Effect of Tranexamic Acid on Rebleeding after Subarachnoid Hemorrhage: A Double-Blind Controlled Clinical Trial

J. van Rossum, MD, A. R. Wintzen, MD, L. J. Endtz, MD,
J. H. R. Schoen, MD, and H. de Jonge, MD

In a double-blind controlled clinical trial on 51 patients with subarachnoid hemorrhage, tranexamic acid, 4 gm per day for ten consecutive days, did not favorably affect the outcome. Neither mortality nor rebleeding rates were improved after a follow-up of three months.

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Antifibrinolytic drugs such as ϵ-aminocaproic acid (EACA) and tranexamic acid have been employed to reduce the risk of rebleeding after subarachnoid hemorrhage (SAH). The rationale has been to prevent dissolution of the blood clot formed at the site of the ruptured aneurysm once the bleeding has stopped [2, 4, 5, 10, 12, 15, 19–22]. This study evaluated the effects of tranexamic acid on the basis of a double-blind controlled clinical trial.

Material and Methods

The investigation was a cooperative trial among the neurology departments of three hospitals. It started in November, 1973, and closed November, 1975. A diagnosis of SAH was made on the basis of hemorrhagic spinal fluid not caused by lumbar puncture and severe headache of acute onset, often accompanied by neck rigidity. Impaired consciousness, pareses, tendon reflex differences, and similar abnormalities were regarded as secondary diagnostic signs.

Treatment was started immediately after the diagnosis was made. In 32 of the 51 patients, treatment was begun on the day of their SAH; in 5 patients it started within 48 hours of the initial bleeding, in 11 patients within one week, and in 3 patients within the second week after the SAH. The trial was set up in a double-blind fashion, drug and placebo being randomly administered in a sequence prescribed by and known only to the statistician (H. de J.). Administration of either placebo or drug was by intravenous infusion or intravenous injection. The drug-treated patients received 4 gm of tranexamic acid in 40 ml of solution daily (1 gm per 10 ml every 6 hours) during ten consectuive days. Placebo-treated patients received physiological sodium chloride solution, 40 ml daily, also for ten consecutive days. It was impossible for medical staff or patients to distinguish between drug- and placebo-containing ampules. Administration of other drugs was avoided as much as possible, but essential medication (e.g., insulin) was given or continued.

Of the 51 patients admitted to the trial, 22 were being treated for diseases or complaints that had existed prior to the onset of SAH. Five were receiving antihypertensives, 4 analgesics, 4 anticoagulants, 3 antidiabetic drugs, 3 glucosides, 2 antiepileptic agents, and 1 each was taking antibiotics, corticosteroids, and tranquilizers. Three patients were taking several kinds of drugs: 1 was on digoxin and anticoagulant therapy, 1 on antidiabetic and diazepam therapy, and 1 used glucoside as well as antihypertensive and analgesic medication. Preexisting diseases in 16 patients included hypertension in 6, diabetes mellitus in 3, cardiac disease in 2, nephritis in 1, rheumatoid arthritis in 1, epilepsy in 2, and bronchial carcinoma in 1. Six patients were taking medication without a firm diagnosis. At the completion of the trial the use of preexisting medication proved to be evenly distributed (11 patients each) between the drug- and placebo-treated groups.

Four patients were on anticoagulant therapy at the time of their SAH because of either a previous cardiac infarction (3 patients) or pulmonary embolism (1 patient); anticoagulation was discontinued at hospital admission. If neurological evaluation led to surgical treatment, drug treatment (tranexamic acid or placebo) was discontinued after the intervention.

When the study was planned, it was acknowledged that some patients would be included in whom subsequent clinical evaluation would change the original diagnosis of SAH to one of, for instance, primary intracerebral hemorrhage or bleeding into a tumor. We hoped that erroneous diagnoses would be evenly divided between the drug- and placebo-treated groups. Originally 54 patients were admitted to the study, but 3 patients had to be excluded because

From the Departments of Neurology of the University Hospital, Leyden, the Municipal Hospitals, The Hague, and the Diaconessenhuis, Voorburg, and the Department of Medical Statistics, University of Leyden, Leyden, The Netherlands.

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Address reprint requests to Dr van Rossum, Department of Neurology, University Hospital, Leyden, The Netherlands.

autopsy findings corrected the original diagnosis to acute subdural hematoma, intracerebral hemorrhage, and multiple hemorrhagic infarcts, respectively.

The clinical follow-up for each patient covered a period of three months, counted from the day of the SAH. Postmortem examination was performed in 16 of the 26 patients who died, 8 of whom had received placebo and 8 drug treatment. In 15 instances an aneurysm was found.

Results

Mortality figures in the placebo- and drug-treated groups are listed in Table 1. Hospital 1 shows a better outcome with drug treatment. However, none of the differences in mortality rates between the placebo-treated and drug-treated patients in any of the three hospitals are significant: $p = 0.31$ (Hospital 1), 0.15 (Hospital 2), and 0.48 (Hospital 3) by the two-sided exact Fisher test. The overall outcome can be analyzed in two ways: by combining the results of the separate tests or by applying the Fisher test to the pooled results of the three hospitals. Both ways of testing yield the nonsignificant p value of 0.48. Consequently, our conclusion from this trial is that administration of tranexamic acid, 4 gm per day intravenously for ten days after SAH, does not influence mortality, as observed three months after SAH.

The mean ages of the placebo- and drug-treated patients (54 and 58 years, respectively) are statistically similar. Six of the 51 patients had been known to have hypertension prior to their SAH. Two died; both were in the drug-treated group. All 4 patients on anticoagulant therapy prior to SAH died. Two (49 and 63 years old) were drug treated and 2 (49 and 67 years old) were placebo treated.

