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.1–5 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 haemorrhage6 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 acid11–15 or tranexamic acid.8,14–16

As we advocated the use of an anti-fibrinolytic agent in SAH patients,8 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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Accepted 13 July 1981
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 haemor-
rhage 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 statisti-
cal analysis by chi-square test for all these three pa-
rameters in each group of EACA and TEA patients,
showed no significant difference. Objective con-
firmation of recurrent haemorrhage was available in
all but two patients out of 13. Objective confirma-
tion 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 Female</td>
<td>Male Female</td>
</tr>
<tr>
<td>Up to 19 yrs</td>
<td>2 1</td>
<td>2</td>
</tr>
<tr>
<td>20 to 39 yrs</td>
<td>10 13</td>
<td>7 6</td>
</tr>
<tr>
<td>40 to 59 yrs</td>
<td>14 28</td>
<td>9 23</td>
</tr>
<tr>
<td>60+ yrs</td>
<td>5 17</td>
<td>5 9</td>
</tr>
<tr>
<td>Total</td>
<td>31 (35%) 59 (65%) 90</td>
<td>23 (37%) 38 (63%) 61</td>
</tr>
</tbody>
</table>

Table 2  Grades at admission

<table>
<thead>
<tr>
<th>Patients</th>
<th>Grading (Hunt and Hess)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I  II III IV Total</td>
</tr>
<tr>
<td>EACA</td>
<td>(62%) 23 8 3 90</td>
</tr>
<tr>
<td>TEA</td>
<td>(54%) 24 3 1 61</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 3-7 days 8-15 days 16+ days Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>EACA</td>
<td>(42%) (31%) (21%) (6%) 90</td>
</tr>
<tr>
<td>TEA</td>
<td>(51%) (28%) (13%) (8%) 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 arteriopathy.

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.5 The haemorrhage from the ruptured aneurysmal sac is sealed by a platelet plug which gradually develops into a bloodclot. 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 medication 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.

The authors thank Mr JP Lanigan, Mr PC Carey, and Mr AR Pate, Consultant Neurosurgeons, St Laurence’s Hospital, Dublin, for allowing us to study patients under their care. We thank Mr MI Kaliszer of Trinity College, Dublin for his help in statistical analysis. We gratefully acknowledge help from KabiVitrum Ltd, and Upjohn Ltd, in searching the literature.

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*J Neurol Neurosurg Psychiatry* 1981 44: 810-813
doi: 10.1136/jnnp.44.9.810

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