ANTIFIBRINOLYTIC TREATMENT IN ANEURYSMAL SUBARACHNOID HEMORRHAGE

ANTIFIBRINOLYTISCHE THERAPIE BIJ SUBARACHNOIDALE BLOEDINGEN DOOR EEN ANEURYSMA

PROEFSCHRIFT

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"It is perhaps no wonder that young doctors, nurtured in an aura of basic science, turn wistfully back to the laboratory where a neat and aesthetically satisfying experiment can be performed, even though the result is of no obvious benefit to the medical practice for which they have been trained."

J.E. Lennard-Jones (176)
Some parts of this thesis were adapted for articles that have been or will be published.

- Vermeulen M, Muizelaar JP:
  Do antifibrinolytic agents prevent rebleeding after rupture of a cerebral aneurysm? A review.

- Vermeulen M, Van Gijn J, Blijenberg BG:
  Spectrophotometric analysis of CSF after subarachnoid hemorrhage: Limitations in the diagnosis of rebleeding.
  Neurology (NY) 33: 112-114, 1983.

- Vermeulen M, Van Gijn J, Hijdra A et al:
  Causes of acute deterioration in patients with a ruptured intracranial aneurysm. A prospective study with serial CT scanning.

- Vermeulen M, Lindsay KW, Murray GD et al:
  Antifibrinolytic treatment in subarachnoid hemorrhage: A multicenter, double-blind, placebo-controlled trial.

- Vermeulen M, Van Vliet H, Lindsay KW et al:
  Degradation products of Fibrin/Fibrinogen in the CSF after subarachnoid hemorrhage: A result of protein leakage rather than local fibrinolytic activity.
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GENERAL INTRODUCTION

Since 1967 antifibrinolytic agents have been used in patients with a subarachnoid hemorrhage (SAH) from a ruptured intracranial aneurysm. Despite many studies on this subject, it is still not clear whether these patients benefit from this treatment. The aim of this study is to elucidate and to solve this controversy.

Chapter I gives a detailed outline of the problem. Aneurysmal subarachnoid hemorrhage is a serious condition with an incidence of 10-20 per 100,000 population per year. One of the main complications in patients who survive the initial hemorrhage is rebleeding which especially occurs during the first two weeks after the presenting hemorrhage and which is associated with a high mortality and morbidity (part I). The short interval between rebleeding and the initial hemorrhage has led to the hypothesis that rebleeding is caused by fibrinolysis of the blood clot which seals the ruptured fundus of the aneurysm.

The principles of the fibrinolytic process are described in part 2.

The current knowledge of the role of fibrinolysis in the pathogenesis of rebleeding and the possibilities to inhibit the fibrinolytic process with antifibrinolytic drugs are summarized in part 3.

The effectiveness of antifibrinolytic therapy can best be studied in a controlled clinical trial. It is useful to distinguish these clinical trials into explanatory and pragmatic trials (part 4).

Fourteen comparative studies of antifibrinolytic treatment had been performed before, but none of these fulfilled simple methodologic standards required in a clinical investigation of therapy (part 5).

A possible measure for the effect of antifibrinolytic treatment might be the influence on the fibrinolytic activity in the cerebrospinal fluid (CSF). Previous studies have concluded that the estimation of fibrin degradation products (FDP) in the CSF is the most useful method of monitoring the fibrinolytic activity after a subarachnoid hemorrhage. However, it has also been suggested that FDP's may reflect a damaged blood-CSF barrier.

I studied the fibrinolytic activity in the CSF and aimed at solving the controversy whether the presence of FDP's in the CSF after SAH reflects a damaged blood-CSF barrier or ongoing fibrinolytic activity. The results of this part of the study are described in Chapter II.
Another approach is to compare the rates of rebleeding in patients on antifibrinolytic therapy and on placebo. In such trials it is mandatory to distinguish rebleeding from other complications after a subarachnoid hemorrhage. In many reports on the effects of antifibrinolytic treatment on the rebleeding rates, it was stated that rebleeding was confirmed by lumbar puncture. However, this may be difficult because [1] CSF may remain blood-stained for as long as 24 days after the hemorrhage; [2] an increased red cell count may result from a traumatic tap; and [3] a rebleed may not be evident in the CSF if the blood is retained in the cerebral parenchyma or the subdural space. The value of serial spectrophotometric analysis of the CSF was investigated in prospective series of patients who did or did not suffer a rebleed, according to serial computed tomography (Chapter III).

Another common method of diagnosing rebleeding is to rely on clinical criteria: an acute deterioration of consciousness is generally regarded as characteristic of a recurrent rupture of the aneurysm, as opposed to other complications. I studied the reliability of this clinical distinction by prospectively comparing acute changes in the clinical condition and changes on computed tomography (Chapter IV).

A final and most important question was whether patients with subarachnoid hemorrhage benefit from treatment with antifibrinolytic drugs by comparing the outcome in the treatment group with that of the placebo group. That is the pragmatic approach. This led to a double-blind, placebo-controlled clinical trial, conducted in several centers.

Apart from the pragmatic approach, which aimed at determining if antifibrinolytic treatment led to improved functional outcome, the incidence of rebleeding, cerebral infarction and other possible complications was also studied (Chapter V).
Subarachnoid hemorrhage (SAH) may be caused by many conditions (167), but non-traumatic SAH has become almost synonymous with hemorrhage from a ruptured berry aneurysm of the circulus of Willis. These aneurysms are not rare: their prevalence rate has been estimated to vary between 1 and 5% (69, 99, 131). Fortunately, not all these aneurysms rupture, but the incidence of aneurysmal hemorrhage is considerable: between 10 and 20/100,000 per year (52, 118, 122). In contrast to the incidence of strokes the incidence of SAH has not decreased since the beginning of this century (122). This suggests that the growth and rupture of an intracerebral aneurysm are not much influenced by hypertension, since the gradual decline of the incidence of stroke has been attributed to the prevention of hypertension by a lower salt intake and to better treatment of hypertension (45, 91).

Congenital factors may play a role in the development of aneurysms, such as defects in the media of the cerebral vessel wall at branching points, but such defects are extremely common. Therefore, apart from congenital factors, acquired factors are operative as well, but these have not been identified (31, 32).

Clinical features

Rupture of an intracranial aneurysm is a serious condition. It has been estimated that of all the patients with an aneurysmal hemorrhage 36% will die or be disabled as a result of the initial insult and that during treatment another 32% will die or be disabled, 11% from rebleeding, 11% from cerebral infarcts, 7% from surgical complications and 3% from medical complications. Thus, of all the patients with an aneurysmal hemorrhage only 32% will survive without major disability, which is half of the patients available for treatment (81). The early mortality (within one day) after SAH is difficult to influence, since these patients usually die from intracerebral hematomas, massive intraventricular hemorrhages or both (73). A small proportion of
early deaths is not associated with intraventricular or intracerebral blood. These patients with only subarachnoid blood may have died from secondary brain damage caused by anoxia and might therefore have been saved by resuscitation (74). For the other patients who die early, there is no treatment and therefore much attention has been called to the symptoms preceding the rupture of an aneurysm (63). These warning signals may be caused by minor bleeds and if these are recognized the aneurysm may be clipped before the major and disastrous bleeding occurs. However, the incidence of these warning leaks and the possibility of diagnosing them have still to be established.

The prognosis of patients who survive the initial insult is to a large extent determined by their neurological condition (122). A reliable grading system is therefore extremely important. However, if patients are assessed with either of two commonly used methods such as the Hunt and Hess (76) or the Nishioka system (114), much inconsistency will result (92). Recently, a new scale has been proposed which is more consistent in practice (148).

Patients with SAH experience a sudden severe headache, such as they have never suffered before. They may remain fully orientated, have transient alterations of consciousness or elapse into a coma from which they never awake. An important sign is the neck stiffness which develops within the first hours after the hemorrhage. Focal signs are not conspicuous in SAH except if an intracerebral hematoma develops.

A CT scan should be the first technical investigation carried out, if SAH is considered. In a series of one hundred consecutive patients with SAH diagnosed on clinical grounds, CT demonstrated in 19 a cause other than a ruptured aneurysm (156). In this series 8 patients had a cerebellar hematoma, which indicates that lumbar puncture may be dangerous in patients with clinical signs of SAH. The distribution of blood in the basal cisterns on CT may predict the absence or presence of an aneurysm and may give information on the site of the ruptured aneurysm (157). Radiological evidence of extravasated blood can be detected in 84-100% of patients in the first two days after a subarachnoid hemorrhage (14, 156, 171). It has been estimated that the probability of recognizing an aneurysmal hemorrhage on CT is 85% after five days, 50% after one week, 30% after two weeks and almost nil after three weeks (158). If the CT scan is negative, a lumbar puncture has to be carried out, but the interpretation of the CSF findings may be cumbersome, since it is difficult to distinguish a traumatic tap from a previous hemorrhage, especially in the first few days (21).

Angiography is at present the most reliable method for identifying an intracranial aneurysm if operation is considered. Recently, intravenous digital angiography has been recommended (23), but the value of this method in the demonstration of aneurysms has still to be established.
Complications

Patients who survive the initial bleeding may have many complications during the first weeks. Of these, rebleeding and infarction are the more important. Other complications are hydrocephalus, edema around an intracerebral hematoma, epilepsy and medical complications.

The incidence of rebleeding is 20% after two weeks and 30% after one month (94). After six months the probability of a rebleed is approximately 3% per year (175). The rate of mortality from rebleeding is about 50% (94).

The pathogenesis of rebleeding has not been established. It has been suggested that rebleeding may be caused by fluctuations in arterial pressure that occur in an attempt to maintain cerebral perfusion (66). Others consider the role of fibrinolysis of the CSF as extremely important (48, 104). Vasospasm has been considered to be a mechanism for preventing rebleeding, and prevention of vasospasm might therefore result in an increased rate of rebleeding.

Vasospasm usually appears 3 to 10 days after SAH and can be demonstrated in 21-62% of the patients depending on the timing of angiography (39, 89). It is generally believed that such focal narrowing can cause cerebral ischemia with neurological deterioration in the form of impairment of consciousness and local signs. This cerebral ischemia is a progressive phenomenon which manifests itself clinically in approximately one quarter of the patients with aneurysmal hemorrhage (37). The agent which induces spasm is not known, but it may be a product released from disintegrated erythrocytes (117). On the other hand, subarachnoid hemorrhage from causes other than a ruptured aneurysm rarely leads to cerebral ischemia.

During vasospasm, cerebral ischemia could also result from increased blood viscosity due to an elevated fibrinogen level, formation of microthrombi, and reduced deformability of red cells (133).

Fisher (47) and Kistler (86) showed a relationship between clinical signs of infarction and the amount and distribution of blood as seen on CT. This has to be confirmed with radiological criteria for infarction. Also, reliable methods have to be developed to grade the amount of blood on CT.

Hydrocephalus may develop within weeks to months after the hemorrhage and is usually characterized by a gradual deterioration of the patients' consciousness (53). Acute hydrocephalus occurring within the first two weeks leads to a rapid deterioration and is not an infrequent complication since the incidence has been reported to be between 10-17.5% (85, 138). The occurrence of acute hydrocephalus has a bad prognosis (85), although others argue that it is not clinically significant, usually resolves spontaneously and does not require shunting (160, 171).

Intracerebral or subdural hematomas formed by the initial hemorrhage may cause a subacute deterioration by tissue damage and/or edema with increasing brain shift (154).
Epileptic fits occur at the onset of aneurysmal hemorrhage in 10-19% of the patients. Epilepsy may also develop during the course of the illness (68, 134).

In a cooperative study on SAH, the most serious medical complications were uremia [3.5%], gastrointestinal hemorrhage [3%], pulmonary embolism [4%] and myocardial infarction [2%] (108). In a series of 100 patients with ruptured aneurysms, the major medical complications were respiratory [54%], genito-urinary [26%] and cardiovascular problems [23%] (169). The genito-urinary problems consisted mainly of cystitis, the cardiovascular complications of arrhythmias and the respiratory problems were mainly caused by pneumonia and pulmonary edema. Much attention has been paid in the literature to cardiac arrhythmia (41). Recently, it has been pointed out that cardiac arrest is an infrequent problem (74).

The intracranial complications after SAH may be difficult to diagnose. The advent of CT has dramatically improved the possibility of distinguishing the different causes of deterioration. This is important not only in studies on the effectiveness of therapies, but it can be decisive for the medical or surgical treatment of the individual patient (154).

Treatment

One of the first problems in treating patients with SAH is whether the patient should be treated in a quiet private room to avoid stress or in an intensive-care or specialized stroke unit, where the patient can be observed closely to record the deteriorations and, the most important, where immediate resuscitation is possible. Stressful influences of the intensive-care unit might be alleviated by sedation.

The respiratory status of the patients must be carefully monitored because a reduction of $pO_2$ in areas of the brain with impaired autoregulation precipitates cerebral infarction (153). Pulmonary edema may develop immediately after the hemorrhage and positive end-expiratory pressure ventilation may be necessary to treat this serious but reversible condition (26, 46, 169). Respiratory arrest after a rebleed requires mechanical ventilation for at least one hour. Return of spontaneous respiration after that time does not occur (74).

The rationale for the treatment of elevated blood pressure in patients with intracranial aneurysms is to reduce the chance of rebleeding by decreasing the pressure against the weakened wall of the aneurysm (66). In addition, turbulence within the aneurysm increases as blood pressure rises, producing vibratory damage and stress on the wall (43). Hypertension might also aggravate the effects of vasospasm by enhancing vasogenic edema (66). On the other hand, regional cerebral blood flow and autoregulation may be abnormal in SAH and therefore lowering of the blood pressure may result in cerebral ischemia by impairing cerebral perfusion (66).
Hyponatremia frequently occurs after SAH and deteriorations of consciousness have been attributed to these low sodium values (7). Hyponatremia is often supposed to be caused by expansion of the extracellular volume. Therefore, fluid restriction is advocated to treat this condition (13). Recently, it has been suggested that this treatment may result in an increased incidence of cerebral infarction (172).

If a patient gradually deteriorates several weeks after the hemorrhage and CT demonstrates ventricular dilatation, there will be little doubt about shunting being an appropriate treatment. Acute hydrocephalus may also occur, but whether this should be treated is still controversial (160).

Many attempts have been made to treat vasospasm. Recently, the use of Nimodipine has been advocated (3), but the study that showed an effect of Nimodipine on the severity of vasospasm is not convincing in terms of an improvement of the overall outcome (163). Another approach is the prevention of ischemia in patients with vasospasm by measures such as an increase of blood pressure, the expansion of blood volume (82) and the decrease of blood viscosity (80). The merits of these treatments have still to be established and it is possible that they are dangerous pre-operatively.

Clipping of the aneurysm is generally believed to be the best treatment to prevent rebleeding. The operative mortality has dramatically improved with modern surgical and anesthetical techniques. The risks of surgery are still related to the condition of the patient and the time of surgery. Operations on the aneurysm are generally not carried out in patients of grades 4 and 5 on the Hunt and Hess scale (76) and there is much controversy about the need for operation in grade-3 patients. The timing of surgery is a well-known controversy in the management of patients with SAH. The disastrous results of early operations in the fifties abandoned acute surgery. Surgery is generally planned after a delay of at least ten days and only on patients in grade 1 or 2 and sometimes patients in grade 3. Recently, acute surgery has attracted new interest because no more favorable outcome can be achieved than thirty years ago (93, 145). The advantages of early operation are that it affords maximum protection against rebleeding, and once the aneurysm has been obliterated arterial pressure can be safely elevated to avoid ischemic complications. It has also been suggested that removal of blood from the cisterns may protect against vasospasm (103). In favor of delayed surgery is that most of the brain edema will have resolved and much of the blood that obscures anatomic detail will have been lysed and washed away, which makes dissection of the aneurysm less difficult. The clot that seals the aneurysm will be organized, with less risk of rupture at operation. It is extremely important to find out if the advantages of early surgery outweigh the disadvantages of surgery on a recently injured brain and in an environment of haste (83).

Antifibrinolytic treatment has been advocated to prevent rebleeding in the pre-operative period and also in patients unsuitable for operation. The effectiveness of antifibrinolytic treatment in SAH is the subject of this thesis.
Part 2. FIBRINOLYSIS AND ANTIFIBRINOLYTIC TREATMENT

When a blood vessel wall is damaged, the hemostatic mechanism starts. This initially involves the adherence of platelets to the damaged wall, followed by the release of substances resulting in aggregation of these platelets (170). As a consequence of this sticking-to-each-other of platelets, a plug is formed that stops the bleeding when the injury to the vessel wall is not too large. Meanwhile, the activation of the coagulation cascade leads to the formation of thrombin. Thrombin converts fibrinogen to fibrin which precipitates as a fibrin polymer. The fibrin network re-inforces the platelet plug and provides a matrix for the reparation by connective tissue (130).

Fibrinolysis is a mechanism that liquifies blood clots and the basic components are plasminogen, plasminogen activators, plasmin and an inhibitor, the $\alpha_2$-antiplasmin [figure 1] (18).

![Diagram](image)

Figure 1.

