Treatment of Subarachnoid Hemorrhage from Ruptured Intracranial Aneurysm with Tranexamic Acid: A Double-Blind Clinical Trial

Benjamin Chandra, MD, PhD

A double-blind clinical trial of tranexamic acid was carried out on 39 patients with fresh subarachnoid hemorrhage from a ruptured aneurysm. Twenty patients received tranexamic acid, 6 gm daily for 14 to 21 days, while 19 patients received conventional therapy of bedrest and dexamethasone when cerebral edema developed, plus isotonic saline. Rebleeding and mortality were reduced by one-fourth and one-fifth, respectively ($p < 0.001$). No side-effects were observed. Tranexamic acid is valuable in the treatment of subarachnoid hemorrhage caused by ruptured intracranial aneurysms.

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Indonesia has a population of 130 million, but only the largest cities have comprehensive neurological centers. The center in Surabaya, the second largest city in the country, serves an area of 60 million people, but has only one neurosurgeon, whose full attention must go to treating brain tumors and traumatic subdural and extradural bleedings. Subarachnoid hemorrhage is usually treated medically.

In 1970 we conducted a preliminary trial with tranexamic acid and obtained encouraging results. The same period saw reports describing the use of ϵ-aminocaproic acid (EACA) in subarachnoid hemorrhage [4]. Because our clinic could not always obtain EACA, a double-blind clinical trial was designed to compare tranexamic acid therapy with conventional therapy.

Materials, Methods, and Results

Patients with subarachnoid hemorrhage resulting from ruptured intracranial aneurysm who were admitted between January 1, 1974, and January 1, 1976, were invited to participate in the trial. Family consent was obtained for unconscious patients. It was explained that one group would receive the conventional treatment of bedrest with intensive nursing care for three weeks with dexamethasone when cerebral edema developed, plus saline injection. The other group would receive bedrest, intensive nursing care, and dexamethasone when cerebral edema developed, plus tranexamic acid injections.

Diagnosis was based on the following criteria:

1. Acute onset of headache
2. Evidence of meningeal irritation
3. Blood-stained cerebrospinal fluid not due to trauma
4. Angiographic demonstration of an intracranial aneurysm
5. Fresh subarachnoid hemorrhage not older than 7 days

None of the patients had a relevant associated illness such as leukemia or other blood dyscrasia.

The patients were allocated at random to two subgroups. Tranexamic acid and isotonic saline solution were prepared in identical ampules and coded so that neither the investigator nor the patient knew which subjects received which substance. The dose of tranexamic acid was 6 gm per day (each ampule contained 250 mg of tranexamic acid), given 1 gm every 4 hours intravenously.

From January 1, 1974, until January 1, 1976, 42 patients met the criteria described. Three declined to participate in the study; the remaining 39 included 21 men and 18 women who ranged in age from 20 to 65 years with a mean of 51 years.

I examined all the patients when they were admitted to the hospital. The following initial laboratory examinations were made before administration of the test drug: complete blood count and differential count, platelet count, urinalysis, and liver function tests. Special attention was given to renal function tests, which included serum creatinine and blood urea nitrogen. The determinations were performed daily while the subject was in the hospital and monthly after discharge. Treatment was continued until 21 days after the last hemorrhage.

Twenty patients received tranexamic acid and 19 received isotonic saline solution. The sex and age distribution of the

From the Department of Neurology, University of Airlangga School of Medicine, Surabaya, Indonesia.

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Table 1. Sex Distribution in the Two Treatment Groups

Sex	Tranexamic Acid	Placebo
Male	11	10
Female	9	9
Total	20	19

Table 2. Age Distribution in the Two Treatment Groups

Age (yr)	Tranexamic Acid	Placebo
30–39	4	3
40–49	6	6
50–59	7	7
60–69	3	3

Table 3. Clinical Conditions in the Two Treatment Groups

Clinical Condition[a]	Tranexamic Acid	Placebo
Grade 1	2	3
Grade 2	10	9
Grade 3	6	5
Grade 4	1	1
Grade 5	1	1

[a]See text for explanation of grades.

Table 4. Mortality and Rebleeding 3 Weeks after the Last Hemorrhage in the Two Treatment Groups

Event	Tranexamic Acid	Placebo
Rebleeding	1	4
Death	1	5

$p < 0.001$.

patients in the two groups showed no significant difference (Tables 1, 2). Patients were classified on admission by the following criteria: (1) asymptomatic or minimal headache and slight neck stiffness; (2) moderate to severe headache, neck stiffness, no neurological deficit other than cranial nerve palsy; (3) drowsiness, confusion, or mild focal deficit; (4) stupor, moderate to severe hemiparesis, possible early decerebrate rigidity, and vegetative disturbances; and (5) deep coma, decerebrate rigidity, or moribund appearance [2]. Table 3 shows the clinical condition of the patients in the two treatment groups. Table 4 gives the results of treatment 3 weeks following the last hemorrhage. No side-effects of tranexamic acid therapy were seen, such as pulmonary embolus or renal artery thrombosis, both of which were described during EACA therapy.

Discussion

The results indicate that tranexamic acid is superior to conventional therapy in subarachnoid hemorrhage and has fewer side-effects than EACA. Our 5% incidence of rebleeding and death accompanying tranexamic acid therapy is similar to Nibbelink's figure of 5.8% using EACA [5]. In both trials, patients were treated who entered the hospital 1 to 7 days after the last hemorrhage. A similar clinical classification was used except that in the EACA study the results were tabulated after 2 weeks, while the tranexamic acid results were assessed after 3 weeks.

Table 5 summarizes the reported side-effects for EACA and tranexamic acid. Emphasis is placed on the duration of treatment. These findings imply that complications of tranexamic acid therapy occur only after long use of the drug, while the side-effects of EACA occur after a few days of use. I used the normal dose of EACA, 24 gm daily, and of tranexamic acid, 6 gm daily. We observed no side-effects in 20 patients who received 6 gm of tranexamic acid from 14 to 21 days.

Tranexamic acid is a transisomer of aminomethyl cyclohexanecarboxylic acid, an antifibrinolytic drug which acts by competitively inhibiting the activator substances that convert plasminogen into the proteolytic enzyme plasmin. The rationale for use of the drug is based on the assumption that rebleeding from an aneurysm is caused by lysis of a clot.

Table 5. Side-Effects of EACA and Tranexamic Acid

Author	EACA	Tranexamic Acid	Duration of Drug Intake
Norlen [6]	Thrombosis, cerebral arteries		10 days
Sonntag [7]	Thrombosis, cerebral arteries		5–14 days
Charytan [1]	Thrombosis, glomeruli		14 days
Davies [3]	Thrombosis, cerebral arteries		5 yr EACA and tranexamic acid

Tranexamic acid theoretically prevents this lysis. Because tendency for recurrent bleeding is known to rise to a maximum around the end of the first week and to decline to a low level after the third week, it is logical to give tranexamic acid for only 3 weeks.

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