TREATMENT OF ACUTE HYDROCEPHALUS AND CEREBRAL ISCHEMIA AFTER SUBARACHNOID HEMORRHAGE

(De behandeling van acute hydrocephalus en
cerebrale ischemie na een subarachnoïdeale bloeding)

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This thesis is the result of the last 4 years of my life
It is dedicated to my family, my parents, and my friends
Whose loyalty and time are more important to me than ever before

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"When I was younger,
so much younger than today
I never needed anybodies
help in anyway
But now those days are gone
and I'm not so self assured ....."
Lennon-McCartney[76]

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GENERAL INTRODUCTION

Only recently has acute hydrocephalus after subarachnoid hemorrhage been recognized as a clinical important problem.[120] The mortality rate in patients with acute hydrocephalus after subarachnoid hemorrhage is higher than in those without, which is mainly caused by cerebral ischemia.[120]

An explanation for the role of acute hydrocephalus in producing fatal cerebral ischemia is offered by the significant correlation between acute hydrocephalus and hyponatremia[134] and between hyponatremia and death from cerebral ischemia,[130] whereas cerebral ischemia is relatively rare in patients with acute hydrocephalus who do not develop hyponatremia.[134] The relation between hydrocephalus and hyponatremia is possibly explained by enlargement of the third ventricle which could interfere with hypothalamic function.[134] Dysfunction of the hypothalamus may result in the release of a natriuretic factor[132] which in turn causes salt wasting and hypovolemia. This hypovolemia may contribute to the development of cerebral ischemia after subarachnoid hemorrhage.[130,131]

Therefore, treatment of acute hydrocephalus should not be aimed only at the reduction of cerebro-spinal fluid pressure, but also at the prevention of a negative sodium- and fluid-balance. This strategy is the subject of this thesis.

Chapter 1 reviews acute hydrocephalus and cerebral ischemia.

Treatment of acute hydrocephalus is discussed in **Chapter 2.** The decision to treat acute hydrocephalus after subarachnoid hemorrhage may be difficult to make for several reasons: 1) impaired consciousness after subarachnoid hemorrhage may result from either the impact of initial bleeding or from hydrocephalus; 2) when the decision to carry out ventricular drainage has been made, the question arises whether this should be done by external drainage or by internal shunting; 3) ventricular drainage may precipitate rebleeding which could be a reason to postpone drainage until the aneurysm has been clipped. In this chapter the results of a study on management problems in 102 patients with acute hydrocephalus are presented.

After it was shown that ventricular drainage in acute hydrocephalus after subarachnoid hemorrhage is accompanied by an increased risk of rebleeding and by serious infection, the effects and complications of treatment with serial lumbar puncture were investigated (**Chapter 3**).

The cause of impaired consciousness in patients with acute hydrocephalus after subarachnoid hemorrhage was investigated by a study on cerebral blood flow (CBF) using single photon emission computed tomography (SPECT) after intravenous administration of technetium-99M

labeled *d,l*-hexamethyl-propylene amine oxime (^{99m}Tc HM-PAO). These results were compared with that in patients with impaired conscious level from cerebral ischemia (**Chapter 4**).

As mentioned before (page 1), cerebral ischemia is a frequent complication in patients with acute hydrocephalus and the volume status plays a major role in the development of cerebral ischemia. The effects of fluid regimen and antihypertensive treatment on cerebral ischemia after subarachnoid hemorrhage were studied and the results are shown in **Chapter 5**.

The relation between hyponatremia and cerebral ischemia was further studied by investigating the influence of fluid intake on this association (**Chapter 6**).

In **Chapter 7**, a study is described which investigated the effects of treatment with fludrocortisone acetate on plasma volume, fluid-, and sodium-balance in patients with subarachnoid hemorrhage.

Chapter 1

ACUTE HYDROCEPHALUS AND CEREBRAL ISCHEMIA AFTER SUBARACHNOID HEMORRHAGE

HYDROCEPHALUS

In 1928, Bagley injected blood into the basal cisterns of 18 dogs and seven of these animals developed hydrocephalus.[8] Bagley was also the first author who reported hydrocephalus in patients with subarachnoid hemorrhage.[9] He presented, among others, four patients with autopsy proven subarachnoid hemorrhage from a cerebral anterior aneurysm, two of these patients had enlarged ventricles. In this report, Bagley also presented four other patients with a headache of sudden onset followed by a gradual deterioration of the level of consciousness (within 24 hours in two patients and within one week in the remaining two). Lumbar punctures, which revealed bloody CSF, were performed because of the presence of papilledema and after lumbar punctures these patients improved. Presumably, these patients suffered from acute hydrocephalus. It took until the early fifties before other reports on hydrocephalus after subarachnoid hemorrhage were published.[6,112] In 1956 Foltz et al[29] reported five cases with hydrocephalus, diagnosed with angiography and pneumoencephalography, which had developed more than 2 weeks after spontaneous subarachnoid hemorrhage. The clinical signs and symptoms of hydrocephalus varied: two patients were lethargic, two were comatose, and one patient had no clinical manifestations of hydrocephalus. In the patient without clinical manifestations of hydrocephalus, evidence of ventricular enlargement was accidentally found on a repeat angiogram. Thereafter, many authors described hydrocephalus after subarachnoid hemorrhage which usually developed after more than 2 weeks after the initial hemorrhage.[11,30,34,36,64,66,69,92,93,107,111,116]

Acute Hydrocephalus

After Bagley's observations,[9] other reports on hydrocephalus which developed within 2 weeks following subarachnoid hemorrhage were published, but not earlier than forty years

later.[72,81,94,100,138] In these reports, the diagnosis was made by angiography and pneumoencephalography. The first report on acute hydrocephalus diagnosed by CT scan appeared in 1979,[121] and in the following years, several other investigators reported on the development of hydrocephalus within 1 week after subarachnoid hemorrhage.[10,19,38,43,54,55,68,73,85,96,110,120]

Frequency of Acute Hydrocephalus

The reported frequency of acute hydrocephalus after subarachnoid hemorrhage varied from 9[110] to 67 %,[10] which may be explained by differences in: 1) criteria used for the diagnosis; 2) patient selection; 3) and timing of the investigation.

1) Criteria for hydrocephalus and for ventricular enlargement on CT were numerous. Vassilouthis[121] used a fixed value of 0.2 for the bicaudate index (the width of the frontal horns at the level of the caudate nuclei divided by the diameter of the brain at the same level) as the upper normal limit of ventricular width, a definition which was also used by other authors.[92,111] A disadvantage of this method is that the normal upper limit is set independently of the patients' age.

2) Some authors included only patients with angiographic proven aneurysm,[10,110,121] others included only those who underwent aneurysm surgery,[34] or excluded patients who died within a few days after subarachnoid hemorrhage.[85] It is to be expected that if all patients with subarachnoid hemorrhage are studied[120] the frequency of acute hydrocephalus will be different from for instance selected patients with an angiographic proven aneurysmal subarachnoid hemorrhage.[10,110,121]

3) The timing of CT scan on which the diagnosis acute hydrocephalus was made varied widely, from less than 4 days[38,43,120,121] to months[138] after the initial subarachnoid hemorrhage.

The frequency of acute hydrocephalus is probably 20% since this was found in a prospective study in 174 unselected consecutive patients with aneurysmal subarachnoid hemorrhage, admitted within 72 hours after the initial hemorrhage. In this study acute hydrocephalus was defined as a bicaudate index above the 95th percentile for age on the admission CT.[120]

Predisposing Factors

Knibestöl et al (1976)[66] reported that patients treated with antifibrinolytics are at a higher risk of developing hydrocephalus after subarachnoid hemorrhage, but in this report hydrocephalus was detected with echoencephalography which is an inaccurate method. The association between treatment with antifibrinolytics and the development of hydrocephalus after subarachnoid hemorrhage was found in a retrospective study in 350 patients with subarachnoid hemorrhage.[98] The problems with this study are that the administration of antifibrinolytics was not randomized and that hydrocephalus was not defined. Other predisposing factors found by Graff-Radford et al (the Cooperative Aneurysm Study)[34] were: increasing age, preexisting hypertension, high blood pressure on admission, intraventricular blood, diffuse or thick focal collection of cisternal blood on admission CT, posterior circulation site of the aneurysm and a decreased level of consciousness on admission. The disadvantage of this study is that, surprisingly, acute hydrocephalus was not defined. Spallone et al (1983)[110] found that the number of hemorrhages and localization of the aneurysm (Internal Carotid Artery and Anterior Communicating Artery) were predisposing factors for the development of hydrocephalus after subarachnoid hemorrhage. However, the authors used many different definitions of hydrocephalus such as: presence of clinical symptomatology; transient improvement after LP;

positive air study; positive RHISA; and positive CT scan. Moreover, the number of patients with hydrocephalus included in the study was very small (n=12) and the association with rebleeding which was suggested, is not convincing since rebleeding was not defined. Another report, which described the association between the amount of cisternal blood on admission and the development of hydrocephalus, was published recently.[125] The problems with this study are that the patients were admitted between Day 1 and Day 13, and that hydrocephalus was not clearly defined. In a study with clearly defined criteria for the diagnosis acute hydrocephalus in which the events after the initial hemorrhage were prospectively studied, the only factor associated with acute hydrocephalus was the presence of intraventricular blood.[120]

Clinical Course

In a retrospective study Vassilouthis et al (1979)[121] concluded that hydrocephalus in the first 14 days after subarachnoid hemorrhage is usually not clinically significant and does not require shunting prior to aneurysm surgery (surgery was planned at the end of the second week). In contrast, van Gijn et al[120] found in a prospective study a decreased level of consciousness in 88% of 34 patients with acute hydrocephalus on admission and on average, the larger the ventricle the greater was the impairment of consciousness. Nine patients with acute hydrocephalus underwent ventricular drainage within 2 weeks after admission. The rebleeding rate in hydrocephalic patients with ventricular drainage was higher, although not significantly, than in those without drainage. Eight of the nine patients with drainage died within 1 month after admission; four of rebleeding and four of cerebral ischemia. As mentioned in the "**GENERAL INTRODUCTION**" (page 1), mortality in patients with acute hydrocephalus (59%) was significantly higher than in those without (35%). The higher mortality was exclusively caused by fatal cerebral infarction (32% versus 9%).[120]

In 1987, Milhorat published a paper on acute hydrocephalus after subarachnoid hemorrhage[85] with different conclusions than the above mentioned study.[120] In a series of 200 patients with subarachnoid hemorrhage, 42 had acute hydrocephalus. Milhorat excluded all patients who had died before cerebral angiography was carried out and he planned aneurysm surgery "as soon as possible" in patients with Grade III or less (Hunt and Hess grading scale[57]). These two factors might explain why rebleeding was not reported in this study. Cerebral ischemia was not mentioned; the only described complication was a *Staphyloccus epidermidis* ventriculitis in one patient. Although ventriculitis as a complication of ventricular drainage is universally known, it was rarely reported as a complication of ventricular drainage in patients with acute hydrocephalus following subarachnoid hemorrhage.[85,109]

Cerebral Blood Flow (CBF)

Whether or not ventricular enlargement found on computed tomogram is the cause of clinical deterioration may be difficult to establish. If the level of consciousness of a patient deteriorates and repeated CT scan shows no abnormality other than a bicaudate index above the 95th percentile for age, the cause of the deterioration may be high pressure hydrocephalus or cerebral ischemia. Cerebral blood flow studies in patients with subarachnoid hemorrhage by means of non-rotating, multiple collimated, scintillation detectors and ^{133}Xenon (^{133}Xe) showed a diffuse decrease of CBF.[31,45,59,67] CBF studies in patients with hydrocephalus after subarachnoid hemorrhage showed contradictory results; diffuse CBF decrease (investigated with multiple collimated scintillation detectors and ^{133}Xe[44,80,84,113]) and depressed frontal CBF (by means of single photon emission computed tomography [effectively SPECT] and ^{133}Xe).[33,127] Positron emission tomography (PET) studies in patients with clinical symptoms of cerebral ischemia after

subarachnoid hemorrhage showed bilateral decrease of regional CBF (rCBF) and of regional cerebral metabolic rate for oxygen ($rCMRO_2$) with increased regional oxygen extraction fraction (rOEF).[99]

CEREBRAL ISCHEMIA

In 1964, Crompton presented the results of his study on the pathogenesis of cerebral infarction following the rupture of cerebral berry aneurysm (159 autopsies; 119 patients with and 40 without cerebral infarction).[16] He concluded that the following factors appear to contribute to the occurrence of cerebral infarction:

- The presence of a large-sized subarachnoid hematoma, especially in the Sylvian fissure.
- Angiographic arterial lumen narrowing ("vasospasm"), probably caused by distortion or stretching of the basal cerebral arteries by subarachnoid hematoma inducing necrosis of the vessel wall. The early changes were: swelling of the endothelial cells and a collection of polymorphonuclear and mononuclear leukocytes between the endothelium and the internal elastic lamina.
- The presence of a hypotensive period, defined as a measured diastolic pressure below 60 mm Hg. Several of the 62 hypotensive patients with cerebral infarction were described in detail: in one patient, a hypotensive period was precipitated by a ganglion-blocking agent, in five other cases atrial fibrillation (two patients), congestive heart failure (one patient), or pulmonary embolism (two patients) were the cause of a drop in the arterial blood pressure.
- Direct aneurysm surgery or carotid ligation, especially in combination with the presence of a postoperative hypotensive period.

Distribution of Cerebral Ischemia

In addition, Crompton observed that bilateral cerebral infarction was present in a substantial proportion of patients.[16] Many years later, Powers et al (using a PET scan, 1985; page 5)[99] and Hijdra et al (a clinicoanatomic study, 1986)[49] confirmed these findings. In a prospectively studied series of 56 patients with cerebral ischemia after subarachnoid hemorrhage, Hijdra et al[49] found diffusely distributed hypodensities on the computed tomograms in six patients, hypodensities in multiple vascular areas were seen in 22 patients (eight unilateral, 14 bilateral), 19 patients had a hypodensity in one vascular area, and CT was normal in nine other patients. Postmortem investigation in 18 patients who died from cerebral ischemia after subarachnoid hemorrhage showed diffuse or multifocal and bilateral cerebral infarction in 16 patients, unilateral multivascular cerebral infarction in one patient, and cerebral infarction in 1 vascular area in another patient.[49]

Amount of Cisternal Blood

The relation between the extent of cisternal blood and the development of cerebral ischemia found by Crompton[16] was later confirmed by others.[3,37,65,87] The problems with these reports were that grading of the amount of cisternal blood was difficult to reproduce and that the diagnosis cerebral ischemia was poorly defined.[3,37,65,87] Only one study dealt appropriately with these two problems.[50] The authors found that the most important predictive variable of the risk of delayed cerebral ischemia was the score of cisternal blood on CT within 72 hours after the initial bleed.

Moreover, they found that the next important predictive variables were the presence of ventricular blood and treatment with long-term tranexamic acid (tranexamic acid administered during the first 28 days).[50]

Vasospasm

Since the description of angiographic arterial lumen narrowing by Crompton,[16] vasospasm is thought to be the major cause of delayed cerebral ischemia after subarachnoid hemorrhage. Unfortunately, many authors referred to different entities when they use the term "vasospasm": angiographic narrowing;[4,10,26,65,86,103,104,128,129] both angiographic narrowing and delayed clinical deterioration after subarachnoid hemorrhage;[46,61,95] any bad clinical condition after subarachnoid hemorrhage;[106] any new neurological deficit which developed after the initial subarachnoid hemorrhage;[99] infarction on CT following subarachnoid hemorrhage;[71,115] or delayed cerebral ischemia after subarachnoid hemorrhage.[7,62,90] Only a few authors[128,129] defined angiographic vasospasm carefully and described the time of appearance and the course of angiographic vasospasm.[128,129] It was found that angiographic vasospasm rarely appeared within 3 days after the initial subarachnoid hemorrhage and that the incidence increased to about 60% in the second week and declined to less than 5% in the sixth week following the initial subarachnoid hemorrhage.[129]

Because of the delayed appearance and prolonged existence of angiographic vasospasm after subarachnoid hemorrhage, neither active constriction of the smooth muscle fibers of the arterial wall nor distortion or stretching of cerebral arteries by subarachnoid hematoma are likely to be the cause. By means of scanning electron micrograph it was shown that intradural arteries lack vasa vasorum,[14] but stomata on the adventitial surface (rete vasorum) were observed, and it was postulated that these structures may be analogous to the systemic vasa vasorum and may contribute to the nutrition of cerebral arteries.[140] The presence of blood in the subarachnoid space may block these stomata[79] and interfere with the metabolism of the cerebral arterial wall followed by arterial wall ischemia and subsequent necrosis.[15,24,56,108] Presumably, the development of structural changes in case of arterial wall ischemia takes a few days. In the first 2 weeks major pathological changes consisted of intimal swelling, subintimal exudation of protein and blood cells and smooth muscle cell necrosis, resulting in a decrease in the diameter of the lumen. Beyond this period, atrophy and fibrosis of the smooth muscle were observed and arterial lumen was wider than in the preceding period.[15,56]

Vasospasm is not the only cause of cerebral ischemia; the development of cerebral ischemia is a multifactorial process and vasospasm is probably just one of these factors.

Volume Status

It is remarkable that it took many years since Crompton's observation of the possible precipitation of cerebral infarction by a hypotensive period after subarachnoid hemorrhage[16] before the importance of blood pressure and volume status in the development and treatment of delayed cerebral ischemia after subarachnoid hemorrhage was recognized.[40,131] As already mentioned in the "**GENERAL INTRODUCTION**" (page 1), the volume status was shown to play an important role in the development of cerebral ischemia.[25,40,130,131] and anti-hypertensive drugs in patients with high blood pressures after subarachnoid hemorrhage may precipitate cerebral ischemia.[40] Moreover, it is common knowledge that cerebral ischemia after subarachnoid hemorrhage can successfully be treated by means of plasma volume expansion with[7,61,70] or without[25] accompanying artificially induced hypertension. The mechanism of this treatment of cerebral ischemia remained obscure. It appeared that plasma volume expansion did not increase

cardiac output.[25] Disappearance of the neurological deficits of cerebral ischemia is correlated with the pulmonary wedge pressure.[25] Presumably, decreased whole blood viscosity,[63,136] as shown by experimental treatment with *isovolemic* hemodilution of ischemic stroke in dogs,[47,58] is responsible for improvement of cerebral blood flow.

