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Low-dose tranexamic acid combined with aprotinin in the pre-operative management of ruptured intracranial aneurysms

A. Spallone, F. S. Pastore, A. Rizzo, B. Guidetti

Division of Neurosurgery, Department of Neurological Sciences, University of Rome, School of Medicine, Rome, Italy

Summary

Among our patients with ruptured intracranial aneurysms 149 were managed pre-operatively with a combination of tranexamic acid (AMCA), 3 gm daily, and aprotinin at an average of 400 000 KIU (Kallikrein inactivating units) daily. Antifibrinolytics were started within three days of the last haemorrhage, and continued for at least six days. The first 91 cases, managed in the years 1971 to 1980, have been evaluated retrospectively. The remaining 58 patients were managed in the period 1981–1985 and carefully watched for possible complications of treatment. No significant differences were noted in the results of patients managed either before or after 1981. The rate of recurrent SAH (10%) was lower than the natural history of aneurysmal SAH. Satisfactory inhibition of fibrinolysis was documented in the CSF collected at the time of operation in 15 patients. This, as well as our previous suggestions that the combination of low-dose AMCA and aprotinin might carry a lesser risk of causing ischaemic complications and hydrocephalus than the conventional antifibrinolytic treatment, might stimulate future studies on fibrinolysis in SAH.

Tranexamsäure-Therapie in Verbindung mit Aprotinin als präoperative Vorbereitung von rupturierten intrakraniellen Aneurysmen

149 Patienten mit rupturierten intrakraniellen Aneurysmen wurden präoperativ mit einer Kombination »tranexamic acid« (AMCA) 3 g pro Tag und Aprotinin mit einer durchschnittlichen Dosierung von 400 000 KIU (Kallikrein inaktivierenden Einheiten) pro Tag behandelt. Die antifibrinolytische Behandlung wurde innerhalb von 3 Tagen nach der Blutung begonnen und mindestens 6 Tage fortgeführt. Die ersten 91 Fälle – zwischen 1971 und 1980 behandelt – wurden retrospektiv ausgewertet. Die verbleibenden 58 Patienten – zwischen 1981 und 1985 behandelt – wurden hinsichtlich möglicher medikamentöser Komplikationen sorgfältig überwacht. Zwischen beiden Gruppen wurden keine signifikanten Differenzen beobachtet. Die Häufigkeit von rezidivierenden SAH (10%) war niedriger als bei unbehandelten aneurysmatischen Subarachnoidalblutungen. Ausreichende Hemmung der Fibrinolyse wurde im Liquor von 15 Patienten nachgewiesen, der während der Operation gewonnen wurde. Diese Tatsache und unsere bereits früher geäußerten Vermutungen, daß die herkömmliche antifibrinolytische Therapie zu ischämischen Komplikationen und Hydrozepahlus führen, sollen weitere Untersuchungen über die Fibrinolyse bei SAB anregen.

Key-Words: Intracranial aneurysm – Subarachnoid haemorrhage – Antifibrinolytic therapy – AMCA – Aprotinin

Introduction

Antifibrinolytic agents have been commonly used in the management of subarachnoid haemorrhage (SAH) caused by intracranial aneurysms, with the aim of reducing the risk of recurrent bleeding in patients awaiting definitive operation. However, the efficacy of antifibrinolytic treatment in aneurysmal SAH has not been unequivocally assessed, in spite of several studies performed over more than ten years (38, 53). E-aminocaproic acid, (EACA) and the more potent tranexamic acid, (AMCA) are the most commonly used antifibrinolytic agents. Both act mainly through a competitive inhibition of the plasminogen activator, although they also exert a minor direct antiplasmin effect. Aprotinin, another antifibrinolytic agent which is mentioned less frequently in the literature about SAH (3, 5, 23, 41, 44), acts mainly through a direct inhibition of plasmin.

