PAPERS AND ORIGINALS

Prolonged antifibrinolysis: an effective non-surgical treatment for ruptured intracranial aneurysms?

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Summary and conclusions

The outcome of treatment with an antifibrinolytic agent (tranexamic acid) for six weeks after rupture of an intracranial aneurysm was assessed in a randomised controlled trial. Twenty-two out of 25 (88%) treated patients survived at follow-up of three to 33 months compared with 14 out of 25 (56%) control patients. Among the patients who did not undergo operation the survival rate was 81% (13 out of 16) in treated patients and 42% (8 out of 19) in controls.

Antifibrinolytic treatment has so far been assumed merely to postpone rebleeding and has been used to enable surgery to be deferred. These findings suggest that tranexamic acid may actually prevent rebleeding without operation. Prolonged antifibrinolysis may therefore prove useful in those patients in good condition whose aneurysms do not lend themselves to surgical obliteration.

Introduction

Only in the last 10-15 years has surgery improved the natural history of ruptured intracranial aneurysms.[1-3] During the same period several studies have shown that antifibrinolytic drugs will reduce the incidence of rebleeding in the first two to three weeks after a haemorrhage.[4-10]

It has been assumed, without good evidence, that antifibrinolytic agents merely postpone rebleeding, thus allowing operation to be deferred more safely.[8 11] A randomised controlled trial of the antifibrinolytic agent tranexamic acid for a longer period suggested that such treatment might permanently modify the future behaviour of ruptured aneurysms. The trial was carried out at St Bartholomew's Hospital, where the management of ruptured aneurysms is still largely non-surgical.

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Patients and methods

Surgical or antifibrinolytic treatment can be expected only to reduce the number of deaths from rebleeding, although many patients who reach hospital after an aneurysmal subarachnoid haemorrhage die from late effects of the first bleed or from unrelated causes. Accordingly, it was decided to admit to the trial only younger patients in good condition with a high risk of rebleeding. All patients admitted with a proved spontaneous subarachnoid haemorrhage were entered into the trial provided they were (*a*) under 65 and without intercurrent disease, (*b*) relatively little disturbed by the first bleed (Botterell grades 1-3),[12] and (*c*) admitted within 96 hours of the first haemorrhage.

Assignment to treatment or control group was by opening a sequentially numbered, sealed envelope containing the decision. Controls received bed rest and sedation. The treated patients also received tranexamic acid 6 g/day for 42 days or until operation, by intravenous infusion for the first seven days and thereafter orally 1·5 g every six hours.

Suppression of fibrinolysis was assessed by serial assay of fibrinogen degradation product (FDP) concentrations in blood and cerebrospinal fluid (CSF). These were measured by the radioimmunoassay method described by Gordon *et al.*[13]

Patients in whom no cause for the subarachnoid haemorrhage could be found or who had angiomas were removed from the trial after angiography. In the former group the risk of recurrent haemorrhage is very small.[14] In the latter group not only is the risk of late bleeding much less than with an aneurysm but surgery is often undertaken with aims other than that of preventing recurrent haemorrhage. A few patients with aneurysms underwent operation, generally late and indirect in type. They remained in the trial. Recurrent haemorrhage was accepted only if confirmed by lumbar puncture or necropsy.

Results

Seventy-nine patients entered the trial from September 1974 to May 1977 (table I). None of the 27 patients removed from the trial after angiography had rebled. One patient with an angioma died after surgery. One with no lesion who was given tranexamic acid died after progressive deterioration assumed to be due to cerebral ischaemia.

The 25 patients with aneurysm who were treated with tranexamic acid matched the 25 controls in age, sex, blood pressure on admission, and site of aneurysm. Twenty-three patients in each group were in

Botterell grades 1 or 2[12]—that is, no neurological deficit, slight to moderate meningism, alert or slightly drowsy.

Nine of the treated group and six of the controls underwent operation a mean of 24 and 16 days respectively after bleeding (range 9-55 and 7-24 days). Only three patients (all in the treatment group) had direct operations to obliterate the aneurysm. The rest had proximal operations (carotid ligation or anterior cerebral artery occlusion), which left the aneurysm supplied with blood.

The numbers of deaths and episodes of rebleeding are shown in table II. There were no operative deaths. One control died after collapsing before lumbar puncture could confirm a rebleed. Permission for necropsy was refused.

