Custom-Tailored Hemodilution With Albumin and Crystalloids in Acute Ischemic Stroke

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Background and Purpose: Hemodilution in the acute phase of ischemic stroke is still controversial. Multicenter studies have failed to demonstrate any benefit. The present study focuses attention on analysis of circulation in stroke and on individual restabilization of circulation.

Methods: The Amsterdam Stroke Study is a prospective, single-center, randomized clinical trial (n=300). Normovolemic hemodilution is accomplished in a customized procedure by administration of 20% albumin plus crystalloids under hemodynamic and rheological monitoring in the acute phase of stroke. All patients receive general intensive care treatment and monitoring with a pulmonary artery catheter. This custom-tailored fluid therapy is guided on the basis of a target pulmonary capillary wedge pressure (12±3 mm Hg) and hematocrit (0.32±0.02). The control group receives only customized rehydration by infusion of crystalloids.

Results: We obtained significant (p<0.05) reduction in mortality at 3 months (from 27% to 16%) and an increase in independence at home (from 35% to 48%) after viscosity reduction by means of hemodilution with albumin in the subgroup with a hematocrit <0.45 (n=201) (specific viscosity effect). We also obtained a significant (p<0.005) reduction in mortality at 3 months (from 27% to 8%) and an increase in independence (from 35% to 59%) after only rehydration with crystalloids in the subgroup with overt dehydration (hematocrit ≥0.45; n=51) as compared with the normal-hematocrit group without signs of dehydration (hematocrit <0.45; n=103) (specific rehydration effect).

Conclusions: This study may provide an explanation for the failures in former hemodilution trials and may re-establish proper hemodilution and rehydration as a valuable therapy in the acute phase of stroke, thus reducing mortality and improving independence after 3 months. (Stroke 1992;23:181-188)
The circulatory filling pressure is also affected by the pharmacodynamic variability of hemodilution therapy. The effect of hemodilution on the peripheral vascular resistance results in a venous vasodilatation with the risk of relative hypovolemia unless adequate additional volume is given. Additional volume becomes even more critical if the patient was already dehydrated before hemodilution was begun. As will be shown, about one third of all stroke patients in this study were dehydrated on admission to the hospital. On the other hand, one should be careful with additional volume in patients with cardiac or circulatory insufficiency, which are present in approximately one third of all stroke patients.

The great variety in mechanisms of cerebral circulatory failure requires individualized analysis and therapy. The differences between the Amsterdam Stroke Study and other recent hemodilution trials in Scandinavia, Italy, and the United States are obvious. Generally, in each of the other three trials there was a hypervolemic regimen in the first hours, resulting in a dangerous circulatory overload in the abovementioned one third of stroke patients with cardiac insufficiency. However, in the postacute phase after several hours or days, especially in the one third of stroke patients with clear dehydration, hypovolemia developed because of the short half-life of dextran 40 or starch used to replace the withdrawn blood. Actually, in two thirds of the patients in the standardized hemodilution trials with dextran or starch, the hemodilution protocol was a threat to the patient.

Subjects and Methods

The Amsterdam Stroke Study was set up as a single-center study of stroke therapy in an intensive-care setting. This has important advantages for the standardization of the various measurement techniques and the use of the different scoring lists. In this protocol, the patients are assigned at random to the hemodilution or control group and stratified with respect to three parameters: Ht <0.45 or >0.45; delay between onset of symptoms and admission less of ≤24 hours, or >24 but <48 hours; and location of the lesion in the carotid or vertebrobasilar regions of the cerebral circulation.

One of the problems with the methodology of hemodilution trials is that a blind control group is not possible, either for the patient or for the medical staff. An attempt was made to eliminate the possible resultant bias by maintaining two separate documentations of the experimental data, one for the method of treatment and one for the results obtained. The two types of information were not coupled until the data were released for automatic processing.

