42%) rebled. We failed to identify factors other than chance to account for this variation. In one patient rebleding was classified as probable; in all other rebleding was definite. Two thirds of the patients who rebled did so after Day 4 of treatment (Figure 1). Six patients had more than one definite additional hemorrhage; only one of these later hemorrhages occurred during TEA treatment. Only the time of the first rebleding is indicated in Figure 1. The results did not change significantly when only patients with a proven aneurysm were considered (11 of 68, 16%).

The rate of delayed cerebral ischemia in the current study closely resembled that after long-term TEA treatment in the previous trial (Table 3). Similar results were obtained when the analysis was restricted to patients with a confirmed aneurysm (24 of 68, 35%). Delayed cerebral ischemia occurred in most patients between Days 2 and 10 after SAH (Figure 2). Of the 33 episodes of cerebral infarction,
21 were classified as definite. No marked differences in the incidences of hydrocephalus, deep-vein thrombosis, or pulmonary embolism were noted between the current study and the previous trial.

When all patients with a positive angiogram were grouped according to the onset of treatment, the distributions of events and outcome among the three treatments were nearly identical. Thus, the interval from SAH to treatment did not contribute to any bias (Table 4).

Discussion

The hypothesis underlying our study was that shortening the duration of antifibrinolytic treatment after SAH might still prevent rebleeding without the risk of ischemic complications. Unfortunately, the reverse proved to be the case. The results of our current prospective study clearly demonstrate that TEA given for only 4 days no longer protects against rebleeding. Most second hemorrhages occurred after stopping TEA; 4 days appears to be insufficient to permit a firm plug to develop. The risk of rebleeding can therefore be diminished only by continued antifibrinolytic treatment throughout the high-risk period in the second week. In contrast, the most important side effect (development of cerebral infarction) remained, even though treatment was stopped before the period during which vasospasm is most frequently encountered. Therefore, TEA may have a harmful effect during the first days after SAH. Why outcome in the current study was not worse than that in the previous trial can be explained by two factors. First, the number of patients in the current study was relatively small. Second, mortality from infarction in the previous trial was confounded by fluid restriction and natriuresis in aneurysmal subarachnoid hemorrhage. Clin Neurol Neurosurg 1988;90:209–214

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The use of historical controls carries substantial disadvantages, but this study was designed to indicate whether we should proceed with a randomized controlled trial. A relatively short period elapsed between the two studies, making radical changes in management policies unlikely, but recognized differences existed. No antihypertensive medication was used in the current study, and all patients received a large fluid intake; this may explain the reduced mortality from cerebral infarction. Our findings leave little doubt that TEA treatment for 4 days has no beneficial and only adverse effects. A full-scale clinical trial of this regimen is therefore no longer attractive. Antifibrinolytic treatment in general is unlikely to be of value until other measures have convincingly been demonstrated to reduce the incidence of cerebral ischemia.

Acknowledgments

We thank the nursing staff and the residents for their efforts, Mrs. E. Budelman-Verschuren for excellent secretarial help, and Dr. Allen H. Ropper for reviewing the manuscript.

References


induced relaxation and involvement of lipooxygenase metabolite(s). Stroke 1987;18:932–937


Key Words • antifibrinolytic agents • cerebral infarction • subarachnoid hemorrhage
Short-term tranexamic acid treatment in aneurysmal subarachnoid hemorrhage.
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*Stroke*. 1989;20:1674-1679
doi: 10.1161/01.STR.20.12.1674

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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