TABLE I—*Details of 79 patients who initially entered trial*

	No of patients	No given tranexamic acid
Patients with aneurysm(s)	50	25
Patients with angiomas	6	2
Patients with no lesion on angiography	21	10
Patients who died before angiography:	2	1
died from rebleeding	1	0
died from effects of first haemorrhage	1	1

TABLE II—*Details of deaths and episodes of rebleeding in each group*

	No of patients	No who died	No who died from confirmed rebleeding*	No who rebled
Treatment group	25	3	3	6
Control group	25	11	10	14

*For comparison between two groups for confirmed rebleeding: P = 0·025 by Fisher's exact probability test.

Overall survival was 88% (22/25) in the treatment group and 56% (14/25) among the controls. Survival amongst those who were not operated on was 81% (13/16) of the treatment group and only 42% (8/19) of the controls.

Patients were followed up for three to 33 months, and 25 of the 36 survivors were followed for over 12 months. Of the total treatment group, 76% (19/25) were alive with no disability, compared with 48% (12/25) in the controls. Three treated patients and two controls were partially disabled.

No case of recurrent haemorrhage occurred later than 55 days. Mean interval until rebleeding was 28·7 days in the treatment group and 24 days in the controls. The mean interval from the presenting bleed to entering the trial was 2·1 days for those treated with tranexamic acid and 2·6 days for the controls. In the treatment group five of the 14 who were admitted within the first 24 hours rebled compared with one of the 11 admitted between 24 and 96 hours. The figures for the control group were 3 out of 6 and 11 out of 19 respectively.

Possible complications of tranexamic acid are shown in table III. Results of serial blood and CSF FDP measurements showed that (*a*) there was no rise in blood FDP concentrations after subarachnoid haemorrhage; (*b*) an initially raised CSF FDP concentration generally fell to normal within the first few days, but occasionally persisted until the third or fourth week; (*c*) persistence of a high CSF FDP concentration after the first week seemed to be associated with a greater risk of rebleeding; (*d*) the CSF FDP concentration did not rise after tranexamic acid was stopped at 42 days; and (*e*) delayed, progressive neurological deterioration was associated with a secondary rise in the CSF FDP concentration.

TABLE III—*Incidence of possible complications of tranexamic acid treatment in each group*

	Treatment group	Control group
Deep vein thrombosis pulmonary embolism	2	2
Communicating hydrocephalus:		
Transient	4	7
Requiring shunting	0	0
Diarrhoea	8	0
Progressive neurological deterioration without rebleeding	8	2
Angiographic evidence of spasm	8	8

Discussion

About 65% of patients admitted to hospital with ruptured aneurysms will die within three years if no treatment is given.[15] Many of the deaths result from the first haemorrhage or from other causes. When a patient survives the first bleed with minimal disturbance (Botterell grade 1) there is initially a 35% chance of his eventually dying from a rebleed, which drops to 10-15% by the middle of the second week.[16] The mortality of direct operations on aneurysm varies from under 5% to over 20%, depending on patient selection and timing of operation.[1 2 17 18] Overall, surgery can now improve the expected mortality by half.[1 3]

Formation of thrombus in and around the aneurysm probably halts the bleeding in those who survive the first haemorrhage.[19] Normally, the leptomeninges show no fibrinolytic activity, but the fibrinolytic system is activated by subarachnoid haemorrhage.[20] Progressive lysis of the thrombus may account for the rise[15] in the rate of rebleeding from 0·7% in the first 24 hours to a peak of 2-3% daily from the fourth to the seventh days. Antifibrinolysis is designed to suppress this process and to allow the thrombus to be replaced by mature fibrous tissue, thus "wrapping" the aneurysm. In two patients in this series who had late direct operations the aneurysms were indeed found to be invested by dense adhesions. Tranexamic acid acts like the more widely used aminocaproic acid by competitively inhibiting plasminogen, but experiments in both man[21] and animals[22] suggest that its potency as an antifibrinolytic agent is 7-10 times as great, and that it produces stronger thrombi.[23]

Several studies, mainly with aminocaproic acid, have shown that antifibrinolytic agents reduce the rebleeding rate in the first two weeks from 15-20% to 5-10%. Most series have been uncontrolled,[4-7 9 11 20 24] but the same striking improvement has been found in controlled trials.[8 10 25 26] The widespread assumption[8 11] that rebleeding is merely postponed does not seem to have been put to the test by continuing the drug and not operating. In the present trial, although surgery was late if at all, "rebound" bleeding in patients given tranexamic acid did not occur; deaths from rebleeding occurred on days one, 10, and 54.