Most of the patients were referred to the trial from the emergency ward of the hospital, while others were referred from the neurological outpatient clinic. Patients were accepted for the trial if the symptoms resulted from an ischemic cerebral lesion, the symptoms were still present when the patient was referred, the delay between onset of symptoms and admission was <48 hours, none of the criteria for exclusion were present, and there was informed consent. To verify the diagnosis of ischemic stroke and exclude hemorrhages and space-occupying cerebral lesions, the clinical examination was supplemented by a computer-assisted tomography done at admission and after 1 week. The total number of patients excluded was 36% (174 of 474 patients). The reasons for exclusions were another diagnosis (32%), delay >48 hours (37%), preference for other therapy (18%), no follow-up possible (8%), no consent (1%), cardiopulmonary contraindications (0.5%), and other reasons (3.5%).

In this trial, hemodilution was achieved by withdrawal of blood and infusion of 20% albumin supplemented with Ringers-glucose to a desired Ht of 0.32±0.02 and a desired wedge pressure of 12±3 mm Hg. Supplementation with crystalloids in the control group was not a defined target in the protocol, but was a consequence of hemodynamic monitoring and proper intensive care. In our opinion, it is unacceptable on ethical grounds to deprive any patient of standard normovolemic circulatory conditions, especially if these can be monitored.

For the purposes of hemodynamic monitoring, all patients were given an intra-arterial line and a pulmonary artery catheter unless there was a contraindication, and all were treated according to a standardized written protocol. In general, we used the following guidelines: all drugs for which no clear indication could be found were withdrawn and the effects of their withdrawal observed for 5 days; drugs for which there was a clear indication, but which could have had a negative effect on the central nervous system, such as hypnotic analgesics or sedatives, were withdrawn if at all possible; drugs for which there was a clear indication, but which were specifically contraindicated under the circumstances of the trial, such as vasoactive agents or diuretics, were also withdrawn; and medication for which there was an indication independent of the state of the circulatory system was continued, but the dosage was subject to adjustment on the basis of improved insight.

The standard treatment was adjusted to the needs of the individual patient whenever necessary. The status of all patients was discussed on a daily basis with representatives of the various clinical and nursing disciplines. We have outlined the standard treatment in detail in order to make clear that the patients of the control group in this study were also treated on an intensive-care basis and that the results of the hemodynamic measurements also played a central role in determining the general policy.

Consent was requested from the patient or relatives after an explanation of what the study entailed. The patient was also informed that he could withdraw from the study at any time. No treatment proven to have a favorable effect was withheld from any of the patients. The protocol of the study was approved by the Committee on Ethics of the hospital involved.
During the 5 days that the patients were treated in the Stroke Care Unit, all parameters were recorded at least once a day. The whole blood viscosity was measured in an automated protocol\textsuperscript{15} using a rotational viscometer (model LS300, Contraves AG, Zurich, Switzerland). The colloid osmotic pressure was measured with a membrane pressure-difference meter (model 4400, Wescor Inc., Logan, Utah). Hemodynamic parameters were measured with the aid of a thermistor-tipped pulmonary artery catheter. Systemic blood pressure was measured continuously through an intra-arterial line. Blood gases, together with the hemodynamic measurements, were determined at least once a day.

In evaluating the results of the Amsterdam Stroke Study, we developed a Prognostic Clinical Outcome Score in which not only the neurological deficit, but also the age of the patient, the delay between onset of symptoms and admission to the hospital, and the Ht were integrated, because these factors also determine to a high degree the prognosis of a patient with an infarction. To measure neurological severity, we used the Initial Severity Score according to Spence and Donner.\textsuperscript{19} We scored consciousness and motor function exactly according to Spence and Donner, but modified the scoring of age and added scoring of delay and Ht. The parameters of the Prognostic Clinical Outcome Score are, therefore, as follows: level of consciousness (0–50 points); motor function (0–60 points); age (0–45 points: <66 years, 66–70, 71–75, and >75 years provide 0, 15, 30, and 45 points, respectively); delay (0–45 points: <6 hours, 6–12, 13–24, and 25–48 provide 0, 15, 30, and 45 points, respectively), and Ht (0–45 points: <0.30, 0.31–0.34, 0.35–0.37, 0.38–0.41, 0.42–0.44, 0.45–0.49, and ≥0.50 provide 45, 30, 15, 0, 15, 30, and 45 points, respectively). This score gives an impression as to the most important risk factors and their contribution to the prognosis and natural outcome of a stroke patient apart from any therapeutic intervention and is considered a more complete initial severity score. According to this score, there were no significant differences between the hemodilution and control groups with respect to their initial severity.