Plasminogen is synthesized in the liver (17). It is a single-chain glycoprotein of which the complete amino-acid sequence, consisting of 791 residues, is known. The activation of plasminogen by urokinase, an activator found in greater quantities in the urine, and presumably other activators occurs by the cleavage of a peptide bond between arginine 561 and valine 562. This activation of plasminogen results in the formation of a two-chain molecule, the plasmin. The activation of plasminogen will occur preferentially, if not solely on the fibrin surface and therefore plasmin will be generated only when fibrin is present (116). Plasminogen and plasminogen activators are both adsorbed on to the surface of fibrin. Plasminogen adheres to fibrin by means of structures which bind amino-acids such as epsilon-aminocaproic acid and lysine; these are termed lysine-binding sites. Presumably, complementary structures resembling epsilon-aminocaproic acid
are exposed on the surface of fibrin molecules and display an affinity for these lysine-binding sites of plasminogen (27).

The plasminogen activator found in the blood is released by the vascular endothelium (149). The concentration of plasminogen activators during clotting determines the rate of fibrinolysis. Fibrin clots prepared from tissue-type plasminogen-activator-rich plasma, lyse spontaneously within a few hours but similar clots, prepared from plasma with a low level of these activators do not lyse within 24 hours, neither spontaneously nor on addition of activators (19). Plasmin is formed on the surface of fibrin, it is a proteolytic enzyme with fibrin as its physiological substrate. The plasmin cleaves some specific peptide bonds in the fibrin molecule. The fibrin becomes soluble and the plasmin that comes free is neutralized by a very rapid reaction with $\alpha_2$-antiplasmin (27). This reaction prevents the extension of the fibrinolytic process beyond the environment of the clot. The antiplasmin in the plasma surrounding a clot cannot react with plasmin during the interaction between plasmin and fibrin since the active sites of plasmin are occupied in this reaction.

The degradation of fibrin by plasmin results in the formation of X-oligomers by the release of peptides from the $A_\alpha$-chain of fibrin. The aggregated X-oligomers are digested further to complexes described as Y-D and [D-D]E (57). These fibrin-fibrinogen degradation products [FDP's] can be demonstrated in blood with immunological techniques. Their presence usually indicates the breakdown of fibrin as for instance in disseminated intravascular coagulation (57).

With the fibrin-plate method (11), estimation of plasminogen activation activity is possible. Test samples are applied on these fibrin plates and after overnight incubation the diameter of the resulting zones of lysis are measured. The lysed area represents the fibrinolytic activity of the sample. Other methods of detecting plasminogen activator activity are measuring the euglobulin clot lysis time (111), and the solid-phase radiometric assay (106).

**Antifibrinolytic treatment**

The two major synthetic antifibrinolytic drugs are 6-aminohexanoic acid or epsilon-aminocaproic acid and trans-P-aminomethyl-cyclohexanecarboxylic acid or tranexamic acid (figure 2). There is a marked structural similarity of lysine with these synthetic inhibitors of fibrinolysis and this explains their action (125). The plasminogen molecules bind to fibrin by a lock-and-key fit between one or more lysine-binding sites on plasmin or plasminogen and complementary sites on the fibrin. Epsilon-aminocaproic acid and tranexamic acid block the lysine sites of plasminogen and as a consequence the binding to fibrin cannot take place (125). Subtle changes in the structure of these antifibrinolytic agents have marked effects since the
molar potency of tranexamic acid is six to tenfold higher than of epsilon-aminocaproic acid and the cis-form of tranexamic acid is ineffective in comparison with the trans-form (125).

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H & \quad H & \quad H & \quad H & \quad H
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Epsilon-aminocaproic acid

\[
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\quad & \quad & \text{COOH}
\end{align*}
\]

Tranexamic acid

**Figure 2.**

### Clinical pharmacology

**Epsilon-aminocaproic acid**

After intravenous injection the biological half-life of epsilon-aminocaproic acid is 77 minutes (110). After intravenous injection 80-100% of the dose can be recovered in the urine within 4-6 hours, in contrast to only 25% after oral ingestion (101). Epsilon-aminocaproic acid is eliminated by glomerular filtration and the major portion of the drug is not metabolized. Epsilon-aminocaproic acid given by mouth is rapidly and almost entirely absorbed from the gastrointestinal tract. If 100 mg/kg body weight is given intravenously, the plasma concentration is 3.9 mg/100 ml after 4 hours. The plasma concentration is 16 mg/100 ml if the same dose is given by mouth. The peak concentration of epsilon-aminocaproic acid is 30 mg/100 ml two to three hours after oral ingestion. In-vitro experiments and clinical experience indicate that a plasma concentration of at least 13 mg/100 ml is required to control fibrinolytic activity (101). The recommended dosage for inhibiting fibrinolysis is 100 mg/kg body weight intravenously at about 3-hourly intervals. Alternatively, after an initial intravenous dose the same dose can be given by mouth at the same time intervals (110). For inhibiting 'local' fibrinolysis 100 mg/kg body weight intravenously or by mouth should be given three to four times a day (110).
Tranexamic acid

The biological half-life of tranexamic acid after intravenous injection is one to three hours. After 24 hours 90% can be recovered in the urine. The maximum serum concentration of tranexamic acid is 2 mg/liter after a dose of 10 mg/kg body weight by mouth; after a dose of 100 mg/kg body weight a plasma concentration of 40 mg/liter is reached within four hours (6, 40). This means that tranexamic acid is not absorbed from the gastrointestinal tract as effectively as aminocaproic acid. Therefore, the oral dose of tranexamic acid given during the third and fourth weeks of treatment in the clinical trial described in Chapter V, was higher than the intravenous dose: 6 grams versus 4 grams a day. Tranexamic acid is eliminated by glomerular filtration, and impairment of renal function considerably prolongs the biological half-life. In-vitro experiments and clinical practice indicate that control of fibrinolysis requires a plasma tranexamic acid concentration of 10-15 mg/liter. Since this drug is rapidly excreted in the urine, it must, like epsilon-aminocaproic acid, be given at short intervals. To inhibit fibrinolysis an intravenous dose of 10 mg/kg body weight every 3-4 hours is recommended, or an oral dose of 30-50 mg/kg body weight every 3-4 hours. For inhibition of 'local' fibrinolysis a much lower dose may be given by mouth owing to its sustained tissue activity: 10-20 mg/kg body weight three to four times daily (6, 40).

Tranexamic acid crosses the blood-CSF barrier in patients with a ruptured cerebral aneurysm and enters the aneurysm clot (51). It has been demonstrated that tranexamic acid given in a dosage of 1 gram intravenously six times daily causes a successive rise in the CSF concentration as the number of injections increases. This cumulation in CSF has also been reported after administration of the drug by intravenous infusions, and by mouth. The peak concentration of tranexamic acid is achieved within the shortest time in the patients who received the drug by intravenous infusion (51). Fodstad assumed that a concentration of at least 1 mg/liter of tranexamic acid is sufficient to inhibit fibrinolytic activity in the CSF. This assumed therapeutic level is reached within 36 hours with intravenous injections or infusion of 6 grams daily and within 48 hours when the drug is administered orally in a dosage of 9 grams daily (51).

Side-effects

In patients on epsilon-aminocaproic acid muscle pain with increased serum enzymes have been reported (55). In a muscle biopsy of a patient with this therapy, hyaline degeneration was found (87). In another patient, an acute delirious state was attributed to epsilon-aminocaproic acid (173). Epsilon-aminocaproic acid and tranexamic acid may cause diarrhea, nasal stuffiness and conjunctival suffusion (164). Occasionally, orthostatic symptoms have been reported (164). Intracranial arterial thrombosis has been de-
scribed in two patients receiving tranexamic acid to control menorrhagia and in a patient with angio-edema (34, 132). In two controlled clinical trials thrombotic complications did not occur more frequently in treated patients. In a study of 201 patients undergoing prostatectomy and treated with tranexamic acid, there was no significant difference in the incidence of thrombosis between the treatment and placebo groups (71). In a double-blind study of 515 other patients after prostatectomy, the mortality due to pulmonary embolism and myocardial infarction was similar in both groups (165).

**Clinical applications**

Epsilon-aminocaproic acid and tranexamic acid are both of value in patients with hemophilia undergoing dental surgery. Their use in these patients has resulted in a saving of coagulation factor concentrates at the time of operation (54, 166). Antifibrinolytic treatment to prevent spontaneous bleeding has not been shown to be effective (15, 144). Epsilon-aminocaproic acid and tranexamic acid both control the hematuria in patients with hemophilia but the risks of renal tract obstruction is considered to be too high (65, 75).

Antifibrinolytic treatment may have a role in the treatment of profuse menstrual bleeding due to dysfunctional bleeding, IUD and inherited coagulation defects (22, 79, 112, 113). Their value in the bleeding complications of pregnancy has not been demonstrated (10). Epsilon-aminocaproic acid and tranexamic acid reduce the blood loss after prostatectomy and this may aid recovery mainly due to better drainage of the bladder which decreases the risk of infection (70, 100). In gastrointestinal hemorrhage antifibrinolytic treatment might reduce the number of patients requiring operation (16). Tranexamic acid is said to be able to inhibit tumor growth (9).

The role of antifibrinolytic treatment in subarachnoid hemorrhage is controversial (161). An illustrative example is that in 1977 four of the seven University departments of neurology in the Netherlands treated patients with antifibrinolytic therapy after SAH, and the other three did not. The reasons for this controversy will be discussed in Part 5.
Part 3. FIBRINOLYSIS AFTER SUBARACHNOID HEMORRHAGE

After an aneurysmal hemorrhage, rebleeding most frequently occurs during the first two weeks (94). This has led to the hypothesis that rebleeding is caused by a premature lysis of the blood clot which seals the aneurysm and that methods which could preserve the clot for a longer period might decrease the rate of rebleeding. Initially, it has been supposed that there is a direct lytic effect of CSF on the blood clot surrounding the aneurysm. De Vivo (36) studied the effects of CSF on in-vitro coagulation in three test systems and found an inhibitory influence of CSF on a prothrombin system and an acceleratory effect on both the thromboplastin generation test system and the thrombin-fibrinogen reaction. From this study it can be concluded that CSF acts either as an accelerator or inhibitor of coagulation depending on which phase of the coagulation system is studied. These investigations on the effects of CSF on the coagulation system take into account only the reactions between blood clots and isolated CSF and not what happens if blood enters the subarachnoid space. It has been shown that the dura mater and pia mater have considerable fibrinolytic activator activity (151). These activators are more important than the effects of isolated CSF on coagulation. When blood enters the subarachnoid space, activators from the damaged meninges react with the plasminogen of the blood, converting this into plasmin. This fibrinolytic activity has been considered responsible for the early clot lysis after SAH (150).

The systemic activation of the fibrinolytic system might also play a role in the lysis of the aneurysm clot, since the fibrin plug is partly exposed to the arterial circulation. Gibbs and O'Gorman (61) measured the diluted blood clot lysis time and found slightly increased values after SAH. Ettinger (42) confirmed these results. In contrast, the fibrinolytic activity in the blood as measured on fibrin plates was found not to be increased in patients with SAH, and FDP’s in the blood were not detectable or had low values (44, 151). In conclusion, there is no firm evidence for activation of systemic fibrinolysis after SAH. The slight enhancement of systemic fibrinolysis that sometimes can be detected is probably aspecific, and comparable with that occurring in other stress-producing situations (151).

The fibrinolytic activity of the CSF after SAH has been estimated by measuring lysis zones on heated and unheated fibrin plates. Fodstad (50) demonstrated an increased fibrinolytic activity of CSF on unheated plates, during the first week after the hemorrhage. These findings are at variance with other studies, and Fodstad explained this by differences in the fibrin plates. He used human fibrin, which he considered more sensitive than the bovine fibrin plates.

FDP’s result from breakdown of fibrin by plasmin. Complete breakdown leads to the formation of D and E fragments. Against antigenic
determinants of these fragments antisera can be raised, which form the basis of the quantitative immunochemical methods of measuring FDP's (90).

Tovi (151) was the first to demonstrate FDP's in the CSF. He demonstrated FDP's in the CSF of patients with SAH up to the end of the third week after the initial bleeding. These FDP's disappeared during the first days of treatment with tranexamic acid. Maurice-Williams (96), using a more specific and sensitive assay, detected FDP's in the CSF in a number of patients up to five weeks after the bleeding. Both these studies concluded that as the fibrinolytic activity in the CSF may continue for several weeks, antifibrinolytic therapy should be given at least as long. Maurice-Williams considered it unlikely that CSF FDP's would linger on for long after active lysis of the clot had ceased, as the total CSF volume is replaced every eight hours and as FDP's have a biological half-life of 15 hours.

The effect of tranexamic acid on FDP levels was studied by Fodstad (50). The FDP levels were reduced after one week in treated patients but after two weeks the amount of FDP was reduced also in a control group. He demonstrated increased FDP levels in CSF on admission without an accompanying increase in fibrinolytic activity on fibrin plates. From these findings he concluded that measurement of FDP's gives a more accurate picture of local fibrinolysis in the CSF than the fibrin plate method. He found high levels of FDP's in the CSF in patients who developed ischemia. Even in the blood of these patients elevated FDP levels were detected. Fodstad suggested that the rise of FDP's in patients with ischemia might be the result or the cause of anoxia. In the latter case, FDP's might possess vasoconstrictive activity and might contribute to the development of vasospasm.

From all the studies on fibrinolytic systems and coagulation abnormalities in SAH, the most consistent finding is the high level of FDP's in the CSF during the first weeks after the hemorrhage. These FDP's are considered to be a reliable measure for the optimal dosage of antifibrinolytic treatment (51), for deciding between surgical and conservative treatment (96) and for monitoring antifibrinolytic therapy in the individual patient (135). The validity of this concept has been tested as part of this thesis (Chapter II).
Part 4. METHODS FOR THE CLINICAL ASSESSMENT OF ANTI-FIBRINOlytic TREATMENT IN SUBARACHNOID HEMORRHAGE

Comparison of different treatments

The effectiveness of some therapies are easy to demonstrate. A new treatment in a fatal disease will be accepted after the first cures are reported. The demonstration of the effectiveness of antifibrinolytic agents in SAH is more complex. Despite twenty-nine clinical studies which appeared in the medical literature this therapy remains controversial (161).

One approach of investigating whether antifibrinolytic therapy has a beneficial effect in patients with SAH is to compare the outcome of patients over different periods of time, with and without treatment. One of the disadvantages of such historical controls is that the diagnostic procedures for the disease and the events under scrutiny may have changed over the years. This is certainly the case in patients with SAH. The advent of the CT scan has dramatically improved the accuracy of diagnosing events after the initial bleeding. Another disadvantage of historical controls is that the referral pattern and the general management of these patients has also changed over the years. Therefore, the best method of studying the effects of antifibrinolytic therapy is to use concurrent controls in a clinical trial. Such trials are difficult to define. Clinicians performing a trial are carrying out an experiment, in contrast to a survey in which a follow-up study is done without prospective design. The allocation of patients to the different treatment groups in the trial requires randomization. Many randomization methods exist but the ideal method is the use of random number tables. In general, it is wise to avoid methods which are related to characteristics of the study subjects, such as surname or date or place of recruitment. If, for instance, the date of admission is used, the allocation to the two groups may be influenced by bias of the referring physicians. Physicians who believe in antifibrinolytic therapy and who know that on even days the admitted patients will be treated with antifibrinolytic therapy might delay referral when seeing a patient on uneven days, while patients in a poor condition would be admitted immediately. Another incorrect randomization criterion is the ward to which the patient is admitted. If the patients of ward A are treated while the patients of ward B are on placebo, it is quite possible that the study would indicate the differences in overall management between the two wards rather than the differences between the two treatments.

After this decision to study the effects of treatment in a clinical trial an important question is whether a double-blind technique should be used. In previous studies on antifibrinolytic therapy in subarachnoid hemorrhage, the differences in rebleeding rate between control and treatment groups have
been used as the major criterion of effectiveness. In such studies the diagnosis of rebleeding becomes extremely important. It is, therefore, surprising that in many studies rebleeding was not even defined. The difficulties in the diagnosis of rebleeding from the CSF or from the clinical features alone will be explained in Chapters III and IV, respectively. These difficulties make it clear that the diagnosis of rebleeding is open to observer bias. To avoid this bias a blind technique is mandatory. It might be argued that the effectiveness of antifibrinolytic therapy can be studied by comparing the mortality rates in the treatment and control groups and that the diagnosis of death is not influenced by observer bias. However, it is possible that a clinician who knows that a patient is on antifibrinolytic treatment will delay surgery in these patients in contrast to patients on placebo. These differences in timing of operation may in turn influence the mortality rates. Similarly, clinicians may treat hypertension more vigorously when antifibrinolytic treatment is omitted because they fear for rebleeding especially in these patients. Treatment with antihypertensives may result in an increased incidence of cerebral infarction and consequently in an increased mortality. All these arguments make it clear that a controlled trial of antifibrinolytic agents should be designed in a blind fashion.

