Original Contributions

Multicenter Trial of Hemodilution in Acute Ischemic Stroke
I. Results in the Total Patient Population

Scandinavian Stroke Study Group

Hemodilution by the combination of venesection and dextran 40 administration has previously been reported to enhance neurologic recovery in the acute phase of ischemic stroke. To study this therapeutic principle in its "natural habitat," a stratified and randomized multicenter trial involving 15 large and small hospitals was performed. Patients with acute ischemic stroke of <48 hours’ duration and with hematocrits of 38–50% on admission were randomized to a hemodilution (183 patients, mean age 72.0 years) or a control group (190 patients, mean age 71.6 years). The two groups did not differ in sex distribution or medical history. Hematocrit, blood pressure, and neurologic score were closely similar at entry. By graded venesection (250–1000 ml) during the first 2 days and dextran 40 infusions (500 ml daily) during 5 days, the mean hematocrit was reduced from 44.2 to 37.1%. Three-month survival expressed as life table product was 0.84 in hemodilution and 0.88 in control patients. In survivors, neurologic score and activities of daily living performance during 3 months of follow-up were not improved by hemodilution. Length of stay in an acute-care hospital and the need for long-term institutional care was not reduced among patients in the hemodilution group. Major cardiovascular events occurred somewhat more often and there was an apparent increase in mortality during the first few days of hemodilution therapy. However, the differences were not significant. We conclude that the present standardized treatment with moderate hemodilution has no overall beneficial effects in general patients with acute ischemic stroke. (Stroke 1987; 18:691–699)

In recent years, hemorheologic factors have attracted much attention as possible contributors to the pathophysiology of ischemic stroke. Cerebral blood flow (CBF) has been shown to be inversely related to hematocrit and whole-blood viscosity. The stroke risk appears to be increased not only in hyperviscosity states such as polycythemia and paraproteinemia but also in individuals with hematocrits in the upper normal range. In patients with ischemic stroke, enhanced aggregation and reduced deformability of erythrocytes have been demonstrated.

In the normal brain, CBF is increased during intentional hemodilution. It has not been determined if this phenomenon represents a regulatory mechanism ensuring a constant supply of oxygen to the brain tissue or if the increase in cerebral blood volume exceeds the decrease in oxygen carrying capacity so that a true enhancement of oxygen and nutrient supply results. In ischemic brain tissue, there is a breakdown of cerebral autoregulation, i.e., CBF is no longer independent of blood pressure. In this situation, if local blood flow is less determined by vascular resistance, it is conceivable that hemorheologic factors emerge as more important in nutrient supply and transportation of waste products. Hemodilution has been shown to reduce cerebral ischemic lesions in experimental animals. In humans, previous investigators have applied hypervolemic hemodilution by administering plasma volume expanders, usually dextran. Beneficial effects as well as no effects have been reported.

Many patients with acute stroke have cardiac disorders making them tolerate volume overload poorly. Therefore, the combination of venesection and infusion of plasma volume expanders has been used to achieve rapid hemodilution with less risk of compromising the systemic circulation. This therapeutic prin-
Priciple has been adopted locally as routine treatment of acute ischemic stroke. In a single-center randomized controlled trial involving 102 patients in a stroke unit, beneficial effects of the combination of venesection and dextran 40 administration were reported. When compared with a control group, treated patients had better early neurologic recovery, they were left with fewer functional impairments, and a larger proportion of patients were able to return home. Mortality, however, was little affected by hemodilution.

These results were sufficiently encouraging to prompt a larger study. The present multicenter trial was therefore initiated using a study protocol similar to that of the single-center trial. The major aims of this study were first, to explore whether beneficial effects of hemodilution in acute ischemic stroke could be verified in a larger group of patients recruited from a more common clinical setting than the research-oriented stroke unit, and second, to obtain a patient sample large enough to permit analyses of subsets of patients. In this article, overall results in the total patient population will be reported. The results in subgroups of patients will be presented in a forthcoming communication.

