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Anti-fibrinolytic treatment in the pre-operative management of subarachnoid haemorrhage caused by ruptured intracranial aneurysm

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SUMMARY One hundred consecutive patients treated with epsilon aminocaproic acid 24 grams daily prior to surgery for ruptured intracranial aneurysms have been compared with the previous 100 patients managed similarly but without anti-fibrinolytic drugs. No other alterations in management were made and the two series are closely comparable in all other respects. Fewer episodes of recurrent haemorrhage and deaths from this cause occurred in the treated patients, but more cases of cerebral ischaemia occurred. Neither difference is statistically significant and overall more deaths occurred in the patients treated with antifibrinolytic drugs. The value of this method of treatment in the management of aneurysmal subarachnoid haemorrhage is questioned.

Although 40% of patients who bleed from ruptured intracranial aneurysm die from the effect of the first haemorrhage, in the remainder the bleeding ceases spontaneously.[1] In these patients clot surrounds the aneurysm and a plug of platelets and fibrin seals the site of bleeding.[2] The blood in the subarachnoid space stimulates fibrinolytic activity in the cerebrospinal fluid (CSF)[3] and dissolution of clot can lead to recurrent bleeding from which one third of survivors of the first haemorrhage die in the next six weeks.[4 5] Intracranial surgery prevents recurrent haemorrhage by sealing the aneurysm or excluding it from the circulation, but otherwise does not assist in recovery unless a large intracerebral haematoma can be removed.[6] The operative mortality of such surgery depends on the neurological state of the patient,[7 8] and the time which has elapsed since the last haemorrhage.[9 10] Early operation, especially in patients in poor condition, results in higher mortality and morbidity[10 11] and delay may reduce the operative risk and allow time for patients to improve their neurological state. Such delay exposes patients to continued risk of re-bleeding, and antifibrinolytic drugs have been advised to retard the dissolution of the protective platelet plug and blood clot around the aneurysm. There is, however, no agreement about the effectiveness of such treatment and while some series have maintained that antifibrinolytic drugs have reduced the incidence of recurrent bleeding[12–26] others have denied this.[27–31] In this study the fate of 100 consecutive patients with aneurysmal subarachnoid haemorrhage (SAH) treated by antifibrinolytic agents prior to operation has been compared with a similar number of control patients. The two groups have been carefully matched, including a prediction of death from re-bleeding in each patient based on grade and period of risk.

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Materials and methods

One hundred patients with SAH due to ruptured aneurysm admitted consecutively to the Regional Department of Neurosurgery at Central Middlesex Hospital between January 1977 and June 1979 have been treated with antifibrinolytic agents. This series of patients has been compared with 100 consecutive patients admitted with the same diagnosis and not treated with antifibrinolytic agents during the preceding period from May 1973 until January 1977. Patients with SAH due to cerebral arteriovenous malformations or without angiographically demonstrated cause have been excluded from both groups. Also excluded are patients admitted in poor grade who died within a few days from the effects of the first haemorrhage without having re-bled, and patients admitted more than 21 days after SAH, since in neither of these groups is antifibrinolytic treatment likely to alter the outcome. During the period of the study all patients with SAH under the age of 70 years have been accepted for admission on the day of referral unless deeply comatose. The age distribution of the patients in the two groups, and the mean ages are

comparable (table 1) as are the sex distribution, incidence of arterial hypertension and incidence of multiple aneurysms. Hypertension has been considered to be present when the diastolic pressure has been found to be consistently raised above 100 mm mercury or where patients have been known to be hypertensive before the onset of SAH. Table 1 shows the grades of the patients at the time of admission, and the intervals between SAH and admission to the department. The grading system of Nishioka[5] has been used to allow the prediction tables of Alvord[32] to be used in predicting the outcome, and the time intervals chosen have been those used by Alvord.[32] The two groups are well matched for age, sex, hypertension and multiple aneurysms, but there are differences in the grading, and in the time of admission, since patients in the earlier control group tended to be referred later and in better grade. To assess the effect of these differences the Alvord[32] prediction tables have been used to determine a notional risk of death in each patient. The period of risk of re-bleeding has been taken to be the time in days between admission to the department and the date of the operation, or in unoperated patients the date of discharge from hospital. In fatal cases the period of risk was the time between admission and death, whether due to re-bleeding, cerebral ischaemia or other cause. In each patient the probability of survival in the grade of admission has been taken from the tables[32] at the beginning and end of the period of risk, and these two figures subtracted to give a notional figure for risk of fatality during the period. The addition of these figures from each patient gives a notional figure for predicted deaths in each group and this is shown in table 1, together with the mean period of risk.