Aneurysm Surgery

Crompton's observation that direct aneurysm surgery precipitates cerebral ischemia[16] is still valid, despite improvement in the technique of aneurysm surgery, anesthesiology, and perioperative care. The occurrence of postoperative cerebral ischemia depends on the timing of surgery; early surgery is accompanied by a higher occurrence of cerebral ischemia when compared with delayed surgery, but this delay is accompanied by more rebleeds.[2,13,27,91] A considerable proportion of these preoperative rebleeds can be prevented by antifibrinolytic treatment, but this treatment is also accompanied by an increased occurrence of cerebral ischemia.[122] Therefore, improvement of outcome can be achieved only if cerebral ischemia can be prevented.

Chapter 2

MANAGEMENT PROBLEMS IN ACUTE HYDROCEPHALUS AFTER SUBARACHNOID HEMORRHAGE

INTRODUCTION

Acute hydrocephalus after subarachnoid hemorrhage is not uncommon. As mentioned on page 4, the frequency depends on the criteria used for the diagnosis and ranges from 9%[110] up to 67%.[10] In a consecutive series of 174 subarachnoid hemorrhage patients admitted within 72 hours after the initial hemorrhage to the Department of Neurology of the University Hospital Rotterdam, computed tomogram (CT) showed ventricular enlargement (defined as bicaudate index exceeding the 95th percentile for age) in 20%.[120]

The decision to treat acute hydrocephalus may be difficult for several reasons. First, impaired consciousness on admission may result from either the impact of initial bleeding or from hydrocephalus. If the impairment of consciousness is caused by hydrocephalus, delay of ventricular drainage could lead to a decrease in cerebral blood flow, precipitating (fatal) cerebral ischemia.[120] Second, when the decision to carry out ventricular drainage has been made, the question arises whether this should be done by external drainage or by internal shunting. Early shunting is probably not effective, since blood and the high protein content of the cerebrospinal fluid (CSF) may block the shunt.[96] Furthermore, not all patients require permanent shunting. On the other hand, external ventricular drainage may be accompanied by serious infections.[82,85,109] Third, it has been suggested that early ventricular drainage may precipitate rebleeding,[96,120] which could be a reason to postpone drainage until the aneurysm has been clipped.

We describe, from a consecutive series of 473 patients, the management problems of 91 patients with acute hydrocephalus after subarachnoid hemorrhage, as judged on the admission CT within 3 days after the initial subarachnoid hemorrhage, and of 11 patients who developed acute hydrocephalus later, but within 1 week after subarachnoid hemorrhage. In patients with a total score on Glasgow Coma Scale (GCS)[114] of <13 on admission, ventricular drainage was

immediately carried out if the impairment of the level of consciousness was thought to be caused by hydrocephalus. In all other patients and in patients with unimpaired (GCS of 14) or slightly impaired (GCS of 13) consciousness on admission, ventricular drainage was performed only if consciousness deteriorated and if no other cause for this deterioration was found.

We tried to answer the following questions. 1) What is the clinical course in patients with acute hydrocephalus, and what proportion requires ventricular drainage? 2) Does spontaneous improvement occur in patients with acute hydrocephalus and an impaired level of consciousness? 3) Is the frequency of cerebral ischemia increased in patients with acute hydrocephalus? 4) Does early ventricular drainage precipitate rebleeding? and 5) What is the risk of infection in patients treated with external drainage without prophylactic antibiotics

PATIENTS AND METHODS

Patients

During a period of 9 years and 5 months (from November 1977 until May 1987) we prospectively studied 473 consecutive patients who fulfilled the following criteria: clinical signs of subarachnoid hemorrhage; CT abnormalities suggesting a ruptured aneurysm[118] or perimesencephalic hemorrhage[119] or xanthochromic CSF (investigated with spectrophotometry);[22,123] and admission to the Department of Neurology of the University Hospital Rotterdam within 72 hours after subarachnoid hemorrhage. Acute hydrocephalus in 34 of the first 174 patients has been reported previously, with emphasis on the diagnosis and predisposing factors.[120]

Definition of Events

Events were recorded during a period of 28 days after the initial subarachnoid hemorrhage, or until death or surgical treatment of the aneurysm. CT scanning was carried out on admission (admission CT) and was repeated after any clinical deterioration. The level of consciousness was assessed by means of the 14-point Glasgow Coma Scale.[78,114] The events were defined as *probable delayed cerebral ischemia*: gradual development of focal neurologic signs, with or without deterioration in the level of consciousness, without confirmation by a CT or an autopsy; *definite delayed cerebral ischemia*: deterioration of consciousness or development of focal signs, or both, with CT or autopsy confirmation of cerebral infarction; *probable rebleeding*: sudden deterioration and death, without the possibility of proof by a CT or if autopsy was refused; *definite rebleeding*: sudden deterioration with increased amount of blood on a repeat CT or at autopsy when compared with a previous CT; *acute hydrocephalus*: bicaudate index measured on the initial CT or on a repeat CT within 1 week after the initial subarachnoid hemorrhage exceeded the normal upper limit (95th percentile) for age[38,43,120] (<36 years of age, 0.16; 36-45 years, 0.17; 46-55 years, 0.18; 56-65 years, 0.19; 66-75 years, 0.20; 76-85 years, 0.21[21,83,120]); and *deterioration from hydrocephalus*: deterioration of consciousness with no detectable cause other than hydrocephalus, confirmed by a repeat CT (relative bicaudate index [patient's bicaudate index divided by the normal upper limit for age] of >1).[38,43,120]

Treatment

From November 1977 until December 1982 the patients were treated with tranexamic acid or placebo during a period of 28 days after admission or until aneurysm surgery (long-term tranexamic acid).[122] From January 1983 until March 1986 the patients did not receive tranexamic acid and from April 1986 until May 1987 tranexamic acid was given during the first 4 days after admission (short-term tranexamic acid).[135]

Until December 1982 the daily fluid intake was between 1.5 and 2 l and the patients were treated with fluid restriction (<1000 ml/24 hr) in case of hyponatremia, defined as a sodium level of <135 mmol/l on at least 2 consecutive days.[130] From January 1983 onward the daily fluid intake was at least 3 l in all patients, and fluid restriction and diuretic medication after admission were avoided.[40] Unless the patient was on antihypertensive medication on admission, this treatment was not given. When signs of cerebral ischemia developed, extra fluid in the form of 20% albumin was administered.

Cerebral angiography and aneurysm surgery were performed depending on the patient's clinical condition. Aneurysm surgery was usually planned on Day 12.

Follow-Up

There was a 3 months follow-up of the survivors, including those who underwent aneurysm surgery. The outcome was assessed according to the 5-point Glasgow Outcome Scale.[60]

Statistics

The fourfold tables were analyzed with Yates' corrected chi-square test. If the expected number in any cell was <5, the fourfold tables were analyzed with the two-sided Fisher's exact probability test.

RESULTS

Frequency of Acute Hydrocephalus

Acute hydrocephalus was measured on the initial CT in 91 (19%) of the 473 patients. Of these 91 patients, 25 (27%) had no impairment of consciousness on admission (GCS of 14), 13 (14%) had a GCS of 13 and in the remaining 53 (58%) the GCS was <13. The degree of ventricular enlargement was not clearly different among these groups (Figure 1). In another 11 patients (3% of the 382 patients without hydrocephalus on admission), ventricular enlargement was found on a repeat CT, after clinical deterioration had developed, within 1 week after the initial hemorrhage.

Angiography was negative in nine (10%) of the 91 patients with acute hydrocephalus on admission, in one of the 11 patients who developed acute hydrocephalus within 1 week after subarachnoid hemorrhage, and in 36 of the remaining 371 patients. The proportion of ventricular enlargement on the initial CT in patients with a negative angiogram is 20% (nine of 46 patients), which is similar to that in all 473 patients.

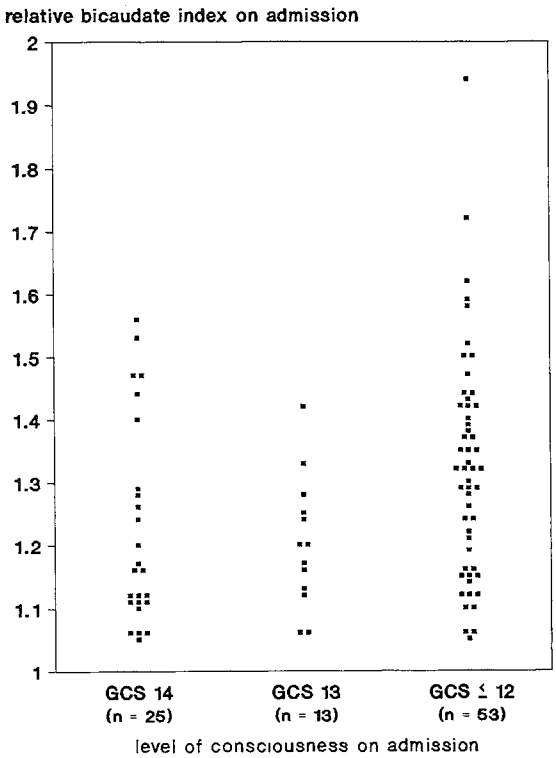
Clinical Course of Patients With Ventricular Enlargement on The Initial CT

25 Patients With GCS of 14 on Admission (Figure 2A)

Eighteen of these 25 patients did not deteriorate from acute hydrocephalus after admission, although seven of these 18 patients deteriorated from other causes. Aneurysm surgery was performed in six patients. The remaining 12 patients remained unoperated because of negative angiogram (6), inoperable proximal basilar aneurysm (1), definite cerebral ischemia (2), rebleeding (1 definite and 1 probable), and age over seventy (1).

Seven of the 25 patients deteriorated after admission from acute hydrocephalus (within 24 hours in two patients, between 1 day and 1 week in the other five patients). In six of these seven patients a ventricular drain was immediately inserted (Figure 2A). In the other patient spontaneous improvement of conscious level occurred. Aneurysm surgery was performed in two patients (24 and 31 days after subarachnoid hemorrhage). The remaining five patients did not undergo aneurysm surgery because of poor clinical condition (2), definite rebleeding (2), and definite cerebral ischemia (1).

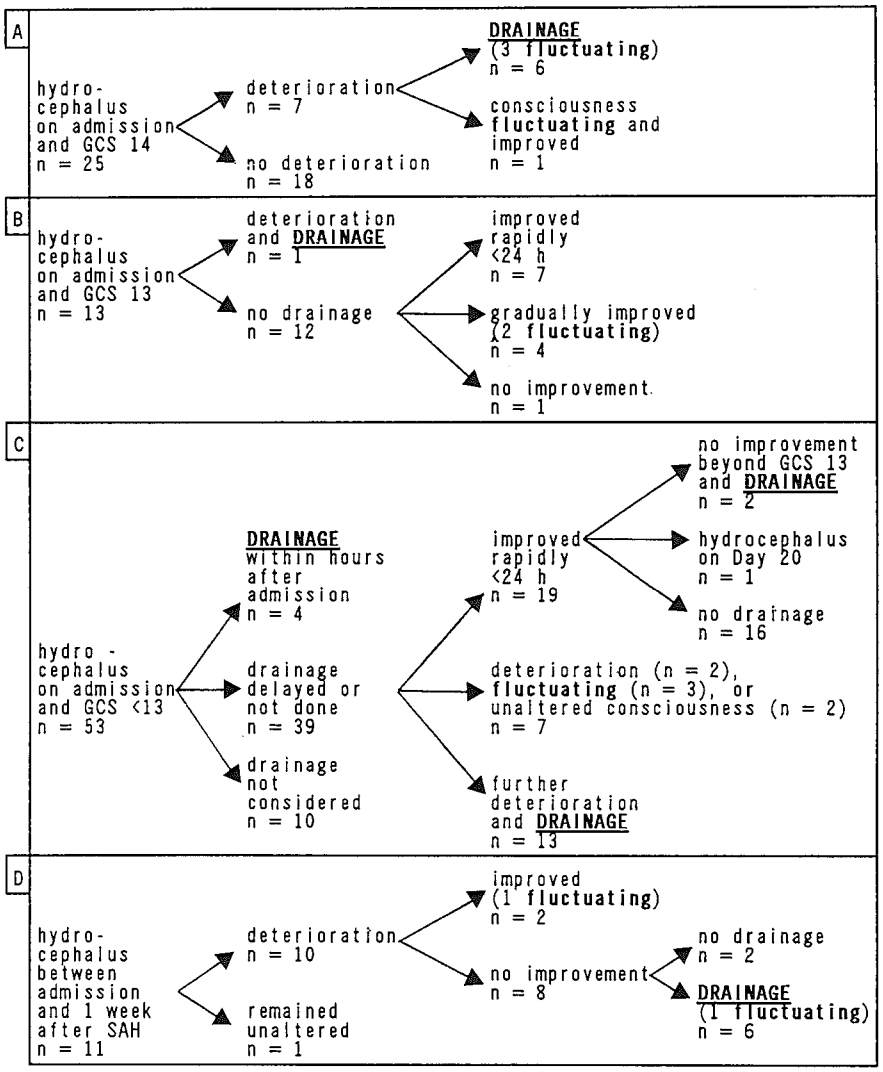
Figure 1. *Scatter plot of relative bicaudate index (patient's bicaudate index divided by upper normal limit [95th percentile] for age) on admission by level of consciousness on admission for 91 patients with acute hydrocephalus after subarachnoid hemorrhage. GCS, Glasgow Coma Score.*



13 Patients With GCS of 13 on Admission (Figure 2 B)

One of these 13 patients deteriorated from acute hydrocephalus within 24 hours after admission, and an emergency ventricular drainage was carried out. Drainage was not performed in the remaining 12 patients: seven improved rapidly (within 24 hours) after admission, four improved gradually, and one patient did not improve; in this patient cerebral ischemia developed 5 days after subarachnoid hemorrhage. Two of the four patient with a gradual improvement had initially improved followed by a deterioration from acute hydrocephalus with fluctuations of level of consciousness and spontaneous recovery. Aneurysm surgery was performed in four of the 13 patients. The remaining nine patients were not operated because of negative angiography (3), rebleeding (1 probable and 1 definite), definite cerebral ischemia (3), or both (1), and in one case because of age over seventy.

Figure 2. *Clinical course of 102 patients with hydrocephalus after subarachnoid hemorrhage (SAH). GCS, Glasgow Coma Score.*



53 Patients With GCS of < 13 on Admission (Figure 2C)

Only four of the 53 patients with GCS of <13 underwent ventricular drainage within hours after admission (Figure 2C). Two of these four patients had downward deviation of the eyes, one had an extremely enlarged ventricular system (relative bicaudate index = 1.62), and one patient, who was admitted 2 days after the initial hemorrhage, had gradually deteriorated before

admission. None of these four patients underwent aneurysm surgery because of definite rebleeding (2), definite cerebral ischemia (1), and age over seventy (1).

In 10 of the 53 patients ventricular drainage was not considered because of massive intraventricular hemorrhage. All were in a poor clinical condition (GCS of <9). Two had a definite rebleed immediately after admission. All died within 48 hours after admission (Figure 2C).

In the remaining 39 of the 53 patients it was not clear, on admission, whether the impaired level of consciousness resulted from the initial hemorrhage or from acute hydrocephalus. Ventricular drainage was initially considered, but omitted or delayed (Figure 2C).

* Nineteen of the 39 patients rapidly recovered (within 24 hours) after admission. Two of these 19 patients did not improve beyond a GCS of 13 and a repeat CT still showed hydrocephalus. Both patients improved after drainage. A third patient, with a rapid initial spontaneous improvement, deteriorated from cerebral ischemia 6 days after the initial subarachnoid hemorrhage, followed by deterioration from hydrocephalus 20 days after subarachnoid hemorrhage; ventricular drainage was not performed.
* Thirteen of the 39 patients in whom drainage was initially considered but delayed, went on to deteriorate with no detectable cause other than hydrocephalus (11 patients within 24 hours, one on Day 2 and one on Day 5). Ventricular drainage was performed and followed by clinical improvement in seven patients.
* In the remaining seven of the 39 patients, ventricular drainage was not performed because the level of consciousness was fluctuating (3) or initially remained unaltered (2), because hydrocephalus was not recognized as the cause of clinical deterioration (1), and because deterioration from acute hydrocephalus was followed by a rebleeding (1).
    ** In the three patients with a fluctuating level of consciousness ventricular drainage was postponed on several occasions, because slight improvements were repeatedly thought to be the beginning of spontaneous and lasting recovery. One had a probable rebleed and died, one recovered spontaneously, and one patient finally went on to a persistent vegetative state, probably as a result of hydrocephalus.
    ** The two patients whose level of consciousness initially remained unaltered deteriorated from probable cerebral ischemia after 4 and 8 days.
    ** The patient in whom the symptoms of acute hydrocephalus were not recognized remained in a poor condition and died from medical complications. Repeated CT showed no abnormality other than hydrocephalus.

Aneurysm surgery was performed in seven of these 39 patients. In the remaining 32 patients surgery was omitted because of deterioration from acute hydrocephalus (8), definite rebleeding (5), cerebral ischemia (definite 6, probable 4), sudden deterioration with unexplained cause (1), and age over seventy (8).

Clinical Course of Patients Who Developed Acute Hydrocephalus After Admission (Figure 2D)

In 11 patients the initial CT did not show ventricular enlargement, but hydrocephalus developed between admission and 1 week after the initial subarachnoid hemorrhage (Figure 2D).

* One of these 11 patients remained disoriented and hydrocephalus was found on a repeat CT scan 3 days after admission. Definite cerebral ischemia developed on Day 8 and definite rebleeding and death on Day 19.

* Four of these 11 patients deteriorated from acute hydrocephalus (two at 3 days, one at 4 days, and one at 5 days after admission), but they did not undergo ventricular drainage. Two of these patients recovered spontaneously (one showed fluctuation of consciousness). Two patients died because of definite rebleeding, in one case rebleeding was preceded by definite cerebral ischemia.
* Six other patients deteriorated from acute hydrocephalus (4 within 24 hours and 2 at 6 days after admission) and ventriculostomy was performed immediately after this deterioration in four patients. In the remaining two patients ventriculostomy was performed with a delay of 7 days in one case (because of fluctuation of the level of consciousness) and 9 days in the other (initially only disorientation, followed by further deterioration after a few days).

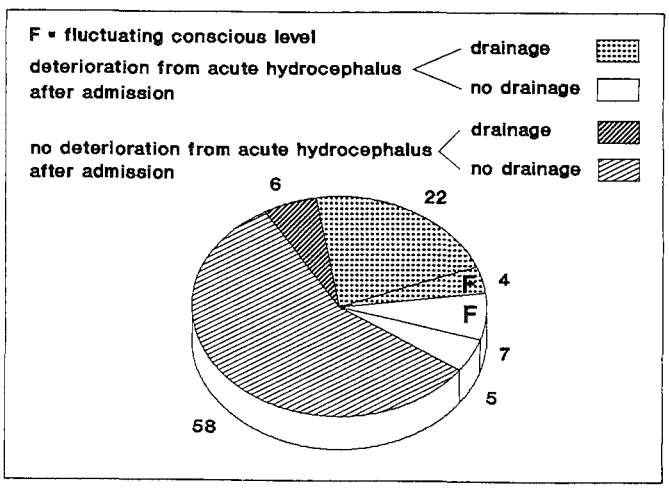
Aneurysm surgery was performed in four of the 11 patients and omitted in seven patients because of negative angiography (1), acute hydrocephalus (1), definite rebleeding (2), definite cerebral ischemia (2), and age over 70 (1).