Subjects and Methods

Three hundred seventy-three patients were included in the trial. The study protocol has previously been presented and commented upon in this journal. Fifteen centers in 4 Scandinavian countries participated; 5 were university hospitals and 10 nonuniversity hospitals. A steering committee was responsible for the conduct of the trial. The investigation was approved by 5 regional ethical research committees.

Patient Inclusion

All patients presenting with focal neurologic deficits of presumed cerebrovascular origin were considered for the study. Inclusion criteria were: 1) start of treatment possible within 48 hours of onset of neurologic symptoms; 2) absence of intracranial hemorrhage demonstrated by computed tomography (CT) scan or cerebrospinal fluid (CSF) spectrophotometry (if a CT scan was not performed before inclusion, the diagnosis was confirmed by a CT scan within a week or by a repeat CSF spectrophotometry on Days 4–7); 3) hematocrit between 38.0 and 50.0%; 4) systolic blood pressure ≤ 250 mm Hg and diastolic pressure ≤ 130 mm Hg; 5) no acute myocardial infarction in the preceding 4 weeks, no severe angina pectoris, and no overt signs of left ventricular failure (significant pulmonary rales, diastolic filling gallop, or x-ray signs of cardiac failure); 6) no ongoing anticoagulant treatment and no clinical indication for this treatment (such as progressing stroke) evident before inclusion; 7) absence of known renal failure (plasma creatinine < 300 μmol/l or serum urea < 14 mmol/l); 8) no concomitant terminal or immediately life-threatening disorder; 9) absence of very severe previous disability precluding meaningful assessment of changes in neurologic deficits and activities of daily living (ADL) function; 10) absence of coma or deep stupor without reaction to speech; and 11) oral consent by patient or, when applicable, family member after oral and written information. There were no age limits.

To estimate how the study population compared with a general stroke population, detailed records of all patients with acute stroke considered for the study were kept at 13 of the 15 centers. Of 1,032 patients presenting with stroke in these centers, 325 (31.5%) were included in the trial. The reasons for excluding patients have been presented in detail previously. Only 1 reason was recorded in each excluded patient; the major reasons were delay of > 48 hours (21.6%), anticoagulant treatment (9.0%), intracranial bleeding (6.5%), previous disease precluding scoring (6.3%), severe cardiac disorder (5.4%), hematocrit < 38 or > 50% (5.1%), coma (4.1%), and consent not given (3.4%). In these 13 centers, the proportion of men was 58.0% in subjects that were included and 50.1% in those excluded, whereas mean age (± SD) was 71.6 ± 8.5 years in included and 73.4 ± 10.5 in excluded patients.

Stratification and Randomization

Once included, patients were stratified by center, age (≤ 65, 66–75, and ≥ 76 years), and a prognostic neurologic score as described previously. Within each stratum, they were then randomized to either the treatment or control group in preset multiples of 4 by drawing envelopes containing a slip assigning a particular patient to one of the two groups.

Hemodilution Treatment

Treatment was started immediately in patients randomized to hemodilution. Twenty milliliters of haptendextran (Promiten, Pharmacia, Uppsala, Sweden) was given to block possible antibodies to dextran, and dextran infusion and venesection were initiated simultaneously. If hematocrit was 38.0–41.9%, a 250-ml venesection was performed. If hematocrit was 42.0–50.0%, 500 ml of blood was taken. During venesection, the same amount of dextran 40-saline (Rheomacrodex, Pharmacia) was infused in the other arm; a rate of blood withdrawal greater than the rate of dextran infusion was cautiously avoided to minimize the risk for hypovolemia. If venesection involved 250 ml, another 250 ml of dextran 40 was administered during the following 2–4 hours. On the following day (Day 1), the hemodilution procedure was repeated, applying the same hematocrit cut-off levels as on the day of entry. If hematocrit was now < 38%, no venesection was performed but 500 ml of dextran 40 was given. On days 2–4, no further venesection was done, but 500 ml of dextran 40 was infused daily over 2–4 hours to maintain hemodilution.

