Comparative clinical trial of epsilon amino-caproic acid and tranexamic acid in the prevention of early recurrence of subarachnoid haemorrhage

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SUMMARY A comparative controlled clinical trial of epsilon aminocaproic acid (EACA), 36 g/day and tranexamic acid (TEA), 6 g/day, was undertaken to assess their effectiveness in reducing early recurrence of subarachnoid haemorrhage (SAH). Of 90 patients treated with EACA recurrent haemorrhage was seen in 8% of these patients and 7% of the patients developed delayed ischaemic deficit. The total pre-operative mortality in EACA-group was 11%. Of 61 patients treated with TEA, 10% had recurrent haemorrhage and delayed ischaemic deficit occurred in 5% of the patients. The total pre-operative mortality in TEA-group was 11%. No difference was found between the effectiveness and side-effects of these drugs.

The use of anti-fibrinolytic drugs for prevention of early recurrence of subarachnoid haemorrhage is becoming widespread.1,2,3 The two drugs used for this purpose are epsilon aminocaproic acid and tranexamic acid. Once a clinician accepts that an anti-fibrinolytic agent is useful for preventing early recurrence of subarachnoid haemorrhage, he faces the dilemma of choice between these two drugs. There has been no published comparative results to show their effectiveness or the prevalence of side-effects. We have shown that epsilon aminocaproic acid is effective in preventing early recurrence of haemorrhage4 and this is in line with some other reports.5,6 The effectiveness of tranexamic acid in preventing recurrence of subarachnoid haemorrhage has been shown by Corkill,7 Smith and Upchurch,8 Nibbelink,9 Schisano,4 and Chandra.10 On the other hand there are various reports which show either minimal or no beneficial effect in prevention of SAH either by epsilon aminocaproic acid,11,12 or tranexamic acid.13

As we advocated the use of an anti-fibrinolytic agent in SAH patients,6 we thought that a comparative clinical trial between these two drugs may be helpful. This clinical trial was undertaken between January 1978 and June 1980.

Materials and methods

Only patients with the diagnosis of SAH, proved by lumbar puncture were taken into this trial. Patients admitted on three days of the working week formed the group who had EACA and patients admitted on two days of the week formed the group who had TEA. The pre-operative treatment and the policy of investigation by angiography and CT scan were similar in the two groups.

EACA was given in a dose of 36 g/day, divided in six equal doses. TEA was given in 6 g/day doses, divided into six equal doses. The oral and intravenous doses were the same. Side-effects, such as nausea, vomiting and diarrhoea were noted. Periodical checks for white cell count, platelet count and haemoglobin levels were done. The incidence of deep-venous thrombosis or pulmonary embolus were carefully recorded. The anti-fibrinolytic drug was continued either to the time of surgery or if surgery was not undertaken, until the patient was discharged. This formed the cut-off point for observation of the patients as far as this trial was concerned.

The criteria of the recurrent haemorrhage were (a) clinical (as outlined in our paper, ref 3), (b) by computed tomography where evidence of a fresh haemorrhage or haematoma was regarded as a positive evidence, (c) by lumbar puncture and examination of CSF, and (d) by post-mortem examination.

"Delayed ischaemic deficit", a term coined by Dr Miller Fischer,17 is defined as a syndrome that may occur with severe arterial constriction in aneurysm patients with SAH. The criteria for delayed ischaemic deficits, used here are as follows:— (a) clinical—gradual onset of drowsiness and unconsciousness or neurological deficits

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like hemiparesis or dysphasia, (b) repeat angiogram after this clinical presentation showed either increase in previous cerebral arterial spasm or onset of cerebral arterial spasm where no spasm existed before, and (c) a repeat CT scan done after the onset of clinical symptoms showed cerebral infarction.

Results

Ninety patients were given EACA and 61 patients were given TEA. The two groups were comparable in age and sex distribution (table 1), clinical grading at the time of admission (table 2) interval between SAH and start of anti-fibrinolytic drug (table 3), and distribution of various types of lesions (table 4). A statistical comparability analysis by chi-square test showed no significant difference between EACA and TEA groups. Recurrent haemorrhage occurred in seven (8%) patients out of 90 in the EACA group and five patients died from the effects of recurrent haemorrhage. Six patients (7%) developed delayed ischaemic deficit in this group. Recurrent haemorrhage occurred in six patients (10%) in the TEA group and all of these six patients died from the effects of recurrent haemorrhage. Delayed ischaemic deficit occurred in three patients (5%). The total mortality before operation was 11% for EACA patients and 11% for TEA patients (table 5). A statistical analysis by chi-square test for all these three parameters in each group of EACA and TEA patients, showed no significant difference. Objective confirmation of recurrent haemorrhage was available in all but two patients out of 13. Objective confirmation of delayed ischaemic deficit was available in all but two patients out of nine.