The criteria selected for a general evaluation were the mortality and the place of residence after 3 months, the latter being subdivided into hospital, nursing home, rehabilitation center (dependent), and the patient’s own home (independent). The place of residence shows a significant correlation with the neurological severity and disability scores, which will be described in detail in a later article. The degree of disability is established with the aid of standardized scales as proposed by Barthel and Rankin.\textsuperscript{20,21} The most important data from the neurological examination carried out on admission are recorded with the aid of a standard form.\textsuperscript{22,23}

The general evaluation was carried out at two levels: 1) comparison between the hemodilution group H (n=148) and the control group C (n=152); and 2) comparison of the four subgroups stratified on the basis of hematocrit. The subgroups are as follows: group N\textsubscript{C} (n=103), normal Ht (<0.45) and control; group N\textsubscript{H} (n=98), normal Ht and hemodilution; group E\textsubscript{C} (n=51), elevated Ht (≥0.45) and control; and group E\textsubscript{H} (n=48), elevated Ht and hemodilution.

Statistical analysis for this general evaluation was performed using the \( \chi^2 \) test for comparing percentages, Student’s \( t \) test for comparison of two mean values, and the \( \chi^2 \) test for trend (Cochran-Mantel-Haenszel test\textsuperscript{24}) for comparison of the percentages dead, dependent, and independent patients.

**Results**

From April 1986 to April 1990, 300 patients were included in the Amsterdam Stroke Study. Table 1 shows the epidemiological characteristics, such as the stratification factors Ht, delay, type of infarction, and distribution according to sex and age. Both the average age of the patients (74.5 years) and the low percentage of exclusion on the basis of the severity of the patient’s condition (only 0.5% excluded for cardiopulmonary insufficiency) indicate that this was definitely a “high risk” group; even patients in coma were not excluded.

As indicated above, it is characteristic for the Amsterdam Stroke Study that normovolemia was achieved in both the control and hemodilution groups (pulmonary capillary wedge pressure of 12±3 mm Hg) and that the reduction of the Ht to 0.32±0.02 in the hemodilution group was realized by withdrawal of blood and its replacement by albumin and crystalloids (Figure 1). Interestingly, there was also a decrease in Ht in the control group due to the administration of crystalloids, with food and drink ad libitum. The pulmonary capillary wedge pressure was essentially identical throughout the 5 days in the control and hemodilution groups.

A high Ht can be the result of either polycythemia or dehydration. Polycythemia is characterized by a high Ht in combination with a normal colloid osmotic pressure, whereas in dehydration, both the Ht and the colloid osmotic pressure are elevated. Figure 2 shows that in the group with a high Ht, the colloid osmotic pressure on admission was significantly higher than in the group with a normal Ht (\( p<0.01 \)), indicating that a high Ht in stroke patients should be interpreted as a sign of dehydration and a contracted circulatory volume rather than of polycythemia.

Concerning the risk factors and medication in the various subgroups, there is a relatively high percentage of chronic obstructive pulmonary disease (16% versus 11%), smokers (54% versus 39%), and a higher incidence of therapy with diuretics (35% versus 28%) and calcium antagonists (9% versus 4%) in the elevated Ht group compared with the normal Ht group. Conversely, there is a relatively higher percentage of hypertension (44% versus 38%) and arrhythmia (41% versus 36%) and more frequent vasodilator therapy (33% versus 21%) in the normal Ht group.
TABLE 1. Epidemiological Data for the Study Subgroups

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<th>Total</th>
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<th>Nc</th>
<th>Nh</th>
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C, control; H, hemodilution; Nc, normal hematocrit (Ht) (<0.45) and control group; Nh, Normal Ht and hemodilution group; Ec, elevated Ht (≥0.45) and control group; and Eh, elevated Ht and hemodilution; see “Subjects and Methods” for further explanation.