Only three of the 50 patients underwent direct aneurysm operations, and a further 12 had indirect operations at a mean interval of 17 days. A retrospective review of patients treated at St Bartholomew's Hospital suggests that indirect surgery is effective only in reducing early bleeding. Such surgery may have only temporary efficacy and may be worthwhile only if carried out early, to carry the patient over the initial high-risk period. If this is so then virtually none of the patients in this series received effective surgery, and indeed the rebleeding rate and mortality in the control group were much as would be expected in an untreated population. The incidence of death and rebleeding was reduced by about two-thirds in the treated group. In those who had no surgery 81% of treated patients survived compared with 42% of controls. The trial was not double-blind, but the criteria of failure of treatment, recurrent haemorrhage, and death permit little subjective bias.

It may be objected that follow-up has not yet excluded very late rebleeding. This may be so, but, although some studies[14 15] report an annual incremental mortality of up to 5% among untreated survivors, others[27-29] suggest that rebleeding after three months is very rare. Deaths from unrelated illness may account for this discrepancy, as many untreated patients are rejected for surgery because of age or intercurrent disease. In any case it does not follow that a patient who survives the initial period after antifibrinolysis has the same later risks as the person who survives that period without such treatment.

Even better results might be obtained if antifibrinolytic treatment could be started at the referring hospital. The mean interval before starting tranexamic acid was two days. The high initial CSF FDP concentrations suggest that considerable clot lysis had already occurred.

Antifibrinolytic drugs should probably be given for at least four weeks to cover the period during which primary or secondary fibrinolysis continues and the risk of breakthrough bleeding is highest. Indeed, rebleeding in a patient who has had antifibrinolytic treatment may be less serious, as the aneurysm is better protected after the first bleed.

Theoretical side effects[30 31] of thromboembolism and communicating hydrocephalus from obstruction of the subarachnoid space were not encountered,[1 10 31] even though antifibrinolytic treatment was continued for longer than usual. Progressive neurological deterioration, usually reversible, was common, however, and does not seem to have been a problem when treatment was given for a shorter period, although cases of cerebral arteriopathy[6 32] and delayed cerebral arterial spasm[10] have been reported.

Progressive cerebral ischaemia may prove to be a serious side effect of prolonged antifibrinolysis in the more obtunded patients, in whom such an occurrence is known to be more frequent. Three of the five patients in Botterell grade 3 who were given tranexamic acid showed this phenomenon, and the failure of large intracerebral clots to dissolve may also prove to be a problem. The death of an obtunded patient given tranexamic acid after the closure of the trial was apparently due to ventricular blockage caused by a persistent clot.

The tentative conclusion to be drawn from these findings, given that the number of patients and length of follow-up were limited, is that prolonged antifibrinolysis may permanently improve the natural history of ruptured aneurysms. If this is so the results of direct aneurysm surgery will have to be measured against a new set of rebleeding and survival risks, and those patients whose aneurysms have configurations or sites not accessible to surgery can be offered an effective non-surgical treatment.

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Endometrial assessment with Isaacs cell sampler

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Summary and conclusions

The value of the Isaacs endometrial cell sampler in the cytological assessment of the endometrium was studied in 121 unanaesthetised patients aged over 40. Satisfactory aspirates for cytological diagnosis of endometrial state were obtainable in 111 patients (91%) whereas endometrial specimens for histological diagnosis were obtained in only 89 patients (79%). In only four out of 83 cases were there diagnostic discrepancies between the aspirates and the curettings. It is concluded that the technique is safe, quick, comfortable, and reliable for assessing endometrial state. It should therefore prove valuable for screening, particularly in the management of menopausal women requiring oestrogen treatment.

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Introduction

Considerable experience of mass screening programmes for carcinoma of the cervix has shown that premalignant and malignant lesions can often be diagnosed at an asymptomatic stage. The success of the Papanicolaou smear is largely due to the ease with which cell samples can be obtained. There has always been a need for a similar screening test to detect asymptomatic premalignant and malignant lesions of the body of the uterus. Such a test would also be valuable in screening postmenopausal women receiving oestrogen treatment, which may be associated with abnormal endometrial hyperplasia[1] and carcinoma.[2-4]

Various methods of obtaining endometrial specimens for