**Explanatory and pragmatic trials**

When a trial on the effects of antifibrinolytic therapy in SAH is designed, a major decision is what kind of trial will be carried out: an explanatory or a pragmatic trial. The contrasts between explanatory and pragmatic approaches have been described by Schwartz, Flamand and Lellouch in their book Clinical Trials (137). They explained that the choice between these types of trials has implications for the selection and the number of patients, the administration of the drugs, and the assessment of events (Table 1). In general, an explanatory approach aims at providing an increase in knowledge or understanding, while a pragmatic approach investigates whether a treatment is beneficial in the average clinical situation and thus ought to be used.

An explanatory approach may also provide information of practical importance but this depends on the results of such trials. Supposing there is a reliable method of determining fibrinolytic activity around the aneurysm and the result of the trial is that treatment has no effect on fibrinolysis, the conclusion is that this treatment is of no practical value. On the other hand, if inhibition of fibrinolytic activity actually occurs, there is still a need to show the beneficial effect on the clinical condition of the patients. A pragmatic trial may also provide an increase in understanding, but only if the result is positive: after having shown an improvement of outcome in patients treated with antifibrinolytic agents, we may suppose that these agents inhibit fibrinolytic activity.
The first implication of the choice between these two types of trials is the selection of patients to be studied. If a purely explanatory approach is adopted in trials on antifibrinolytic treatment, patients with a high fibrinolytic activity in the CSF will be selected and the effects of treatment on this fibrinolytic activity will be studied. Another explanatory approach is to select patients with an aneurysm and to compare the rebleeding rates. From a pragmatic viewpoint it will be essential to choose patients who are representative of those to whom the antifibrinolytic treatment will be administered in practice. This implies that patients can be included in the trial who have clinical signs and symptoms of a subarachnoid hemorrhage but who eventually fail to show an aneurysm on angiography. Likewise, patients in whom angiography will not be carried out because they are not fit for surgery, will also be included in a pragmatic trial, although it remains uncertain whether an aneurysm is present or not.

The choice between an explanatory and a pragmatic approach may also depend upon the route of administration of the drugs. In a pragmatic trial we

Table 1. Contrasts between an explanatory and a pragmatic approach in studying the effects of antifibrinolytic treatment in SAH.

<table>
<thead>
<tr>
<th>Aim of study</th>
<th>Explanatory</th>
<th>Pragmatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required number of patients</td>
<td>Type I and II errors are of importance</td>
<td>Type III error is of importance</td>
</tr>
<tr>
<td>Selection of patients</td>
<td>Patients with fibrinolytic activity in CSF or with an aneurysm</td>
<td>Patients with SAH probably due to aneurysm</td>
</tr>
<tr>
<td>Route of drug administration</td>
<td>i.v. greatest biological effect</td>
<td>i.v. and oral as in practice</td>
</tr>
<tr>
<td>Assessment of treatment</td>
<td>Measurements of CSF fibrinolytic activity or counting confirmed rebleeds</td>
<td>Estimation of outcome</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Increase of knowledge of mechanism of rebleeding</td>
<td>Improves decision how to treat SAH</td>
</tr>
<tr>
<td>Increase of knowledge</td>
<td>Always</td>
<td>If Outcome improves</td>
</tr>
<tr>
<td>Improves clinical decision</td>
<td>If no effect</td>
<td>Always</td>
</tr>
</tbody>
</table>

*AF = Antifibrinolytic
Table 2. The three different conclusions and the six possible errors in an explanatory trial.

<table>
<thead>
<tr>
<th>REALITY</th>
<th>CONCLUSIONS FROM A STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>comparison between antifibrinolytic treatment and placebo</td>
</tr>
<tr>
<td></td>
<td>more effective</td>
</tr>
<tr>
<td>more</td>
<td>equally effective</td>
</tr>
<tr>
<td>effective</td>
<td>type II error</td>
</tr>
<tr>
<td>equally</td>
<td>type I error</td>
</tr>
<tr>
<td>effective</td>
<td>type III error</td>
</tr>
<tr>
<td>less</td>
<td>type I error</td>
</tr>
<tr>
<td>effective</td>
<td>type II error</td>
</tr>
</tbody>
</table>
give the drugs in a way which is usual in practice, in an explanatory trial we choose the route of administration which will give the greatest biological effect, even if side-effects develop. In an explanatory trial of patients with SAH, the drugs will be given intravenously even if they have no neurological deficits or disturbed consciousness, while in a pragmatic trial the drugs will be given by mouth when the patients can swallow and do not vomit.

The course of the disease will be followed in biological terms in an explanatory trial, which means that in patients with SAH we shall determine the fibrinolytic activity or the number of rebleeds. In a pragmatic trial the advantages and disadvantages of the treatment are assessed. This is done by comparing the general condition of the patients with SAH after treatment with and without antifibrinolytic drugs.

The contrasts between an explanatory and a pragmatic trial have been explained above by comparison between extreme cases. Mixed designs are also possible: sometimes a trial can be more pragmatic than explanatory, or vice versa.

If we decide to assess only the rate of rebleeding, the trial is mainly explanatory, whereas a comparison of fibrinolytic activity is a purely explanatory approach. Trials assessing the rate of rebleeding have therefore practical consequences only if the results show no effects on the rebleeding rate. When the results demonstrate a decrease in the rate of rebleeding, there is still a need for a pragmatic trial to investigate if this treatment really improves the outcome of the patients.

Required number of patients

In the design of a trial, the calculation of the number of patients required is of crucial importance. In Part 5 it will be explained that many trials on antifibrinolytic therapy in SAH were too small for conclusions to be possible. In such calculations the contrasts between an explanatory and a pragmatic approach again operate. In an explanatory trial we may reach three different conclusions with six possible errors (Table 2). If placebo and antifibrinolytic treatments are truly equivalent, we may conclude from a trial that antifibrinolytic treatment is more effective or that this treatment is less effective than placebo (error of the first kind). If antifibrinolytic treatment is actually more effective or less effective than placebo, we may find no difference (error of the second kind), or we may find the opposite (error of the third kind). To minimise the possibility of concluding that a difference exists when this is not actually so, we choose a small value for the error rate of the first kind (\( \alpha \)). Conversely, if antifibrinolytic therapy is effective, we do not wish to conclude that there is no difference. Therefore, we also have to fix the probability \( \beta \) which is the probability of not detecting a real difference (type II error). After having fixed \( \alpha \) and \( \beta \) within small values, the error rate \( \gamma \)
(third kind) becomes negligible. However, before fixing the $\alpha$ and $\beta$ error rates we have to decide what difference we at least wish to detect. It is not realistic to go to great lengths for concluding that one treatment is 1% better than the other. A usual aim is that the number of patients should be sufficient to show a 50% reduction of unwanted events or other end-points, depending on the nature of the trial. If we do not wish to miss a reduction in the rebleeding rate of at least 50%, we take the chance of considering a treatment resulting in a reduction of less than 50% as ineffective. And even if we assume a 50% difference between the two treatments, we must accept the probability $\alpha$ of incorrectly concluding that one treatment is better than the other, and the probability $\beta$ of still missing a true difference of this magnitude.

The required number of patients for the trial described in Chapter V, was calculated after finding that the overall rebleeding rate of patients treated with placebo or tranexamic acid was around 17%. We decided to aim at detecting a reduction in rebleeding of at least 50%. In that case the rebleeding rate in the placebo group would be 22.6% and in the treatment group 11.3%. Then we fixed the error rates $\alpha$ at 5% and $\beta$ at 10%. With equation 1 we can calculate the required number of patients,

\[
Equation 1: \quad n = \frac{(\epsilon_{10} + \epsilon_{13})^2}{2(\sin^{-1}\sqrt{P_B} - \sin^{-1}\sqrt{P_A})^2}
\]

where the symbols are as follows: $n$ is the number of patients in each group, $\epsilon_0$ and $\epsilon_1$ are the Normal deviates corresponding to the required error rates $\alpha$ and $\beta$, $P_B$ and $P_A$ are in this example the assumed rebleeding rates 22.6% and 11.3%, and $\sin^{-1} P_B$ denotes the angle in radians whose sine is equal to the square root of $P_B$.

The required number of patients is:

\[
Equation 2: \quad n = \frac{(1.90 + 1.282)^2}{2(\sin^{-1}\sqrt{0.226} - \sin^{-1}\sqrt{0.113})^2} = 225
\]

which means 225 patients in each group, or 450 patients in total.

In a pragmatic trial the $\alpha$ and $\beta$ error rates are not important. If the two treatments are equally effective, we cannot make a mistake when we recommend one of the treatments, therefore an error of the first kind is of no importance. With this approach we always reach a conclusion so that the error rate $\beta$ is zero. Failing to reach a conclusion in favor of antifibrinolytic treatment simply means to conclude in favor of placebo treatment. In these circumstances the error rate of the third kind becomes of vital importance: the only mistake that can be made is that an inferior treatment is recommended. The required number of patients in a pragmatic trial must therefore be calculated after choosing a small value for $\gamma$. 
We did not calculate the required number of patients in a pragmatic way because we did not know the mortality rate nor the proportion of patients dying from rebleeding. If we use the mortality rates of the trial described in Chapter V we can calculate the numbers required for a new, pragmatic trial. In the explanatory approach we wished to detect a difference in the rebleeding rate of at least 50% and since half of the patients who rebled died from rebleeding, a reduction in rebleeding of 50% will result in a reduction in mortality of 25%. The overall mortality was 36%, a reduction with 25% is therefore achieved if the mortality rate in the placebo group is 41% and in the treatment group 31%. Using equation 3, we can calculate the required number of patients in a pragmatic way,

Equation 3:  
\[ n = \frac{\epsilon^2 \gamma}{2(\sin^{-1}\sqrt{p_B} - \sin^{-1}\sqrt{p_A})^2} \]

where \( \epsilon \) is the Normal deviate corresponding to the error rate \( \gamma \) and \( p_B \) and \( p_A \) are the mortality rates 41% and 31%.

If we choose the value 0.05 for \( \gamma \), the required number of patients is

Equation 4:  
\[ n = \frac{1.645^2}{2(\sin^{-1}\sqrt{0.41} - \sin^{-1}\sqrt{0.31})^2} = 124 \]

which means 124 in each group.

Statistical significance and therapeutic gain

When the results of two treatments are compared, it is possible that the difference is highly significant in a statistical sense. However, a high statistical difference does not mean that the one treatment is far superior to the other. To determine how much better the treatment is, we may estimate the therapeutic gain (176). If, for example, the rebleeding rate in the control group is 30% and it is 10% in the treatment group, the therapeutic gain is 20%. Random variation will play its role, so we should like to know within what limits the true difference may be expected to lie. This can be calculated by estimating the 95% confidence limits of the difference between the rebleeding rates. These limits can be determined by first calculating the standard error of the difference. The 95% confidence limits will lie between the observed difference and \( \pm 2 \) standard errors. Therefore, the number of patients in each group determines the width of the 95% confidence interval. If the rebleeding rate was reduced from 30% to 10% in a study with 20 patients in each group, the 95% confidence interval for the therapeutic gain of 20% lies between -4% and 44%. This would mean that no reduction in rebleeding rate is still
possible. If the same results were obtained in a study with 100 patients in each group, the limits would lie between +9% and 31%, which means that the reduction in rebleeding rate would be at least one third. Confidence limits inform us about the probable size of the difference and we can see if the therapeutic gain is worthwhile. Another advantage of calculating the 95% confidence limits of the difference is that it also provides information on the value of a trial with a negative result. We may, for example, find that the rebleed rate in the placebo group of a trial is 25% and conclude that there is no difference between antifibrinolytic therapy and placebo in preventing rebleeding. The 95% confidence limits may lie between -18% and +22%, indicating that the treatment may nearly double the rate of rebleeding but could also decrease the rebleeding rate to only a few percent. This is as much as we knew before the trial started. These confidence limits have been calculated for differences found in previous trials on antifibrinolytic therapy in SAH and are shown in Part 5 of this chapter.

It is to be expected that if equation 4 is used to calculate the required number of patients for a pragmatic trial, the sample sizes will be small. This will result in wide confidence intervals and therefore with this method we may not be able to quantify the benefits of a treatment.

In conclusion, the best method of determining the effects of antifibrinolytic treatment in SAH is to carry out a double-blind, randomized, placebo-controlled trial with a sufficient number of patients and to use a pragmatic analysis, which assesses the influence of treatment on the overall outcome of the patients.
Gibbs and O’Gorman [1967] (61) published the first report on antifibrinolytic treatment in subarachnoid hemorrhage, and since then twenty-nine reports have appeared in the English medical literature. These studies can be divided into two groups, studies with and without concurrent controls. The disadvantages of historical controls have been explained in Part 4.

The 15 studies without concurrent controls are summarized in Table 3.

Table 3. Studies of antifibrinolytic treatment without concurrent controls.

<table>
<thead>
<tr>
<th>Author (et al.) (ref.)</th>
<th>No. of patients</th>
<th>Rebleeding %</th>
<th>Overall % mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mullan (104)</td>
<td>35</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Norlén (115)</td>
<td>14</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Ransohoff (129)</td>
<td>50</td>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>Tovi (152)</td>
<td>34</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Geronemus (60)</td>
<td>27</td>
<td>19</td>
<td>—</td>
</tr>
<tr>
<td>Corkill (28)</td>
<td>20</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Shaw (140)</td>
<td>9</td>
<td>56</td>
<td>33</td>
</tr>
<tr>
<td>Profeta (126)</td>
<td>135</td>
<td>?</td>
<td>70</td>
</tr>
<tr>
<td>Nibbelink (108)</td>
<td>502</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Post (124)</td>
<td>85</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Mullan (105)</td>
<td>103</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Schisano (136)</td>
<td>58</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Adams (1)</td>
<td>1114</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Ameen (4)</td>
<td>100</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Guidetti (57)</td>
<td>123</td>
<td>11</td>
<td>—</td>
</tr>
</tbody>
</table>

Mullan (104) and Norlén (115) both prudently concluded that antifibrinolytic treatment might diminish the rate of rebleeding and that this treatment seemed sufficiently free from side-effects to warrant a larger study.

Ransohoff (129) admitted that his study was too small to be conclusive, but he considered the mortality rate of 35% lower than expected and therefore thought his results encouraging. Although the series of Tovi (152) was equally small, the conclusions were less prudently formulated. Geronemus (60) gave as his opinion that “antifibrinolytic treatment is a most useful early treatment in SAH”. Corkill (28) considered his results to be in favor of antifibrinolytic treatment. Shaw (140) felt that his series showed such poor results that he was deterred from proceeding with a therapeutic trial and he asked in a letter in the Lancet for the opinion of others. The conclusions of Profeta (126) were surprising. He concluded that antifibrinolytic treatment did not protect the patient from the risk of rebleeding during the first weeks after the hemorrhage, but that it produced a faster improvement after the initial bleeding.
### Table 4. Studies with concurrent controls and positive results.

<table>
<thead>
<tr>
<th>Author (et al.)</th>
<th>Randomization</th>
<th>Double</th>
<th>No. of patients</th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nibbelink (109)</td>
<td>+</td>
<td>69</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sengupta (139)</td>
<td>+</td>
<td>76</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TVIauricc-</td>
<td>+</td>
<td>25</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams</td>
<td>+</td>
<td>23</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chowdary (25)</td>
<td>+</td>
<td>82</td>
<td>83</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. Studies of antifibrinolytic treatment with concurrent controls and negative results.

<table>
<thead>
<tr>
<th>Author (et al.)</th>
<th>Randomization</th>
<th>Double</th>
<th>No. of patients</th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibbs (61)</td>
<td>+</td>
<td>22</td>
<td>64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gibbs (62)</td>
<td>+</td>
<td>22</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gilvin (64)</td>
<td>+</td>
<td>27</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Rossum (159)</td>
<td>+</td>
<td>2.5</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chandra (24)</td>
<td>+</td>
<td>19</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaste (84)</td>
<td>+</td>
<td>32</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gclmcrs (59)</td>
<td>+</td>
<td>26</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shucart (141)</td>
<td>+</td>
<td>55</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fodstad (49)</td>
<td>+</td>
<td>29</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Rebleeding (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Treatment</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>Control</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Treatment</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>Control</td>
<td>39</td>
<td>4</td>
</tr>
<tr>
<td>Treatment</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>Control</td>
<td>39</td>
<td>4</td>
</tr>
<tr>
<td>Treatment</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>Control</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>Treatment</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td>Control</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Treatment</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

Note: Studies with concurrent controls and positive results.
Post (124), Mullan (105) and Nibbelink (108) concluded that antifibrinolytic therapy reduced the rate of both rebleeding and death. Schisano (136) suggested that antifibrinolytic therapy prevented rebleeding but he feared the ischemic complications. He concluded that a lower dose of tranexamic acid combined with aprotinin is effective in preventing rebleeds and is free from severe side-effects. Adams (1) estimated the incidence of rebleeding and of mortality in 1114 patients. He concluded that this treatment was useful in the preoperative care of patients with SAH and that this therapy was not associated with severe neurological complications. In particular, an increased incidence of cerebral ischemia or infarction was not found. Ameen (4) compared the rates of rebleeding and mortality between historical controls and a series of a hundred patients treated with antifibrinolytic agents. He concluded that antifibrinolytic treatment reduced the rate of rebleeding but increased the rate of infarctions, resulting in a slightly increased incidence of mortality in the treatment group: 13 patients died in the treatment and 11 in the control group, while 15 patients developed cerebral ischemia in the control group and 18 in the treatment group. The rebleeding rate was reduced from 15 to 8%. None of these differences reached statistical significance.