Data are % unless indicated otherwise.

In contrast to the substantial differences in risk factors and medication, the subgroups were not significantly different with regard to the prognostic outcome score as defined on the basis of the following five factors: level of consciousness, motor function, age, delay, and Ht.

As shown in Figure 3, the clinical outcome is not significantly different in the hemodilution and control groups as a whole. However, the results of the evaluation at the level of the four subgroups (hemodilution versus control at either normal or elevated Ht in accordance with the prior stratification), as shown in Figure 4, reveal both a significant effect and a very interesting phenomenon. First, in two thirds of the stroke patients (those with a normal Ht, i.e., <0.45), hemodilution therapy (group Nh) yielded significantly better results (p<0.05) than in those patients in the control group (Nc). However, in one third of the stroke patients (those with an elevated Ht, i.e., ≥0.45), the results in the control group (Ec) seem to be better, but not significantly, than those in the hemodilution group (Eh).

It is clear that, if the hemodilution and control groups are recombined on the basis of the initial Ht, the average score with an elevated Ht (Ec+Eh) is better, although not significantly so, than with a normal Ht (Nc and Nh) (mortality-dependency-independence: 21–37–42% versus 13–35–52%). This is interesting, since previous studies have demonstrated that a stroke with an elevated Ht has a less favorable natural course and leads to larger infarctions, if deprived of adequate cardiovascular therapy.

We found that a reduction in mortality leads to a similar improvement in independence at home and not to any increase in disability (Figure 4). The relatively high mortality in the hemodilution group with elevated Ht (Eh) is obvious. Hypovolemia after

FIGURE 1. Time course of hematocrit during the first 5 days of intensive-care treatment. &: Before hemodilution; #, after hemodilution.

FIGURE 2. Bar graph of colloid osmotic pressure (COP) on admission in groups with high and normal hematocrit (Ht).
extreme bloodletting probably plays a role in this already-dehydrated group, but even in the hemodilution group with normal Ht (NH, not dehydrated), in which bloodletting was less extreme, this mechanism of induced hypovolemia can play a role. Our analysis of the subgroups has made it clear that viscosity and circulatory volume are pivotal pathogenetic factors, which sometimes potentiate (Ec, normovolemic rehydration and slight viscosity decrease) and sometimes counteract each other (NH and EH, induced hypovolemia and strong viscosity reduction). If one looks only at the Ht in the four subgroups (Figure 5), there is clearly no simple relationship between Ht and clinical outcome (Figure 4). The rapid increase in Ht in the EH group, compared with the NH group, in the first weeks is interesting and indicates a problem with volume control, especially in the EH group.

Consideration of all patients yields new information with respect to the effect of delay before admission. While confirming that the prognosis of a cerebral infarction in response to adequate therapy becomes less favorable as the onset of treatment is delayed, many authors have emphasized the "time window" for therapy,25 the maximal delay being 6–12 hours before onset of treatment. However, this by no means implies that a longer delay is a contraindication to treatment or will always mean a poor prognosis. Our study even shows a more favorable, not significant, prognosis after delayed admission. The percentages of mortality–dependency–independence after 3 months in case of a short delay (≤24 hours) were 20–37–42% compared with 13–33–54%, respectively, in case of a longer delay (>24 hours and ≤48 hours). In fact, in our experience it is in the milder infarctions that treatment tends to be delayed longer; obviously, the family physician, the patient, and the relatives often want to "wait and see," since the symptoms may not yet be so alarming.

**Discussion**

The starting point of the Amsterdam Stroke Study was an individually adjusted, optimal hemodilution technique as described by Grotta for the Hemodilution in Stroke Study Group.13 In comparison with earlier studies, there are quite a few important differences, such as the hemodiluent used (albumin versus modified starch or dextran) and the fact that the control group also received hemodynamic monitoring and proper care with the aid of a pulmonary artery catheter. This regimen had inevitable consequences for the treatment of the control patients, especially the dehydrated patients with a contracted circulatory volume syndrome.26 Nevertheless, the point of departure of the Amsterdam trial can be compared with that of the American hemodilution trial.13 The diagnosis of dehydration and hypovolemia could be established on the basis of the Ht (high), colloid osmotic pressure (high), and wedge pressure (low), with the result that crystalloids often had to be administered in large doses. The control group in our study is thus a real intensive-care group.