The present study was designed to evaluate the results of clinical use of AMCA at reduced dosage combined with aprotinin, in the pre-operative management of ruptured intracranial aneurysms. In a previous paper (18) we suggested that such a combination might perhaps reduce the risk of rebleeding without increasing in the same time the incidence of delayed ischaemic dysfunctions and of hydrocephalus, as the other more commonly used antifibrinolytics appear to do (2, 12, 13, 19, 21, 27, 37, 52).

Material and Methods

Of our patients harbouring ruptured intracranial aneurysms 149 were considered for the present study. They represented approximately one third of the total of intracranial aneurysms observed in the same period. These cases were admitted as possible candidates for delayed operation and managed pre-operatively with a combination of low-dose AMCA, 3 gm/day, and aprotinin, at an average of 400 000 Kallikrein inactivating units (KIU) daily.

Prerequisites for inclusion in this study were also commencement of antifibrinolytic treatment as above, either on admission or in the referring hospital, within three days from the last SAH, and its continuation for at last six consecutive days. Those cases were excluded in which a complicated operation was the likely cause of the patients deterioration after operation, as well as a few cases which very recently received prophylactic nimodipine for ischaemic complications. The first 91 cases managed in the years 1971 to 1980 have already been evaluated in previous papers (18, 45, 47), where the results of two different forms of antifibrinolytic treatment were compared retrospectively. The remaining 58 patients were managed by the present authors during the last five years and carefully observed clinically. The management protocol was remarkably similar in these patients.

Antifibrinolytics were administrated by continuous intravenous infusion until operation, death or discharge. In cases requiring prolonged antifibrinolytic treatment aprotinin was discontinued after approximately three weeks and AMCA given orally thereafter, for no more than six weeks. Other measures included bed rest, mild sedation when required, careful pharmacological reduction of abnormally raised blood pressure,

and osmotic diuretics when needed. A steroid cover before and immediately after the operation was also given to most cases. Delayed ischaemic complications were tentatively managed with plasma volume expanders. For the purpose of the study, we evaluated the incidence of rebleeding, cerebral ischaemic complications (CIC), posthaemorrhagic hydrocephalus and thromboembolic complications. Diagnosis of rebleeding required lumbar puncture and/or CT scan confirmation. CIC were diagnosed by clinical criteria, in deteriorating patients in which recurrent SAH, electrolytic derangement and hydrocephalus were convincingly excluded as possible causes of the clinical deterioration. This required the use of other diagnostic tools, such as echoencephalography and CT in the more recent cases. As a rule, angiography was not performed in deteriorating patients. CIC were classified as mild if regressing within 48 hours, or severe if lasting longer, regardless of the final outcome of the patient.

As far as hydrocephalus, we considered only cases requiring a shunt. Thromboembolism was usually diagnosed clinically and/or at autopsy.

The antifibrinolytic activity in the CSF was assessed in 17 cases by determination of fibrinogen degradation products (FDPs) as described by *Sawaya* et al. (40). As a rule, the samples were collected through the spinal drainage at the time of operation, in order to avoid repeated LPs in patients with unprotected aneurysms. Pre-operative samples were obtained in four patients, two of which died subsequently from recurrent SAH, but in no case was the antifibrinolytic treatment actually monitored.

Results

Patients characteristics

For reasons explained in previous papers (18, 45), there was a male predominance in the first 91 patients (52 : 39), while sex incidence was similar in the more recent cases (28 males : 30 females). Age of patients (Tab. 1) and location of aneurysms (Tab. 2) were comparable to the largest series from the literature (17, 20, 21, 32, 33). The vast majority of the patients were admitted in reasonably good condition (Tab. 3).

Duration of treatment

Antifibrinolytics were administrated for an average of 11 days (range 6–36 days). Definitive operation was the ultimate goal in the management of the present patients. This was achieved in more than 80% of the cases (Tab. 4). In the group of more recently managed patients refusal of operation was less common, a fact which explains the difference in the rate of cases discharged without surgical treatment.