Guidetti (67) also concluded that the rebleeding rate was lower in patients on antifibrinolytic treatment but that the risk of ischemic complications was higher since 9% of his patients on treatment died from ischemia as compared with 6 to 8% reported in the literature. Like Schisano (136), he advocated the use of a lower dosage of tranexamic acid in combination with aprotinin to maintain the beneficial effect on the rate of rebleeding while reducing the ischemic complications.

Studies with concurrent controls that demonstrated a significant reduction in the rate of rebleeding are shown in Table 4. None of these five studies had a blind design. The disadvantages of non-blind studies have been explained in Part 4. Three of the five studies had an acceptable method of randomization (random number tables). The effectiveness of antifibrinolytic therapy was investigated by Nibbelink (109) by comparing the overall mortality as well as the rebleeding rates. In both rates a significant reduction was demonstrated when the patients were treated with antifibrinolytic drugs but without induced hypotension. The same conclusions were reached by Maurice-Williams (95). Fodstad (48) demonstrated a lower rate of rebleeding in treated patients but the decreased mortality in the treatment group did not reach statistical significance. He concluded that there was an obvious effect of the drug on the rebleeding rates but that this beneficial effect must be weighed against the possibility of increasing the rate of cerebral ischemia. Sengupta (139) and Chowdary (25) studied the effects of antifibrinolytic treatment by comparing the rebleeding rates only.

Controlled studies without an effect on the prevention of rebleeding are shown in Table 5. Only three of these nine studies included an acceptable
randomization method and a blind procedure. In the study of Gibbs and O’Gorman (61) the effects of therapy were mainly investigated by comparing the rebleeding rates. No influence of treatment on the rate of rebleeding or mortality was detected but this was attributed to insufficient inhibition of fibrinolysis. In a second study Gibbs (62) concluded that antifibrinolytic therapy was effective in preventing fatal rebleeds, although the difference in rebleeding rates did not reach statistical significance. In this study only death from rebleeding was recorded and not the number of patients with rebleeds who survived. The overall mortality showed a significant difference in favor of treatment.

Girvin (64) concluded that there is no evidence that antifibrinolytic treatment prevents rebleeding. In fact, as can be seen in Table 8, he demonstrated that antifibrinolytic therapy increased the rate of rebleeding.

The studies of Van Rossum (159), Chandra (24) and Kaste (84) are the best designed clinical trials with both a blind procedure and an accepted method of randomization. The conclusions of Van Rossum and of Kaste are that tranexamic acid has no influence on the mortality rate or on the rate of rebleeding. Chandra concluded that antifibrinolytic treatment significantly reduced rebleeding and mortality, but his conclusions cannot be confirmed after recalculating his results.

In the study of Gelmers (59) a risk reduction for rebleeding of more than 50% was achieved but since this difference did not reach a statistically significant level, he concluded that this treatment was not effective. The influence on the overall mortality was not reported. Shucart (141) came to similar conclusions, and in his report information on overall mortality is also lacking. Fodstad (49) studied the effects of tranexamic acid in a second trial by comparing the rates of rebleeding, delayed ischemia and hydrocephalus in treatment and control groups. He concluded that tranexamic acid might prevent rebleeding, although he could not conclusively demonstrate this. An increase in the number of cerebral ischemic complications was detected in the treatment group and the overall mortality was also higher in this group. Fodstad suggested that tranexamic acid should be administered until operation, not longer than one or two weeks, that it should not be given to elderly patients, and not to patients who develop signs of cerebral ischemia, and that it should be discontinued after rebleeding.

The incidence of delayed cerebral ischemia was studied in 5 of the 14 controlled trials (Table 6). All these five studies showed an increased incidence in the treatment group. Four studies reported the incidence of hydrocephalus, in one study a slightly increased incidence was found in the treatment group (Table 7). Venous thrombosis was reported in 11 studies, and 2 showed an increased incidence in the treatment group.

Fourteen controlled trials used the rate of rebleeding as a measure for the efficacy of antifibrinolytic treatment. In four of these studies the diagnosis rebleeding was not defined. Ten of these 14 trials also compared the mortality
Table 6. Incidence of infarction in 5 controlled studies of antifibrinolytic treatment.

<table>
<thead>
<tr>
<th>Author (et al.)</th>
<th>(ref.)</th>
<th>No. of patients</th>
<th>Infarction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibbs</td>
<td>(61)</td>
<td>22</td>
<td>64</td>
</tr>
<tr>
<td>Girvin</td>
<td>(64)</td>
<td>27</td>
<td>39</td>
</tr>
<tr>
<td>Maurice-Williams</td>
<td>(95)</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Fodstad</td>
<td>(48)</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Fodstad</td>
<td>(49)</td>
<td>29</td>
<td>30</td>
</tr>
</tbody>
</table>

*Fatal infarctions only.

Table 7. Incidence of hydrocephalus requiring shunt in 4 controlled studies of antifibrinolytic treatment.

<table>
<thead>
<tr>
<th>Author (et al.)</th>
<th>(ref.)</th>
<th>No. of patients</th>
<th>Hydrocephalus %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maurice-Williams</td>
<td>(95)</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Fodstad</td>
<td>(48)</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Kaste</td>
<td>(84)</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Fodstad</td>
<td>(49)</td>
<td>29</td>
<td>7</td>
</tr>
</tbody>
</table>

rates of the treatment and control groups. In only three studies the outcome of the patients was given in more detail (48, 49, 95). The outcome was better in the treatment group in two of these three studies (48, 95).

Table 8 shows the nine studies that showed no effect of treatment on the rebleeding incidence, with the 95% confidence limits for the differences between the rebleeding rates in the treatment and the control groups. It can be seen that seven of the nine studies were too small to be conclusive. The two studies that were conclusive showed a paradoxical increase in the rate of rebleeding.

Table 8. Studies of antifibrinolytic treatment with negative results: confidence limits.

<table>
<thead>
<tr>
<th>Author (et al.)</th>
<th>(ref.)</th>
<th>95% confidence limits for difference between rebleeding rates</th>
<th>Observed difference %</th>
<th>Rebleeding % control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibbs</td>
<td>(61)</td>
<td>-14 — +18</td>
<td>+ 2</td>
<td>32</td>
</tr>
<tr>
<td>Gibbs</td>
<td>(62)</td>
<td>- 3 — +31</td>
<td>+14</td>
<td>18</td>
</tr>
<tr>
<td>Girvin</td>
<td>(64)</td>
<td>-42 — 0</td>
<td>-21</td>
<td>15</td>
</tr>
<tr>
<td>Van Rossum</td>
<td>(159)</td>
<td>-24 — +18</td>
<td>- 3</td>
<td>16</td>
</tr>
<tr>
<td>Chandra</td>
<td>(24)</td>
<td>-5 — +37</td>
<td>+16</td>
<td>21</td>
</tr>
<tr>
<td>Kaste</td>
<td>(84)</td>
<td>-23 — +17</td>
<td>- 3</td>
<td>19</td>
</tr>
<tr>
<td>Gelmers</td>
<td>(59)</td>
<td>-3 — +41</td>
<td>+19</td>
<td>35</td>
</tr>
<tr>
<td>Shucart</td>
<td>(141)</td>
<td>-32 — - 4</td>
<td>-18</td>
<td>9</td>
</tr>
<tr>
<td>Fodstad</td>
<td>(49)</td>
<td>-17 — +25</td>
<td>+ 4</td>
<td>24</td>
</tr>
</tbody>
</table>

The 95% confidence limits for the differences between the rebleeding rates; a ‘+’ sign means a decrease and a ‘-’ sign indicates an increase in rebleeding.
Most of the trials aimed at demonstrating an effect on rebleeding, which implies an explanatory approach, at least in part. The diagnosis of rebleeding was "confirmed by lumbar puncture or autopsy" or made on clinical grounds. The pitfalls of these criteria are investigated and explained in Chapters III and IV, respectively.

In conclusion, only 14 of the 29 clinical studies of antifibrinolytic agents were controlled, only 3 of the 14 controlled trials were carried out with a double-blind procedure and with an accepted method of randomization, and these three studies were too small to be conclusive.
Chapter II

DEGRADATION PRODUCTS OF FIBRIN AND FIBRINOGEN IN THE CEREBROSPINAL FLUID AFTER SUBARACHNOID HEMORRHAGE: A RESULT OF PROTEIN LEAKAGE RATHER THAN LOCAL FIBRINOLYTIC ACTIVITY

Introduction

Rebleeding from intracranial aneurysms occurs especially during the first two weeks after the initial hemorrhage (94). This has led to the hypothesis that rebleeding is caused by lysis of the clot surrounding the ruptured aneurysm and that inhibition of clot lysis might reduce the incidence of rebleeding (104). If tranexamic acid can prevent rebleeding, it is likely that fibrinolytic activity plays a role in the pathogenesis of recurrent bleedings.

Determination of fibrinolytic activity in blood and cerebrospinal fluid (CSF) after a subarachnoid hemorrhage (SAH) as measured on unheated fibrin plates has led to conflicting results (50). On the other hand, high concentrations of fibrin/fibrinogen degradation products (FDP's) in the CSF have been an invariable finding (44, 50, 96, 135). The monitoring of FDP levels in the CSF has been recommended for controlling the efficiency of antifibrinolytic therapy (51, 135) and for identifying patients at high risk of rebleeding (96). However, Anderson (5) suggested that FDP's in the CSF might not be a reliable index of increased fibrinolytic activity as these FDP's may reflect protein leakage across a damaged blood-CSF barrier. Recently, the conclusions of Anderson were criticized (96, 135) as they were not based on studies in patients with SAH and as he could not demonstrate FDP's together with other low molecular weight proteins in three patients with SAH 4 to 16 days after the initial bleeding. In addition, it has been suggested that this explanation is unlikely because increased FDP levels in the CSF are not more persistent in more obtunded patients (96).

This study aimed at solving the controversy whether the presence of FDP's in the CSF after SAH reflects a damaged blood-CSF barrier or ongoing fibrinolytic activity in the subarachnoid spaces. I approached this problem in several ways. If the presence of FDP's in the CSF is mainly the result of a defective blood-CSF barrier, the following should be expected: [1] no difference in the concentration of FDP's between patients with and

Patients and Methods

During the second week after the presenting hemorrhage, CSF was obtained by lumbar puncture (LP) in 48 patients with SAH. The diagnosis of SAH was based on clinical signs and symptoms and on the presence of subarachnoid blood as confirmed by computerized tomography (CT) (157). In 31 of these 48 patients an aneurysm was demonstrated by angiography or at autopsy. In the other 17 patients an aneurysm was highly probable by the predominance of extravasated blood in the interhemispheric, suprasellar or Sylvian cisterns on CT. Angiography was not undertaken in these 17 patients because surgical treatment was not considered due to age (over 65), impaired consciousness or ischemic cerebral deficits.

The 48 patients were a consecutive series of patients with SAH who fulfilled the following criteria: [1] treatment with placebo or tranexamic acid was started within 72 hours of the presenting hemorrhage; [2] at least seven days of treatment with placebo or tranexamic acid was given before the lumbar puncture was done during the second week after the presenting hemorrhage; [3] no clinical signs and symptoms of rebleeding had occurred between admission and the LP during the second week, and the amount of blood on CT made during the second week had decreased compared with the CT scan made on admission; [4] no contraindication for LP (brain shift on CT). These patients were part of a randomized double-blind placebo-controlled trial on the effectiveness of tranexamic acid (Chapter V).

Placebo or tranexamic acid was administered by intravenous bolus six grams a day in six doses during the first week, and four grams a day in four doses during the following three weeks or until operation or death. On the day of the LP the clinical condition of the patient was assessed by grading the level of consciousness with the Glasgow Coma Scale (147) and by examining the patient for neurological deficits. CT was performed on admission and repeated seven days later, before the LP was done.

During the period of drug administration we recorded any deterioration in the level of consciousness or the development of focal signs. Whenever possible, these events were investigated by CT scanning. We defined a definite rebleed as a sudden deterioration with increased hemorrhage on the CT scan or at autopsy, when compared with a previous CT scan.

Tranexamic acid or placebo treatment remained ‘blind’ during the measurements of total protein, FDP’s, plasminogen and when recording rebleeding.
**CSF studies**

Cerebrospinal fluid was obtained by lumbar puncture carried out between day 9 and day 15 from the presenting hemorrhage (mean day 12). The CSF was collected directly into three plastic tubes. The first contained a mixture of thrombin and trasyloL (6.4 U and 1000 K IE/ml, respectively) for FDP measurement. This tube was left at 37°C for at least one hour to eliminate interfering fibrinogen by clotting. The second tube contained a 1/10 volume 3.8% citrate solution for measuring plasminogen and the third tube was used to measure the total protein. FDP’s were estimated immunochromatically according to Laurell (90) with antifibrinogen antiserum (Clotimmune®-fibrinogen, Behringwerke AG). Values were calculated to a detection limit of 2 mg/L CSF in reference to standard amounts of FDP’s obtained by degrading fibrinogen with plasmin (1 CU per 10 mg/ml). Plasminogen was determined amidolytically with the chromogenic substrate S-2251 (Kabi Vitrum, Amsterdam) on the PA-80 (Vitatron, Dieren), essentially as described by Friberger (56) (values expressed in milliunits). The total protein was determined according to the Folin-Ciocalteau technique (119). Ten patients with a variety of neurological disorders were used as a ‘control’ group. All had normal CSF total protein values (less than 0.60 g/L) and these CSF samples contained no red cells and had no xanthochromia as measured spectrophotometrically.

**Results**

Of the 48 patients with SAH 22 received tranexamic acid and 26 placebo. We found no differences in FDP values in the CSF in these two groups of patients. FDP’s were even more often absent in patients on placebo (table 9). The mean concentration of FDP was 5 mg/L (range 0-20) in the placebo group, and 4 mg/L (range 0-22) in the tranexamic acid group. If only the patients with detectable FDP’s are taken into account, the mean concentration of FDP was 11 mg/L (range 4-20) in the tranexamic acid
group, and 12 mg/L (range 7-22) in the placebo group. The CSF total protein values were significantly higher in patients with detectable FDP's than in patients without FDP's (fig. 3) (p < 0.01 Wilcoxon-Mann-Whitney

![Graph](image)

**Figure 3.** The relation between absence or presence of fibrin/fibrinogen degradation products in the CSF and the total CSF protein value.
test). Similarly, the plasminogen values were higher in patients with FDP's (fig. 4) \( p < 0.01 \) Wilcoxon-Mann-Whitney test. In the 'control' group of 10 patients no FDP's were detected and the range of plasminogen values was between 14 and 16 milliunits.

![Figure 4. Plasminogen values in patients with and without fibrin/fibrinogen degradation products in the CSF after SAH and in patients with a variety of neurological disorders and a normal CSF total protein.](image)

According to the clinical condition on the day of the lumbar puncture, the 48 patients were divided into those with intact brain function (maximum Glasgow Coma Score and no focal deficits) and those with impaired consciousness or with focal neurological deficits. FDP's occurred in a significantly greater proportion of patients with a depressed conscious level and/or neurological deficits (table 10) \( p_2 = 0.04 \) Fisher's test; taking the asymmetry of the null distribution into account.

After the lumbar puncture in the second week, no rebleeding was observed in the patients with an unimpaired consciousness and without focal neurological deficits. Of the 27 with impaired consciousness or with focal neurological deficit, 10 had a rebleed. All these rebleeds were confirmed by
Table 10. Relation between clinical state and the presence of fibrin/fibrinogen degradation products in the CSF.

<table>
<thead>
<tr>
<th>Clinical State</th>
<th>Number of patients with FDP's in CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alert without neurological deficit, ( n = 21 )</td>
<td>16 (absent) 5 (present)</td>
</tr>
<tr>
<td>Impaired consciousness and/or focal neurological deficits, ( n = 27 )</td>
<td>12 (absent) 15 (present)</td>
</tr>
</tbody>
</table>

Table 11. Relation between rebleeding and tranexamic acid in 27 patients with SAH followed by impaired consciousness or focal neurological deficits.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients</th>
<th>Tranexamic Acid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleeding</td>
<td>10</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>No Rebleeding</td>
<td>17</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>14</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 12. Relation between rebleeding and the presence of fibrin/fibrinogen degradation products in the CSF in 27 SAH patients with impaired consciousness or focal neurological deficit.

<table>
<thead>
<tr>
<th>FDP's in CSF</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>10</td>
</tr>
<tr>
<td>No Rebleeding</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
</tr>
</tbody>
</table>
CT. In these 27 patients rebleeding was less frequent in those who were treated with tranexamic acid ($p < 0.01$) (table 11). No such relation was found between the presence or absence of FDP's and rebleeding (table 12). Of these 27 patients 15 had FDP's in the CSF.

The FDP values in patients with detectable FDP and subsequent rebleeding ($n = 6$, $\bar{X} = 11$, range 5-22) were not different from the FDP values in patients with FDP's and without rebleeding ($n = 9$, $\bar{X} = 11$, range 4-20).