Treatment was interrupted if an adverse reaction to the treatment was evident or suspected, if intracranial bleeding was diagnosed after inclusion, if the diagnosis of cerebrovascular disease was disproved, if anticoagulant treatment was judged by the attending physician to be clearly indicated, if acute myocardial infarction was diagnosed before inclusion, or if the patient was considered unsuitable for the present procedure. In case of an adverse reaction, the venesection was stopped, and dextran 40 infusion was cautiously avoided to minimize the risk for hypovolemia. If venesection involved 250 ml, another 250 ml of dextran 40 was administered during the following 2–4 hours. On the following day (Day 1), the hemodilution procedure was repeated, applying the same hematocrit cut-off levels as on the day of entry. If hematocrit was now < 38%, no venesection was performed but 500 ml of dextran 40 was given. On days 2–4, no further venesection was done, but 500 ml of dextran 40 was infused daily over 2–4 hours to maintain hemodilution.
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infarction, plasma creatinine levels > 300 µmol/l, or blood pressure > 250/130 mm Hg occurred, or if the patient wanted to withdraw from the study. Patients in whom treatment was interrupted are presented in “Results.” Only if a patient was proven to have a diagnosis other than stroke (e.g., brain tumor), was he or she excluded from the data analysis. In all other instances (even if treatment could not be performed or was interrupted very early), the patient remained in the hemodilution group, thus adhering strictly to the intention-to-treat principle.24

Patients in the control group were in the same wards as the hemodilution patients, and the regimes for basic medical care, nursing, activation, and rehabilitation were identical. No sham procedures were involved.

Evaluation of Treatment

The following variables were evaluated: 1) hematocrit and blood pressure during the treatment period (Days 0-5) and at 3 months after entry; 2) neurologic scores (see below) before randomization (Day 0), on Day 5, and at 3 months; 3) ADL proficiency assessed by the Maryland Disability Index (Barthel score)25 on Day 5 and at 3 months; 4) occurrence of recurrent strokes, major cardiac events, peripheral vein thrombosis, pulmonary embolism, and diabetes during the first 3 months; 5) drug intake and cerebrovascular surgery during 3 months; and 6) deaths, causes of death, and need for long-term care in a hospital, nursing home, or other institution in the first year (only results from the first 3 months are reported here). For neurologic assessment, a 0 to 48 point scoring system, as presented earlier,21 was used. Initial scorings were performed before randomization; thereafter, scorings were done by a rater who was unaware of the group to which the patient had been assigned. Consistency between centers was obtained by joint neurologic and ADL scoring exercise sessions before the trial was started. An electrocardiogram (ECG) was obtained in all patients at least once in the first 3 days.

Handling and Quality of Data

Data protocols were submitted to the coordinating center at Umeå University and checked for completeness, number of errors, and delay from expected follow-up to submission. Data quality was, in general, excellent and showed no major differences between nonuniversity and university centers. The mean number of errors per protocol was 0.13 in university and 0.08 in nonuniversity centers, and the mean number of missing data per protocol was 1.48 and 0.38, respectively. The proportion of protocols submitted within 1 month of expected follow-up was 67% in both university and nonuniversity centers.

Sample Size Calculations and Statistics

The sample size chosen for this study (approximately 200 in each group) gives a 95% confidence interval for a 50% proportion of ± 7% (43–57%), which was regarded as sufficiently narrow to detect differences in the statistical calculations that were also clinically important. To describe distributions of data, standard deviation (SD) has been used for variables assumed to be symmetrically distributed. Quartile distances have been used for score data. Groups have been compared by χ² analysis, analysis of variance, and log rank tests as indicated in the text.