Rebleeding

Recurrent SAH occurred in 15 patients (10%), in 7 of which (4.7%) it was the cause of death. No difference was noted between patients managed either before or after 1981.

Cerebral ischaemic complications (CICs)

Forty patients (26.8%) suffered from delayed ischaemic dysfunctions. The incidence of mild CIC, unlike that of severe CIC, was higher in the more recently managed cases (17% vs 12%), but the difference was not significant. CIC represented the main cause of death in eight cases (5%).

Tab. 1 Age of the patients

Age	1971–1980		1981–1985		Total	
	N.	%	N.	%	N.	%
< 40 yrs	20	22	15	25.9	35	23.5
40–60 yrs	56	61.5	33	56.9	89	59.7
> 60 yrs	15	16.5	10	17.2	25	16.8
Total	91	100	58	100	149	100

Tab. 2 Location of aneurysms

Location	1971–1980		1981–1985		Total	
	N.	%	N.	%	N.	%
ICA	20	22	16	27.6	36	24.2
ACA	42	46.2	25	43.1	67	45
MCA	16	17.5	7	12.1	23	15.4
VB	3	3.3	4	4.6	7	4.7
Multiples	10	11	6	10.3	16	10.7
Total	91	100	58	100	149	100

ICA – Internal carotid artery.
MCA – Middle cerebral artery.
ACA – Anterior cerebral/anterior communicating artery.
VB – Vertebro-basilar system.

Tab. 3 Clinical grading (Hunt and Hess scale)

Grade	1971–1980		1981–1985		Total	
	N.	%	N.	%	N.	%
I	9	9.9	5	8.7	14	9.4
II	46	50.6	29	50	75	50.3
III	28	30.8	18	31	46	30.9
IV	8	8.8	6	10.6	14	9.4
Total	91	100	58	100	149	100

Tab. 4 Reasons for termination of antifibrinolytic treatment

Reason	1971–1980		1981–1985		Total	
	N.	%	N.	%	N.	%
Operation	75	82.4	50	86.2	125	83.9
Death	6	6.6	5	8.6	11	7.4
Discharge*	10	11	3	5.2	13	8.7
Total	91	100	58	100	149	100

* Due to general containdications to, or refusal of, operation.

Posthaemorrhagic hydrocephalus

Nine patients (6%) developed a clinically significant ventricular dilatation, with no difference between the patients managed in different periods.

Thromboembolic complications

Deep venous thrombophlebitis were observed in 11 cases (7.4%), with an increased incidence in the more recent cases (5.5% vs 10.3%, not significant). Four cases (2.7%) also suffered from pulmonary embolism. All but one of these patients received antifibrinolytics for more than two weeks.

Overall clinical results

The results are summarized in Tab. 5. As already mentioned, no difference was noted between the first 91 patients and the remainder, except for an insignificant increase in the incidence of mild CIC and of thrombophlebitis observed in the more recent cases.

Determination of antifibrinolytic activity in the CSF

Tab. 6 summarizes the main data of the patients submitted to CSF FDPs determination at the time of operation. The mean

Tab. 5 Overall clinical results

Complication	1971–1980 N.	%	1981–1985 N.	%	Total N.	%
Rebleeding	10	11	5	8.6	15	10.1
Deaths from rebleeding	4	4.6	3	5.2	7	4.7
CIC (cerebral ischaemic complications)	22	24.2	18	31	40	26.8
Mild CIC	11*	12.1	10*	17.2	21	14.2
Severe CIV	11	12.1	8	13.8	19	12.8
Deaths from CIC	5	5.5	3	5.2	8	5.4
Hydrocephalus	6	6.5	3	5.2	9	6
Thrombophlebitis	5*	5.5	6*	10.3	11	7.4
Pulmonary embolis	2	2.2	2	3.4	4	2.7
Total	91	100	58	100	149	100

* Differences statistically not significant.