In summary, clinical deterioration from hydrocephalus occurred in 38 (37%) of the 102 patients, and fluctuations of the level of consciousness occurred in 11 of these 38 patients (Figure 3). In three patients, the deterioration was of sudden onset, defined as <5 minutes, mimicking a rebleed; in the remaining 35 patients the onset was gradual (at least hours). There were also 38 patients with an unimpaired (GCS of 14; 25 patients) or a slightly impaired level of consciousness (GCS 13; 13 patients), of whom 28 (74%) did not show fluctuations or deterioration of the consciousness level from acute hydrocephalus, despite ventricular enlargement on admission (Figure 2, A and B).

Ventricular Drainage

Of the 102 patients with acute hydrocephalus, 32 (31%) underwent ventricular drainage (7% of the total group of 473 patients) (Figure 3). One of these 32 patients had a negative angiogram. Eight patients received a primary internal shunt and 24 patients an external ventricular drain. The decision to treat hydrocephalus by external drainage or by internal shunting was influenced mainly by the interval since the initial bleeding. Thus, in only two of the eight patients who had internal shunting was the shunt implanted within 10 days after the hemorrhage compared with 22 of the 24 patients with external drainage. In nine of the 24 patients the external drainage was later replaced by an internal shunt.

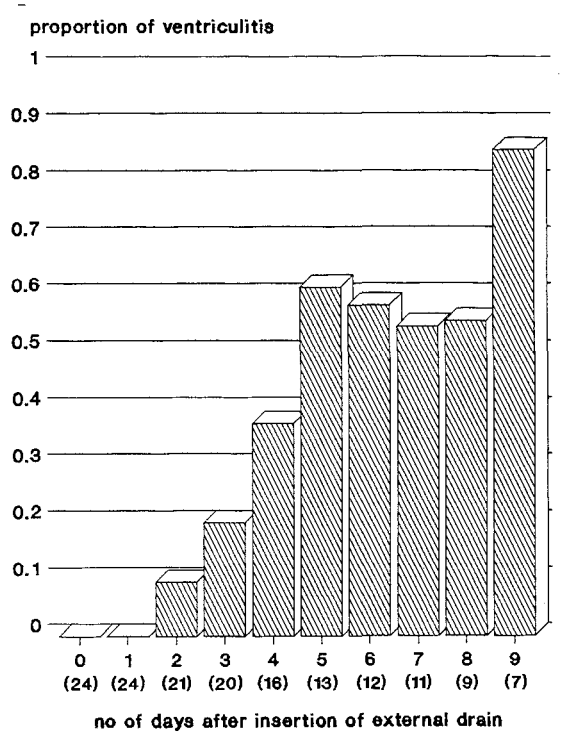
Figure 3. *Pie chart of proportion of patients with ventricular drainage among patients with and without deterioration of the level of consciousness from acute hydrocephalus after admission.*



Twenty-five (78%) of the 32 drained patients showed an initial improvement of consciousness after ventriculostomy. In the remaining seven patients ventricular drainage had no such favorable effect.

* One of these seven patients had been intermittently disoriented from 1 day after subarachnoid hemorrhage; 18 days later this patient remained disoriented for a prolonged period, and an internal shunt was inserted without success.
* In two of these seven patients clinical improvement after ventricular drainage was precluded by the development of definite cerebral ischemia (1 day before drainage in one patient and 5 days after drainage in the other).
* In two other patients: one did not show an immediate improvement of the clinical condition and the other developed ventriculitis 3 days after ventriculostomy. The external drain was removed 3 days after insertion and was followed by clinical deterioration and death in both patients, 8 and 25 days after subarachnoid hemorrhage. These two patients had not developed focal signs, and the repeated CT scan showed no abnormalities other than hydrocephalus.
* Another patient rebled 1 day after the insertion of ventricular drainage and died.
* The seventh patient developed ventriculitis 2 days after drainage, which was successfully treated with antibiotics. However, this patient remained in a poor clinical condition and died 25 days after subarachnoid hemorrhage.

Figure 4. *Bar graph of proportion of externally drained patients with acute hydrocephalus after subarachnoid hemorrhage developing ventriculitis over time. Number of patients with external catheter still in situ in parenthesis.*



Complications After Treatment of Acute Hydrocephalus

Infection

Twelve (50%) of the 24 externally drained patients, but none of the eight internally drained patients developed ventriculitis , confirmed by positive bacterial cultures of the CSF (*Staphylococcus epidermidis* in most patients). Especially if drainage was maintained for more than 3 days (Figure 4). In five (42%) of these 12 patients, the ventricular catheter was removed because of the infection. In one patient ventriculitis was followed by a lethal septic shock. Two other patients suffered nonfatal deterioration from ventriculitis.

Rebleeding

The factors known to affect the risk of rebleeding are long-term tranexamic acid treatment[122] and, clipping of the aneurysm. No other factors[52] (including short term tranexamic acid treatment[135]) have been reliably identified. The frequency of rebleeding within the first 12 days (the period before operation) was compared between groups of patients with aneurysmal subarachnoid hemorrhage with and without long-term tranexamic acid treatment (75 rebleeds, 31 ventricular drains) (Table 1). In patients without long-term tranexamic acid treatment, the rebleeding rate of patients with ventricular drainage was significantly higher than that in patients without acute hydrocephalus (43% vs. 20%, $X^2=5.521$, $p=0.019$) and in patients with acute hydrocephalus without ventricular drainage (43% vs. 15%, $X^2=5.446$, $p=0,020$). In patients who were treated with long term tranexamic acid, the numbers were too small for statistical comparison (Table 1)

Table 1. Rebleeds With or Without Treatment With Long-term Tranexamic Acid in Relation to Acute Hydrocephalus and Ventricular Drainage in 427 Patients After Aneurysmal Subarachnoid Hemorrhage.

	Ventricular drainage					
	No				Yes	
	No hydrocephalus		Hydrocephalus < 1 week		Hydrocephalus < 1 week	
Long-term tranexamic acid treatment	rebleeds n	no. %	rebleeds n	no. %	rebleeds n	no. %
Yes	70	4 6	9	0 0	8	0 0
No	265	53 20*	52	8 15#	23	10 43

Hydrocephalus within 1 week after subarachnoid hemorrhage; drainage within 12 days after subarachnoid hemorrhage.

*# p <0.02, =0.02, respectively, different from hydrocephalus with drainage without long-term tranexamic acid treatment.

Table 2. Outcome 3 Months After Subarachnoid Hemorrhage In Relation to Acute Hydrocephalus In 427 Patients With Aneurysmal Subarachnoid Hemorrhage.

	Acute hydrocephalus		
	Yes		No
	Ventricular drainage		
Outcome	Yes no. %	No no. %	
Dead	17 55	37 60	158 47
Initial SAH	0 0~	8 22~	35 22~
Rebleeding	7 41~	12 32~	61 38~
Cerebral ischemia	3 18~	7 19~	22 14~
Hydrocephalus	5* 29~	2* 5~	4# 3~
Other	2 12~	8 22~	36 23~
Dependent	6 19	4 7	31 9
Independent	8 26	20 33	146 44$
Total	31	61	335

In parentheses % of total, except ~: % of dead patients.

* Includes patients who died of ventriculitis or drain removal following ventriculitis.

Hydrocephalus that developed >1 week after subarachnoid hemorrhage

$ p <0.05 different from acute hydrocephalus

Delayed Cerebral Ischemia

Among the 427 patients with aneurysmal subarachnoid hemorrhage, delayed cerebral ischemia developed in eight (all definite) (26%) of the 31 hydrocephalic patients with ventricular drainage, in 18 (four probable and 14 definite) (30%) of the 61 hydrocephalic patients without ventricular drainage and in 63 (19%) of the 335 patients without acute hydrocephalus (the two groups with acute hydrocephalus vs. that without acute hydrocephalus $X^2=3.359$, $p=0.067$).

Outcome after 3 months

Aneurysmal Subarachnoid Hemorrhage

Outcome after 3 months in 427 patients with aneurysmal subarachnoid hemorrhage is shown in

Table 2. The proportion of patients who were independent 3 months after subarachnoid hemorrhage was significantly lower in patients with acute hydrocephalus with or without ventricular drainage than in those without acute hydrocephalus ($X^2=4.637$, $p=0.031$; Table 2). The higher proportion of patients without drainage dying from the initial hemorrhage was offset by the higher proportion of patients dying of complications after ventricular drainage (Table 2).

Patients With Negative Angiography

Only one of the 10 patients with acute hydrocephalus and negative angiography showed clinical deterioration from acute hydrocephalus and underwent ventricular drainage. Neither rebleeding nor delayed cerebral ischemia was observed and outcome of these patients after 3 months was invariably good.

DISCUSSION

In our unselected consecutive series of 473 patients admitted to the Department of Neurology within 72 hours after subarachnoid hemorrhage, CT showed hydrocephalus on admission in 19%. The same frequency of acute hydrocephalus was found in a subgroup of 46 patients with clinical signs and symptoms of subarachnoid hemorrhage and blood in the basal cisterns, but with a negative angiogram. In these 46 patients acute hydrocephalus was the only cerebral complication.

The risk of deterioration from hydrocephalus between 3 days and 1 week after subarachnoid hemorrhage in patients without ventricular enlargement on admission is low (3%).

Acute hydrocephalus was not symptomatic in all 91 patients with enlarged ventricles on admission. The level of consciousness was unimpaired in 27%, slightly impaired in 14%, and moderately to severely impaired in 58%. There was no relation between the level of consciousness and the degree of enlargement of the ventricles. The majority of the patients with an unimpaired or a slightly impaired level of consciousness did not subsequently deteriorate from acute hydrocephalus.

Of the 53 patients with a GCS of <13, in 19% ventricular drainage was not considered because blood clot completely filled all ventricles; in 8% ventricular drainage was immediately performed. In the remaining 73%, the decision to treat acute hydrocephalus was delayed; half of these patients recovered spontaneously. The degree of ventricular enlargement did not predict spontaneous recovery.

A remarkable feature in the 38 patients with deterioration from acute hydrocephalus was that 29% had fluctuations in their level of consciousness. This made the decision to treat acute hydrocephalus difficult, because our policy was to start treatment only if patients deteriorated from acute hydrocephalus or failed to improve; because any improvement was repeatedly considered as the beginning of spontaneous and lasting recovery, ventricular drainage was often delayed, which led in some cases to persistent impairment of consciousness.

In 31% of the 102 patients with acute hydrocephalus on CT (7% of all 473 patients with subarachnoid hemorrhage) ventricular drainage was performed. Ventricular drainage resulted in clinical improvement in 78%, but the outcome after 3 months remained poor.

The most frequent adverse events after ventricular drainage were rebleeding and infection. The risk of rebleeding was significantly increased after ventricular drainage, and in 42% of the

12 externally drained patients developing ventriculitis the drain had to be removed because of infection. After 3 months the outcome of patients with acute hydrocephalus, with or without ventricular drain, was worse than that of patients without acute hydrocephalus.

The frequency of acute hydrocephalus in our series is in accordance with the findings of one other study[85] and is different from those of many others.[10,30,34,66,69,72,93,100,111,121,138] These differences can be explained by the less reliable criteria (if any) used for the diagnosis, by patient selection, and by timing of the investigations.

Remarkably, only little has been written on the indications for ventricular drainage in acute hydrocephalus after subarachnoid hemorrhage. In our series the decision to treat acute hydrocephalus was delayed in the majority of the patients. We found that most patients with an unimpaired level of consciousness on admission do not need ventricular drainage and that even patients with an impaired level of consciousness on admission may spontaneously improve. The delay of ventricular drainage need not be unduly long since the majority of patients who recover spontaneously do so within 24 hours after admission (Figure 2, B and C). Not only those who fail to recover within 24 hours, but also those who then again deteriorate without evidence of complications other than hydrocephalus, are serious candidates for ventricular drainage.

Could the higher rebleeding rate after ventricular drainage be explained by factors other than drainage? Probably not. Factors such as the level of consciousness and the amount of cisternal and intraventricular blood on admission are associated with delayed cerebral ischemia and outcome;[3,49] short-term tranexamic acid treatment is associated with cerebral ischemia,[135] but none of these factors are associated with rebleeding. No factor other than medical (long-term tranexamic acid) or surgical intervention have been reliably associated with rebleeding.[52] After corrections for these factors, the rebleeding rate was significantly higher in patients with than in patients without ventricular drainage, with or without acute hydrocephalus.

In a previous report on the first part (37%) of this series[120] the frequency of delayed cerebral ischemia and mortality from cerebral ischemia was very high in patients with ventricular drainage. In this extended series, the frequency of and mortality due to delayed cerebral ischemia in patients with acute hydrocephalus was still higher, but no longer significantly so, than in patients without acute hydrocephalus, probably (as described and investigated in **Chapter 5**) because fluid restriction was no longer applied in patients with hyponatremia,[40,130] a frequent complication of hydrocephalus in subarachnoid hemorrhage.[41,120,134] There was no difference in this respect between patients with or without ventricular drainage for acute hydrocephalus. Therefore, it is unlikely that a short delay in the treatment of acute hydrocephalus will result in an increased frequency of cerebral ischemia.

What can be done to improve the outcome of patients with acute hydrocephalus? Although the risk of rebleeding can be diminished by long-term antifibrinolytic treatment, the benefit is negated by an increased frequency of delayed cerebral ischemia.[122] To improve outcome, it might be necessary to combine antifibrinolytic agents with plasma volume expansion[25] or calcium antagonists,[90,95,97] but even if this treatment combination is effective, it remains to be seen whether such a combined regimen would be effective after ventricular drainage. An alternative could be to have treatment of hydrocephalus by ventricular drainage soon followed by, or simultaneously performed with, clipping of the aneurysm.[85] Such a policy will improve outcome only if early surgery is not accompanied by increased mortality and morbidity.[2,27,91]

It has also been suggested that rebleeding after ventricular drainage can be prevented if the CSF pressure does not fall below 15-25 mm Hg.[96,124] We could not confirm this, since the CSF pressures after drainage in our series were within this "safe" range.

Infection was a frequent complication in the externally drained patients, especially if drainage was maintained for more than 3 days. Ventriculitis as a possible serious complication following drainage in hydrocephalus after subarachnoid hemorrhage was discussed by Diaz in a comment on the paper by Milhorat.[85] Diaz suggested that ventriculitis can be prevented by using a long subcutaneous tunnel. Others preferred antibiotic prophylaxis,[72,82,109,137] and a short duration of external drainage.[82,137]

Another possibility might be to treat hydrocephalic patients with serial lumbar puncture,[69,100,110] provided the CSF blockage is in the subarachnoid space and not in the ventricular system and provided there is no hematoma with mass effect. The risk of infection with this procedure is small, and the fall in CSF pressure is probably more gradual. The results of treatment acute hydrocephalus after subarachnoid hemorrhage with this simple procedure is presented in **Chapter 3**.

APPENDIX

An editorial on acute hydrocephalus after subarachnoid hemorrhage by RC Heros was published in the same issue by *Stroke* (June 1989).[48]

Chapter 3

TREATMENT OF ACUTE HYDROCEPHALUS AFTER SUBARACHNOID HEMORRHAGE WITH SERIAL LUMBAR PUNCTURE

INTRODUCTION

Acute hydrocephalus is a frequent complication following subarachnoid hemorrhage.[38,120] In a series of 473 patients with subarachnoid hemorrhage admitted within 72 hours of the initial bleed, hydrocephalus (defined as a bicaudate index on computed tomogram (CT) exceeding the 95th percentile for age) occurred in 20% (**Chapter 2**).[2] Management of these patients presents problems. Not all patients with acute hydrocephalus and with a decreased level of consciousness on admission required treatment. Approximately 40% improved spontaneously within 24 hours.[38] Yet in some, delay in reducing the high intracranial pressure could produce deleterious effects resulting in irreversible brain damage or death from fatal cerebral ischemia.[120] But external ventricular drainage carries a risk of ventriculitis and rebleeding.[38] Despite this, in a recent editorial, Heros recommended "immediate ventricular drainage" in patients with a significant hydrocephalus and a decreased level of consciousness.[48] Serial lumbar puncture provided an alternative and simpler approach.[29,100] In this study we investigate whether serial lumbar puncture is effective in restoring the level of consciousness in patients with acute hydrocephalus and assess the complications of this treatment.

PATIENTS AND METHODS

We entered 104 consecutive patients with subarachnoid hemorrhage admitted within 72 hours into this study; 26 patients were admitted to the Department of Neurosurgery of the Royal Free Hospital, London, and 78 to the Department of Neurology of the University Hospital Dijkzigt,

Rotterdam. All had clinical signs of subarachnoid hemorrhage and abnormalities suggesting a ruptured aneurysm on CT.[118] Patients with a perimesencephalic hemorrhage[119] or a negative angiogram, and patients who were moribund on admission were excluded.

Events were prospectively recorded during a 28 day period after the initial subarachnoid hemorrhage, or until death or surgical treatment of the aneurysm. CT scanning was carried out on admission (initial CT) and was repeated after any clinical deterioration. The amount of cisternal blood on the initial CT was graded on a scale of 0 to 3 separately for each of the 10 cisterns (maximum score of 30).[40,53] Similarly, intraventricular blood was graded separately for each of the 4 ventricles (maximum score 12 points).[40,53] We assessed the level of consciousness with the 14-point Glasgow Coma Scale.[78,114] A decreased level of consciousness was defined as a decrease of at least one point in the motor or in the verbal score on the Glasgow Coma Scale. We defined events as follows; *probable delayed cerebral ischemia:* gradual development of focal neurological signs, with or without deterioration in the level of consciousness, without confirmation by CT or autopsy; *definite delayed cerebral ischemia:* deterioration of consciousness or development of focal signs, or both, with CT or autopsy confirmation of cerebral infarction; *probable rebleeding:* sudden deterioration and death, without the possibility of proof by a CT or if autopsy was refused; *definite rebleeding:* sudden deterioration with an increased amount of blood on a repeat CT or at autopsy when compared with a previous CT; *acute hydrocephalus:* an increase in the bicaudate index beyond the upper limit (95th percentile) for age, measured on the initial CT or on a CT repeated within 1 week after the initial subarachnoid hemorrhage.[38,43,120] The upper limits were: <36 years of age, 0.16; 36-45 years, 0.17; 46-55 years, 0.18; 56-65 years, 0.19; 66-75 years, 0.20; 76-85 years, 0.21.[21,38,83,120] The relative bicaudate index was obtained by dividing the patient's bicaudate index by the upper limit for age;[38,43,120] *deterioration from hydrocephalus:* deterioration in the level of consciousness with no detectable cause other than hydrocephalus, confirmed by a repeat CT (relative bicaudate index >1).