Hemodilution with colloids instead of crystalloids has definitely produced less cerebral edema in animal experiments.27 However, in a clinical setting, working with patients who exhibit much more variable initial conditions, dehydration must be suspected in one third of the stroke patients. Rehydration may require several liters a day, which should first be given in the form of crystalloids.

In our experience, given hemodynamic control, there are hardly any cardiac contraindications to hemodilution; on the contrary, normovolemic hemodilution appears to be an adequate therapy even in the presence of a poor cardiopulmonary status. It often brings the patient back to physiological conditions and creates the possibility of reducing the cardiac afterload in such a way that the dosage of vasoactive and diuretic agents can be reduced to an absolute minimum. It should be mentioned that in
the Amsterdam trial, after the acute intensive care phase of 5 days, the "old" regimen of diuretics, vasodilating agents, and β-blockers was often re instituted by the cardiologist or internist. The underlying reason for this is that the interests of the heart and brain are often not entirely congruent, and there is a tendency to let the requirements of the heart prevail.

The terminological confusion regarding isovolemic, normovolemic, and hypervolemic hemodilution can be clarified somewhat by adding criteria into which the initial conditions of the patient have been incorporated. An isovolemic exchange in a hypervolemic patient remains a hypovolemic hemodilution. For this reason, we prefer the term "normovolemic hemodilution," defined on the basis of optimal measured values in the patient: an Ht of approximately 0.32, a pulmonary capillary wedge pressure of approximately 12 mm Hg, and a normal colloid osmotic pressure of 22–24 mm Hg. To achieve this, we recommend a "custom-tailored" hemodilution.

With regard to the choice of albumin, in addition to the important advantages related to erythrocyted and thrombocyte-aggregation, the capture of oxygen radicals, and the buffering of the microcirculation, a stable, long-term normovolemia can only be achieved with the aid of a natural colloid that is neither broken down nor excreted to a large extent. This has been a crucial defect in practically all of the clinical hemodilution trials reported to date8-13; a strongly hypervolemic regimen at the beginning, followed after a few hours or days by a hypovolemia resulting from the withdrawal of blood and the short half-life of the hemodiluent used. Even in the Amsterdam Stroke Study, where albumin was administered, a secondary hypovolemia developed after 2–3 weeks, manifested most clearly in the elevated Ht (Eh) of the hemodilution group (Figure 5). The results were rather good in this group (Figure 4), but less favorable than in the control group Ec receiving only crystalloids, without withdrawal of blood. We must concludes that patients with a high Ht seem to be more sensitive to secondary hypovolemia because they are already hypovolemic. The hemodilution protocol we used must therefore be adjusted for these patients with an Ht of ≥0.45, so that there is less withdrawal of blood and more rehydration. In the normovolemic group with an Ht of <0.45, the protocol in the acute phase may be left unchanged. It is extremely important to recognize that there are two underlying aspects in any hemodilution therapy: a reduction of the viscosity and an optimization of the circulating volume. These two factors make stroke with a normal Ht a different phenomenon than stroke with a high Ht.

Concerning the risk factors, the subgroups with a normal Ht (Nc and Nh) also had a higher average age and more severe neurological symptoms initially compared with the subgroups with an elevated Ht (Ec and Eh). The delay before admission was approximately the same in both groups. The groups with an elevated Ht were also characterized by a more frequent use of diuretics and less frequent use of vasodilating agents. This group also contained more patients with chronic obstructive pulmonary disorders and smoking problems. These combinations of risk factors are probably not accidental. With a normal Ht and normal circulatory filling, the main limiting factor is the vascular system. This is accompanied by a higher age and a larger initial infarction zone. With an elevated Ht and hypovolemia, the onset of a stroke is caused not only by the sclerotic vascular bed, but even more by the elevated blood viscosity and the reduced flow, so that the stroke takes place at a younger age. Medication (particularly diuretics), smoking, and chronic pulmonary disease lead to dehydration, polycythemia, or a combination of the two.