Tab. 6 Cases undergoing CSF FDPs evaluation at ther time of surgery

	Sex	Age	Location	Duration of *AF treatment	CSF FDPs level	CIC
1	F	53	ICA-MCA	8 days	8 μg/ml	severe
2	F	52	AcoA	7 days	< 4 μg/ml	NO
3	F	50	AcoA-MCA	12 days	4 μg/ml	NO
4	M	33	AcoA	12 days	< 4 μg/ml	NO
5	F	58	AcoA	11 days	< 4 μg/ml	NO
6	M	42	AcoA	7 days	4 μg/ml	NO
7	M	52	AcoA	9 days	< 4 μg/ml	NO
8	M	51	AcoA	9 days	4 μg/ml	mild
9	F	23	AcoA	9 days	< 4 μg/ml	NO
10	F	56	ICA	8 days	< 4 μg/ml	NO
11	F	57	AcoA	11 days	< 4 μg/ml	NO
12	F	47	ICA	7 days	4 μg/ml	NO
13	F	50	MCA	6 days	4 μg/ml	NO

*AF – Antifibrinolytic

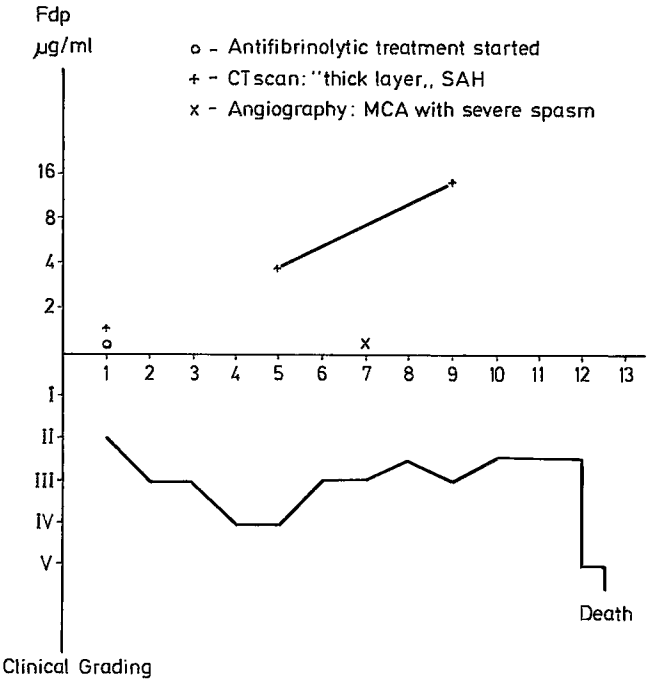

Fig. 1

interval between SAH and operation was ten days. We observed generally a satisfactory inhibition of fibrinolysis. The highest FDPs value was detected in a patient who had CIC pre- and postoperatively. Pre-operative CSF samples were collected in another four cases. Two of these were subsequently operated on, and their FDPs levels were low (≤ 4 μg/ml) pre- and perioperatively. The remaining two cases rebled and died before an operation could be performed. One of these cases, a 43-year-old man with a basilar aneurysm, showed normal FDPs values (< 4 μg/ml) in the CSF collected six days after the SAH. He had been admitted in grade IV, and required several days to improve. He died from rebleeding two days before the scheduled operation, 21 days after the first SAH. Fig. 1 summarizes the clinical history of the remaining patient, a 46-year-old woman with a MCA aneurysm. She suffered from severe CIC from which she was recovering at the time of death. The last FDPs determination, performed three days before the fatal recurrent SAH, had shown slightly elevated values (16 μg/ml).