Treatment with serial lumbar puncture was performed when acute hydrocephalus appeared to cause impairment of conscious level in the absence of a hematoma with mass effect and provided that blood did not completely fill the third or fourth ventricle, obstructing the ventricle system.[20] Each time a maximum of approximately 20 ml of cerebro-spinal fluid (CSF) was removed. Of the 104 patients, 101 received tranexamic acid. Fluid intake was maintained at 3 liters a day in all patients; fluid restriction and diuretic medication after admission were avoided. Patients on antihypertensive therapy on admission, continued to receive treatment, otherwise none was given. Cerebral angiography and aneurysm operation were performed at times dependant on the patients clinical condition. Aneurysm operation was usually planned between Day 7 and Day 10 in London and on Day 12 in Rotterdam. All survivors were followed-up at three months and graded according to the five-point Glasgow Outcome Scale.[60]

The fourfold tables were analyzed with the two-sided Fisher's exact probability test.

RESULTS

Measurement of the CT scans on admission indicated acute hydrocephalus in 24 (23%) of the 104 patients. Of these 24 patients, six (25%) had no impairment of consciousness on admission (a total score on the Glasgow Coma Scale [GCS] of 14), five (21%) had a GCS of 13 and in the remaining 13 (54%) the GCS was <13. In another nine patients (11% of the 80

patients without hydrocephalus on admission) a repeat CT within 1 week of the initial hemorrhage demonstrated delayed ventricular enlargement.

Patients with acute hydrocephalus had a higher incidence of impaired consciousness on admission, a higher score of cisternal blood and a higher frequency of ventricular blood than those with normal ventricular size (Table 1). Clinical deterioration occurred after admission in seven (29%) of the 24 patients with acute hydrocephalus on the initial CT and in six of the nine patients who had delayed ventricular enlargement (i.e. 8% of the 80 patients without acute hydrocephalus on the initial CT).

Table 1. Entry Characteristics 104 Patients With Aneurysmal Subarachnoid Hemorrhage by Presence of Acute Hydrocephalus and by Treatment With Serial Lumbar Puncture

	Serial Lumbar Puncture					
	No				Yes	
	No Hydrocephalus n=71		Hydrocephalus n=16		Hydrocephalus n=17	
	no.	%	no.	%	no.	%
GCS on admission						
12	20	28	8	50	9	53
13	16	23	2	13	5	29
14	35	49	6	38	3	18
Score of cisternal blood on initial CT						
0- 6	11	15	2	13	1	6
7-12	10	14	2	13	1	6
13-18	26	37	7	44	6	35
19-24	14	20	2	13	5	29
25-30	6	8	3	19	4	24
not scored	4	6	0	0	0	0
Ventricular blood	7	10	7	44	7	47

GCS, sum score on the 14-point Glasgow Coma Scale

Serial lumbar puncture was performed in 17 patients:

* five of these 17 patients had a decreased conscious level on admission and serial lumbar puncture was performed immediately. In the remaining 13 of the 18 hydrocephalic patients with a decreased conscious level on admission (GCS <14) lumbar puncture was not performed: six patients improved spontaneously after admission; in four patients there was doubt whether the decreased level of consciousness was caused by hydrocephalus; three patients died <24 hours after admission: one had a massive ventricular clot and two had an early rebleeding (one of these two patients had a hematoma with mass effect).
* in 12 of the 17 patients serial lumbar puncture was started within 1 week after admission.

The duration that lumbar punctures were performed and number of lumbar punctures required in each patient is summarized in Figure 1.

Conscious level improved after serial lumbar puncture in 12 (71%) the 17 patients (i.e. in 10 (77%) of the 13 patients with deterioration from acute hydrocephalus): six patients fully recovered (GCS of 14) after serial lumbar puncture; six other patients did not improve beyond a GCS of 13 (disoriented), in two of these patients, an internal shunt was inserted, followed by sustained improvement in the level of consciousness (GCS of 14), and in the remaining four patients death occurred from other complications several days after serial lumbar puncture was started. In five (29%) of the 17 patients, serial lumbar puncture had no effect: two of these patients received an internal shunt followed by sustained improvement (GCS of 14); in the three other patients, death from other complications occurred several days after commencing serial lumbar puncture.

In summary, four (12%) of the 33 patients with acute hydrocephalus received an internal shunt (4% of all patients). None of the patients who underwent serial lumbar puncture or who

received an internal shunt developed clinical signs of meningitis or ventriculitis. Although 5 patients failed to improve after lumbar puncture, none deteriorated from transtentorial herniation within the subsequent days following serial lumbar puncture.

Analysis of (probable and definite) rebleeding was restricted to the first 12 days. The incidence of rebleeding in hydrocephalic patients treated with serial lumbar puncture was not higher than that in patients without acute hydrocephalus (two [12%] of 17 v.s. nine [13%] of 71 patients) (Table 2), rebleeding occurred more frequently in hydrocephalic patients who were not treated with serial lumbar puncture when compared with those without acute hydrocephalus (Table 2), but this difference was not statistically significant ($p = 0.999$, Fisher's exact probability test).

The incidence of (definite and probable) cerebral ischemia in patients with acute hydrocephalus was no higher than in those without hydrocephalus (9 [27%] of 33 v.s. 22 [31%] of 71 patients); and the frequency of cerebral ischemia in hydrocephalic patients treated with serial lumbar puncture was similar to that of patients without acute hydrocephalus (6 [35%] of 17 v.s. 22 [31%] of 71 patients, Table 2). Cerebral ischemia in patients with acute hydrocephalus treated with serial lumbar puncture was more often fatal (four [67%] of six patients) than in patients without hydrocephalus (seven [32%] of 22 patients), but the number of patients is small and the difference was not statistically significant ($p = 0.141$, Fisher's exact probability test).

Only 24% of the hydrocephalic patients compared with 62% of those without acute hydrocephalus had their aneurysm clipped by Day 28. The

Figure 1. *Scatter plot of the length of period in which lumbar punctures were required (left) and the number of lumbar punctures (right) performed in each patient*

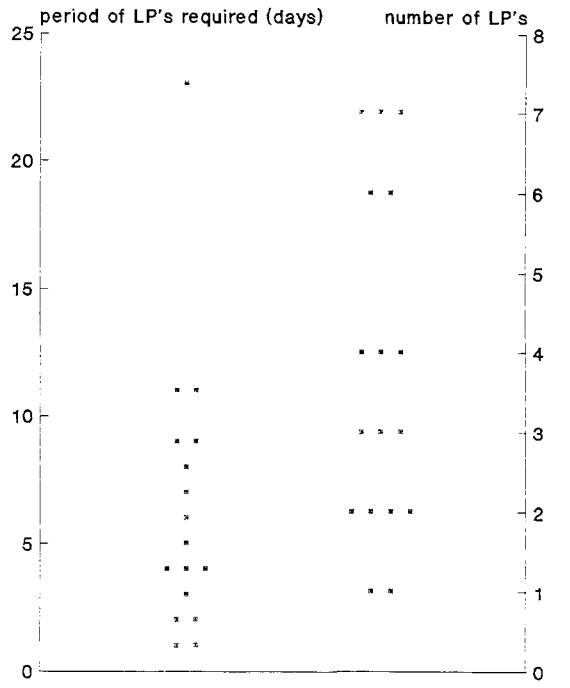


Table 2. Rebleeds and Cerebral Ischemia in Relation to Acute Hydrocephalus and Serial Lumbar Puncture in 104 Patients With Aneurysmal Subarachnoid Hemorrhage

	Serial Lumbar Puncture					
	No				Yes	
	No Hydrocephalus n=71		Hydrocephalus n=16		Hydrocephalus n=17	
	no.	%	no.	%	no.	%
rebleed* Day 12	9	13	4	25	2	12
Cerebral ischemia*	22	31	3	19	6	35

* definite and probable

proportion of patients with independent outcome at 3 months in patient without acute hydrocephalus was significantly higher than that in hydrocephalic patients treated with serial lumbar puncture (Fisher's exact probability test $p=0.033$) (Table 3).

Table 3. Outcome in 104 Patients With Aneurysmal Subarachnoid Hemorrhage Related to Acute Hydrocephalus and Treatment With Serial Lumbar Puncture

	Serial Lumbar Puncture					
	No				Yes	
	No hydrocephalus n=71		Hydrocephalus n=16		Hydrocephalus n=17	
Outcome	no.	%	no.	%	no.	%
Dead	21	30	8	50	10	59
Dependent	7	10	0	0	2	12
Independent	42	59*	8	50§	5	29
Missing	1	1	0	0	0	0

*§$p=0.033$, 0.296, respectively, by Fisher's exact probability test

DISCUSSION

In this consecutive series of patients with aneurysmal subarachnoid hemorrhage, serial lumbar puncture performed in 17 patients with acute hydrocephalus resulted in an improvement of conscious level in 12 (71%). Half of the patients fully recovered. The other half improved but not beyond a GCS of 13 (i.e. remained disoriented). Of all 104 patients, only 4% required internal shunting. In patients with a hematoma occluding the fourth, third, or lateral ventricles, an obstructive element exists and lumbar puncture is contraindicated. We observed blood within these structures in some patients, but in no instance did this appear to cause obstruction.

The frequency of acute hydrocephalus in this series matches other recent studies[85,120] and the frequency of acute hydrocephalus described in **Chapter 2**.[38] The extent to which patients with acute hydrocephalus on admission appeared to affect conscious level closely approximated that of a previous series of patients with acute hydrocephalus (**Chapter 2**).[38] The proportion of patients who improved after lumbar puncture is similar to the proportion improving patients in the previous series after ventricular drainage (**Chapter 2**).[38] A direct comparison of treatment of acute hydrocephalus with external ventricular drainage with treatment with lumbar puncture is not feasible. It is likely that serial lumbar puncture is carried out more readily and with less delay than external ventricular drainage in hydrocephalic patients with impaired conscious level; some of these patients might have improved spontaneously if treatment had been delayed. However, the beneficial effect of lumbar puncture cannot be attributed to spontaneous improvement in all patients, since progressive deterioration in the level of consciousness from acute hydrocephalus halted and improved in 77% of the patients shortly after lumbar puncture.

In the series of patients treated with ventricular drainage the risk of rebleeding was significantly increased during the first 12 days (**Chapter 2**);[34] Several factors may play a role: a rapid fall in the CSF pressure and a rapid decrease of the ventricular size may lead to displacement of the aneurysm clot; insertion of the ventricular catheter may induce intracranial fibrinolytic activity resulting in lysis of the aneurysm clot; Heros[48] suggested that this increased risk could be attributed to a difference in neurological grade between the treated and the untreated groups.[1,101] But, in a large series of patients in which the occurrence of rebleeding was prospectively studied with clearly defined criteria for rebleeding, no association between rebleeding and the initial condition could be demonstrated.[50] In the present study, we observed no such difference in rebleeding rate between those undergoing lumbar puncture and those not. A possible explanation for this could be that the drop in the CSF pressure after treatment with

lumbar puncture is more gradual than after the insertion of a ventricular catheter and/or that lumbar puncture does not induce intracranial fibrinolytic activity. However, this cannot be concluded with certainty since there is an important difference between this study and the previous study (**Chapter 2**).[38] In the latter study, analysis of the patients treated with ventricular drainage was restricted to those not receiving antifibrinolytic treatment, whereas in the present study nearly all patients had tranexamic acid.

A high CSF pressure in patients with acute hydrocephalus after subarachnoid hemorrhage may reduce cerebral perfusion and theoretically contribute to ischemic complications. Continuous ventricular drainage should ensure a constant reduction in CSF pressure. Despite the fact that serial lumbar puncture may leave a small defect in the dura allowing CSF to escape continuously, it may risk intermittent increases in CSF pressure. In this series, the incidence of cerebral ischemia was not different between patients with and patients without acute hydrocephalus despite a higher rate of risk factors for cerebral ischemia in the former group.[3,50] On the other hand, when cerebral ischemia did develop, it was more fatal among patients with acute hydrocephalus.[120]

In conclusion, ventricular drainage produces a significant risk of ventriculitis and may increase the risk of rebleeding (**Chapter 2**).[38] In contrast, none of the patients in this study developed ventriculitis or meningitis and the incidence of rebleeding was not increased after serial lumbar puncture. None of the patients deteriorated from coning resulting from lumbar puncture. Serial lumbar puncture is therefore a simple, safe and effective way of treating acute hydrocephalus. This "conservative" treatment readily identifies those patients in whom the hydrocephalus will spontaneously recover and those who will require an internal shunt.

Chapter 4

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY IN PATIENTS WITH ACUTE HYDROCEPHALUS OR WITH CEREBRAL ISCHEMIA AFTER SUBARACHNOID HEMORRHAGE

INTRODUCTION

Many patients with cerebral ischemia after subarachnoid hemorrhage have an impaired level of consciousness.[49] As mentioned on page 5, computed tomography (CT) scanning and autopsy studies in these patients demonstrated that brain damage was rarely restricted to single vascular territories, but was usually a multivascular and diffuse process[49]. These findings were confirmed by cerebral blood flow (CBF) study by means of positron emission tomography (PET) in patients with cerebral ischemia after subarachnoid hemorrhage.[99] These multiple and bilateral lesions explain the impairment of consciousness in these patients. As described in **Chapter 2** and 3, acute hydrocephalus may also be accompanied by impaired consciousness,[38,43,120] perhaps mediated by a more global kind of ischaemia, since a reduction of cerebral blood flow by enlarged ventricles has been demonstrated and in studies with ^{133}Xenon (^{133}Xe).[33,44,80,84,113,127]

Recently, a new method to investigate changes in the regional cerebral blood flow was introduced, by means of intravenously administered technetium-99M labeled *d,l*-hexamethyl-propylene amine oxime (^{99m}Tc HM-PAO) and by the measurement of its regional cerebral uptake by single photon emission computed tomography (SPECT).[88]

The aim of this study was to compare the pattern of cerebral blood flow, as depicted by SPECT scanning and ^{99m}Tc HM-PAO, in patients with acute hydrocephalus with that of those with cerebral ischemia after subarachnoid hemorrhage.

PATIENTS AND METHODS

We studied eight patients with subarachnoid hemorrhage, four of them with delayed cerebral ischemia, and four with acute hydrocephalus. All patients had suffered a deterioration of consciousness after admission, defined as a sum score of 12 or less on the 14-point Glasgow Coma Scale.[78,114] Aneurysmal subarachnoid hemorrhage was confirmed by CT scanning on admission (initial CT).[117] SPECT studies were performed when cerebral ischemia or hydrocephalus was suspected to be the cause of the deterioration. *Cerebral ischemia* was defined as a deterioration of consciousness with or without focal neurological signs, and without hydrocephalus or an enlarging hematoma on CT. Ongoing deterioration immediately after admission was not regarded as cerebral ischemia. *Acute hydrocephalus* was diagnosed if the bicaudate index, which was measured on the initial CT or on a repeat CT within 1 week after the initial SAH, exceeded the normal upper limit (95th percentile) for age,[21,38,83,120] and if deterioration of consciousness occurred with no detectable cause other than hydrocephalus. Technetium labelled HM-PAO is prepared by adding 1110 megabecquerel freshly eluted sodium pertechnetate to a vial containing freeze dried 0.5 mg *d,l*-hexamethyl-propylene amine oxime (HM-PAO), 7.6 microgram stannous chloride dihydrate, and 4.5 mg sodium chloride (Ceretec). From this mixture, 740 megabecquerel was intravenously administered within 30 minutes after preparation. SPECT scanning was performed 10 to 20 minutes later to avoid possible interference from cerebral uptake of free sodium pertechnetate. Data acquisition was done by means of a single-head rotating gamma-camera (Siemens) with a low energy all purpose collimator and a PDP 11/73 computer. Software: SPETS-11 running under TSX+, Nuclear Diagnostics. Total acquisition angle: 360°; 60 projections of 30 seconds each; 64 x 64 matrix; pixel size: 6 mm; spatial resolution <10 mm. Acquired images were filtered by means of a Wiener filter (EMTFLT version 4.1, by Sten Carlsson, Department of Medical Physics, S451-80 Udevalla, Sweden). Transversal (parallel to orbito-meatal line), and coronal slices were reconstructed with a ramp filter, after correction for attenuation, by calculation of the geometric means. Slice thickness: 12 mm. The upper threshold was kept at 100% and the lower at 5%. The reconstructed images were studied in the multi-slice, absolute scaling mode.

RESULTS

Patients

Cerebral ischemia was diagnosed in four patients (Cases 1-4). Deterioration from ischemia occurred between Day 3 and Day 9 after subarachnoid hemorrhage. All had focal neurological signs: one patient had a right hemiparesis and aphasia (Case 1); Case 2 had paresis of the left arm; Case 3 had a left hemiparesis; and the fourth patient (Case 4) had a paralysis of the left leg and a right hemiparesis. None of the four patients had an impaired level of consciousness before deterioration from cerebral ischemia. A repeat CT failed to show cerebral infarction in two (Cases 1 and 3) of these four patients. A repeat CT in Case 2 showed a hypodense area in the territory of the right middle cerebral artery and in Case 4 repeat CT showed a hypodense area in the territory of the left anterior cerebral artery. Both hypodensities correlates with one of the areas with decreased cerebral uptake of ^{99m}Tc HM-PAO (Figure 1) and with the focal neurological deficits of these two patients.

Another four patients deteriorated from hydrocephalus (Cases 5-8). The relative bicaudate indexes in these patients were: 1.30, 1.30, 1.05, and 1.41. Deterioration from acute hydrocephalus occurred between Day 1 and Day 4 after subarachnoid hemorrhage. After serial lumbar puncture, three of the four patients showed improvement of the level of consciousness. The remaining patient (Case 8) developed cerebral ischemia a few days after the onset of deterioration from acute hydrocephalus.

Spect Studies

In patients with cerebral ischemia, multiple circumscribed areas with decreased uptake of ^{99m}Tc HM-PAO were seen on the SPECT scan. The posterior watershed areas were involved in all patients and the anterior watershed areas in three (Cases 1, 2, and 4). Three patients (Cases 2, 3, and 4) had bilateral areas with decreased uptake of ^{99m}Tc HM-PAO (Figure 1).