Discussion

This study demonstrates in the first place that during the second week after aneurysmal hemorrhage the presence of FDP's in the CSF did not depend on whether the patients were treated with tranexamic acid or with placebo. This is not to be expected if FDP's reflect ongoing fibrinolysis in the CSF. Tranexamic acid has been shown to enter the CSF (51), and if given in the dosage we used, it is regarded as a potent inhibitor of fibrinolysis (51). Moreover, tranexamic acid reduced the incidence of rebleeding, in a subgroup from the present study (table 11) [as well as in the trial population as a whole (Chapter V)]. It is therefore more likely that these FDP's in the CSF arise outside the subarachnoid space, in ischemic brain tissue where tranexamic acid cannot penetrate. From these ischemic areas FDP's may leak across a damaged blood-CSF barrier into the CSF. Consistent with this theory are three other findings. Firstly, the total protein in the CSF is higher in patients with detectable FDP's. The high total protein in patients with detectable FDP's cannot be explained by the contribution of FDP's as this is too small to have a significant effect. Secondly, plasminogen which is a protein of similar molecular size as FDP's was also found to be raised in these patients. If the FDP's are generated in the subarachnoid space by an ongoing fibrinolytic activity one might expect that the level of plasminogen would not be increased but decreased, since plasminogen would be converted to plasmin. Thirdly, there is a clear relationship between impaired consciousness or neurological deficits and the presence of FDP's in the CSF of patients without a recent hemorrhage.

Anderson (5) determined FDP's in the CSF of 252 patients with a variety of neurological diseases and found that FDP's appear in the CSF together with other low molecular weight proteins such as plasminogen and factor IX. The appearance in the CSF of FDP's under pathological conditions has been confirmed in patients with meningitis (20).

Anderson compared his findings with the source of FDP's in the urine of patients with glomerulonephritis (107), in the peritoneal fluid of patients with ovarian carcinoma (146) and in the pleural fluid of patients with lung
tumors (8). In these conditions FDP's are also found with increasing protein values.

It has been argued that the lack of relation between FDP levels in blood and CSF in patients with SAH makes it improbable that FDP's leak into the CSF across a damaged blood-CSF barrier (96). However, intravascular thrombosis and clot lysis within cerebral vessels may generate a high local concentration of FDP's that can leak into CSF but cannot reach or may be diluted in the systemic circulation.

Patients with raised FDP levels are said to be especially at risk of rebleeding (96, 135). Our patients in a good condition had no rebleeds, which is not surprising since these patients as a rule were operated on soon after the lumbar puncture, on an average on day 12 from the presenting hemorrhage. In contrast, the 27 patients with an impaired consciousness or with focal neurological deficits, were not operated on and remained longer at risk of rebleeding. Ten patients in this group had rebleeds. FDP's were not more frequent and the FDP levels were not higher in patients with subsequent rebleeding. It might be argued that a number of 27 patients is too small to be conclusive, but it is striking that in this group of patients the effect of tranexamic acid in the prevention of rebleeding was statistically significant.

In conclusion, persistent FDP's in the CSF after SAH reflect a damaged blood-CSF barrier and not local fibrinolytic activity in the subarachnoid space. Therefore, FDP's are unreliable for monitoring antifibrinolytic treatment in SAH and cannot be used for selecting patients at high risk of rebleeding.
Chapter III


Introduction

Many studies of patients with SAH state that rebleeding was confirmed by lumbar puncture (LP), but this may be difficult, because CSF may remain grossly blood-stained for as long as 24 days after the hemorrhage (168). Red cell counting seems to be a more objective method, but an increased RBC may result from a traumatic LP. Conversely, recurrent hemorrhage may not be evident in the CSF if blood is retained in cerebral parenchyma or subdural space.

It has been suggested that spectrophotometric analysis of CSF is of value in detecting rebleeding by showing an interruption of the normal resolution of the blood pigments oxyhemoglobin and bilirubin (155). Another measure of rebleeding is CT if a baseline scan is available for comparison. We performed serial spectrophotometry in patients who did or did not suffer a rebleed, according to both clinical features and CT.

Patients and Methods

Patients. We examined the time course of xanthochromia after a single SAH in 15 patients (from a consecutive series of 100 patients with a ruptured aneurysm) who met the following criteria: [1] initial lumbar puncture performed on the second or third day after the SAH (day 0 = day of bleeding); [2] lumbar puncture performed weekly for at least three weeks after the first SAH; [3] no clinical evidence of rebleeding; and [4] no evidence of rebleeding on CT at weekly intervals. In four patients the aneurysm was demonstrated by angiography, and in 11 it was strongly suggested by CT evidence of blood in the basal cisterns (157).

We compared the results in this group with serial studies of CSF in six patients with clinical and CT signs of rebleeding. Eleven other patients also suffered rebleeding, but the course of CSF xanthochromia could not be investigated because of sudden death (seven patients), traumatic puncture
(one patient with a clot in the test tube), the presence of a large hematoma on CT precluding another LP (two patients), or lack of CSF samples taken before the rebleed (one patient).

Spectrophotometry. CSF was centrifuged immediately after the lumbar puncture. The supernatant was examined with a Beckman double-beam spectrophotometer Model 25 to record the absorption spectrum between 400 and 700 nm. All results were checked regularly for absorption results (cobalt sulphate) and wavelength setting (holmium oxide) (127). The xanthochromic index was estimated according to the method of Van der Meulen as the sum of the absorption values at 415 nm (oxyhemoglobin) and 460 nm (bilirubin) (155). The contribution of methemoglobin is ignored in this approach. The xanthochromic index was corrected for the CSF protein content, which may contribute to the absorption at these wavelengths. Protein was determined by a Folin-Ciocalteau procedure (119). With the formula of Van der Meulen (155), the relative percentages of oxyhemoglobin and bilirubin contributing to the xanthochromia were calculated. At different times after the hemorrhage, these values follow the rate of conversion of oxyhemoglobin to bilirubin. The results of spectrophotometry were also expressed according to the method of Kronholm and Lintrup (88), in which the concentration of hemoglobin (oxyhemoglobin and methemoglobin) and bilirubin are estimated from the absorption at the wavelengths 400, 412 and 480 nm.

Results

Patients without rebleeding. In the 15 patients with a single SAH, the course of the xanthochromic index fell into three different patterns. In five patients, the index decreased after the initial value obtained 2 or 3 days after SAH; in eight patients, the index increased until the ninth or tenth day and then fell; and in two patients, the index increased progressively up to the sixteenth or seventeenth day (table 13). These three different patterns were independent of the initial value; both high and low initial values could be followed by a steep increase or decrease of the xanthochromic index.

The oxyhemoglobin percentage of the total xanthochromia varied widely throughout the first four weeks after the hemorrhage (table 14). Of the 15 patients, only two showed the previously reported pattern of a decrease in the oxyhemoglobin percentage after the second or third day. In the other patients, the oxyhemoglobin percentage spontaneously rose during the first, second, and third weeks; in eight, this occurred after a previous fall. As late as three weeks after the hemorrhage, the percentage of oxyhemoglobin could still be 82.

It has been suggested that a hemorrhage confined to the subarachnoid
Table 13. Xanthochromic index in 15 patients without rebleeding.

<table>
<thead>
<tr>
<th>Days after SAH</th>
<th>2 or 3</th>
<th>9 or 10</th>
<th>16 or 17</th>
<th>23 or 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.870</td>
<td>0.392</td>
<td>0.182</td>
<td>0.097</td>
<td></td>
</tr>
<tr>
<td>0.590</td>
<td>0.540</td>
<td>0.097</td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td>0.895</td>
<td>0.756</td>
<td>0.122</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>0.810</td>
<td>0.335</td>
<td>0.220</td>
<td>0.047</td>
<td></td>
</tr>
<tr>
<td>0.287</td>
<td>0.269</td>
<td>0.101</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>0.290</td>
<td>0.372</td>
<td>0.247</td>
<td>0.199</td>
<td></td>
</tr>
<tr>
<td>0.875</td>
<td>5.220</td>
<td>3.330</td>
<td>0.138</td>
<td></td>
</tr>
<tr>
<td>0.333</td>
<td>0.343</td>
<td>0.300</td>
<td>0.251</td>
<td></td>
</tr>
<tr>
<td>0.287</td>
<td>1.480</td>
<td>0.455</td>
<td>0.223</td>
<td></td>
</tr>
<tr>
<td>0.910</td>
<td>2.960</td>
<td>1.518</td>
<td>0.430</td>
<td></td>
</tr>
<tr>
<td>0.328</td>
<td>4.482</td>
<td>1.660</td>
<td>0.503</td>
<td></td>
</tr>
<tr>
<td>0.185</td>
<td>0.300</td>
<td>0.207</td>
<td>0.205</td>
<td></td>
</tr>
<tr>
<td>0.109</td>
<td>0.259</td>
<td>0.217</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>0.111</td>
<td>0.335</td>
<td>0.470</td>
<td>0.075</td>
<td></td>
</tr>
<tr>
<td>0.099</td>
<td>0.197</td>
<td>0.287</td>
<td>0.050</td>
<td></td>
</tr>
</tbody>
</table>

Table 14. Percentage of oxyhemoglobin in 15 patients without rebleeding.

<table>
<thead>
<tr>
<th>Days after SAH</th>
<th>2 or 3</th>
<th>9 or 10</th>
<th>16 or 17</th>
<th>23 or 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>86</td>
<td>75</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>19</td>
<td>2</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>36</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>33</td>
<td>66</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>26</td>
<td>36</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>39</td>
<td>99</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>50</td>
<td>70</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>26</td>
<td>36</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>31</td>
<td>35</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>93</td>
<td>25</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>67</td>
<td>70</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>37</td>
<td>67</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>79</td>
<td>93</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>98</td>
<td>98</td>
<td>39</td>
<td></td>
</tr>
</tbody>
</table>
space may be distinguished from one with an intracerebral hematoma by the preponderance of bilirubin in the former and the preponderance of oxyhemoglobin in the latter (155). Therefore, we divided the patients into two groups, depending on the presence or absence of intracerebral blood on the initial CT (table 15). We found no preponderance of either pigment on 16 or 17 days after SAH in patients with or without an intracerebral hematoma.

The absolute concentrations of hemoglobin and bilirubin, taken together, closely followed the xanthochromic index. The course of the hemoglobin concentration was similar to that of the oxyhemoglobin percentage, with rising values occurring even during the second or the third week and occasionally preceded by an initial fall.

Table 15. Relative percentages of CSF oxyhemoglobin and bilirubin in patients with and without an intracerebral hematoma.

<table>
<thead>
<tr>
<th>CSF 16 or 17 days after SAH</th>
<th>No.</th>
<th>Intracerebral blood on CT</th>
<th>No intracerebral blood on CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxyhemoglobin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>more than 50%</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>more than 50%</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

**Patients with rebleeding.** Six patients had a second SAH, and CSF could be compared with two earlier samples, because the time of rebleeding varied from day 11 to day 24. Five of them showed an increase in the xanthochromic index after an initial fall. The increase in the oxyhemoglobin percentage and hemoglobin concentration, however, did not exceed the values found in patients without a rebleed. The sixth patient showed a decrease in the xanthochromic index after rebleeding and also of the oxyhemoglobin percentage and the hemoglobin concentration.

**Discussion**

For a confident diagnosis of rebleeding from spectrophotometric analysis of one or two CSF samples, measurement of some substance or index should provide a normal background pattern of a gradual decrease after the first few days of the hemorrhage, against which a sudden increase can stand out. We were unable to find any reliable measure, at least for the first three weeks, during which most recurrent ruptures occur. The xanthochromic index measures the total amount of pigments from red cell breakdown and may continue to rise up to the sixteenth or seventeenth day after SAH.
Therefore, suspected rebleeding cannot be confirmed merely by demonstrating an increase in xanthochromia. The percentage of oxyhemoglobin increased in most of our patients without a rebleed up to the third week and in some up to the fourth. Oxyhemoglobin could even be the predominant pigment three weeks after the hemorrhage, in contrast to one report. Surprisingly, and at variance with the course of the xanthochromic index, the oxyhemoglobin percentage showed a second rise after an initial fall in one half of the patients. Measurement of the hemoglobin concentration showed the same unpredictable time course. Thus, neither oxyhemoglobin percentage nor hemoglobin concentration can help in the diagnosis of rebleeding.

Van der Meulen (155) also noted that the rate of conversion of oxyhemoglobin to bilirubin may vary. He assumed that in patients with only subarachnoid blood, close contact with cells of the mesothelial lining resulted in rapid conversion of oxyhemoglobin to bilirubin, in contrast to patients with intraparenchymal blood. In our study, however, CT failed to confirm a relationship between the presence of intracerebral blood and the rate of conversion of oxyhemoglobin.

Lumbar puncture confirmed recurrent SAH in only 5 of 17 patients with CT evidence of rebleeding for several reasons. First, the puncture may be contraindicated if a hematoma is suspected. Second, time must elapse before xanthochromia develops, and it is necessary to wait at least six hours after the suspected rebleed. Meanwhile, the patient may die. Third, we found that the xanthochromic index is the most predictable spectrophotometric measure, but a rise of this index is of no diagnostic value unless it is preceded by a previous fall. This requires at least two previous CSF samples, and the initial rise can continue until the seventeenth day. Even then, absence of a secondary increase does not exclude rebleeding.
years), impaired level of consciousness, or ischemic cerebral deficits. The patients were studied for a four-week period after the presenting hemorrhage, or until death or operation within this time. During this period all patients were under continuous observation in an intensive-care unit. Most operations were carried out on the twelfth day after the presenting hemorrhage. CT was performed on admission and was repeated weekly and also within six hours of an acute clinical deterioration.

If the attention of the nursing staff was attracted by a sudden change (within less than five minutes) in a patient's condition, the physician in charge was called to examine the patient and one of us was notified immediately. Only clinical changes that were compatible with rebleeding are reported. This was almost invariably a sudden impairment of consciousness; the exceptions are given below. We defined an impaired level of consciousness as a drop of at least one point on the motor score of the Glasgow Coma Scale (GCS) (147). Rebleeding was diagnosed only if we found fresh blood on CT in comparison with the previous scan.

Results

Acute deteriorations

Sixty-two episodes of acute deterioration were observed in 46 of the 150 patients (table 16). Thirty-three patients had 1 episode, ten had 2, and three had 3. The clinical features consisted of an acute impairment of consciousness in 59 episodes and in two patients of an acute increase in severe headache, followed by confusion. In addition, we included one comatose patient who showed a sudden and obvious change in the normal breathing pattern. One other comatose patient suffered an asymptomatic rebleed as observed on serial CT scanning and was excluded from this study. Fifty-six of these acute deteriorations were investigated by CT scanning. This demonstrated rebleeding in 36 episodes, including the patient who showed a sudden change in respiration. In the 20 remaining events the amount of hemorrhage revealed on the scan had not increased. Of the 36 episodes in which rebleeding was proved by CT, 16 were fatal (14 within 24 hours), whereas a fatal outcome occurred in only 3 of the 20 episodes without CT evidence of rebleeding (one within 24 hours).

Six episodes of deterioration were not investigated by CT; all these patients died within twelve hours. In one of them autopsy showed massive intraventricular blood that had not been present on the last CT scan. In the remaining five patients permission for autopsy was not granted. All five had suffered one or more confirmed rebleeds before the fatal episode. As death within 12 hours was always caused by rebleeding in the other patients, a further rebleed was highly probable.
Table 16. Features of 62 episodes of acute deterioration in 46 of 190 patients with SAH.

<table>
<thead>
<tr>
<th>CT Findings</th>
<th>Clinical Features</th>
<th>No. of Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 fresh blood</td>
<td>Sudden onset of severe headache and confusion</td>
<td>1</td>
</tr>
<tr>
<td>6 CT not performed</td>
<td>Sudden impairment of consciousness</td>
<td>26</td>
</tr>
<tr>
<td>18 no fresh blood</td>
<td>Sudden onset of confusion and confusion</td>
<td>9</td>
</tr>
<tr>
<td>2 no fresh blood</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td>16</td>
</tr>
</tbody>
</table>

Note: CT findings compare the amount of hemorrhage with that on previous scans.

**Decrease of at least one point on the modified scale of the Glasgow Coma Scale.

***Rebleeding in one patient was confirmed at autopsy by comparison with previous CT in the few other patients; rebleeding was highly probable.

because of early death after deterioration, all were had a previous CT-proven rebleed.
Rebleeding

The 42 episodes of rebleeding occurred in 33 patients: 25 had 1, 7 had 2, and 1 had 3 rebleeds. Four anatomical types of rebleeding could be distinguished: intraventricular [in 24], intracerebral [in 4], a combination of intracerebral and intraventricular hemorrhage [in 4], and subarachnoid blood only [in 5]. As mentioned above, in five fatal cases neither CT nor autopsy was performed, so the diagnosis could not be confirmed. The mortality rate according to the types of rebleeding is shown in table 17.

<table>
<thead>
<tr>
<th>Type of rebleeding</th>
<th>No. of death</th>
<th>No. of survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>intraventricular</td>
<td>9*</td>
<td>15</td>
</tr>
<tr>
<td>intracerebral</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>combination: intraventricular and intracerebral</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>purely subarachnoid</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>total</td>
<td>17**</td>
<td>20</td>
</tr>
</tbody>
</table>

*In one patient the intraventricular blood was observed at autopsy.
**Five more patients died from rebleeding but neither CT nor autopsy was performed.