Discussion

The management of ruptured intracranial aneurysms in still matter of great debate. The policy of delaying direct surgical treatment, adopted until very recently by most neurosurgeons is being reconsidered at present in view of the results of the new Cooperative study, which showed that early operation does not *per se* increase the risk of ischaemic complications (20), as was suggested in the past (11, 17, 30). The lack of convincing evidence of the effectiveness of antifibrinolytic treatment for ruptured intracranial aneurysms (38, 53) has also contributed to the renewed interest in early operation for intracranial aneurysms. Conflicting results have been reported by previously published papers (5, 6, 8, 15, 16, 22, 27, 32, 41–43, 50, 51), a fact which may well be explained in terms of deficiencies in the methods used (38). Therefore, it is not surprising that more carefully conducted recent studies have been rather uniform in showing that conventional antifibrinolytic treatment, either EACA or AMCA at the commonly suggested dosages (9, 32, 50), actually decreased the risk of rebleeding, but also increased the incidence of ischaemic complications and of hydrocephalus, thus leaving unaffected the outcome in SAH patients (2, 12, 21, 52). In an attempt to stimulate new research on antifibrinolysis for ruptured intracranial aneurysms, we reported in 1981 the results of a retrospective study comparing two different methods of antifibrinolytic therapy: the conventional full-dose AMCA treatment versus the combination of low-dose AMCA and aprotinin (18). This study was affected by severe bias, and we cautioned against accepting its results as definitive. Nevertheless it was remarkable that the incidence of ischaemic complications and hydrocephalus was reduced in patients receiving the combination low-dose AMCA-Aprotinin, while the rates of recurrent SAH and of thromboembolism were similar in the two groups of patients.

The theoretical basis for the possible beneficial action of aprotinin in SAH has been extensively discussed in previous papers (18, 45, 47) and will only be mentioned briefly here. Aprotinin might interfere favourably with the process of erythrocyte breakdown within the basal cisterns, which is likely to be a major causative factor for both subarachnoid fibrosis leading to hydrocephalus (19, 37) and release of vasoactive substances causing ischaemia (7, 34, 35) after SAH. Aprotinin appears also to exert a protective action against post-ischaemic oedema (10, 26). In addition, reducing the dosage of the "spasmogenic"

AMCA (12, 13) might also contribute to improving the results as far as ischaemic complications are concerned. Since there are very few papers reporting the use of aprotinin, either alone or in combination, in SAH (3, 5, 18, 23, 41, 44, 45, 47), to confirm its effectiveness as an antifibrinolytic agent for ruptured intracranial aneurysms would require further evidence to be produced. Present data showed a similar rebleeding rate in both retrospective and prospective studies. Satisfactory inhibition of CSF fibrinolysis was documented in the patients undergoing FDP determination in the CSF collected at the time of operation. The 10% rebleeding rate observed in present cases compares favourably with the 18 to 30% incidence of recurrent SAH observed at two weeks in untreated patients (21, 28–30, 33, 36). We noticed a slight, insignificant increase in the rates of mild CIC and of thrombophlebitis in the more recently managed cases, probably as a result of more close clinical observation.

The lack of increased incidence of ischaemic complications (20, 35, 48) as well as continuing research in the field of clinical management of the so-called "symptomatic vasospasm" (1, 4, 14, 24, 46, 49) are strong arguments in favour of early operation for intracranial aneurysms, the only therapeutic measure which permits effective management of the problem of recurrent SAH. However authors also strongly favouring early operation recently reported a fair proportion of patients – 20% to 30% – who were submitted to delayed surgical treatment for clinical and/or logistic considerations (4, 25). It is obvious that these patients, who are faced by the risk of recurrent bleeding while awaiting operation, would require some form of pharmacological prevention, possibly different from the conventional antifibrinolytic treatment. From the present results we may conclude that the antifibrinolytic combination low-dose AMCA and aprotinin is no worse than the conventional full-dose AMCA treatment as far as rebleeding rate. This, as well our previous suggestions (8, 45, 47) that the incidence of ischaemic complications and possibly hydrocephalus might be possibly reduced by using the antifibrinolytic combination given to the present patients, appear to offer arguments for conducting prospective randomized studies of this combination in patients with ruptured intracranial aneurysms.

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Dott. Aldo Spallone
Cattedra di Neurochirurgia
2° Università degli Studi di Roma
"Tor Vergata"
Via Orazio Raimondo, 8
00193 Roma