In the four patients with acute hydrocephalus, decreased uptake of ^{99m}Tc HM-PAO was seen predominantly around the third ventricle, bilaterally in the basal parts of the temporal lobes, around the temporal horns of the lateral ventricles, and in the basal parts of the frontal lobes. This pattern of areas with decreased uptake is especially visible on the coronal slices (Figure 1). These areas with decreased uptake of ^{99m}Tc HM-PAO were by far larger than the size of the third ventricle on CT. In these patients there were only slight flow voids at the convexity of the brain. Serial lumbar puncture, which initially revealed high cerebro-spinal fluid pressures (40-50 cm H_2O), was performed in all four patients. Repeated SPECT scanning after serial lumbar puncture showed an improvement of the uptake of ^{99m}Tc HM-PAO in the basal parts of the brain in Case 6 and 7, and a slight improvement in case 5. These changes were especially visible on the coronal slices. Repeated SPECT scanning of the remaining patient (Case 8), who developed symptoms of cerebral ischemia, showed decreased uptake of ^{99m}Tc HM-PAO in both posterior watershed areas, predominantly on the left side, in the territory of the right middle cerebral artery, and in the right anterior watershed area.

DISCUSSION

Several studies have shown that cerebral uptake of ^{99m}Tc HM-PAO reflects cerebral blood flow.[75,88] Decreased cerebral uptake of ^{99m}Tc HM-PAO in cerebro-vascular disease has been shown to correspond well with the results of other methods such as PET scanning,[89,139] and ^{133}Xe cerebral blood flow measurements.[5]

In our patients with impaired consciousness from cerebral ischemia, SPECT scanning showed multiple regions with decreased uptake of ^{99m}Tc HM-PAO, mainly in the watershed areas, reflecting impairment of cerebral blood flow between the territories of the cerebral arteries. These areas with decreased uptake of ^{99m}Tc HM-PAO are in agreement with the distribution of cerebral infarction described in postmortem studies in patients with subarachnoid hemorrhage who had clinical symptoms of cerebral ischemia before death[49], with one other SPECT study using ^{99m}Tc HM-PAO[17], and with CBF studies with PET[99] in patients with cerebral ischemia after subarachnoid hemorrhage.

Multiple and bilateral distribution of areas with decreased cerebral blood flow and subsequent brain ischemia explains deterioration in the level of consciousness in cerebral ischemia after subarachnoid hemorrhage but what is the cause of impaired consciousness in

acute hydrocephalus? Decreased cerebral blood flow has been demonstrated in patients with high[44] and normal-pressure hydrocephalus,[33,80,84,113,127] and may also be present in acute hydrocephalus, which would explain impairment of the level of consciousness. SPECT scanning indeed showed regions with decreased uptake of ^{99m}Tc HM-PAO in our hydrocephalic patients, but the pattern was different from that in patients with cerebral ischemia. In patients with acute hydrocephalus, a decreased uptake was seen predominantly in the basal parts of the brain. The areas with decreased uptake of ^{99m}Tc HM-PAO in the basal parts of the brain improved convincingly in two patients (Case 6 and 7) and slightly in another patient (Case 5), when compared to the higher parts of the brain, after treatment with serial lumbar puncture. This was accompanied by clinical improvement in these three patients. The patient who did not improve had developed cerebral ischemia.

Decreased radio-activity in the basal areas in patients with acute hydrocephalus cannot be explained by compression of brain tissue by the enlarged ventricles without reduction of the regional blood flow, because in that case each unit of volume of the compressed brain tissue would have shown a higher radio-activity on the SPECT scan. Moreover, brain tissue does not compress but shifts outward and upward displacing CSF. The decreased uptake cannot be explained by a partial volume phenomenon from the third ventricle because the area of decreased uptake is by far larger than that of the third ventricle on CT. The decreased uptake most likely reflects decreased cerebral blood flow, but the question is whether there is a primarily decreased cerebral blood flow or a decreased blood flow secondary to hypometabolism. A primary disturbance of cerebral blood flow is the most likely explanation since it was shown in patients with recent-onset obstructive hydrocephalus associated with cerebral neoplasia that the levels of cortical blood flow were inappropriately low compared with

Figure 1

Without Complications

SPECT scan of cerebral uptake of ^{99m}Tc HM-PAO in a patient with subarachnoid hemorrhage, who has no complication

Cerebral Ischemia

Areas with decreased cerebral uptake of ^{99m}Tc HM-PAO in patients with cerebral ischemia after subarachnoid hemorrhage (*coronal and transversal slices*):

- Case 1: left middle cerebral artery and left anterior and left posterior watershed areas
- Case 2: in the territory of the right middle cerebral artery, right anterior and both posterior watershed areas
- Case 3: right middle cerebral artery and both posterior watershed areas
- Case 4: left and right middle cerebral artery and anterior cerebral artery, right anterior watershed area

Acute Hydrocephalus, Before Serial Lumbar Puncture

Areas with decreased cerebral uptake of ^{99m}Tc HM-PAO in patients with acute hydrocephalus after subarachnoid hemorrhage, before serial lumbar puncture

Case 5, 6, 7 and 8:

transversal slices: around the ventricles, especially around the posterior horn of the lateral ventricles. Case 5: diffusely distributed areas with decreased uptake of ^{99m}Tc HM-PAO

coronal slices: around the third ventricle and the temporal horn of the lateral ventricles in the basal parts of the brain. Case 7: a small area on the left side of the lateral ventricle

Acute Hydrocephalus, After Serial Lumbar Puncture

Areas with decreased cerebral uptake of ^{99m}Tc HM-PAO in patients with acute hydrocephalus after subarachnoid hemorrhage, after serial lumbar puncture

Case 5, 6, and 7 (*coronal slices*):

changed pattern of ^{99m}Tc HM-PAO uptake in the basal parts of the brain (slightly in Case 5, convincingly in Case 6 and 7)

Case 8 (*transversal and coronal slices*):

new multifocal areas with decreased cerebral uptake of ^{99m}Tc HM-PAO, in the territory of the right middle cerebral artery, in the right and left posterior-, and in the right anterior-watershed areas

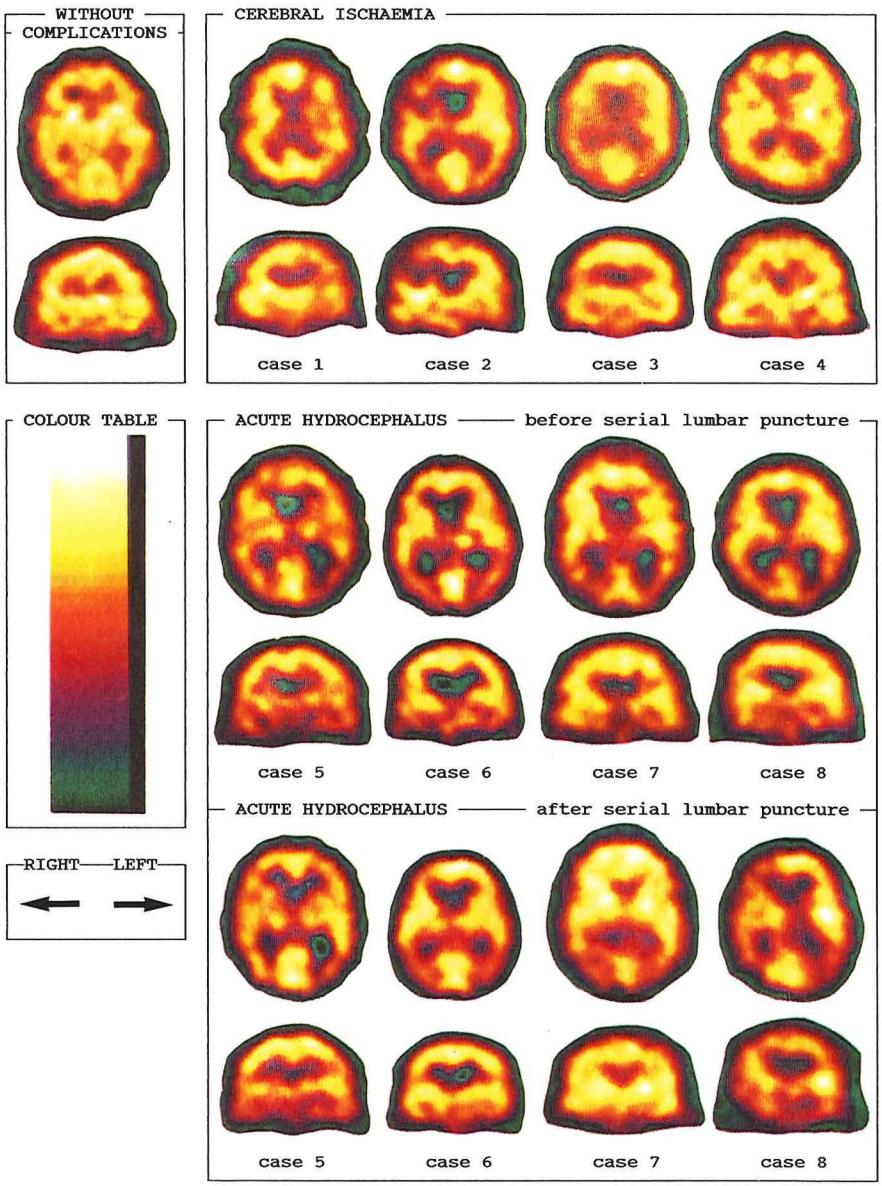


Figure 1. *Results of single photon emission computed tomography in patients with cerebral ischemia and in those with acute hydrocephalus after subarachnoid hemorrhage.*

the levels of cortical oxygen utilization.[12] The pattern of regional cerebral blood flow impairment that we found in patients with hydrocephalus has not been reported before. In most studies,[44,80,84,113] however, non rotating, multiple collimated scintillation detectors were used, and

cerebral blood flow values of the gray matter were estimated by calculating the initial slope index of the ^{133}Xe clearance curve[31,74] or by analyzing the gray matter part of the bicompartmental model.[31,74] Obviously changes in the blood flow to the deep regions of the brain cannot be detected with this method. Others measured regional cerebral blood flow by means of SPECT and ^{133}Xe,[33,127] but calculated regional cerebral blood flow from slices of at least 5 cm above the orbito-meatal line. These slices are well above the areas of decreased regional cerebral blood flow found in our patients.

Apart from showing that impaired consciousness in acute hydrocephalus results from a disturbance predominantly in the basal parts of the brain, this study may also have practical implications. If a patient has deteriorated from acute hydrocephalus and does not respond to treatment, the explanation may be that insufficient cerebro-spinal fluid drainage or another complication such as cerebral ischemia has developed. The latter is most likely if SPECT scanning shows decreased regional cerebral blood flow elsewhere than in the basal parts of the brain, even if CT shows no evidence of infarction.

Chapter 5

EFFECT OF FLUID INTAKE AND ANTIHYPERTENSIVE TREATMENT ON CEREBRAL ISCHEMIA AFTER SUBARACHNOID HEMORRHAGE

INTRODUCTION

Cerebral ischemia is a major complication after subarachnoid hemorrhage.[3,51] Recently, it has been suggested that volume status is important in the development of cerebral ischemia.[7,25,46,61,130,131] Patients with hyponatremia after subarachnoid hemorrhage had an increased risk of developing cerebral ischemia when treated with fluid restriction.[130] Case reports described improvement of clinical deficits attributed to cerebral ischemia after plasma volume expansion.[25] In addition, induced hypertension may also reverse symptoms of cerebral ischemia.[7,61,70]

These observations prompted us to change our management of patients with subarachnoid hemorrhage. Before 1983, daily fluid intake was 1.5-2 l and antihypertensives were administered when hypertension developed. Moreover, fluid restriction was applied in case of hyponatremia, on the (incorrect)[131,132] assumption that low serum sodium levels were caused by dilution (inappropriate secretion of antidiuretic hormone) rather than by sodium loss. After December 1982, daily fluid intake was at least 3 l, fluid restriction was not applied, and antihypertensives were administered only when a patient was receiving this treatment before admission.

A randomized clinical trial is the best method to compare the effects of these different management regimens on cerebral ischemia and outcome. However, in view of our previous analysis,[130] we felt that it was no longer ethical to randomize patients to treatment with fluid restriction and low daily fluid intake. To assess the effect of the new treatment regime on cerebral ischemia and on outcome in general, we compared the management results of patients treated before 1983 with result of those patients treated after December 1982.

PATIENTS AND METHODS

We prospectively studied 384 consecutive patients with the clinical features of subarachnoid hemorrhage, confirmed by initial computed tomogram (CT on admission)[117] or by xanthochromic cerebro-spinal fluid (investigated with spectrophotometry).[22,123] Treatment with tranexamic acid is an important variable related to cerebral ischemia[3,50,122] and since treatment with tranexamic acid differed among these 384 patients (patients received long-term tranexamic acid treatment or placebo before 1983,[122] and short-term tranexamic acid or no treatment after December 1982[135]), our analysis of the effect of the different regimens on cerebral ischemia and outcome was restricted to the 244 patients who did not receive tranexamic acid. Patients with a negative angiogram or with evidence on the initial CT scan of subarachnoid hemorrhage other than ruptured aneurysm were not included.[118,119] All patients were admitted within 72 hours after the initial subarachnoid hemorrhage to the Department of Neurology of the University Hospital Rotterdam (from November 1977 until May 1987). If death appeared imminent, entry into the study was delayed.

During the observation period, which lasted 4 weeks or until death or surgery, all patients were under continuous observation in an intensive care unit. The level of consciousness was assessed by means of the 14-point Glasgow Coma Scale;[78,114] a score on the Glasgow Coma Scale (GCS) of >12 indicated a good clinical condition. Most operations were carried out on Day 12 after the presenting subarachnoid hemorrhage. When a patient's clinical condition deteriorated, physical examination and CT were repeated. Outcome was assessed after 3 months, according to the 5-point Glasgow Outcome Scale.[60]

In 185 (76%) of the 244 patients, an aneurysm was demonstrated by angiography or by postmortem examination. In the remaining 59 patients, angiography and surgery were not considered because of advanced age (>70 years) or impaired level of consciousness. However, in these patients rupture of an aneurysm was considered highly probable because CT showed extravasation in the interhemispheric, suprasellar, or sylvian cisterns[117] without evidence of other causes of subarachnoid hemorrhage.[118,119] The amount of cisternal blood on the initial CT was graded on a scale of 0 to 3 separately for each of the 10 cisterns (maximum sum score 30 points) as previously described.[50,53,120] Similarly, intraventricular blood was graded separately for each of the four ventricles (maximum score 12 points).[50,53,120] Because an intraventricular score of 1 reflects sedimentation of blood in the ventricle, we considered only a score of >1 for at least one of the four ventricles to be relevant, and we referred only to this as "presence of intraventricular blood".

Clinical events were defined as 1) *probable delayed cerebral ischemia:* gradual development of focal neurologic signs, with or without deterioration in the level of consciousness, without confirmation by CT or autopsy; 2) *definite delayed cerebral ischemia:* deterioration in the level of consciousness or development of focal signs, or both, with CT or autopsy confirmation of cerebral infarction; 3) *probable rebleeding:* sudden deterioration and death without the possibility of confirmation by CT or if autopsy was refused; 4) *definite rebleeding:* sudden deterioration with an increased amount of blood on a repeat CT or at autopsy compared with a previous CT; 5) *acute hydrocephalus* bicaudate index obtained by CT on admission or within 1 week after the initial subarachnoid hemorrhage exceeding the normal upper limit (95th percentile) for age[38,43,120] (upper limits were: <36 years of age, 0.16; 36-45 years, 0.17; 46-55 years, 0.18; 56-65 years, 0.19; 66-75 years, 0.20; 76-85 years, 0.21);[21,38,43,83,120] 6) *deterioration from hydrocephalus:* deterioration

in the level of consciousness with no cause other than hydrocephalus, confirmed by a repeat CT giving a relative bicaudate index of >1 (*relative bicaudate index*: the patient's bicaudate index divided by the normal upper limit for age).[38,43,120]

During the first study period, from November 1977 through December 1982, antihypertensive treatment was started if a single recording showed a diastolic blood pressure of >110 mm Hg. Clonidine was then administered intramuscularly in doses of 150-900 microgram. If diastolic blood pressure remained >110 mm Hg, oral or intravenous beta-blocking agents or diuretics were added. Daily fluid intake during the first study period was 1.5-2 l and the patients were treated with fluid restriction (<1000 ml/day) in case of hyponatremia, defined as a sodium level of <135 mmol/l on at least 2 consecutive days. The rationale for fluid restriction was the (incorrect)[131,132] assumption that hyponatremia was caused by inappropriate secretion of antidiuretic hormone.[130] During the second study period, daily fluid intake was at least 3 l in all patients and fluid restriction or diuretic medication after admission was avoided. Unless the patient was receiving antihypertensives on admission, such treatment was not given. When signs of cerebral ischemia developed, extra fluid (20% albumin) was administered.

The fourfold contingency tables were analyzed with Yates' corrected chi-square test. If an expected value was <5, the fourfold tables were analyzed with Fisher's two sided exact probability test.

RESULTS

Entry variables related to the occurrence of cerebral ischemia and poor outcome at 3 months are the amount of cisternal blood on the initial CT,[3,50] the presence of intraventricular blood on the initial CT,[50] and the score on Glasgow Coma Scale.[50] The presence of hydrocephalus on the initial CT is related to the occurrence of fatal cerebral ischemia and poor outcome.[120] These variables are shown separately for patients admitted during the two study periods in

Table 1. Entry Characteristics of 244 Patients With Subarachnoid Hemorrhage by Study Period

	Admitted in Nov 77-Dec 82		Admitted in Jan 83-Apr 87	
	n=89		n=155	
	no.	%	no.	%
Sex				
Male	31	35	61	39
Female	58	65	94	61
Mean age (in years)	50.6		51.4	
Score on Glasgow Coma Scale				
3-12	28	31	40	26
12-14	61	69	115	74
Aneurysm confirmed	70	79	115	74
carotid artery	24	34	32	28
middle cerebral artery	11	16	19	17
anterior cerebral artery	31	44	50	43
posterior circulation	4	6	14	12
Initial computed tomogram				
Cisternal blood*				
0 - 6	35	39	35	23
7 - 12	25	28	42	27
13 - 18	19	22	32	21
19 - 24	9	10	29	19
25 - 30	1	1	15	10
not scored	0	0	2	1
Ventricular blood				
present#	16	18	45	29
2- 3	2	2	9	6
4- 6	7	8	13	8
7- 9	5	6	10	6
10-12	2	2	13	8
absent	73	82	110	71
not scored	0	0	2	1
Hydrocephalus	16	18	27	17

* Total score, amount of blood in all 10 cisterns
\# Total score, amount of blood in all 4 ventricles

Table 1. Patients admitted in the second study period had more cisternal blood and more often had intraventricular blood on the initial CT than those admitted during the first study period. The frequency of hyponatremia among the 155 patients admitted during the second study period was 35%, and the frequency of fluid restricted hyponatremia among the 89 patients admitted during the first study period was 33%. Antihypertensive treatment was administered in nine (6%) of the 155 patients admitted during the second study period and in 52 (58%) of the 89 patients admitted during the first study period.