Recurrent hemorrhages that invaded the brain parenchyma were relatively often followed by death, but this pattern was seen in less than half of all fatal cases. The distribution of rebleeding related to time since the presenting hemorrhage is shown in figure 5. There is an obvious peak around the end of the first week. To some extent, however, this peak is caused by a cluster of second rebleeds that occurred soon after the first (mean interval 2 days) and also by the decreasing number of patients at risk of having a first rebleed. To eliminate these two factors we calculated the proportion of first rebleeds on a given day among the patients at risk on that day (figure 6). It is clear that there is still a maximum in the incidence of first rebleeds at the end of the first week. In addition, another peak seems to emerge during the third week. This may have been caused by chance as there were relatively few patients at risk during this time.
Figure 5. Distribution of rebleeding in time: absolute numbers.

Figure 6. Distribution of rebleeding in time: relative numbers (first rebleeds only).
Acute deteriorations without CT signs of rebleeding

In 10 of 20 acute episodes without CT signs of rebleeding another definitive diagnosis could be established. Six patients had convulsions during the acute loss of consciousness and it is probable that epilepsy caused rather than accompanied the clinical deterioration. In one patient electrocardiographic monitoring showed ventricular fibrillation, and defibrillation restored consciousness. In three patients CT revealed radiolucent areas within three days of the acute episode, and eventually all these patients died from cerebral infarction.

Ten unexplained events occurred in nine patients. Subsequently, rebleeding occurred in three of these patients, cerebral infarction in three, and three patients had no other complication. Epilepsy was later observed in one patient who also had a rebleed and in another patient after a cerebral infarct. Five of these nine patients showed enlargement of the cerebral ventricles at the time of the acute deterioration. We measured ventricular size using the bicaudate index (38, 102), and ventricular enlargement was defined as more than 2 standard deviations above the mean for the patient's age.

The clinical features of the ten unexplained episodes were compared with those in the twenty patients who survived a rebleed. We recorded changes in consciousness (measured with the GCS), changes in blood pressure (unchanged, increased or decreased), pupillary reactions (present or absent) and pupil size (small, normal or wide), changes in breathing pattern, and rate of recovery (within one hour, between 1 and 6 hours, more than 6 hours). As mentioned above, one patient rebled while in deep coma, and the clinical signs consisted only in a sudden onset of irregular breathing. All the other patients with CT-proven rebleeding deteriorated at least one point on the GCS motor scale, which means that none of them obeyed commands. Of the ten patients with unexplained events, eight also deteriorated at least one point on the GCS motor scale. Two patients still obeyed commands. Both suddenly complained of a severe headache after which they were confused. Apnea occurred in five of the 20 patients who survived a CT-proven rebleed and was not seen in patients with an acute deterioration without CT evidence of rebleeding. All the other clinical features were equally frequent in both groups.

Rebleeding may be difficult to detect by CT if large clots are already present in the basal cisterns. Therefore, we graded the amount of cisternal blood on CT scans made before and after the deteriorations for which no cause could be found. With our method, ten cisterns and fissures are separately graded from 0 (no blood) to 3 (completely filled with blood), so that the maximum score is 30. On five scans the blood had disappeared from the CSF spaces, in four the clot had decreased to a slight amount (1/30, 2/30, 4/30 and 6/30) and in only one patient an extensive hemorrhage (23/30) was unchanged two days after the initial hemorrhage.

The time after the presenting hemorrhage at which unexplained deterioration occurred is indicated in figure 7. This figure also shows the time
of rebleeds that remained confined to the subarachnoid space (only after the sixth day) and the time of acute deterioration from known causes other than rebleeding (mainly during the first week).

Figure 7. Time of acute deterioration from known causes other than rebleeding (top), time of acute deterioration from unknown cause (center), and time of rebleed confined to the subarachnoid space (lower).
Discussion

In this report we have included only episodes of acute deterioration that, on clinical grounds, clearly suggested rebleeding. For the detection of rebleeds, we used serial CT scanning, which is far superior to other techniques (156). Rebleeding could not be detected by CT in 20 of the 62 acute events (32%), and if the 25 fatal episodes are excluded, an even larger proportion of abrupt deterioration episodes could not show to be caused by rebleeding: 17 (46%) of 37 non-fatal events.

Defined causes of acute deterioration other than rebleeding in 10 patients were epilepsy, cardiac arrhythmia, and, surprisingly, cerebral ischemia. Cerebral ischemia after SAH usually presents with a gradual onset of deterioration. In contrast, three patients in our series had acute impairment of consciousness, remained stable for a few hours and then suffered a further gradual deterioration, while evidence of infarction developed on serial CT. Perhaps acute vasospasm accounted for the sudden impairment of consciousness, mimicking rebleeding.

In ten other non-hemorrhagic episodes of acute deterioration no certain cause could be determined. It might be argued that in these cases CT was not sensitive enough to demonstrate an increased amount of blood. This does not apply to the five unexplained episodes in patients who no longer showed extravasated blood on CT. After the disappearance of previously visualized blood, it is likely that rebleeding can be confirmed by CT because on first rupture aneurysmal hemorrhage is practically always detected (158). In 4 of the 5 remaining episodes, CT showed a decreased amount of blood in the cisterns. A small additional hemorrhage in the cisterns might still have caused symptoms without radiological changes. However, this explanation is unlikely for two reasons. Firstly, confirmed rebleeding during the first week was never confined to the subarachnoid space (figure 7). It is improbable that all early rebleeds that were purely subarachnoidal would be invisible radiologically. A more reasonable assumption is that the presence of a subarachnoid clot forces the blood from a fresh rupture into the brain parenchyma or into the ventricular system (30). Secondly, only one patient with an unexplained deterioration showed a large pre-existing hemorrhage on CT.

Even then CT scanning can be quite sensitive, as demonstrated in a patient who had two confirmed rebleeds on consecutive days while the first hemorrhage had not yet resolved (figure 8).

The subsequent course of the disease in the nine patients with 10 deteriorations of unknown cause was far from uniform: epilepsy, rebleeding and infarction all occurred. Abrupt changes of intracranial pressure might also have played a role, as hydrocephalus was present at the time of deterioration in five of the nine patients.

It is clear that, if too much dependence is placed on clinical signs and symptoms, the incidence of rebleeding will be overestimated: the diagnosis
Figure 8. Three successive hemorrhages in one patient, clearly distinguished by serial CT scanning. Upper row (day 8): partial resorption of the initial hemorrhage (not shown), with a residual hematoma in the right frontal and temporal lobes (suggesting an aneurysm of the right middle cerebral artery), and in the right lateral ventricle and the posterior horn of the left lateral ventricle. Center row (day 12, after a sudden and transient loss of consciousness with fixed pupils): fresh blood is seen in the third ventricle and in the left lateral ventricle. Lower row (day 13, after another acute episode of impaired consciousness): the intracerebral hematoma is enlarged, and a rim of fresh blood in both lateral ventricles outlines the less dense clots of the two previous hemorrhages.
Rebleeding will be wrong in every third patient. A similar conclusion was put forward in a recent report (97), but based on incomplete evidence, as a distinction between abrupt and gradual deteriorations could not be made with confidence and as the presence or absence of rebleeding was inferred in some patients from repeated CT scanning, but in others from lumbar puncture or autopsy—with inherent limitations. Our study demonstrated a higher rate of rebleeding (two thirds of acute events versus less than one third of all deteriorations), with the previously recognized peak incidence of rebleeding around the end of the first week (94), and with a substantially lower mortality rate (50% versus 90%).

The conflicting results of the two studies emphasize again how difficult the diagnosis of deteriorations after SAH can be. Therefore, studies on the effect of treatment to prevent some of these complications may lead to different conclusions, mainly because of different methods of diagnosing these complications. One of the controversies in the treatment of SAH patients is whether antifibrinolytic treatment prevents rebleeding. Most studies on this subject compare the incidence of rebleeding in the treated and control groups. This requires that the mode of onset of the deterioration is known, which is possible only if the patients are under close observation, and that the diagnosis of rebleeding is established by serial CT scanning. An alternative method is to measure outcome after SAH in terms of functional ability (77). Such a pragmatic assessment (137) also takes into account the possible side-effects of treatment.
Chapter V

ANTIFIBRINOLYTIC TREATMENT IN SUBARACHNOID HEMORRHAGE: A MULTI-CENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL IN 479 PATIENTS

Introduction

It is important to establish if antifibrinolytic treatment is beneficial in patients with subarachnoid hemorrhage: a reduction in the rate of rebleeding would permit a delay of aneurysm surgery until the risks are less, and antifibrinolytic treatment is the only possibility of preventing rebleeding in patients who are unsuitable for operation. However, antifibrinolytic agents might result in an increased incidence of cerebral ischemia and hydrocephalus.

The effects of the antifibrinolytic drug tranexamic acid was studied in a double-blind, placebo-controlled trial. The design and conduct of this multi-center trial took account of the contrasts between ‘pragmatic’ and ‘explanatory’ studies as described in Chapter I part 4. A ‘pragmatic’ approach was adopted and the aim was to determine if, in practical clinical circumstances, antifibrinolytic treatment led to improved functional outcome in patients who presented with subarachnoid hemorrhage. In addition, the incidence of rebleeding, ischemia and other possible complications was investigated.

In calculating the required number of patients for this trial we aimed at a risk of not more than 10% of failing to show a true reduction of rebleeding by 50%, with 95% confidence (Chapter I part 4).

Patients and Methods

The trial commenced in November 1977 in Rotterdam, in October 1979 in Amsterdam, in October 1980 in Glasgow and in January 1982 in London and ended in these four centers on the 31st of December 1982.

Criteria for eligibility

Patients eligible for this study were admitted to one of the centers, with
symptoms and signs of subarachnoid hemorrhage and with confirmatory evidence on the initial CT scan or in the CSF. If the CT scan was negative and therefore doubt existed as to whether an aneurysm had ruptured (157), angiography was carried out before randomization.

Reasons for exclusion were: elapse of 72 hours since the presenting hemorrhage; the presence of deep vein thrombosis, coagulation disorders, renal insufficiency or pregnancy; previous treatment with antifibrinolytic agents; CT-scan evidence of another cause of subarachnoid hemorrhage (e.g. AVM, tumor) or negative angiography carried out before randomization (see above). If death appeared imminent, entry was delayed.

Randomization

Using random number tables (121), the pharmaceutical firm supplied each center with boxes containing a complete four-week course of either tranexamic acid or placebo. In each batch of six boxes the two groups were balanced. These boxes were numbered consecutively, without other distinctions, and administered to eligible patients in that order. For each patient the trial period commenced on opening the treatment box. The contents of the box (phials or tablets) were marked only with the trial number. The trial code was broken in May 1983, after all events and outcomes had been recorded.

Treatment

Treatment was always started within 72 hours of the hemorrhage. The maximum duration of treatment was four weeks. In Rotterdam and Amsterdam the drugs were administered by intravenous bolus for four weeks, in Glasgow and London by intravenous bolus for two weeks and orally thereafter. Six grams a day in six doses were given during the first week and four grams a day in four doses thereafter. The oral equivalent given in the third and the fourth week was six grams a day in four doses (48). Treatment was discontinued: when an operation for the aneurysm commenced, if a diagnosis other than aneurysm was established, if the angiogram was negative, or if a venous thrombosis or pulmonary infarct developed.

We checked the efficiency of drug administration by comparing the number of phials and tablets prescribed with the numbers used up from the allocated treatment box. Since other drugs can affect the fibrinolytic and clotting systems, we limited the drugs used to treat hypertension to clonidine, and for pain pethidine or a codeine derivative was given.
**Investigations**

A CT scan was carried out on admission and was repeated at weekly intervals and after clinical deterioration. Four-vessel angiography was performed depending on the patient's clinical condition.

**Assessment of outcome and of events during the trial**

Outcome was assessed at three months according to the five-point Glasgow outcome scale (77). For the purpose of analysis this scale was shortened into three groups, viz. dead, persistent vegetative state/severe disability (dependent), and moderate disability/good recovery (i.e. independent).

During the trial period, i.e. the period of drug administration, we recorded any deterioration in the level of consciousness or the development of focal signs. Whenever possible, these events were investigated with CT scan and sometimes also with lumbar puncture. A sudden marked increase in the severity of the patient's headache was not considered as an episode of clinical deterioration. Intracranial complications were recorded, such as rebleeding, infarction, hydrocephalus, local edema from a hematoma, epilepsy or other.

A diagnosis of rebleeding was, if possible, confirmed by repeated CT scanning. The appearance of the CSF at lumbar puncture or spectrophotometric analysis was considered insufficient to diagnose or exclude rebleeding (162). Autopsy was considered diagnostic of rebleeding only when it showed extravasated blood that was clearly absent on a previous CT scan. We distinguished rebleeding or infarction into definite and probable episodes, according to the available evidence.

**Definite rebleeding:** Sudden deterioration with increased hemorrhage on CT scan or at autopsy when compared with a previous CT scan.

**Probable rebleeding:** Sudden deterioration and death without the possibility of proof by CT scan and when autopsy was refused.

**Definite infarction:** The gradual development of focal neurological signs and/or deterioration in conscious level with infarction confirmed by CT scan or at autopsy.

**Probable infarction:** The gradual development of focal neurological signs with or without deterioration in conscious level and without confirmation on CT scan or at autopsy.

**Extracranial events** were recorded as cardio-respiratory, metabolic, gastro-intestinal bleeding or other. We discussed details of individual patients when doubt existed about the cause of deterioration. I reviewed the record of each patient who deteriorated.
Statistical methods

The significance of the treatment effect on mortality, rebleeding, infarction and hydrocephalus was assessed using logistic regression (29), in order to control for any imbalance in the two groups. Interactions of all possible orders were fitted, but in no case were any significant. Hence the final analyses were based on linear logistic regression. The quoted $X^2$ statistics are based on asymptotic likelihood ratio tests for assessing the significance of the treatment term in the regression model (29).

Results

Of 904 patients with subarachnoid hemorrhage admitted to the four centers during the period of study, 479 (53%) were entered into the trial. The principal reasons for exclusion were: elapse of more than 72 hours between bleed and admission (205 patients), a cause for SAH other than aneurysm (87 patients), death within a few hours in a patient already 'in extremis' (55 patients) and operation within 72 hours of bleeding (51 patients).

Characteristics on entry: comparison of patients in the 4 centers

The majority (89%) of patients in the trial were studied in either Rotterdam (44%) or in Glasgow (45%) (table 18). The smaller numbers in the other two centers reflect a shorter duration of study, a lower number of admissions or a policy of early operation (Amsterdam).

Entry to the study was within 24 hours of the bleed in 39% of all patients. Differences between local referral patterns resulted in a larger proportion of early admissions in Rotterdam (60%) than in Glasgow (23%). Primary care physicians or neurologists usually referred patients directly to the Rotterdam neurological unit, whereas in the remaining centers the patients had been admitted primarily to another hospital or specialty and then transferred to the neurosurgical unit with a view to investigation and operation. Thus, 21 (10%) of the Rotterdam series were over 70 years of age, whereas such patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients in the four centers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rotterdam</td>
</tr>
<tr>
<td>Placebo</td>
<td>104</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>106</td>
</tr>
<tr>
<td>Total</td>
<td>210</td>
</tr>
</tbody>
</table>
were not admitted in Glasgow. As a consequence the rate of angiography was 64% in Rotterdam and 91% in Glasgow (overall 77%), and 33% of the patients in Rotterdam underwent operation compared to 53% in Glasgow (overall 43%).