Operation was performed intracranially in 76 patients and by carotid ligation in five patients in the treated group and in 79 and two respectively in the control group. The reasons for non-operation are given in table 1. Clinical details of most of the patients in this study have been described elsewhere.[33]

Epsilon aminocaproic acid (EACA) was given by mouth or nasogastric tube in a dose of 3 grams 3-hourly to all the patients in the treated group from the time of admission until operation, or until discharge or death in non-operated patients. This dose has been shown to be sufficient to produce an effective therapeutic blood level for antifibrinolysis within two hours,[34] and has been stated to be effective in preventing recurrent SAH.[9 12 13 15 17 18 21] If drowsiness or vomiting prevented oral or nasogastric administration amino-methyl cyclohexane carboxylic acid (AMCA, tranexamic acid) was substituted in a dose of 1 gram by intravenous infusion 8-hourly. Patients in both groups received complete bed rest with full medical management including control of hypertension, and this management has not changed over the period of the study. Angiography was performed as early as possible but was sometimes delayed if patients were felt to show clinical evidence of cerebral ischaemia. CT scans were performed in most patients in the EACA treated group. Recurrent bleeding was recognised by sudden severe headache and increased neck stiffness, often associated with sudden deterioration in clinical condition or conscious level. Lumbar puncture was used in most cases and repeated CT scanning was also used in the treated group. Cerebral ischaemia was recognised by slow deterioration in conscious level or in neurological signs without any sudden incident resembling re-bleeding. CT scanning was useful in these circumstances in showing cerebral swelling or areas of diminished density.

Results

Thirteen deaths occurred in the group of treated patients compared with 11 in the control group (table 2). Eight recurrent haemorrhages with four fatalities occurred in the treated group, as against 15 with six fatalities in the controls. Eighteen patients were affected by severe delayed cerebral ischaemia with eight deaths in the treated group compared with 15 such patients with four deaths in the controls.

Thrombo-embolic complications were seen in both groups. In the treated group 12 patients developed a deep vein thrombosis (DVT) and four of these resulted in pulmonary embolism with one death. In the control group there were seven DVTs, with five pulmonary emboli and one death. In addition to the three postoperative deaths due to cerebral ischaemia there was another due to pulmonary embolism and one due to technical difficulties in the operation, an operative mortality of 3% in 162 patients. Three postoperative deaths occurred in the control group and two in the treated group. Approximately 10% of patients taking EACA had some nausea with occasional vomiting and diarrhoea, but most managed to continue taking the tablets.

Discussion

One of the problems in the surgical treatment of ruptured intracranial aneurysms is that the earlier intracranial operation is performed the worse the results in terms of operative mortality and morbidity,[10 11] and yet the longer surgery is delayed the greater the risk of recurrent bleeding.[4 32] If antifibrinolytic treatment reduces the risk of recurrent haemorrhage operation can safely be delayed until patients have recovered from the effects of the first haemorrhage and are in optimum condition for intracranial surgery. Following SAH the blood in the CSF stimulates local fibrinolysis and raised levels of fibrinogen degradation products (FDP) can be found in the CSF.[35] Focal cerebral damage may also increase fibrinolysis[3] and could explain the increased risk of re-bleeding in patients in poor neurological condition. Antifibrinolytic drugs are readily absorbed from the gastrointestinal tract and pass the blood CSF barrier.[36 37] Their action is to inhibit the activator which converts plasminogen into the proteolytic enzyme plasmin.[3] This reduces the breakdown of the fibrin plug in the aneurysm at

Table 1 *Detailed comparisons between treated and control patients*

	Age distribution								
Age groups (yr)	0–10	11–20	21–30	31–40	41–50	51–60	61–70	Total	Mean
Treated patients	0	1	7	23	22	28	19	100	47·50
Control patients	1	2	4	18	27	31	17	100	48·61
	Sex, hypertension (diastolic over 100), multiple aneurysms								
	M	F			Hypertension		Multiple aneurysms		
Treated patients	20	80			33		17		
Control patients	30	70			39		18		
	Grades on admission								
Grading	1	2	3		4	5	Mean	(SD)	
Treated patients	1	49	36		14	0	2·63	(0·73)	
Control patients	0	60	23		17	0	2·57	(0·76)	
	Interval between SAH and admission								
Days	< 1	1–3	3–7		7–21		Mean	(SD)	
Treated patients	39	38	18		5		2·62	(3·88)	
Control patients	35	35	22		8		3·14	(3·26)	
	Period of risk: predicted and actual deaths								
	Mean period of risk in days	(SD)			Predicted deaths (see text)		Actual deaths		
Treated patients	12.37	(7.74)			21.60		13		
Control patients	14·20	(13·54)			21·20		11		
	Reasons for non-operation								
	Died from rebleeding	Disabled by rebleeding		Died from cerebral ischaemia		Disabled by cerebral ischaemia		Disabled by first haemorrhage	Total
Treated patients	4	2		7		1		5	19
Control patients	6	1		2		4		6	19