Table 2. Incidence of Clinical Events and Outcome Among 244 Patients With Subarachnoid Hemorrhage by Study Period

	Admitted in Nov 77-Dec 82		Admitted in Jan 83-Apr 87	
	n=89		n=155	
	no.	%	no.	%
Cerebral ischemia	19	21*	16	10
Rebleeding	#28	31	~44	28
Acute hydrocephalus	16	18	32	21
Outcome at 3 months				
death	41	46	56	36
dependent	9	10	13	8
independent	39	44	86	55

* p=0.030, different from second study period by Yates' corrected X^2 test
\# all definite
~ 39 definite, 5 probable

Despite the presence of more cisternal blood and despite the higher frequency of intraventricular blood on the initial CT scan, the occurrence of cerebral ischemia was lower among patients admitted during the second study period (16 [10%, 13 definite, three probable] of 155) than among those admitted during the first study period (19 [21%, 18 definite, one probable] of 89; $X^2=4.732$, $p=0.030$; Table 2). This led to a slightly better outcome among patients who were admitted during the second study period, but the difference is not significant ($X^2=2.629$, $p=0.104$; Table 2). The frequency of cerebral ischemia among patients in a good clinical condition on admission was 18% (11 [10 definite, one probable] of 61 patients) during the first study period and 8% (nine [seven definite, two probable] of 115 patients) during the second study period.

The proportion of fatal ischemia had also decreased by the second period, from 32% (six of 19 patients) to 19% (three of 16 patients), but this difference did not reach significance (Fisher's exact probability test, $p=0.46$; Table 3). The other major complications (rebleeding and acute hydrocephalus) occurred with the same frequency in all 244 patients and in patients with cerebral ischemia admitted during both periods (Table 2 and 3). Outcome in all 244 patients and in patients with cerebral ischemia was better during the second study period, whereas the incidence of other complications in these patients was not different (Table 2 and 3).

Mortality after 3 months in patients with cerebral ischemia (analysis restricted to

Table 3. Mortality, Clinical Events, and Outcome Among 35 Patients With Subarachnoid Hemorrhage and Cerebral Ischemia by Study Period

	Admitted in Nov 77-Dec 82		Admitted in Jan 83-Apr 87	
	n=19		n=16	
	no.	%	no.	%
Fatal ischemia	6	32	3	19
Rebleeding	*4	21	*3	19
Acute hydrocephalus	5	26	4	25
Outcome at 3 months				
death	12	63	6	38
dependent	3	16	4	25
independent	5	21	6	38

* all definite

patients without rebleeding) among the patients admitted during the second study period was lower than that among those admitted during the first study period (Table 4), but the difference was not significant ($X^2=1.362$, $p=0.243$). Mortality among patients with rebleeding (analysis restricted to patients without cerebral ischemia) and among patients with acute hydrocephalus did not differ between periods (Table 4).

Table 4. Mortality of Clinical Events Among 244 Patients With Subarachnoid Hemorrhage

	Admitted in Nov 77-Dec 82			Jan 83-Apr 87		
	n	no.	%	n	no.	%
Cerebral ischemia	15	9	60	13	4	31
Rebleeding	24	20	83	41	34	83
Acute hydrocephalus	16	9	56	32	16	50

Analysis restricted to patients without rebleeding for cerebral ischemia and to patients without cerebral ischemia for rebleeding.

DISCUSSION

A change in the management of patients with subarachnoid hemorrhage, consisting of increased daily fluid intake and restriction of the use of antihypertensives, significantly decreased the occurrence of cerebral ischemia between study periods. The outcome of patients who developed cerebral ischemia and of all patients improved, although not significantly. The occurrence and mortality of other major complications (rebleeding and acute hydrocephalus) did not change.

In a nonrandomized study such as ours, it is important to investigate whether variables related to cerebral ischemia and to poor outcome were equally distributed between the two periods. Patients admitted during the second study period not treated with tranexamic acid in whom the effects of the different management regimens were investigated were at a higher risk of developing cerebral ischemia. Despite this, the observed frequency of cerebral ischemia among these patients was lower. Moreover, all 244 consecutive patients were prospectively studied in the same institution and the entry criteria, the assessment of clinical deterioration and the assessment of outcome had not changed over time. The additional treatment regimen had not changed; in particular Nimodipine which has recently been demonstrated to be effective in patients after subarachnoid hemorrhage,[97] and other calcium antagonists were not administered. Therefore, we attribute the decreased occurrence of cerebral ischemia during the second study period to the combination of increased daily fluid intake and the restricted use of antihypertensives.

We do not know whether the same results can be achieved by a restricted use of antihypertensives or by a large daily fluid intake alone. It has been suggested that either plasma volume expansion or artificially increased blood pressure may reverse the clinical symptoms of cerebral ischemia.[7,25,61,70] It may be that the combination of these two measures is even more effective. How an improved volume status prevents cerebral ischemia after subarachnoid hemorrhage is not known. Cardiac output may increase or blood viscosity may decrease; both may result in an increased cerebral blood flow.[25,47,58,63,136]

During the second period of the study, with the exception of nine patients, we did not administer antihypertensives in patients who were not receiving this treatment before admission. A rise in blood pressure may be a compensatory mechanism to increase perfusion pressure in the presence of arterial spasm or cerebral ischemia. If this compensation exists, the harmful

effect of antihypertensives would be explained. On the other hand, since blood flow in the proximal basal arteries (where the aneurysm is located) would seem to be unimpaired, hypertension might result in a higher frequency of rebleeding. Nevertheless, the frequency of rebleeding in our series remained unchanged with a restricted use of antihypertensives during the second period.

During the second study period, the occurrence of cerebral ischemia among patients who were in a good grade on admission (Glasgow Coma Scale Score of >12) was remarkably low (8%). This means that the administration of calcium antagonists[97] in this subgroup of patients can hardly improve outcome by further diminishing the risk of cerebral ischemia. Calcium antagonists may be particularly beneficial to patients at an increased risk of developing cerebral ischemia, such as patients with a Glasgow Coma Scale Score of <13 on admission and those who are treated with antifibrinolytic agents. Even short-term treatment with tranexamic acid increases the occurrence of cerebral ischemia.[135]

In conclusion, this study strongly suggest a beneficial effect of a regimen of increased daily fluid intake and restricted use of antihypertensives in patients after subarachnoid hemorrhage. From a theoretical point of view a study with randomized controls would have provided stronger evidence, but in view of our earlier finding that both fluid restriction and antihypertensive treatment are probably harmful,[130] we did not feel justified in continuing that regimen in our patients.

Chapter 6

HYPONATREMIA IS ASSOCIATED WITH CEREBRAL ISCHEMIA IN PATIENTS WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE

INTRODUCTION

Cerebral infarction after aneurysmal subarachnoid hemorrhage occurs often in patients who develop hyponatremia. Furthermore, patients with cerebral infarction and hyponatremia have a higher mortality rate than patients with cerebral ischemia and normal sodium values. This was demonstrated in a large series of patients with subarachnoid hemorrhage who had a daily fluid intake of 1.5-2.0 l.[130] In this series of patients, fluid restriction was applied in case of hyponatremia, on the (incorrect) assumption that the low serum levels of sodium were caused by dilution as a result of inappropriate secretion of antidiuretic hormone.[130] The question is whether hyponatremia is associated with cerebral ischemia or whether the treatment of hyponatremia by fluid restriction is responsible for this association.

The aim of this study was to investigate the association of hyponatremia and cerebral infarction in patients with subarachnoid hemorrhage who had a daily fluid intake of at least 3 liters and who were not treated with fluid restriction when hyponatremia developed.

PATIENTS AND METHODS

We prospectively studied 208 consecutive patients with the clinical features of subarachnoid hemorrhage, confirmed by computed tomogram (CT)[117] or by xanthochromic cerebro-spinal fluid (investigated with spectrophotometry).[22,123] Patients with negative findings on angiography or with evidence on CT of subarachnoid hemorrhage other than ruptured aneurysm[118,119,120] and patients who were moribund on admission were excluded. All patients were admitted within 72

hours after the initial subarachnoid hemorrhage. In 150 (72%) of the 208 patients an aneurysm was demonstrated by angiography or postmortem examination. In the remaining patients angiography and surgical treatment were not considered because of age or impaired level of consciousness. However, rupture of an aneurysm was considered highly probable because CT showed extravasated blood in the interhemispheric, suprasellar, or Sylvian cisterns,[117] without evidence of other causes of subarachnoid hemorrhage.[118,119] The amount of cisternal blood and intraventricular blood on the initial CT was graded as described on page 34.[50,53,120] During the study period, which lasted for 4 weeks or until death or operation, all patients were under continuous observation in an intensive care unit. The level of consciousness was assessed by means of the 14 point Glasgow Coma Score.[78,114] Most operations were carried out on the twelfth day after the presenting hemorrhage. CT scanning was performed on admission and when a patient's clinical condition deteriorated. Cerebral ischemia was diagnosed as described on page 34.[38,39,40,43,130]

From January 1983 until April 1986 the patients did not receive tranexamic acid and from April 1986 until May 1987 tranexamic acid was given during the first 4 days after admission. The daily fluid intake was at least 3 liters in all patients. Fluid restriction or diuretic medication was prohibited. Antihypertensive drugs were prohibited unless the patients was on this treatment before admission. When signs of cerebral ischemia developed, extra fluid in the form of albumin 20% was administered. Calcium antagonists were not given.

Hyponatremia was defined as a sodium level lower than 135 mmol/l on at least 2 consecutive days in the absence of hyperlipidemia or paraproteinemia. Serum sodium levels were measured daily in the first two weeks after admission.

The fourfold tables were analyzed with the Yates' corrected chi-square test. If one of the expected value is lower than 5 the fourfold tables were analyzed with the two sided Fisher's exact probability test.

Table 1. Relationship Between Hyponatremia and Cerebral Ischemia in 208 Patients With Aneurysmal Subarachnoid Hemorrhage

	Cerebral ischemia		
	Yes no.	No no.	total
serum sodium level			
> 134 mmol/l	17*	121	138
< 135 mmol/l	17	53	70
total	34	174	208

* significantly different from number in hyponatremic group by chi-square test ($X^2=4.028$, $p=0.045$)

RESULTS

Hyponatremia developed in 70 (34%) of the 208 patients. Cerebral infarction was diagnosed in 34 (16%) of the 208 patients and confirmed by CT or autopsy in 27 (13%). The occurrence of cerebral ischemia in patients with hyponatremia, 17 (24%) of 70 patients, was significantly higher than in patients without hyponatremia, 17 (12%) of 138 patients ($X^2=4.028$, $p=0.045$) (table 1). Fatal ischemia did not occur significantly more often in patients with hyponatremia than in patients without hyponatremia: 5 (29%) of 17 patients with cerebral ischemia in the hyponatremic group, and 4 (24%) of 17 patients in the group without hyponatremia died from cerebral infarction. The frequency of cerebral ischemia was significantly related to the amount of cisternal blood on the initial CT ($X^2=5.925$, $p=0.015$) and to treatment with tranexamic acid ($X^2=14.458$, $p=0.0001$), but not to the presence of intraventricular blood (Table 2). The amount of cisternal blood, the presence of ventricular blood, and treatment with tranexamic acid did not

increase the frequency of hyponatremia (table 2).

Table 2. Frequency of Cerebral Ischemia and Hyponatremia Related to Amount of Cisternal Blood on The Initial CT scan, to Presence of Ventricular Blood, and to Treatment With Tranexamic Acid

	Cerebral ischemia			Hyponatremia		
	n	no.	%	n	no.	%
Score of cisternal blood on initial CT						
0 - 15	105	10*	10	105	35	33
16 - 30	100	23	23	100	34	34
not scored	3	1		3	1	
Ventricular blood on initial CT						
absent	149	24	16	149	48	32
present	56	9	16	56	21	38
not scored	3	1		3	1	
Treatment with tranexamic acid						
No	155	16#	10	155	54	35
Yes	53	18	34	53	16	30

* significantly different from number in high-scoring group by chi-square test ($X^2=5.925$, $p=0.015$).

\# significantly different from number in treatment group by chi-square test ($X^2=14.458$, $p=0.0001$).

DISCUSSION

Hyponatremia after subarachnoid hemorrhage is not rare; in this and in a previous study,[130] hyponatremia occurred in one third of the patients. This study demonstrates that hyponatremia following subarachnoid hemorrhage remains significantly associated with cerebral ischemia even if a large daily fluid intake is given and if no fluid restriction is applied in case of hyponatremia. Other identified factors associated with cerebral ischemia are the amount of blood in the basal cisterns on the initial CT,[3,50] the presence of ventricular blood,[50] and treatment with antifibrinolytics.[3,50,122] In this study, the amount of blood in the basal cisterns and antifibrinolytic treatment were associated with an increased risk of cerebral ischemia, but not with an increased incidence of hyponatremia. Therefore, the association between hyponatremia and cerebral ischemia cannot be explained by an association between hyponatremia and one of these predictive variables of ischemia.

The cause of hyponatremia is probably the release of a natriuretic factor, which results in renal salt wasting.[18,102,132] Subsequent passive diuresis may lead to hypovolemia[131] and this may impair cerebral blood flow, resulting in cerebral ischemia. The association between hypovolemia and cerebral ischemia is supported by reports which described successful treatment of cerebral ischemia by plasma volume expansion.[25]

It remains to be established that cerebral ischemia in patients with hyponatremia after subarachnoid hemorrhage can be prevented by starting plasma volume expansion as soon as hyponatremia develops. Another approach could be to try prevent hyponatremia by inhibition of sodium excretion.[39,133] The effect of the inhibition of sodium excretion with the mineralocorticoid fludrocortison acetate in patients with subarachnoid hemorrhage is presented in Chapter 7.[39]

Chapter 7

EFFECT OF FLUDROCORTISONE ACETATE IN PATIENTS WITH SUBARACHNOID HEMORRHAGE

INTRODUCTION

Delayed cerebral ischemia is a major complication occurring after aneurysmal subarachnoid hemorrhage (**Chapter 5**).[3,40,49,50,51,122] One possible causal factor is a decrease in plasma volume,[131,133] associated with excessive natriuresis[131,132,133] and hyponatremia.[28,41,120,130,134] Hyponatremia in patients with subarachnoid hemorrhage with or without fluid restriction is related to an increased risk of cerebral infarction (**Chapter 6**).[41,130] Several authors have reported a partial or complete reversal of signs and symptoms of cerebral ischemia after plasma volume expansion, with[7,61,70] or without[25] induced arterial hypertension. Maintenance of an adequate intravascular volume is therefore important in patients with subarachnoid hemorrhage. In a small non-randomized study,[133] the mineralocorticoid fludrocortisone acetate[77,126] appeared to prevent plasma volume depletion in the first 6 days after hemorrhage. The aim of our study was to investigate the effect of fludrocortisone acetate on sodium balance, fluid balance, and plasma volume in a randomized trial of patients with subarachnoid hemorrhage.

PATIENTS AND METHODS

The trial commenced in January 1986 and ended in May 1987. Three centers participated: the Department of Neurosurgery, Royal Free Hospital, London, United Kingdom; the Department of Neurology, University Hospital Rotterdam, The Netherlands; and the Department of Neurology, University Hospital, Utrecht, the Netherlands. The ethics committee in each center approved the study.

Patients with signs and symptoms of subarachnoid hemorrhage and with confirmatory evidence on the initial computed tomogram (CT on admission)[117,118,119] or in the cerebro-spinal fluid (investigated with spectrophotometry[22,123]) were eligible. Reasons for exclusion were a lapse of >72 hours since the presenting hemorrhage; age of >70 years; previous treatment with diuretics or corticosteroids; presence of endocrine, renal, or cardiac disease; or computed tomographic evidence of a cause for subarachnoid hemorrhage other than aneurysm.[118,119] If death appeared imminent, entry was delayed.

The amount of cisternal blood on the initial CT was graded separately for each of the 10 cisterns on a scale of 0 to 3 (maximum score 30 points).[50,53,120] Similarly, intraventricular blood was graded separately for each of the four ventricles (maximum score 12 points).[50,53,120] Four vessel angiography and aneurysm surgery were performed depending on the patient's clinical condition. Surgery was planned between Day 7 and Day 10 in London, and on Day 12 in Rotterdam and Utrecht. The level of consciousness was assessed at entry by means of the 14 point Glasgow Coma Scale.[78,114]

Eligible patients were randomized after informed consent was obtained. Randomization was stratified per center, according to random number tables by means of a sealed-envelope technique.

Treatment with fludrocortisone acetate was always started within 72 hours after the hemorrhage. The drug was administered intravenously or orally, 400 microgram/day in two doses, for a maximum duration of 12 days. Treatment was discontinued if signs of heart failure developed. Anticoagulants, platelet aggregation inhibitors, and diuretics were prohibited throughout the study period. Antihypertensive drugs were given only if the patient was receiving this treatment before admission. Glucocorticosteroid treatment was started (in those who were eligible for aneurysm operation) 48 hours before the operation. All patients received tranexamic acid intravenously for the first 4 days after admission, in six doses of 1 g/day. During the first 12 days, the fluid intake was maintained at 3 l/day either orally or intravenously (isotonic saline). For every degree of body temperature above 38°C, an additional 500 ml/day fluid was administered. When signs of cerebral ischemia developed, extra fluid in the form of dextran 40, polygelin (Haemaccel) (in London), or 20% albumin (in Rotterdam and Utrecht) was given. Serum electrolytes, blood urea nitrogen, serum creatinine, and routine blood hematologic values were measured daily.

Plasma volume was measured during the first 24 hours after admission and was repeated on Days 6 and 12. Plasma volume was determined by the isotope dilution technique. A total dose of 148 kBq of 5 mg radioiodinated human serum albumin (Iodine-125 in London and Iodine-131 in Rotterdam and Utrecht) in isotonic saline was injected intravenously.[105] Blood was sampled before injection and at given times after injection (in London at 10, 20, 30, and 60 minutes; in Rotterdam and Utrecht at 8 and 13 minutes). Isotope activity was analyzed with a Gammatrac 1191 (Tracor Analytic, Elk Grove Village, Illinois, USA).[32] We expressed the results as total plasma volume and calculated the percentage change between the second (Day 6) and the first measurements, and between the third (Day 12) and the first measurements. Because bed rest alone may cause a certain decrease in plasma volume after 1 week,[35] we considered only a drop in plasma volume of >10% relevant, and we referred only to this as "decreased plasma volume".