**Characteristics on entry: comparison of patients in treatment and control groups**

241 patients received tranexamic acid and 238 patients received placebo. Important prognostic factors were well matched in each group (table 19), although some differences occurred despite randomization. In Table 19. Comparison of entry characteristics in the treatment and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 241</td>
<td>n = 238</td>
</tr>
<tr>
<td>SEX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>95 (39%)</td>
<td>94 (39%)</td>
</tr>
<tr>
<td>Female</td>
<td>146 (61%)</td>
<td>144 (61%)</td>
</tr>
<tr>
<td>AGE (Mean)</td>
<td>50.3</td>
<td>50.2</td>
</tr>
<tr>
<td>Interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24 hours</td>
<td>95 (39%)</td>
<td>91 (38%)</td>
</tr>
<tr>
<td>25-48 hours</td>
<td>86 (36%)</td>
<td>75 (32%)</td>
</tr>
<tr>
<td>49-72 hours</td>
<td>60 (25%)</td>
<td>72 (30%)</td>
</tr>
<tr>
<td>Loss of consciousness at Ictus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>110 (48%)</td>
<td>111 (48%)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>42 (17%)</td>
<td>37 (16%)</td>
</tr>
<tr>
<td>II</td>
<td>93 (39%)</td>
<td>87 (37%)</td>
</tr>
<tr>
<td>III</td>
<td>61 (25%)</td>
<td>71 (30%)</td>
</tr>
<tr>
<td>IV/V</td>
<td>45 (19%)</td>
<td>43 (18%)</td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 and 13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>128 (53%)</td>
<td>122 (51%)</td>
</tr>
<tr>
<td>Worst diastolic blood pressure in first 24 hours</td>
<td>&gt;100</td>
<td>90 (37%)</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hunt and Hess grading system**

- **Grade Description**
  1. Asymptomatic, or minimal headache and slight neck stiffness
  2. Moderate to severe headache, neck stiffness, no neurological deficit (except cranial nerve palsy)
  3. Drowsiness, confusion, or mild focal deficit
  4. Stupor, moderate to severe headache, possibly early de cerebrate rigidity and vegetative disturbances
  5. Deep coma, de cerebrate rigidity, moribund

**Hunt and Hess grading system**

<table>
<thead>
<tr>
<th>Grade Description</th>
<th>Glasgow Coma Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye opening</td>
<td>E</td>
</tr>
<tr>
<td>Spontaneous speech</td>
<td>4</td>
</tr>
<tr>
<td>To speech</td>
<td>3</td>
</tr>
<tr>
<td>Pain</td>
<td>2</td>
</tr>
<tr>
<td>Nil</td>
<td>1</td>
</tr>
<tr>
<td>Motor response</td>
<td>M</td>
</tr>
<tr>
<td>Obeys</td>
<td>5</td>
</tr>
<tr>
<td>Localizes</td>
<td>4</td>
</tr>
<tr>
<td>Sideslies</td>
<td>3</td>
</tr>
<tr>
<td>Extensor response</td>
<td>2</td>
</tr>
<tr>
<td>Nil</td>
<td>1</td>
</tr>
<tr>
<td>Verbal response</td>
<td>V</td>
</tr>
<tr>
<td>Oriented</td>
<td>5</td>
</tr>
<tr>
<td>Confused</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td>Nil</td>
<td>1</td>
</tr>
</tbody>
</table>

Coma Score: (E + M + V) = 5 to 14
particular, a preceding history of hypertension requiring treatment was more frequent in the placebo group (26% versus 17%).

**Cause of subarachnoid hemorrhage**

Angiography was carried out in 370 patients, 181 (75%) in patients on tranexamic acid and 189 (79%) patients in the control group (table 20). The median interval from randomization to angiography was two days in both groups. The investigation was carried out within three days of randomization in 82% of the treatment group and in 80% of the controls. An aneurysm was demonstrated on angiogram in a significantly greater proportion of patients in the control group (155 or 65%) as opposed to 130 (54%) on tranexamic acid. However, the early timing of the angiography strongly suggests that this discrepancy resulted from a chance imbalance of randomization and not from a treatment effect; and we have analysed the data accordingly. Autopsy showed a further 41 aneurysms in patients who did not undergo angiography. The distribution of aneurysm sites corresponds to previous series and randomization produced an even proportion in each group. Of the 152 patients with demonstrated aneurysms in the treatment group 64 (42%) aneurysms arose from the anterior cerebral artery, 48 (32%) from the carotid artery, 26 (17%) from the middle cerebral artery and 14 (9%) from the posterior circulation, as opposed to 70 (40%), 53 (30%), 34 (20%) and 17 (10%) respectively for comparable sites in the control group (174 patients). Of the patients with demonstrated aneurysms, 32 (21%) in the treatment group and 26 (15%) in the control group had more than one aneurysm.

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm demonstrated</td>
<td>130 (54%)</td>
<td>155 (65%)</td>
</tr>
<tr>
<td>Negative</td>
<td>51 (21%)</td>
<td>34 (14%)</td>
</tr>
<tr>
<td>No angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm demonstrated at autopsy</td>
<td>22 (9%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>No aneurysm demonstrated</td>
<td>38 (16%)</td>
<td>30 (13%)</td>
</tr>
<tr>
<td>Total</td>
<td>241</td>
<td>238</td>
</tr>
</tbody>
</table>

**Efficiency of treatment administration**

Of 241 patients in the treatment group, 20 missed one or more doses. Three patients in the placebo group mistakenly received a few doses
tranexamic acid. Three patients randomized to placebo treatment were later found to have received previous treatment with tranexamic acid. None of the above patients was excluded from the final analysis.

Treatment was stopped before the 28th day in 190 (40%) patients who had an operation, in 112 (23%) who died, in 63 (13%) whose angiogram was negative, and in 5 (1%) because of the development of a complication (deep vein thrombosis, pulmonary embolus). In 17 (4%) treatment was stopped after another diagnosis was established, and in 4% for various other reasons. Only 74 (15%) patients completed the full 28 day course.

The imbalance in the number of aneurysms demonstrated in the treatment and control groups almost certainly accounted for the different number of patients in each group in whom treatment was stopped as a result of operation (84 (35%) in the treatment group and 106 (45%) in the control group). Similarly, treatment was stopped in more patients (15%) following negative angiography in the tranexamic acid group than in the control group (11%). Other reasons for stopping treatment (other cause established, death or thrombotic complication) were well matched in each group.

'Blinding' was effective as neither patients nor doctors were aware of the treatment: placebo or tranexamic acid. Few patients developed diarrhea, so this did not upset the blinding.

Outcome

Review three months after the hemorrhage showed that there was no difference in outcome between treatment and control groups (table 21). Of 173 patients who died, 84 had received tranexamic acid and 89 had received placebo. The slight difference in mortality rates was not significant ($X^2 = 0.64$ on 1 d.f. $p = 0.42$). If analysis is restricted to those patients with an

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Tranexamic acid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients n = 479</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>84 (35%)</td>
<td>89 (37%)</td>
</tr>
<tr>
<td>Dependent</td>
<td>30 (12%)</td>
<td>23 (10%)</td>
</tr>
<tr>
<td>Independent</td>
<td>127 (53%)</td>
<td>126 (53%)</td>
</tr>
<tr>
<td>Total</td>
<td>241</td>
<td>238</td>
</tr>
<tr>
<td>Patients with Aneurysm on n = 285</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>37 (28%)</td>
<td>50 (32%)</td>
</tr>
<tr>
<td>Dependent</td>
<td>16 (12%)</td>
<td>18 (12%)</td>
</tr>
<tr>
<td>Independent</td>
<td>77 (59%)</td>
<td>87 (56%)</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
<td>155</td>
</tr>
</tbody>
</table>

*For this study the Glasgow outcome scale was shortened into three groups, viz. dead, dependent (persistent vegetative state and severe disability) and independent (moderate disability and good recovery).
aneurysm demonstrated at angiography, there was also no significant
difference between treatment and control groups in all outcome categories.
Similarly, there was no significant difference in the outcome of
treatment and control groups in any of the individual centers. The overall
mortality was higher in Rotterdam (42%) than in Glasgow (29%), reflecting
the greater proportion of old patients and early admissions.

*Events in treatment and control groups*

Despite the similarity in outcome there were marked differences in the
frequency of rebleeding and infarction occurring during the trial period in
the tranexamic acid and control groups (table 22).

<table>
<thead>
<tr>
<th>EVENTS</th>
<th>Tranexamic acid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 241</td>
<td>n = 238</td>
</tr>
<tr>
<td>Rebleed</td>
<td>21 (9%)</td>
<td>56 (24%)</td>
</tr>
<tr>
<td>Infarct</td>
<td>59 (24%)</td>
<td>36 (15%)</td>
</tr>
<tr>
<td>Hydrocephalus requiring shunt</td>
<td>35 (15%)</td>
<td>29 (12%)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>12 (5%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>8 (3%)</td>
<td>9 (4%)</td>
</tr>
</tbody>
</table>

Rebleeding was significantly reduced in the treatment group ($X^2 = 18.07$ on 1 d.f. $p < 0.001$) (table 22). The results were the same when only patients with an aneurysm demonstrated at angiography were considered; 13 (10%) of 130 patients on tranexamic acid rebled compared to 35 (23%) of 155 patients on placebo.

Rebleeds were 'definite' in 17 (81%) of the treatment group and in 51 (91%) of the control group. Multiple rebleeds are not accounted for in this analysis. More than one rebleed occurred in 15 patients, 3 in the tranexamic acid group and 12 in the control group. Of the 77 patients who rebled, 82% died within three months of the initial bleed, with an equal distribution in the two groups. Figure 9 shows the cumulative proportion of patients rebleeding in each group, for all randomized patients and also for those patients with an aneurysm demonstrated on angiography.

The graphs show divergence of the treatment and control groups from the 4th day after randomization, irrespective of whether an aneurysm had been conclusively demonstrated or not. From the 4th to the 18th day rebleeding almost ceased in patients on tranexamic acid, but continued at a higher rate in patients in the control group.
Figure 9. Cumulative proportion of rebleeding during the trial in A, all patients, and B, in patients with a positive angiogram.
Cerebral infarction occurred more frequently in the treatment group ($X^2 = 8.07$ on 1 d.f. $p < 0.01$) (table 22). When only the results in patients with an aneurysm demonstrated on angiogram are considered, the findings were similar; 37 (28%) of 130 patients in the treatment group developed infarction as compared to 19 (12%) of the 155 patients in the control group.

In the tranexamic acid group 76% of the infarcts were 'definite' compared to 78% in the control group. Tranexamic acid had no effect on the severity of the infarct: after three months, 61% of patients with infarcts had died in the treatment group and 53% in the control group ($0.4 < p < 0.5$).

Figure 10 shows the cumulative proportion of infarcts occurring within each group during the treatment period for all randomized patients and for patients with an aneurysm on angiography. The graphs of patients on tranexamic acid diverge from the control group on the 6th day of treatment. Few infarcts developed after fourteen days in either group.

Causes of death

Rebleeding and infarction together had caused 73% of all deaths at three months. The differences in frequency of rebleeding and infarction in the two groups were reflected in differences in causes of death. Table 23 shows that the reduction in deaths due to rebleeding in the tranexamic acid group is counter-balanced by an increase in deaths due to infarction. In the remaining 27% a variety of other causes of death were identified, including extracranial causes (9%) and complications of operation or anesthesia (6%). There was no obvious difference for such events between the treatment and control groups, but together these other causes occurred more frequently in the tranexamic acid group.

Possible complications of treatment (excluding infarction)

More patients in the treatment group developed hydrocephalus
Figure 10. Cumulative proportion of cerebral infarction during the trial in A, all patients, and B, in patients with a positive angiogram.
requiring CSF drainage at three months (table 22), but this difference did not reach statistical significance ($X^2 = 1.21$ on 1 d.f. $p = 0.27$).

Only 21 patients developed clinical evidence of deep vein thrombosis at three months and there was not a difference in incidence between the treatment and control groups. The same applied to pulmonary embolus. Although some patients developed mild diarrhea during treatment, this was never so severe that treatment had to be stopped.

**Discussion**

This study demonstrates that antifibrinolytic therapy with tranexamic acid did not improve outcome in patients with subarachnoid hemorrhage. There was no difference in the proportion of patients with moderate disability and good recovery in the treatment and control groups. The observed difference in mortality was 2.5% in favor of tranexamic acid. The 95% confidence interval for this difference is -6% to 11%. The tightness of this interval means that unlike previous studies where a non-significant difference merely reflected the inadequate patient numbers, our study has demonstrated that any beneficial effect of treatment is too small to be clinically significant. This lack of benefit was not due to a lack of antifibrinolytic effect, because rebleeding was reduced from 24% in the control group to 9% in the treatment group, but was the result of a concurrent increase in the incidence of ischemic complications.

In the design of the trial we adopted the pragmatic approach (137) and looked at the overall usefulness of the drug by assessing patient outcome three months after the ictus. Thus any potential benefit from the antifibrinolytic therapy was weighed against deleterious effects. With this method all randomized patients are included in the final analysis despite any diagnostic errors and other protocol violations such as errors of drug administration. These inevitably occur in ‘real life’ situations. The results of such a trial directly apply to clinical practice. One possible disadvantage of the pragmatic approach is that dilution of the high risk group (i.e. patients with an aneurysmal SAH) may mask a specific drug action. Despite this, our results conclusively demonstrated an effect of tranexamic acid in preventing rebleeding.

Many patients of this study were randomized before an aneurysm had been demonstrated angiographically, especially in Rotterdam where angiography was carried out only if surgical treatment was considered. However, there was no difference in the effect of treatment irrespective of whether all randomized patients or only patients with an angiographically proven aneurysm were analysed.

Randomization provided an equal distribution of important prognostic factors including age, clinical state and blood pressure on admission. Some
disparities between groups did arise, with more patients having a preceding history of hypertension in the control group. We consider the discrepancy in the number of patients with a proven aneurysm in each group to have occurred by chance and have analysed the data accordingly. However, to guard against the possibility of this discrepancy being a result of treatment, we re-analysed the data without adjusting for the imbalance and this in no way altered our conclusions.

In this study most rebleeds were confirmed by CT scan (88%) and in addition observer bias was eliminated by the trial being 'blind'. In most previous studies the diagnosis of rebleeding was based only upon lumbar puncture findings or autopsy. These methods do not provide conclusive evidence of rebleeding, especially when, as is usual, the deterioration occurs within the first three weeks. At this stage, a fresh hemorrhage is seldom obvious because the cerebrospinal fluid (CSF) may remain grossly blood-stained for as long as 24 days after the initial hemorrhage (168) and an increased red-blood cell count may result from a traumatic puncture. Analysis of CSF xanthochromia is of limited value (162). The diagnosis of rebleeding by autopsy may also be difficult and requires that the interval between the first hemorrhage and rebleeding is not too short and the interval between rebleeding and death not too long.

A reduction in the rate of rebleeding was also found in 5 of the 14 controlled trials previously reported. However, none of these five studies was double blind. The only three studies that were randomized and blind did not show a significant difference in rebleeding between the two groups. Mortality was analysed in ten studies and in three was reported to be significantly decreased by antifibrinolytic treatment. These findings were not substantiated in our study. An important shortcoming of the previous studies that failed to show benefit in either rebleed rate or in outcome with antifibrinolytic therapy was that the number of patients in the treatment and control groups were too small. In such studies the chance of failing to show a significant difference is unacceptably high (161). The increase in cerebral ischemia we observed, confirms the report of Fodstad (49). We also found a slightly higher incidence of hydrocephalus, but this difference did not reach statistical significance. Although systemic thrombotic complications of antifibrinolytic therapy have been occasionally reported, this study and all previous studies in patients with subarachnoid hemorrhage did not show a significant increase in the treatment group.

The effects of antifibrinolytic therapy are likely to depend upon the dose and the agent used. The dosage of tranexamic acid in this study was based upon studies of Tovi (150). Although a lower dose might decrease complications, it is likely that there would be less effect on rebleeding. It remains to be seen whether epsilon-aminocaproic acid is as effective as tranexamic acid and has fewer side-effects.

The use of antifibrinolytic therapy after SAH depends on the views
about the benefits of surgical treatment and in particular the merits of operation at different times. There is increasing employment of early operation (within three days) but whether this improves outcome is not yet clear. Moreover, it is likely that operation will always be delayed or contra-indicated in some patients, especially those in poor clinical condition. For such patients to benefit from antifibrinolytic therapy, it would be necessary to devise a method of minimising the complications of treatment, while preserving the beneficial effect in preventing rebleeding. In this study patients who had raised blood pressure and who received antihypertensive drugs were especially at risk of infarction if treated with tranexamic acid, as were those who had fluid restriction to treat hyponatremia. Avoidance of drops in blood pressure or perhaps even deliberate expansion of circulating fluid volume might reduce the risk of infarction, as might preventive treatment with an agent such as Nimodipine (3). On the other hand, it would need to be shown in further large well-conducted studies that such measures did not negate the preventive effect of antifibrinolytic treatment on rebleeding and that real benefits did ensue.
GENERAL SUMMARY

The aim of this study was to elucidate and to solve the controversy whether patients with a subarachnoid hemorrhage (SAH) benefit from antifibrinolytic treatment.

In Chapter I the current knowledge of SAH and antifibrinolytic therapy is reviewed. Aneurysmal subarachnoid hemorrhage has an incidence of 10-20 per 100,000 population per year. It has been estimated that of all the patients 36% will die or be disabled as a result of the initial bleeding, 32% will die or be disabled during treatment and 32% will survive without major disability. The early mortality is difficult to influence; some can be saved by resuscitation and some others if early warning signals of aneurysm rupture can be recognized.

Patients who survive the initial hemorrhage may have many complications, especially during the first two weeks. Rebleeding and cerebral infarcts are the most frequent secondary events. Thirty per cent of the patients will have rebled after one month and about 50% of these will die. Cerebral ischemia is clinically manifest in about 25% of the patients.

Hydrocephalus may develop weeks to months after the hemorrhage, but acute hydrocephalus also occurs. The other complications are hematomas, epileptic fits and medical complications such as pulmonary edema, cardiac arrhythmias, pulmonary embolism and gastrointestinal hemorrhage. Problems in the management of patients with SAH are: the treatment of elevated blood pressure, hyponatremia, vasospasm and cerebral ischemia, the timing of surgery and the use of antifibrinolytic agents.

In Part 2 of Chapter I the principles of fibrinolysis and antifibrinolytic treatment are described.

