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 haemorrhage³ and this is in line with some other reports.^{2,5,6} 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,¹¹⁻¹³ or tranexamic acid.^{6,14-16}

As we advocated the use of an anti-fibrinolytic agent in SAH patients,³ 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.

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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

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

Age-group	EACA patients			TEA patients		
	Male	Female	Total	Male	Female	Total
Up to 19 yrs	2	1	3	2	0	2
20 to 39 yrs	10	13	23	7	6	13
40 to 59 yrs	14	28	42	9	23	32
60+ yrs	5	17	22	5	9	14
Total	31 (35%)	59 (65%)	90	23 (37%)	38 (63%)	61

Table 2 Grades at admission

Patients	Grading (Hunt and Hess) ²²				
	I	II	III	IV	Total
EACA	56 (62%)	23 (26%)	8 (9%)	3 (3%)	90
TEA	33 (54%)	24 (39%)	3 (5%)	1 (2%)	61

No patient was admitted in Grade V.

Table 3 Interval between SAH and start of drug

Patients	First 48 hr	3-7 days	8-15 days	16+ days	Total
EACA	38 (42%)	28 (31%)	19 (21%)	5 (6%)	90
TEA	31 (51%)	17 (28%)	8 (13%)	5 (8%)	61

Table 4 Distribution of lesions

Lesion	EACA pts	TEA pts
Ant cerebral and ant communicating aneurysm	12	13%
Middle cerebral aneurysm	12	13%
Int carotid and post communicating aneurysm	23	26%
Vertebro-basilar aneurysm	5	6%
Multiple aneurysms	10	11%
Artero-venous malformation	4	5%
No lesion found	24	26%
Total	90	100%

Table 5 Results

Patients	Total No	Rebleed	Death from rebleed	Delayed deficit	Total mortality*
EACA	90	7 (8%)	5†	6 (7%)	10 (11%)
TEA	61	6 (10%)	6	3 (5%)	7 (11%)

*Includes all deaths up to the cut-off point for this trial.

†72% of patients who rebled with EACA medication died.

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.³ 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 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 8 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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