Sodium balance was calculated daily for the first 12 days or until aneurysm surgery by subtracting sodium excretion from sodium intake. Patients who were well enough to eat were placed on a specially prepared low-sodium diet as well as on intravenous fluids to minimize

errors in sodium intake calculations. Sodium excretion was measured in 24 hour urine samples. Fluid balance was calculated daily by subtracting total urine production from total fluid intake. Cumulative sodium and fluid balances were analyzed for the first 6 days and for the entire 12-day study period.

Clinical deterioration occurring within 28 days or until aneurysm surgery was investigated by clinical examination and, where possible, by a repeat CT. Cerebral events were defined as *probable delayed cerebral ischemia* (gradual development of focal neurological signs, with or without deterioration in the level of consciousness, without confirmation by a CT or an autopsy) and definite delayed cerebral ischemia (gradual or sudden deterioration in the level of consciousness or the development of focal signs, or both, with CT or autopsy confirmation of cerebral infarction). Outcome was assessed according to the 5-point Glasgow Outcome Scale.[60]

The fourfold tables were analyzed with Fisher's exact probability test.

Table 1. Comparison of Entry Characteristics of Control and Fludrocortisone-Treated Patients With Aneurysmal Subarachnoid Hemorrhage

	Control n = 45		Treated n = 46	
	no.	%	no.	%
Sex				
Male	19	42	20	43
Female	26	58	26	57
Mean age (in years)	50.0		49.8	
Hours to entry				
0 - 24	28	62	29	63
25 - 48	11	25	9	20
49 - 72	6	13	8	17
Loss of consciousness at ictus	17	38	22	48
History of hypertension	4	9	5	11
Glasgow Coma Scale Score				
3 - 12	10	22	8	17
12 - 13	10	22	12	26
14	25	56	26	57
Evidence of aneurysm (angio/autopsy)				
Not investigated	9	20	9	19
No aneurysm	7	16	11	24
Aneurysm	29	64	26	57
site of ruptured aneurysm				
*anterior cerebral artery	10	35	5	19
*carotid artery	7	24	12	46
*middle cerebral artery	8	28	7	27
*posterior circulation	3	10	1	4
*unknown	1	3	1	4
Cisternal blood score				
0 - 6	10	22	14	30
7 - 12	9	20	9	20
13 - 18	11	25	7	15
19 - 24	7	16	8	18
25 - 30	6	13	6	13
not scored	2	4	2	4
Intraventricular blood score				
0 - 3	41	91	41	89
4 - 6	2	4	2	4
7 - 9	0	0	3	7
10 - 12	2	4	0	0

* % of those with evidence of aneurysm

RESULTS

Ninety-one patients were randomized: 46 (treated) patients received fludrocortisone and 45 (control patients) did not. Except for a slightly higher proportion of treated patients with a low amount of cisternal blood (score 0-6) and a higher proportion of control patients with cisternal blood score of 13-18 on the initial CT entry characteristics were well matched between the groups (Table 1). Antibiotic treatment was administered in one of the 46 treated patients and in four of the 45 control patients without fludrocortisone. No other drug that might affect renal function was administered.

We measured plasma volume in 82 patients on Day 1, in 64 patients on Day 6, and in 47 patients on Day 12, which enabled us to calculate plasma volume changes in 62 patients for the

first 6 days and in 46 patients for entire 12-day study period. In the remaining patients, measurements were omitted because of early death, aneurysm surgery, the finding of a cause for subarachnoid hemorrhage other than aneurysm, or technical problems. Fluid balance and sodium balance were calculated for the first 6 days in 78 and 77 patients, respectively, and for the entire 12-day study period in 62 and 61 patients, respectively. These included all patients with complete measurement of plasma volume. Cumulative sodium balance and decreased plasma volume could be correlated in 61 patients for the first 6 days and in 46 patients for the entire 12-day study period; we were able to compare cumulative sodium balance and fluid balance in 77 patients for the first 6 days and in 61 patients for the entire 12-day study period.

Table 2. Comparison of Control and Fludrocortisone-treated Patients With Aneurysmal Subarachnoid Hemorrhage

	Control			Treated		
	n	no.	%	n	no.	%
Negative cumulative sodium balance						
First 6 days	40	25	63*	37	14	38
Entire 12-day period	33	23	70#	28	8	29
Negative cumulative fluid balance						
First 6 days	40	3	8	38	5	13
Entire 12-day period	33	4	12	29	1	3
Decreased plasma volume (>10%)						
Day 6	32	11	34	30	8	27
Day 12	25	8	32	21	3	14
Cerebral ischemia	45	14	31	46	10	22

*# $p<0.05$, <0.003, respectively, different from control by Fisher's exact probability test.

Fluid intake and sodium intake were well matched in the groups. Mean daily fluid intake in the fludrocortisone group was 3,261 ml during the first 6 days and 3,352 ml during the entire 12-day study period; in the control group these values were 3,341 and 3,264 ml, respectively. Mean daily sodium intake in the fludrocortisone group was 219 mmol during the first 6 days and 222 mmol in the entire 12-day study period. In the control group these values were 208 and 202 mmol, respectively.

Fludrocortisone treatment significantly reduced the incidence of a negative cumulative sodium balance in the first 6 days ($p=0.041$) and in the entire 12-day study period ($p=0.0023$, Table 2). There was no effect of fludrocortisone treatment on the cumulative fluid balance.

Table 3. Correlation of Cumulative Sodium Balance With Plasma Volume and Fluid Balance After Aneurysmal Subarachnoid Hemorrhage

	Cumulative sodium balance					
	Negative			Positive		
	n	no.	%	n	no.	%
Decreased plasma volume (>10%)						
Day 6	27	13	48*	34	6	18
Day 12	23	10	43#	23	1	4
Negative fluid balance						
First 6 days	39	7	18*	38	0	0
Entire 12-day period	31	4	13	30	0	0

*# $p<0.02, <0.005$, and $p<0.02$, different from positive cumulative sodium balance

A negative cumulative sodium balance during the first 6 days correlated with decreased plasma volume (48 vs. 18 %, $p=0.014$) and with a negative cumulative fluid balance (18% vs. 0%, $p=0.012$, Table 3). During the entire 12-day study period, a negative sodium balance correlated significantly with decreased plasma volume ($p=0.004$) but not with a negative fluid balance ($p=0.113$, Table 3).

Despite the relation between fludrocortisone treatment and sodium balance and between sodium balance

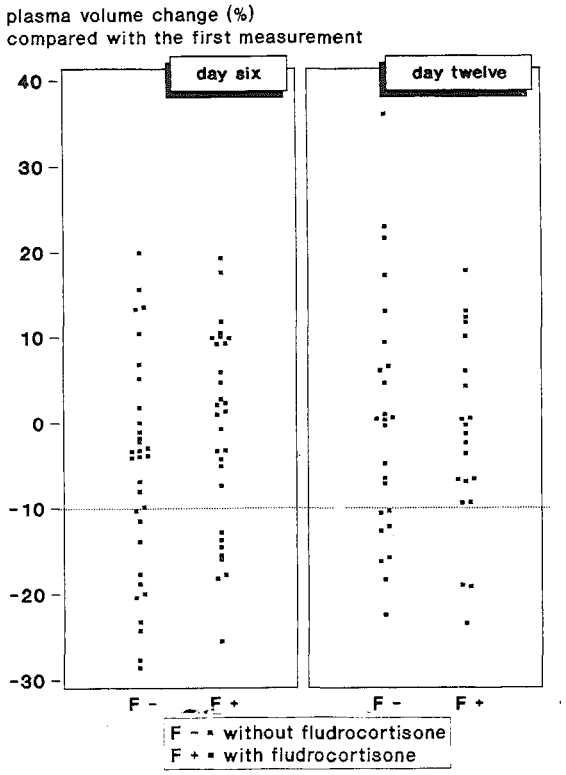
and plasma volume, the direct relation between fludrocortisone treatment and plasma volume was not significant ($p=0.588$ and $p=0.188$, respectively, for the first 6 days and for the entire 12-day study period, Table 2, and Figure 1).

Of the 46 patients treated with fludrocortisone only seven (15%) received plasma volume expanders, compared with 11 (24%) of the 45 control patients. Plasma volume expanders were administered to 14 (58%) of the 24 patients with probable or definite cerebral ischemia and to four (6%) of the 66 patients without cerebral ischemia.

The incidence of cerebral ischemia was lower in the treated group, but the difference was not significant. Of the 46 treated patients, 10 (22%) developed delayed cerebral ischemia (seven definite and three probable) compared with 14 of the 45 control patients (31%, seven definite and seven probable, $p=0.349$; Table 2). This trend was seen in each center.

Outcome was similar in the two groups; independent outcome was achieved in 29 (63%) of the 46 treated patients and in 30 (67%) of the 45 control patients ($p=0.827$).

Figure 1. *Scatter plot of percentage plasma volume change (difference between plasma volume measured on Day 6 or Day 12 and that on Day 1 divided by plasma volume measured on Day 1) by treatment with (+) or without (-) fludrocortisone*



Fludrocortisone treatment was discontinued in two patients because of pulmonary edema, but in the control group pulmonary edema also occurred in two patients. No other side effects developed except hypokalemia. The effect of fludrocortisone treatment on blood pressure was investigated by comparing mean blood pressure on Days 1, 6, and 12, in patients admitted in Rotterdam (44% of all patients). No differences in mean blood pressure between the groups were found.

DISCUSSION

Our study confirms that patients with subarachnoid hemorrhage may have excessive natriuresis, as almost half of our patients in whom it was assessed had a negative sodium balance during the first 6 days after admission. This excessive natriuresis cannot be explained by a high sodium intake before admission followed by a low intake after admission since the

mean daily sodium intake in our patients matched that in the average North American and Western European population (174-261 mmol).[23] The release of a natriuretic factor after subarachnoid hemorrhage is a more likely explanation for this sodium loss.[18,120,130,132,134]

A negative sodium balance was correlated significantly with a negative fluid balance during the first 6 days and with decreased plasma volume during both the first 6 days and the entire 12-day study period. It is therefore reasonable to assume that any means of preventing the development of a negative sodium balance would help maintain plasma volume. Fludrocortisone treatment significantly reduced the occurrence of a negative sodium balance, during both the first 6 days and the entire 12-day study period. Although the results did suggest that plasma volume depletion was reduced by fludrocortisone treatment, the difference was not significant.

The effect of fludrocortisone in preventing plasma volume depletion may have been masked by the administration of plasma volume expanders. These were administered when the clinicians in charge suspected that cerebral ischemia was developing, and fewer treated patients received plasma volume expanders than control patients.

A decrease in plasma volume may lead to an increase in hematocrit, an increase in blood viscosity, and impaired cerebral blood flow, especially in the microcirculation.[47,58,63,136] Inhibition of sodium excretion is directed at preventing such a decrease in plasma volume in the hope that the risk of cerebral ischemia can be minimized. The design of our study did not aim at demonstrating a reduced incidence of cerebral ischemia. To show such a benefit would have required many more patients in each group. Despite this, it is of interest that the proportion of patients with cerebral ischemia was lower in the fludrocortisone-treated group and that this trend was observed not only between the two groups in the study as a whole, but also between the two sub-groups in each of the three participating centers.

In conclusion, we have confirmed the relation between natriuresis and a decrease in plasma volume in a relatively large number of patients. Fludrocortisone significantly reduced sodium excretion and therefore remains of possible therapeutic benefit in patients with subarachnoid hemorrhage.

GENERAL DISCUSSION

Acute hydrocephalus after subarachnoid hemorrhage is not an infrequent problem. The study described in **Chapter 2**[38] confirmed that the occurrence is approximately 20%. In the majority of these patients the level of consciousness was impaired, but not all patients needed ventricular drainage. A considerable proportion of patients improved spontaneously, which was usually apparent within 24 hours after the initial bleed. In patients who needed treatment, ventricular drainage was effective in three quarter of the patients, but the beneficial effects of this treatment were negated by complications such as an increased risk of rebleeding and ventriculitis. The cause of the increased rebleeding rate in these patients is unknown. Several factors may play a role: 1) a rapid fall in the CSF pressure and a rapid decrease of the ventricular size may cause displacement of the clot surrounding the aneurysm, or 2) insertion of the ventricular catheter may induce fibrinolytic activity resulting in lysis of the aneurysm clot.

Treatment of acute hydrocephalus with serial lumbar puncture appeared to be as effective as ventricular drainage in restoring the level of consciousness (**Chapter 3**[43]). Complications such as increased risk of rebleeding and ventriculitis were not observed. Yet, the outcome of patients with acute hydrocephalus after subarachnoid hemorrhage remained worse than that of patients without acute hydrocephalus, which is mainly explained by: a higher occurrence of fatal cerebral ischemia in patients with acute hydrocephalus.[120] Therefore, outcome can be improved if cerebral ischemia can be prevented or can be treated when it occurs.

As already mentioned in the "**GENERAL INTRODUCTION**" (page 1), there is a significant correlation between acute hydrocephalus and hyponatremia,[134] and between hyponatremia and death from cerebral ischemia.[130] The relation between acute hydrocephalus and hyponatremia was explained by enlargement of the third ventricle[134] which might interfere with hypothalamic function and which might result in the release of a natriuretic factor[132] leading to salt wasting and hypovolemia.[131] The problem with this explanation was that the association between hyponatremia and cerebral ischemia had been demonstrated in patients who were treated with fluid restriction when hyponatremia developed. Therefore, the question remained whether it was hyponatremia or the treatment of hyponatremia (fluid restriction) that was associated with cerebral ischemia. In **Chapter 6**[41] it was demonstrated that the association between cerebral ischemia and hyponatremia is also present in patients with a large daily fluid intake and without fluid restriction.

Is it possible to prevent excessive natriuresis? In **Chapter 7**[39] it was shown that fludrocortisone reduces natriuresis in patients with subarachnoid hemorrhage, but the effect of fludrocortisone on plasma volume could not be demonstrated. The explanation could be that in patients who were not treated with fludrocortisone the frequency of cerebral ischemia and the occurrence of treatment of cerebral ischemia with plasma volume expansion were more frequent than in those who did receive fludrocortisone. Another explanation could be that higher doses of fludrocortisone are required to demonstrate an effect on plasma volume. However, the importance of a large fluid intake was clearly demonstrated (**Chapter 5**[40]). Therefore in patients who are at a higher risk of developing fatal cerebral ischemia, such as patients with acute hydrocephalus, the fluid balance should carefully be monitored. Apart from a large fluid intake combined with a restricted use of antihypertensive drugs, cerebral ischemia can also be prevented by the administration of calcium antagonists: treatment with nimodipine was shown to improve overall outcome of patients with aneurysmal subarachnoid hemorrhage by preventing cerebral ischemia.[90,95,97] Therefore, cerebral ischemia in patients with acute hydrocephalus will probably occur less often when these treatment regimens are applied. Moreover, when cerebral ischemia occurs, despite preventive measures, attempts can be made to reverse this condition by hypervolemic treatment, with[7,61,70] or without[25] artificially induced hypertension, since it has repeatedly been reported that dramatic improvement followed this treatment.[7,25,61,70]

When a patient with acute hydrocephalus shows deterioration of the level of consciousness, it is not always clear whether this is caused by the effects of the increased ventricle size or by cerebral ischemia. Moreover, deterioration may start with the effects of ventricular enlargement, and later on cerebral ischemia may develop worsening the patient's clinical condition. During this process, it is hard to tell when the effect of hydrocephalus ends and when the effect of cerebral ischemia start. By means of SPECT studies with ^{99m}Tc HM-PAO (**Chapter 4**[42]) it was shown that patients with acute hydrocephalus have a decreased rCBF which is predominantly confined to the basal parts of the brain. In contrast, patients with cerebral ischemia had a decreased rCBF at higher levels. Therefore, SPECT studies with ^{99m}Tc HM-PAO can be used to distinguish acute hydrocephalus from cerebral ischemia.[42] Patients with acute hydrocephalus without cerebral ischemia may benefit from serial lumbar puncture alone. This does not mean that serial lumbar puncture should be omitted in patients with enlarged ventricles who developed cerebral ischemia, because acute hydrocephalus can contribute to the development of cerebral ischemia and serial lumbar punctures should be performed in these patients combined with hypervolemic hemodilution.

Probably treatment of acute hydrocephalus with a simple and safe procedure such as lumbar puncture combined with measures to prevent ischemia or with treatment of cerebral ischemia, will result in an increased proportion of patients who are fit enough to undergo aneurysm surgery without excessive delay to prevent rebleeding. As rebleeding is another complication of subarachnoid hemorrhage with a high mortality and a high morbidity, prevention of rebleeding should ultimately improve the overall outcome in patients with acute hydrocephalus.

SUMMARY

Acute hydrocephalus following subarachnoid hemorrhage is a serious complication with high mortality. This high mortality is mainly caused by an increased frequency of fatal cerebral ischemia.[120] The subject of this thesis is the treatment of acute hydrocephalus and cerebral ischemia following aneurysmal subarachnoid hemorrhage.

In **Chapter 1**, the complications of subarachnoid hemorrhage were reviewed. Hydrocephalus following subarachnoid hemorrhage was already reported in 1928. It took until the early fifties before other reports on hydrocephalus were published. The first report on acute hydrocephalus diagnosed by CT scan was published in 1979. Acute hydrocephalus was not considered to be of clinical significance by some authors, but the opposite was shown by a publication 1985. In this study, acute hydrocephalus on CT made within 72 hours after subarachnoid hemorrhage appeared to be a frequent complication since it was found in 20% of the patients. Although the patients initially improved after ventricular drainage, 88% of the drained patients died within one month after admission, mainly because of fatal cerebral ischemia.

In 1964, Crompton published the results of his study on the pathogenesis of cerebral infarction following subarachnoid hemorrhage. Although most of his conclusions were ignored over the years, many have recently been confirmed. The most important conclusions were that cerebral infarction after subarachnoid hemorrhage is not confined to a single vascular territory, that the development of cerebral ischemia is a multifactorial process, and that narrowing of the arterial lumen after subarachnoid hemorrhage is probably caused by ischemic changes of the cerebral vessel wall.

The plasma volume status and antihypertensive treatment appeared to play an important role in the development of cerebral ischemia. Other important factors for the development of cerebral ischemia are measures taken to prevent rebleeding. Early aneurysm surgery and antifibrinolytic agents precipitate cerebral ischemia to such an extent that the results of these preventive measures are negated by the increased frequency of cerebral ischemia.