Studies on the fibrinolytic activity in blood and CSF after SAH are reviewed in Part 3 of Chapter I. The most consistent finding is that high levels of FDP's can be found in the CSF during the first weeks after the hemorrhage. These FDP's in the CSF are considered a reliable measure for the optimal dosage of antifibrinolytic treatment, for deciding between surgical and conservative treatment and for monitoring antifibrinolytic therapy in individual patients.

In Part 4 of Chapter I the methods for the clinical assessment of antifibrinolytic therapy in SAH are reviewed. The use of concurrent controls, adequate randomization and double-blind procedures has many advantages in the comparison of treatments. The contrasts between explanatory and pragmatic trials as described by Schwartz, Flamant and Lellouch, and the consequences of these different approaches in studying the effects of
antifibrinolytic treatment are summarized. In general, an explanatory trial aims at providing an increase in knowledge, while a pragmatic trial investigates whether a treatment is beneficial to the patients.

Many trials on the effects of antifibrinolytic treatment in SAH were too small (Part 5). It is shown how the required number of patients can be calculated. In addition, the advantages of calculating the therapeutic gain rather than the statistical significant difference between treatments are explained.

In Part 5 the previous studies on the effects of antifibrinolytic therapy are reviewed. Twenty-nine studies appeared in the literature, and 14 included concurrent controls. Of these 14, only three were carried out with both a blind procedure and an acceptable method of randomization. However, these three studies were too small to be conclusive.

If the effects of antifibrinolytic treatment are studied from an explanatory viewpoint, this might be done by determining the influence of treatment on the fibrinolytic activity or on the rebleeding rate.

The study described in Chapter II investigates whether the presence of fibrin/fibrinogen degradation products in the CSF after SAH reflects a damaged blood-CSF barrier or continuing fibrinolytic activity in the subarachnoid space. In 48 patients with SAH, fibrin/fibrinogen degradation products (FDP), total protein and plasminogen were determined in the CSF between days 9 and 15 after the presenting hemorrhage. Of these 48 patients, 22 were treated with tranexamic acid. No difference in FDP levels was found between patients on tranexamic acid and those in the control group. The total protein and plasminogen values were higher in patients with FDP's in the CSF than in those without FDP's. FDP's in the CSF were found more frequently in patients with an impaired consciousness or neurological deficit. No relation was found between the presence of FPD's and the later occurrence of rebleeding, while a significant reduction in rebleeding was seen in patients on tranexamic acid.

All these findings indicate that FDP's in the CSF reflect a damaged blood-CSF barrier rather than ongoing local fibrinolysis in the subarachnoid space. Therefore, FDP's in the CSF are unreliable in monitoring antifibrinolytic treatment in SAH and cannot be used for selecting patients at high risk of rebleeding.

The possibility of diagnosing rebleeding by spectrophotometric analysis of the CSF was investigated in the study presented in Chapter III. The course of CSF xanthochromia after subarachnoid hemorrhage was studied by serial spectrophotometric analysis of lumbar CSF in 15 patients without clinical or CT evidence of rebleeding. The xanthochromic index rose in some patients up to the seventeenth day, and the proportion of oxyhemoglobin or the absolute concentration of hemoglobin often fluctuated. Therefore, rebleeding can be demonstrated in lumbar CSF only by increased xanthochromia, if previous samples had shown a decrease. These criteria could be applied in
only 6 of 17 consecutive patients with rebleeding as demonstrated by CT, and they were met in 5.

Another common method of diagnosing rebleeding is to rely on clinical criteria. In Chapter IV a study is described which compares changes in the clinical condition and on CT. In 150 patients with aneurysmal hemorrhage acute deteriorations were studied. The patients were closely observed for a four-week period or until death or operation. Forty-six patients suffered 62 episodes of deterioration that developed within five minutes; 59 consisted of a severe impairment of consciousness. Computed tomography was performed within a few hours of the event. Base-line scans had been obtained at least weekly. Rebleeding was diagnosed in 42 episodes (68%), including 6 patients who died rapidly without a repeat CT scan. In other acute episodes the final diagnosis was epilepsy [6], acute onset of ischemia [3], and ventricular fibrillation [1]. Ten unexplained events occurred in nine patients. Rebleeding could be excluded with confidence in nine of these events, because the residual clots had disappeared or markedly decreased on CT. The conclusion is that a purely clinical diagnosis of rebleeding will be wrong in about every third patient, even if these patients are under close observation.

Chapter V presents the results of a multi-center, double-blind, placebo-controlled trial in 479 patients, which took five years to complete. The aim of the trial was to determine if in practical clinical circumstances, antifibrinolytic treatment led to improved functional outcome in patients who presented with subarachnoid hemorrhage. In addition, the incidence of rebleeding, cerebral ischemia and other possible complications were investigated. The outcome assessed at three months was not statistically different between tranexamic acid and control groups.

Of the 173 patients who died, 84 received tranexamic acid and 89 placebo. The observed difference in mortality was 2.5% in favor of tranexamic acid. The 95% confidence interval for this difference is -6% to 11%. The tightness of this interval means that any beneficial effect of treatment is too small to be clinically significant unlike previous studies where a non-significant difference merely reflected the inadequate patient numbers. Similarly, no statistical difference occurred when analysis was restricted to patients with an angiographically demonstrated aneurysm. This absence of effect was not due to a lack of antifibrinolytic action as rebleeding was reduced from 24% in the control group to 9% in the tranexamic acid group, but resulted from a concurrent increase in the incidence of ischemic complications (15% in the control group, 24% in the tranexamic acid group). The conclusion is that until some method can be found to minimise ischemic complications, tranexamic acid is of no benefit in patients with subarachnoid hemorrhage.
SAMENVATTING

Dit onderzoek werd ingegeven door de controverse of patiënten met een subarachnoidale bloeding gebaat zijn bij behandeling met antifibrinolytica.

In Hoofdstuk I wordt een overzicht gegeven van de huidige kennis van subarachnoidale bloedingen en antifibrinolytische therapie. De incidentie van subarachnoidale bloedingen door een gebarsten aneurysma is 10-20 per 100.000 inwoners per jaar. Geschat wordt dat van alle patiënten 36% overlijdt of ernstig wordt geïnvalideerd door de eerste bloeding, 32% overlijdt of wordt ernstig geïnvalideerd in een latere fase en 32% overleeft zonder ernstige afwijkingen. De vroege sterfte is moeilijk te beïnvloeden, sommigen kunnen worden gered door beademing en enige anderen als waarschuwende bloedingen tijdig worden herkend.

Patiënten die de eerste bloeding overleven, kunnen vele complicaties hebben, vooral tijdens de eerste twee weken.

De belangrijkste daarvan zijn de recidief-bloedingen en de cerebrale infarcten. Na een maand heeft 30% van de patiënten een recidief-bloeding gehad en ongeveer 50% van hen overlijdt hieraan. Cerebrale infarcering is klinisch manifest bij 25% van de patiënten.

Hydrocephalus kan weken tot maanden na de bloeding ontstaan, maar ook acute hydrocephalus komt voor. De andere complicaties zijn intracerebrale hematomen, epilepsie en complicaties als longoedeem, longembolieën, hartritmestoornissen en maag/darm-bloedingen. Problemen bij de behandeling van patiënten met een subarachnoidale bloeding zijn: de behandeling van verhoogde bloeddruk, hyponatriëmie, vasospasme, cerebrale infarcering; het tijdstip van operatie en het gebruik van antifibrinolytica.

In deel 2 van Hoofdstuk I worden de beginselen van fibrinolyse en antifibrinolytische therapie beschreven.

Onderzoeken naar de fibrinolytische activiteit van bloed en liquor na een subarachnoidale bloeding worden samengevat in deel 3 van Hoofdstuk I. Telkens weer worden hoge fibrinedegradatieproduct (FDP)-waarden in de liquor gevonden tijdens de eerste weken na de bloeding. Deze FDP's in de liquor worden wel gezien als een goede maat voor het bepalen van de optimale antifibrinolytische dosering, voor de keuze tussen conservatieve en chirurgische therapie en voor het controleren van antifibrinolytische medicatie.

In deel 4 van Hoofdstuk I worden methoden besproken voor het beoordelen van antifibrinolytische therapie. Het gebruik van een gelijktijdige
controlegroep, effectieve randomisatie en een dubbel-blinde methode heeft vele voordelen bij het vergelijken van behandelingen. De tegenstelling tussen explanatoire en pragmatische onderzoeken zoals beschreven door Schwartz, Flamant en Lellouch, en de gevolgen van deze benadering bij het onderzoek naar de effecten van antifibrinolytische therapie worden opgesomd. Over het algemeen zal een explanatoir onderzoek streven naar het verkrijgen van nieuwe kennis, terwijl een pragmatische aanpak onderzoek of patiënten baat vinden bij de behandeling.

Vele voorgaande onderzoekingen naar het effect van antifibrinolytische therapie bij subarachnoidale bloedingen zijn te klein opgezet. Het vereiste aantal patiënten kan vooraf worden berekend en dit wordt met een voorbeeld toegelicht. Tevens worden de voordelen van het berekenen van de therapeutische winst uiteengezet.

In deel 5 wordt een overzicht gegeven van de tot nu toe verrichte onderzoekingen naar de effecten van antifibrinolytische therapie. In de Engelstalige literatuur verschenen 29 verslagen van onderzoeken, waarvan 14 met een controlegroep. Van deze 14 werden slechts drie onderzoeken dubbel-blind en met een aanvaardbare randomisatiemethode uitgevoerd. Deze drie onderzoeken waren echter te klein om tot een conclusie te kunnen leiden.

Als de antifibrinolytische therapie op een explanatoire wijze wordt onderzocht, dan kan dit worden gedaan bij voorbeeld door de invloed vast te stellen van de behandeling op de fibrinolytische activiteit of op het aantal recidief-bloedingen.

Het onderzoek beschreven in Hoofdstuk II gaat na of de aanwezigheid van FDP’s in de liquor na een subarachnoidale bloeding een uiting is van een beschadigde bloed/liquor-barrière of van aanhoudende fibrinolytische activiteit in de subarachnoidale ruimte. Bij 48 patiënten met een subarachnoidale bloeding werden FDP, totaal eiwit en plasminogeen bepaald in de liquor, afgenomen tussen de 9e en 15e dag na de bloeding. Van deze 48 patiënten werden 22 met tranexaminezuur behandeld. Geen verschil in FDP-waarden werd gevonden tussen patiënten behandeld met tranexaminezuur en de controlegroep. Het totale eiwitgehalte en de plasminogeenwaarden waren hoger bij patiënten bij wie FDP’s werden gevonden dan bij patiënten zonder FDP’s in de liquor. FDP’s werden vaker gevonden bij patiënten met een verlaagd bewustzijn of focale neurologische uitvalverschijnselen. Geen verband werd gevonden tussen FDP’s en recidief-bloedingen, terwijl een significante daling van recidief-bloedingen werd gezien bij patiënten behandeld met tranexaminezuur.

Al deze bevindingen wijzen erop dat FDP’s in de liquor uiting zijn van een beschadigde bloed/liquor-barrière en niet van aanhoudende lokale fibrinolyse in de subarachnoidale ruimten. Daarom zijn FDP’s in de liquor onbetrouwbaar als middel om de werkzaamheid van antifibrinolytische therapie te controleren en kunnen ze ook niet gebruikt worden bij het
identificeren van patiënten met een verhoogd risico op een recidief-bloeding.

De mogelijkheid om recidief-bloedingen met spectrofotometrisch onderzoek van de liquor vast te stellen werd onderzocht in het onderzoek beschreven in Hoofdstuk III. Het beloop van de xanthochromie van de liquor verkregen door lumbale punctie bij 15 patiënten zonder klinische of CT- tekenen van een recidief-bloeding werd bestudeerd. De xanthochromie-index steg bij enkele patiënten tot aan de 17e dag na de bloeding, en het gedeelte van de xanthochromie bestaande uit oxyhemoglobine en de absolute concentratie van hemoglobine schommelde. Daardoor kunnen recidief-bloedingen alleen worden aangetoond in de liquor als de xanthochromie is toegenomen in vergelijking met twee voorafgaande liquor-monsters waarin een daling werd aangetoond. Deze criteria konden bij slechts 6 van de 17 opeenvolgende patiënten met een recidief-bloeding worden toegespitst, en 5 van hen voldeden daaraan.

Een andere veel gebruikte methode bij het diagnostiseren van recidief-bloedingen is het afgaan op klinische criteria. In Hoofdstuk IV wordt een onderzoek beschreven waarin veranderingen in de klinische toestand van patiënten worden vergeleken met die op CT-scans. Bij 150 patiënten met een bloeding door een gebarsten aneurysma werd de oorzaak van elke acute klinische achteruitgang nader onderzocht. Deze patiënten werden nauwlettend geobserveerd gedurende een periode van maximaal vier weken of korter, in geval van operatie of overlijden. Zesenvijftig patiënten hadden 62 episoden van verslechtering binnen vijf minuten, en 59 hiervan bestonden uit een ernstige bewustzijnsdaling. Computertomografie werd verricht binnen enkele uren na de acute gebeurtenis. Wekelijks werden scans gemaakt om als vergelijking te dienen. Een recidief-bloeding werd gediagnostiseerd bij 42 episoden (68%) met inbegrip van zes patiënten die snel overleden zonder herhaling van de CT-scan. Bij de andere patiënten met acute verslechtering was de uiteindelijke diagnose epilepsie (bij 6), acuut begonnen ischemie (bij 3) en ventrikel-fibrillatie (bij 1). Tien acute episoden bij 9 patiënten bleven zonder verklaring. Recidief-bloedingen konden bij negen van deze gebeurtenissen betrouwbaar worden uitgesloten omdat het bloed verdwenen was of aanzienlijk afgenomen op CT. De conclusie luidt dat een uitsluitend op klinische criteria gebaseerde diagnose "recidief-bloeding" onjuist is bij ongeveer een derde van de patiënten, zelfs als deze patiënten nauwlettend waren geobserveerd.

In Hoofdstuk V worden de resultaten beschreven van een zogenaamde "multicenter dubbel-blinde placebo-gecontroleerde trial", waarin in de loop van vijf jaar 479 patiënten werden opgenomen. Het doel van deze trial was vast te stellen of antifibrinolytische therapie leidt tot verbeterde validiteit van patiënten met een subarachnoïdale bloeding. Tevens werd de frequentie onderzocht van recidief-bloedingen, cerebrale ischemie en andere mogelijke complicaties. De afloop, drie maanden na de bloeding, was niet statistisch
verschillend tussen met tranexaminezuur en met placebo behandelde patiënten. Van de 173 patiënten die overleden werden 84 met tranexaminezuur en 89 met placebo behandeld. Het waargenomen verschil in sterfte was 2,5% in het voordeel van tranexaminezuur. Het 95% betrouwbaarheidsinterval voor dit verschil ligt tussen -6 en 11%. Dit nauwe interval betekent, dat het gunstige effect van behandeling te klein is om klinisch van betekenis te kunnen zijn, in tegenstelling tot onderzoeken waarbij een niet significant verschil slechts het gevolg is van een te geringe steekproef-grootte. Eveneens werd geen statistisch significant verschil gevonden als de analyse beperkt werd tot patiënten met een angiografisch aangetoond aneurysma. Deze afwezigheid van een nuttig effect was niet het gevolg van een ontbreken van antifibrinolytische werking, aangezien het percentage recidief-bloedingen daalde van 24% in de controlegroep naar 9% in de tranexaminezuur-groep, maar was het gevolg van een gelijktijdige toename van het aantal ischemische complicaties (15% in de controlegroep, 24% in de tranexaminezuur-groep). De conclusie is dat patiënten met een subarachnoidale bloeding niet gebaat zijn bij behandeling met tranexaminezuur, tenzij ischemische complicaties kunnen worden voorkomen.
REFERENCES


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CURRICULUM VITAE

De schrijver van dit proefschrift werd 18 oktober 1946 te Rotterdam geboren. Hij bezocht te Rotterdam het Johannes Calvijn Lyceum, waar hij in 1964 het HBS B-diploma behaalde. Hij studeerde geneeskunde aan de Vrije Universiteit te Amsterdam en werd in 1974 tot arts bevorderd. Na zijn semi-arts-examen was hij als assistent werkzaam in het psychiatrisch ziekenhuis Vogelenzang (Dr. F. van Ree). Van november 1973 tot april 1976 was hij assistent op de afdeling Interne van het Diaconessenhuis te Voorburg (Dr. P.C. Brinkerink). Vervolgens was hij assistent op de afdelingen Neurologie en Psychiatrie van het Academisch Ziekenhuis Dijkzigt te Rotterdam (Prof. Dr. A. Staal en Prof. Dr. G.A. Ladee). Augustus 1980 werd hij in het specialistenregister voor neurologie ingeschreven. Daarna was hij, in verband met het in dit proefschrift beschreven onderzoek, werkzaam in het Institute of Neurological Sciences te Glasgow (Prof. B. Jennett en Prof. G.M. Teasdale). Hij keerde terug naar het Dijkzigt Ziekenhuis te Rotterdam en gedurende een jaar verbleef hij op de afdeling Klinische Neurofysiologie aldaar (Prof. Dr. M. de Vlieger). Thans is hij als staflid verbonden aan de afdeling Neurologie.