The clinical outcome will clearly be less favorable in the presence of a poor vascular system because the vascular factor is only correctable with difficulty, if at all. In the case of dehydration and hyperviscosity, the causes of the stroke can be alleviated with ease, which logically also results in a better clinical outcome after treatment. This is all the more striking because without rheological intervention, the natural clinical outcome of patients with an elevated Ht is generally poorer than in those with normal Ht.25,29 There are also studies that deny a relationship between Ht and natural clinical outcome.30,31 One reason is that some patient groups with symptomatic obstructive cerebrovascular disease, most commonly internal carotid occlusion,31 are more limited in their vascular factor than in the viscosity factor. Another explanation could be that Ht is just one of the determinants of clinical outcome, and the general negative influence of a high Ht can be counteracted by a lower age and a smaller infarction, as shown in this trial. This is comparable with the longer delay generally associated with a smaller initial deficit,
which does not mean that a long delay is favorable. It is important to take into consideration all the relevant determinants contributing to the final clinical outcome: the initial neurological deficit, the age, the hematocrit, the delay before treatment, and the treatment itself, with a viscosity component and a hydration component.

It should be realized that the figures given are percentages of the total group. However, a decrease in mortality from 27% to 16% by viscosity reduction (i.e., −11%) and from 27% to 8% (i.e., −19%) by rehydration means a reduction in mortality by 41% and 70%, respectively. In the same way, an increase in independence from 35% to 48% (i.e., +13%) by viscosity reduction and from 35% to 59% (i.e., +24%) by rehydration means an increase in independence by 37% and 69%, respectively. The overall reduction in mortality and increase in independence with adequate custom-tailored viscosity reduction and rehydration can be estimated at >50%. An indication of the clinical outcome at 3 months for a non-intensive-care control group can be taken from the Tilburg Epidemiological Study of Stroke:32 31% mortality and an equal percentage of 34% for both dependency and independence. These data are comparable with the results of the Scandinavian trial:10 if the high percentage of excluded patients in this trial (69%) is taken into account. The prognosis of the stroke patient (mortality–dependency–independence) at 3 months can be improved from about \( \frac{1}{2} \) to \( \frac{1}{4} \) to \( \frac{3}{4} \) to \( \frac{1}{2} \) respectively.

On the basis of the Amsterdam Stroke Study, we can draw several conclusions. Hemodilution must be performed in a customized rather than a standard manner, using a long-acting hemodiluent such as albumin. The higher the hematocrit, the more the therapy should be focused on rehydration with crystalloids, rather than on viscosity reduction by means of bloodletting. In 66% of stroke patients (i.e., those with an Ht of <0.45), normovolemic hemodilution with albumin and crystalloids (NH), guided on the basis of the hematocrit (0.32±0.02) and the pulmonary capillary wedge pressure (12±3 mm Hg), gives a statistically significant better clinical outcome compared with the control group (NC): the viscosity effect. In 33% of stroke patients (i.e., those with an Ht of ≥0.45, dehydration), normovolemic hemodilution (EH) also gives good results compared with the general intensive-care group without specific circulatory therapy (NC), but these good results are surpassed by the results of treatment with large doses of crystalloids alone (EC): the rehydration-effect is therefore statistically significant. In the group with elevated Ht, one should be careful with the withdrawal of blood because of the danger of secondary hypovolemia.

Acknowledgments

The authors gratefully acknowledge the assistance of B.J.J. Ansink, C.J. Snijders, J.A.L. Vanneste, and J. Vos, neurologists; G.A.G. Davies, neuroradiologist; and H. van Duyn, neurophysiologist, of the St. Lucas Hospital, Amsterdam, The Netherlands.

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**KEY WORDS** • viscosity • albumin • cerebral ischemia • hemodilution • viscosity
Custom-tailored hemodilution with albumin and crystalloids in acute ischemic stroke.

*Stroke*. 1992;23:181-188
doi: 10.1161/01.STR.23.2.181

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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