Management problems in acute hydrocephalus were studied in a consecutive series of 473 patients admitted within 72 hours after a subarachnoid hemorrhage (**Chapter 2**[38]). In this group of patients, 91 (19%) had hydrocephalus on the initial computed tomogram. Consciousness was unimpaired in 25 (28%) of the 91 patients. In 11 more patients acute hydrocephalus developed within 1 week after subarachnoid hemorrhage. Thirty-eight (8%) of all 473 patients subsequently showed clinical deterioration because of acute hydrocephalus; 11 of these 38 had fluctuations

in the level of consciousness. Of the 66 patients with acute hydrocephalus and impaired consciousness on admission, 26 (39%) spontaneously improved within 24 hours. Ventricular drainage was performed in 32 (31%) of the 102 patients with acute hydrocephalus (7% of all 473 patients). The degree of ventricular dilatation was not directly related to the level of consciousness and did not predict the need for ventricular drainage. Consciousness improved after ventricular drainage in 25 (78%) of 32 patients. Ventriculitis developed in 12 of the 24 patients with external drainage, mainly after >3 days of drainage, and in none of the eight patients with an internal shunt. Among the 340 patients with aneurysmal subarachnoid hemorrhage and no long-term tranexamic acid treatment, the frequency of rebleeding in patients with ventricular drainage (43% of 23) was significantly higher than in hydrocephalic patients without drainage (15% of 52; $X^2=5.446$, $p=0.020$), and patients without acute hydrocephalus (20% of 265 patients; $X^2=5.521$, $p=0.019$).

The conclusion is that spontaneous improvement occurs in almost half of the patients with acute hydrocephalus and impaired consciousness on admission, which is usually apparent within 24 hours, and that the outcome of patients who need ventricular drainage will improve if rebleeding and infection after insertion of the ventricular drain can be prevented.

Treatment of acute hydrocephalus after subarachnoid hemorrhage with serial lumbar puncture was studied in **Chapter 3**.[43] Acute hydrocephalus was demonstrated by computed tomography within 72 hours of subarachnoid hemorrhage in 24 (23%) of 104 patients; of these 24 patients, six (25%) had no impairment of conscious level. In nine (11%) of the remaining 80 patients, acute hydrocephalus developed within 1 week after subarachnoid hemorrhage. With the exception of three patients, all 104 patients received antifibrinolytic treatment. Delayed clinical deterioration from acute hydrocephalus occurred in seven (29%) of the 24 patients with acute hydrocephalus on admission and in six (8%) of the remaining 80 patients. Serial lumbar puncture was performed in 17 patients. Improvement in the level of consciousness was achieved in 10 (77%) of the 13 patients with delayed deterioration from acute hydrocephalus after admission (12 [71%] of the 17 patients treated with serial lumbar puncture); an internal shunt was required in four of these 17 patients (4% of all 104 patients). None of the patients deteriorated from coning following serial lumbar puncture. Rebleeding rate within 12 days after subarachnoid hemorrhage in hydrocephalic patients with serial lumbar puncture was not higher than in those without hydrocephalus (two [12%] of 17 v.s. nine [13%] of 71). Neither meningitis nor ventriculitis was observed.

The conclusion was that provided neither a hematoma with a mass effect nor an obstructive element exists, CSF drainage with serial lumbar puncture is the optimal method of treating acute hydrocephalus after subarachnoid hemorrhage.

Using single photon emission computed tomography (SPECT), cerebral blood flow was studied in eight patients with gradual deterioration in the level of consciousness after subarachnoid hemorrhage (**Chapter 4**[42]). Four had cerebral ischemia and four had acute hydrocephalus. In patients with cerebral ischemia, single photon emission computed tomography scanning showed multiple regions with decreased uptake of technetium-99M labeled *d,l*-hexamethyl-propylene amine oxime (^{99m}Tc HM-PAO) mainly in watershed areas. In patients with acute hydrocephalus, decreased uptake was seen mainly in the basal parts of the brain: around the third ventricle, around the temporal horns of the lateral ventricles, and in the basal part of the frontal lobe. After serial lumbar puncture, there was improvement of the uptake of

^{99m}Tc HM-PAO in these basal areas in three (convincingly in two and slightly in the other) of the four patients accompanied by clinical improvement in these three patients.

These results suggest that patients with acute hydrocephalus and impaired consciousness after SAH, in contrast to patients with cerebral ischemia, have decreased cerebral blood flow predominantly in the basal parts of the brain.

The effects of fluid intake and antihypertensive treatment was studied in 244 consecutive patients with subarachnoid hemorrhage who were admitted within 72 hours to the same institution between November 1977 and May 1987 and who were not treated with antifibrinolytics (**Chapter 5**[40]). From November 1977 through December 1982 (the first study period), daily fluid intake was 1.5-2 l and fluid restriction was applied when hyponatremia developed; antihypertensives were administered to all patients with high blood pressure. From January 1983 through April 1987 (the second study period), daily fluid intake was at least 3 l, fluid restriction was not applied, and antihypertensives were administered only when patients were receiving this treatment before admission; calcium antagonists were not administered. Entry variables of the patients admitted during the two study periods were not significantly different, although patients admitted during the second study period were at slightly increased risks of developing cerebral ischemia and of having a poor outcome. Despite this, cerebral ischemia occurred less frequently among patients admitted during the second study period than among those admitted during the first (16 [10%] of 155 patients vs. 19 [21%] of 89 patients; $p=0.030$). Overall mortality decreased from 46% to 36% while mortality among patients with cerebral ischemia decreased from 60% to 31% (difference not significant). Rebleeding and acute hydrocephalus occurred with the same frequency among patients admitted during both study periods.

The conclusion is, that the combination of increased fluid intake and the avoidance of antihypertensives helps prevent cerebral ischemia after subarachnoid hemorrhage.

The association between hyponatremia and cerebral ischemia was investigated in a consecutive series of 208 patients with subarachnoid hemorrhage who had a daily fluid intake of at least 3 liters and in whom fluid restriction, to correct hyponatremia, was not applied (**Chapter 6**[41]). Hyponatremia occurred in 70 (34%) of the 208 patients. The occurrence of cerebral ischemia in patients with hyponatremia, 17 (24%) of 70 patients, was significantly higher than in patients without hyponatremia, 17 (12%) of 138 patients (X =4,028, $p=0.045$). Cerebral ischemia was not more often fatal in hyponatremic patients than in patients without hyponatremia.

The conclusion was, that patients with hyponatremia are at increased risk of developing cerebral ischemia even if fluid restriction is not applied.

In this study, (**Chapter 7**[43]), with randomized controls, fludrocortisone acetate was administered to 46 of 91 patients with subarachnoid hemorrhage in an attempt to prevent excessive natriuresis and plasma volume depletion. Fludrocortisone significantly reduced the frequency of a negative sodium balance during the first 6 days (from 63% to 38%, $p=0.041$). A negative sodium balance was significantly correlated with decreased plasma volume during both the first 6-day ($p=0.014$) and the entire 12-day study period ($p=0.004$). Although fludrocortisone treatment tended to diminish the decrease in plasma volume, the difference was not significant ($p=0.188$). More patients in the control group developed cerebral ischemia (31%

vs. 22%) and, consequently, more control patients were treated with plasma volume expanders (24% vs. 15%), which may have masked the effects of fludrocortisone on plasma volume.

Fludrocortisone therefore reduces natriuresis and remains of possible therapeutic benefit in the prevention of delayed cerebral ischemia after subarachnoid hemorrhage.

SAMENVATTING

Acute hydrocephalus na een subarachnoïdeale bloeding (SAB) is een ernstige complicatie met een hoge mortaliteit. Deze hoge mortaliteit wordt hoofdzakelijk veroorzaakt door een verhoogde frequentie van dodelijke hersenischemie. Het onderwerp van dit proefschrift is de behandeling van acute hydrocephalus en hersenischemie na een doorgemaakte SAB uit een gebarsten intracraniële aneurysma.

In **Hoofdstuk 1** wordt een overzicht gegeven van de complicaties van een SAB. Hydrocephalus na een SAB werd reeds vermeld in 1928. Het duurde echter tot het begin van de vijftiger jaren voordat andere publikaties over hydrocephalus na een SAB verschenen. De eerste met CT vastgestelde acute hydrocephalus werd in 1979 gepubliceerd. Acute hydrocephalus werd door sommige auteurs klinisch niet van belang geacht. Het tegenovergestelde werd echter in een publikatie uit 1985 aangetoond. Uit dit onderzoek bleek dat met CT aangetoonde acute hydrocephalus binnen 72 uur na de bloeding een veel voorkomende complicatie is, aangezien deze gevonden werd bij 20% van de patiënten. Hoewel de patiënten aanvankelijk verbeterden na ventrikeldrainage, overleden acht van de negen gedraineerde patiënten binnen één maand na opname, hoofdzakelijk door hersenischemie. In 1964 publiceerde Crompton de resultaten van zijn onderzoek over de pathogenese van herseninfarcten na een SAB. Zijn conclusies werden ten onrechte vele jaren genegeerd, een aantal ervan werd onlangs bevestigd. De belangrijkste conclusies waren dat herseninfarcten na een SAB niet beperkt blijven tot een bepaalde vaatgebied, dat het ontstaan van hersenischemie van meerdere factoren afhankelijk is, en dat vernauwing van het arteriële lumen na een SAB wordt waarschijnlijk veroorzaakt door ischemische veranderingen van de cerebrale vaatwand. De volume-status en hypertensie behandeling blijken een belangrijke rol te spelen bij het ontstaan van hersenischemie. Andere belangrijke factoren zijn maatregelen die worden genomen om een recidief bloeding te voorkomen: vroege operatie en antifibrinolytische therapie. Echter, het verwachte gunstig effect van deze maatregelen ter preventie van een recidief bloeding wordt te niet gedaan door toename van cerebrale ischemie.

Problemen bij de behandeling van acute hydrocephalus werden bestudeerd in een opeenvolgende serie van 473 patiënten opgenomen binnen 72 uur na een SAB (**Hoofdstuk 2**[38]). In deze patiëntengroep hadden 91 (19%) hydrocephalus op de eerste CT-scan. Vijfentwintig (28%) van de 91 patiënten hadden geen gedaald bewustzijn. Elf patiënten ontwikkelden een acute hydrocephalus binnen een week na de SAB. Achtendertig (8%) van de 473 patiënten

hadden vervolgens een klinische achteruitgang door acute hydrocephalus; 11 van deze 38 patiënten hadden schommelingen van het bewustzijnsniveau. Van de 66 patiënten met acute hydrocephalus en gedaald bewustzijn bij opname, verbeterden 26 (39%) spontaan binnen 24 uur. Ventrikeldrainage werd toegepast bij 32 (31%) van de 102 patiënten met acute hydrocephalus (7% van de 473 patiënten). De mate van ventrikelverwijding was niet direct gerelateerd aan het bewustzijnsniveau en voorspelde niet de noodzaak tot ventrikeldrainage. Het bewustzijn verbeterde na ventrikeldrainage bij 25 (78%) van de 32 patiënten. Ventriculitis ontstond bij 12 (50%) van de 24 patiënten met externe drainage, vooral na 3 dagen en bij geen van de 8 patiënten met een interne "shunt". Bij de 340 patiënten met een SAB uit een aneurysma en zonder langdurende behandeling met tranexamine zuur, was het voorkomen van een recidief bloeding bij patiënten met ventrikeldrainage (43% van de 23) niet alleen significant hoger dan bij hydrocephalus patiënten zonder drainage (15% van de 52; $X^2=5.446$, $p=0.020$), maar ook bij patiënten zonder acute hydrocephalus (20% van 265 patiënten; $X^2=5.521$, $p=0.019$).

De conclusie is dat bij bijna de helft van de patiënten met acute hydrocephalus en gedaald bewustzijn bij opname spontane verbetering optreedt. Dit wordt gewoonlijk binnen 24 uur duidelijk. De uiteindelijke toestand van patiënten die ventrikeldrainage nodig hebben zal verbeteren, als recidief bloedingen en infecties na het inbrengen van een ventrikeldrain voorkomen kunnen worden.

De behandeling met lumbaal puncties van acute hydrocephalus na een SAB vormt het onderwerp van **Hoofdstuk 3.**[43] Acute hydrocephalus (binnen 72 uur na de SAB) werd gemeten op de opname CT-scan bij 24 (23%) van de 104 patiënten. 101 van deze 104 patiënten werden behandeld met antifibrinolytische therapie. Zes van de 24 hydrocephalus patiënten hadden geen bewustzijnsdaling bij opname. Bij 9 andere patiënten ontstond hydrocephalus binnen een week na de SAB. Klinische achteruitgang door acute hydrocephalus kwam voor bij 29% van de 24 patiënten bij opname en bij 6 (8%) van de resterende 80 patiënten. Lumbaal puncties werden uitgevoerd bij 17 patiënten (bij 5 van de 18 hydrocephalus patiënten met een bewustzijnsdaling bij opname en bij 12 andere patiënten na een achteruitgang door acute hydrocephalus). Verbetering van het bewustzijnsniveau werd bereikt bij 10 (77%) van de 13 patiënten met een achteruitgang door acute hydrocephalus na opname (12 [71%] van de 17 patiënten behandeld met lumbaal puncties) en 4 van de 17 patiënten die behandeld werden met lumbaal puncties kregen uiteindelijk een interne "shunt". De frequentie van recidief bloedingen binnen 12 dagen na een SAB bij hydrocephalus patiënten die behandeld werden met lumbaal puncties was niet hoger dan die van patiënten zonder hydrocephalus (6 [35%] in 17 tegen 22 [31%] in 71). Met uitzondering van drie patiënten, werden alle behandeld met antifibrinolytica. Noch meningitis noch ventriculitis werd gezien bij die patiënten die behandeld werden met lumbaal puncties of een interne "shunt".

De conclusie is dat behandeling met lumbaal puncties van acute hydrocephalus na een SAB een goed alternatief is voor behandeling met externe drainage mits er geen contra-indicatie voor een lumbaal punctie bestaat.

Middels "single photon emission computed tomography" (SPECT) onderzoek werd de cerebrale bloeddoorstroming bestudeerd bij 8 patiënten met geleidelijke bewustzijnsdaling na een SAB (**Hoofdstuk 4**[42]). Vier patiënten hadden hersenischemie en 4 hadden acute hydrocephalus. Bij de patiënten met hersenischemie toonde SPECT-onderzoek meerdere

gebieden met verminderde opname van technetium-99M gelabeld *d,l*-hexamethyl-propylene amine oxime (^{99m}Tc HM-PAO) hoofdzakelijk in waterscheidingsgebieden. Bij patiënten met acute hydrocephalus werd verminderde opname gezien overwegend in het basale gedeelte van de hersenen, rond de derde ventrikel, rond de temporaal hoorns van de zijventrikels en in het basale gedeelte van de frontaalkwab. Na lumbaal puncties was er een merkbare verbetering van de opname van ^{99m}Tc HM-PAO in deze basale gebieden tegelijk met klinische verbetering bij 3 van de 4 patiënten.

Deze resultaten geven aan dat patiënten met een acute hydrocephalus en een gedaald bewustzijn na een SAB, in tegenstelling tot patiënten met hersenischemie. een gestoorde opname van ^{99m}Tc HM-PAO hebben overwegend in het basale gedeelte van de hersenen.

Het effect van vochtinname en antihypertensiva werd bestudeerd bij 244 opeenvolgende patiënten met een SAB, die werden opgenomen binnen 72 uur tussen november '77 en mei '87 en die niet werden behandeld met antifibrinolytica (**Hoofdstuk 5**[40]). Van november '77 tot en met december '82 (de eerste studieperiode) was de dagelijkse vochtinname 1,5-2 liter en vochtbeperking werd toegepast wanneer hyponatriëmie ontstond; antihypertensiva werden toegediend aan alle patiënten met hypertensie. Van januari '83 tot en met april '87 (de tweede studieperiode) was de dagelijkse vochtinname tenminste 3 liter, vochtbeperking werd niet toegepast en antihypertensiva werden alleen toegediend wanneer patiënten deze therapie voor opname al hadden; calciumantagonisten werden niet toegediend. Patiënten die opgenomen werden gedurende de tweede studieperiode hadden een verhoogd risico voor cerebrale ischemie en voor een slechte afloop. Desondanks, kwam hersenischemie minder vaak voor bij patiënten uit de tweede studieperiode, dan bij patiënten opgenomen in de eerste studieperiode (16 [10%] van de 155 patiënten tegen 19 [21%] van de 89 patiënten; $p=0.030$). De totale mortaliteit daalde van 46% naar 36%, terwijl de mortaliteit bij patiënten met hersenischemie afnam van 60% naar 31% (geen significant verschil). Recidief bloeding en acute hydrocephalus kwamen in dezelfde frequentie voor bij patiënten opgenomen gedurende beide studieperioden.

De conclusie is dat de combinatie van ruime vochttoediening en het achterwege laten van antihypertensiva bijdragen tot het voorkomen van hersenischemie na een SAB.

De correlatie tussen hyponatriëmie en hersenischemie werd onderzocht in een opeenvolgende serie van 208 patiënten met een SAB, die een dagelijkse vochttoediening van 3 liter hadden en bij wie vochtbeperking niet werd toegepast (**Hoofdstuk 6**[41]). Hyponatriëmie kwam voor bij 70 (34%) van de 208 patiënten. De frequentie van hersenischemie bij patiënten met hyponatriëmie, 17 (24%) van de 70 patiënten, was significant hoger dan bij patiënten zonder hyponatriëmie, 17 [12%] van de 38 patiënten ($X^2=4.028, p=0.045$). De mortaliteit van hersenischemie was in beide groepen gelijk.

De conclusie is dat patiënten met hyponatriëmie een verhoogde kans hebben op hersenischemie zelfs indien vochtbeperking niet wordt toegepast.

In een gerandomiseerd onderzoek werd fludrocortison acetaat toegediend aan 46 van de 91 patiënten met een SAB in een poging excessieve natriurese en plasma volume depletie te voorkomen (**Hoofdstuk 7**[39]). Fludrocortison verminderde significant het voorkomen van een negatieve natriumbalans gedurende de eerste 6 dagen (van 63% naar 38%, $p=0.041$). Een negatieve natriumbalans was significant gecorreleerd met een plasma volume afname gedurende zowel de eerste 6 dagen ($p=0.014$) als de gehele studieperiode van 12 dagen ($p=0.004$). Hoewel

het leek dat door fludrocortison de plasma volume daling afnam, was het verschil niet significant ($p = 0.188$). Meer patiënten in de controle groep ontwikkelden cerebrale ischemie (31% vs. 22%) en bijgevolg werden meer controle patiënten behandeld met plasma volume "expanders" (24% vs. 15%) waardoor het effect van fludrocortison op plasmavolume mogelijk werd gemaskeerd.

Fludrocortison vermindert derhalve de natriurese en blijft van mogelijke therapeutische waarde voor de preventie van cerebrale ischemie na een SAB.

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