Table 2 *Results: rebleeding; cerebral ischaemia; thromboembolic complications*

	Rebleeds	(*Deaths*)	*Cerebral ischaemia*	(*Deaths*)	*DVT*	(*PE*)	(*Deaths*)	*Total deaths*
Treated patients	7	(4)	18	(8)*	12	(4)	(1)	13
Control Patients	15	(6)	15	(4)*	7	(5)	(1)	11

*Includes 3 post-operative patients with 1 death in EACA treated group, and 5 post-operative patients with 2 deaths in control group.
Analysis by Fishers test of exact probability shows no significant differences between the treated and control patients.

the site of bleeding, and dissolution of the surrounding blood clot;[3] reduction of FDP in the CSF has been demonstrated.[3]

The problem in evaluating the effects of antifibrinolytic drugs in preventing recurrent haemorrhage after SAH is the variability of the natural outcome. Although the risk of fatal re-bleeding depends on the time since the last haemorrhage and the clinical grade of the patient,[4 32] the recurrence of such bleeding in any patient appears to be fortuitous. It follows that in every clinical study of the effects of any treatment of aneurysmal SAH the treated patients must be compared with a carefully matched series of control patients, and that the numbers involved must be large enough to eliminate results due to chance. Matching of treated patients and controls is more important than random selection or double blind studies and the validity of such matching can be assessed by using the prediction tables of Alvord.[32] Of the previously published series describing the effectiveness of antifibrinolytic drugs only five[14 21 24-26] have control groups of untreated patients, and in three of these series[14 24 25] the number of patients in each group is 25 or less. The two larger series with control groups[21 26] show large differences in the re-bleeding rates between the treated and control patients, but in one,[26] 29% of the patients included did not have aneurysms and in neither study is information about the period of risk given. Four of the studies reporting no benefit from the use of antifibrinolytic drugs have control groups,[27 28 30 31] but in three of these the numbers are small.[27 28 31] The other series [30] is the largest with 135 patients compared with 166 controls, but very little data are given in the publication.

Cerebral ischaemia, although a well-known complication of SAH,[33] is mentioned as a problem in only two series. Schisano[23] describes cerebral ischaemia in 10 patients with nine deaths out of 58 patients treated with antifibrinolytic drugs (17·2%) and Maurice-Williams[25] had eight patients with cerebral ischaemia out of 25 in the treated group (32%), as against two out of 25 in the controls (8%). This latter series is unique in that antifibrinolytic treatment was used as a substitute for operation and was continued for 42 days. This may explain the high incidence of ischaemic complications in the treated group of patients. Girvin[28] reports death from cerebral ischaemia in three out of 39 treated patients (7·7%), and Tovi[16] reports two cases, and Norlen and Thulin,[13] and Sengupta *et al*[21] one each. No incidence is recorded in the series of Chowdhary *et al.*[26] In the present series delayed cerebral ischaemia was more common in the treated patients with 18 cases and eight deaths out of 100, compared to 15 cases with four deaths in 100 control patients. The incidence of ischaemia in the treated patients was 18%, similar to that described by Schisano.[22] In the present series the patients who developed cerebral ischaemia did not differ from the other patients in age or grade on admission, but were more usually hypertensive.[33] CT scanning was used in most of the EACA treated patients but contrast injection was used in only half of these. No excess of cerebral ischaemia was seen in patients given intravenous contrast.

Venous thrombo-embolic complications have also been described,[17 19-22 25 26] but the numbers are small. In the present series DVTs occurred in 12 patients with four pulmonary emboli and one death as against seven, five and one in controls. Differences in the incidence of hemiplegia in the two groups cannot explain this since 25 patients with hemiplegia developed five DVTs in each group. Vomiting and diarrhoea have been described as a complication of oral EACA,[25 26] and also affected about 10% of patients in this series in some degree.