The side-effects seen with EACA and TEA were diarrhoea and vomiting. Approximately the same percentage of patients (4-5%) had to have the route of administration changed from oral to intravenous to control the diarrhoea. Nausea and vomiting, which were usually transient were again seen in approximately equal percentage in the two groups of patients. Clinical deep-vein thrombosis was seen in 6% of patients in each group and one patient in each group died of pulmonary embolus while having the medication and one patient in EACA group died of pulmonary embolus during the first week of the post-operative period, but the patient was not at that time on anti-fibrinolytic drugs. No haematological disturbances such as neutropaenia, agranulocytosis or platelet deficiency were noted in either of the

Table 1 Age and sex distribution

<table>
<thead>
<tr>
<th>Age-group</th>
<th>EACA patients</th>
<th>TEA patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Up to 19 yrs</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>20 to 39 yrs</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>40 to 59 yrs</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>60+ yrs</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>31 (35%)</td>
<td>59 (65%)</td>
</tr>
</tbody>
</table>

Table 2 Grades at admission

<table>
<thead>
<tr>
<th>Patients</th>
<th>Grading (Hunt and Hess)&lt;sup&gt;39&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>EACA</td>
<td>56 (62%)</td>
</tr>
<tr>
<td>TEA</td>
<td>33 (54%)</td>
</tr>
</tbody>
</table>

No patient was admitted in Grade V.

Table 3 Interval between SAH and start of drug

<table>
<thead>
<tr>
<th>Patients</th>
<th>First 48 hr</th>
<th>3-7 days</th>
<th>8-15 days</th>
<th>16+ days</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>EACA</td>
<td>38 (42%)</td>
<td>28 (31%)</td>
<td>19</td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>TEA</td>
<td>31 (51%)</td>
<td>17 (28%)</td>
<td>8</td>
<td>5</td>
<td>61</td>
</tr>
</tbody>
</table>

Table 4 Distribution of lesions

<table>
<thead>
<tr>
<th>Lesion</th>
<th>EACA pts</th>
<th>TEA pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ant cerebral and ant communicating aneurysm</td>
<td>12</td>
<td>13%</td>
</tr>
<tr>
<td>Middle cerebral aneurysm</td>
<td>12</td>
<td>13%</td>
</tr>
<tr>
<td>Int carotid and post communicating aneurysm</td>
<td>23</td>
<td>26%</td>
</tr>
<tr>
<td>Vertebro-basilar aneurysm</td>
<td>5</td>
<td>6%</td>
</tr>
<tr>
<td>Multiple aneurysms</td>
<td>10</td>
<td>11%</td>
</tr>
<tr>
<td>Arterio-venous malformation</td>
<td>4</td>
<td>5%</td>
</tr>
<tr>
<td>No lesion found</td>
<td>24</td>
<td>26%</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>100%</td>
</tr>
</tbody>
</table>
groups. None of these patients in either series had shown radiographic evidence of arteropathy.

Discussion

In spite of controversy regarding the efficiency of anti-fibrinolytic drugs in preventing recurrence of haemorrhage, the use of these drugs is becoming more widespread and had been advocated by many neurosurgeons.1–4 6 We published a controlled clinical trial with EACA in 1979 with very good prevention of recurrent haemorrhage. The haemorrhage from the ruptured aneurysmal sac is sealed by a platelet plug which gradually develops into a blood clot. Blood in the subarachnoid space stimulates fibrinolytic activity and this leads to lysis of the clot which had sealed the ruptured aneurysm. This lysis of clot leads in some patients to recurrent haemorrhage which can be catastrophic and fatal.18 There is evidence that the fibrinolytic activity in the CSF may increase abnormally following subarachnoid haemorrhage.9 8 Both the drugs act by inhibiting this process of fibrinolysis. Both drugs penetrate the CSF very well.9 19 20

We undertook this trial to see if some difference existed between the drugs either in their effectiveness in preventing recurrent haemorrhage in the early stages, or in the complication rate, especially the delayed ischaemic deficit. As the drug was stopped on the day of operation, this has been taken as the cut-off point for patients undergoing surgery. For patients who did not have surgery, the cut-off point was taken as the day of discharge from our department. As the aim of giving an anti-fibrinolytic drug is to allow the patients to improve to their best clinical condition prior to surgery, preventing recurrent haemorrhage during the period of waiting, we think that these two cut-off points are reasonable. We do not think that anti-fibrinolytic drugs is a long-term alternative to surgery,1 although we have always advised the referring doctor to continue anti-fibrinolytic medication for a total of six weeks when the patients were transferred back to his care.

We did not encounter any increased incidence of deep-vein thrombosis, as previously reported.1 3 5 15 16 21 Nausea and vomiting and diarrhoea also occurred approximately in equal numbers in each group and were easily treated symptomatically.

We think that the use of anti-fibrinolytic drugs is beneficial in the total care of subarachnoid haemorrhage patients and we have found EACA and TEA equally effective in preventing early recurrence of haemorrhage.

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