Table 2 shows that for both the patients who died and those who survived, the neurological condition at the time of their SAH was about the same for placebo- and drug-treated patients. However, there was a clear-cut correlation between state of consciousness and survival. Of the 21 patients who were alert immediately following SAH, only 1 died; of the 17 who were drowsy, 13 died; and of the 13 comatose patients, only 1 was living after three months.

Thirty-five of the 51 patients underwent angiography. In another 5 patients angiography had been performed several years before, demonstrating an aneurysm (4 patients) or arteriovenous malformation (1 patient) [7], and the investigation was not repeated at the time of the SAH. In the remaining 11 patients angiography was not carried out because of either poor clinical condition or anticoagulant therapy. The percentage of nonvisualized aneurysms was equal in the two groups (30%).

Angiography showed an aneurysm in 13 patients in the placebo-treated group, of whom 8 were alive and 5 had died at three months, and in 11 patients in the drug-treated group, of whom 7 were alive and 4 had died at three months. Five patients in the placebo-treated group and 6 in the drug-treated group did not show an aneurysm on angiography.

Rebleeding episodes occurred in 9 of the 51 patients. The diagnosis of recurrent SAH was made on clinical grounds; a repeat lumbar puncture showing hemorrhagic spinal fluid was obtained in 8 of these 9 patients. In the drug-treated group 5 patients had rebleeding episodes, 4 of which were fatal. In the placebo-treated group, 4 patients suffered from re-

Table 1. Mortality in the Placebo- and Drug-treated Groups

	Hospital 1			Hospital 2			Hospital 3			Total		
Status	PT	DT	Total	PT	DT	Total	PT	DT	Total	PT	DT	Total
Died	6	2	8	5	11	16	0	2	2	11	15	26
Alive	3	5	8	9	5	14	2	1	3	14	11	25
Total	9	7	16	14	16	30	2	3	5	25	26	51

PT = placebo-treated; DT = drug-treated.

Table 2. Neurological Condition at Hospital Admission and Mortality after Three Months (Total Three Hospitals)

Status at Admission	Died			Alive		
	PT	DT	Total	PT	DT	Total
Alert	1	0	1	11	9	20
Drowsy	5	8	13	2	2	4
Comatose	5	7	12	1	0	1
Total	11	15	26	14	11	25

PT = placebo-treated; DT = drug-treated.

bleeding and 3 died. There is no difference in the frequency or mortality of rebleeding between the two groups.

In the placebo-treated group, 8 patients died from the initial bleeding episode and 3 from rebleeding. In the drug-treated group these figures were 10 and 4, respectively. One patient died from a myocardial infarction. We therefore feel justified in concluding that there was no difference between the placebo- and drug-treated groups with regard to early death or death from rebleeding from a ruptured aneurysm.

In our series, unwanted side-effects of tranexamic acid were observed in 2 of 26 treated patients; in the placebo-treated group of 25, no side-effects were noted. One patient complained once of dizziness for a few minutes following the intravenous injection, and another developed superficial thrombophlebitis on the eighth day of therapy at the site of his infusion.

Discussion

Nilsson et al [13] reviewed the use of such antifibrinolytic drugs as EACA and tranexamic acid in nonneurological diseases. Norlén and Thulin [14] described the beneficial effect of EACA during operation on 2 patients with arteriovenous malformations who started to bleed and whose hemorrhage could not be stopped by any other means. Work by Gibbs and O'Gorman [4] indicated that the prognosis in SAH was not changed by EACA administration in 109 patients. Patterson and Harpel [16] demonstrated that EACA or tranexamic acid augmented the "strength" of an experimentally induced thrombus within an aneurysm.

A limited number of papers on the use of EACA or tranexamic acid in SAH from ruptured intracranial aneurysm have appeared [2, 4, 5, 10, 12, 15, 20–22]. None of these studies include controls. Gibbs and Corkill [5] compared two groups of patients with SAH from ruptured aneurysm, 1 treated surgically and the other conservatively with tranexamic acid. The latter group was made up largely of patients who, for various reasons, were considered unable to tolerate operation. Nibbelink et al [12] reported a cooperative study in which 502 patients with ruptured intracranial aneurysm from thirteen institutions received EACA or tranexamic acid. Unfortunately, their conclusion that antifibrinolytic therapy provides beneficial effects in patients with SAH is based on a follow-up period of only fourteen days.

Sengupta et al [19] have presented the only study in which results of EACA treatment in patients with ruptured intracranial aneurysm were compared with controls, though a double-blind procedure was not performed. They did not present details of duration of EACA treatment or of the length of follow-up. An important point to note is that their control group contained twice as many severely ill patients (Botterel grade III) as the EACA-treated group (16 vs 8 patients). Also, their grade II group comprised 30 control patients and only 20 from the EACA group. This means that 18 patients in the control group of 76 were more severely ill on admission than the drug-treated patients, affecting Sengupta's conclusions inasmuch as the prognosis in SAH relates to initial clinical severity [9]. Furthermore, 88% of Sengupta's EACA group underwent surgery compared with 60% of the control group, indicating poorer clinical condition in the latter patients. Under the circumstances, Sengupta's finding that rebleeding did not occur in the 66 patients with aneurysm in the EACA group whereas it was noted in 17 of the 76 control patients is difficult to interpret.

In our study, no difference was noted in the rate of rebleeding between patients treated with tranexamic acid and the control group. As used in the present study, tranexamic acid has a much stronger antifibrinolytic action than EACA [3, 8, 22]. More serious side-effects of antifibrinolytic drugs than were noted in the present study have been published occasionally, predominantly thrombotic [1, 6, 11, 17, 18] and arteriopathic complications [21].

Tranexamic acid (Cyclocapron) and placebo solutions were generously supplied by the manufacturer, KABI, Stockholm, Sweden.

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