Despite the previous encouraging reports of the effectiveness of antifibrinolytic drugs in preventing recurrent bleeding in aneurysmal SAH we have not been able to show a significant difference from controls in our series of 100 patients treated with EACA. Although less re-bleeding with fewer deaths occurred in patients in the EACA treated group there were more instances of progressive cerebral ischaemia, often leading to death, and this determined the worse overall results in this group. Neither event showed a statistically significant difference between the two groups of patients, but overall the EACA treated patients fared slightly less well. We have concluded that there must still be doubt about the value of EACA for routine use in the management of aneurysmal SAH. Rational use might be to withhold antifibrinolytic treatment from good grade patients who are less at risk of recurrent haemorrhage, and aim instead for earlier operation. Antifibrinolytic

Table 3 *Previous publications on the use of antifibrinolytic treatment in aneurysmal subarachnoid haemorrhage*

Authors	*Drug**	*Daily dose*	*Treated patients*						*Control patients*						*Matched series*	*Double blind*
			No	*Rebleeds*	*(Deaths)*	*Cerebral ischaemia*	*(Deaths)*	*DVT (PE)*	*No*	*Rebleeds*	*(Deaths)*	*Cerebral ischaemia*	*(Deaths)*	*DVT (PE)*		
Mullan and Dawley[12]	EACA	24 g	35(†)	2	(1)	0		0								
Norlen and Thulin[13]	EACA	16–20 g	14	0		1	(1)	(‡)								
	AMCA	30–40 mg/Kg														
Gibbs and Corkill[14]	AMCA	3 g	25		(1)	0		0	22		(4)	0		0	No(§)	No
Ransohoff, *et al.*[15]	EACA	24 g	50	6	(5)	(‡)		(‡)								
Tovi[16]	AMCA	4–6 g	34	6	(2)		(2)	0								
Smith and Upchurch[17]	EACA	24 g	21	1		(‡)		1								
Nibbelink[18]	EACA	24–36 g	242(‖)		(5·8%)	(‡)		(‡)	(11)			(‡)		(‡)	No	No
	AMCA															
Nibbelink, *et al.*[19]	EACA	24–36g	471	11·6%	(27)	16·8%		1·1%								
	AMCA							(0·4%)								
Utley and Richardson[20]	EACA	24 g	42	8	(7)	(‡)		(1)								
	AMCA	12 g	182	22	(14)	(‡)		0								
Sengupta, *et al.*[21]	EACA	24 g	66	0		1	(1)	1(1)	76	17	(4)	0		0	No(§)	No
Post, *et al.*[22]	EACA	24–36 g	85	10	(4,	(‡)		3(0)								
Schisano[23]	EACA	24 g	58	1	(1)	10	(9)	(‡)								
	AMCA	2–4 g														
Chandra[24]	AMCA	6 g	20	1	(1)	0		0	19	4	(5)	0		0	No(§)	Yes
Maurice-Williams[25]	AMCA	6 g	25	6	(3)	8		2	25	14	(10)	2		2	No	No
Chowdhary, *et al.*[26]	EACA	36 g	83(¶)	3	(1)	0		5%(1)	82¶	22	(10)	0		5%(1)	No(§)	No
Gibbs andO'Gorman[27]	EACA	36 g	32	8	(8)	(‡)		(‡)	22	8	(8)	(‡)		(‡)	No	No
Girvin[28]	EACA	(P)	39	14	(6)	3	(1)	(‡)	27	4	(3)	1	(1)	(‡)	No	No
Shaw and Miller[29]	EACA	36 g	9	5		(‡)		(‡)	(‡)							
Profeta, *et al.*[30]	EACA	10–15 g	135		(*)	(‡)		(‡)	166		(**)	(‡)		(‡)	No	No
Van Rossum, *et al.*[31]	AMCA	6 g	25(††)	5	(4)	(‡)		0	26(††)	4	(3)	(‡)		0	No	Yes

* EACA = epsilon aminocaproic acid, AMCA = Amino-methyl cyclohexane carboxylic acid (tranexamic acid).
† 30 patients had aneurysms.
‡ Not stated.
§ Insufficient data.
‖ This study compared deaths in patients treated with anti-fibrinolytic drugs (5·8%) with those in patients with induced hypertension (28·9%), and in those with anti-fibrinolytics plus hypotension (23·8%). Total patients in all 242.
¶ The treated group includes 20 patients without aneurysms, and the control group 28 without aneurysms.
P Dose not stated.
** No difference between control and treated groups, but no details given.
†† Only 11 patients in treated group, and 13 in control group had aneurysms on angiography.

drugs could be reserved for patients in whom surgery is delayed because of poor neurological state. If persistence of blood clot around the site of the aneurysm is a factor in initiating cerebral arterial spasm and ischaemia, CT scanning may be of value in identifying patients particularly at risk.

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