Results

Comparability of the Study Groups

One hundred eighty-three patients were randomized to the hemodilution and 190 to the control group. As shown in Table 1, mean ages were closely similar in the two groups, and there was a male predominance among both hemodilution and control patients. The distribution of previous cardiovascular disorders did not show any significant differences (Table 1). A history of transient ischemic attack (TIA) and smoking was somewhat more common in hemodilution patients, and diabetes occurred more often in control subjects. However, none of these differences reached significance (p values 0.15–0.28 by χ² test). By history, approximately one-fifth of the individuals in both groups had atrial fibrillation. ECGs obtained in the first days after admission revealed atrial fibrillation in 41 (22%) of hemodilution and 39 (21%) of control patients. In the prognostic neurologic score used for stratification, 16% of the patients allocated to the hemodilution group and 12% of those in the control group had scores of < 10 points, signifying poor prog-

Table 1. Sex, Age, Medical History, Smoking Habits, and Side of Neurologic Deficits in 183 Hemodilution and 190 Control Patients With Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Hemodilution</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>63</td>
<td>55</td>
</tr>
<tr>
<td>Females</td>
<td>37</td>
<td>45</td>
</tr>
<tr>
<td>Age, mean ± SD (years)</td>
<td>72.0 ± 8.4</td>
<td>71.6 ± 9.5</td>
</tr>
<tr>
<td>Medical history (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manifest stroke</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers*</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Side of predominant neurologic deficits (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>Left</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Bilateral</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

*Including subjects who stopped smoking in the preceding year.
†Side of body.
nosis quo ad vitam (maximum is 22 points). Hematocrit and blood pressure at entry are compared below.

**Diagnostic and Hemodilution Procedures**

The diagnosis of a cerebral ischemic event was supported by a CT scan in 111 of the hemodilution patients (61%) and in 122 of the control patients (64%). In all remaining subjects, CSF spectrophotometry was performed. The interval from the onset of symptoms to the start of hemodilution treatment is shown in Figure 1. Median interval was 20 hours. Treatment was initiated within 12 hours in 28% and within 24 hours in 67% of the patients.

In Table 2, the amounts of blood taken during hemodilution is shown. On the day of entry, the great majority of patients underwent a 500-ml venesection. On the following day (Day 1), 500 ml of blood was taken in approximately one-third and 250 ml in one-fourth, and in one-third of the patients no phlebotomy was performed because hematocrit had dropped to <38%.

Hemodilution treatment was interrupted in 21 patients (11%). In 6 patients the reason was early death, in 1 a suspected anaphylactic reaction that readily reversed on termination of dextran infusion without further intervention, in 8 acute myocardial infarction or left ventricular failure, in 4 intracranial bleeding detected after inclusion, in 1 start of anticoagulant treatment, and in 2 on request of the patient.

**Hematocrit and Blood Pressure**

At entry, hematocrit was $44.3 \pm 3.2\%$ (mean $\pm$ SD) in the hemodilution group and $44.7 \pm 3.5\%$ in the control group. Changes in hematocrit are demonstrated in Figure 2. By Day 5, hematocrit was reduced to $37.1 \pm 3.8\%$ in the hemodilution group but had returned to pretreatment levels by 3 months after hemodilution. Mean hematocrit was essentially unchanged throughout the observation period in control subjects.

Blood pressure was closely similar in the two groups at inclusion (Figure 3). The well-recognized decline in blood pressure in the first few days after stroke occurred in both groups. Mean reduction was somewhat greater in hemodilution patients (change between Days 0 and 2, 18/10 vs. 13/6 mm Hg), but this difference did not reach significance. At 3 months' follow-up, almost identical blood pressures were again recorded (Figure 3).

**Neurologic Outcome**

In our neurologic rating system, the maximum score of 48 points signified no deficit in the assessed functions. Figure 4 shows the distribution of scores at entry. Mean neurologic score was 28.4 points in the hemodilution group and 29.6 points in the control group (no significant difference).

In the evaluation of neurologic outcome, only patients surviving at least 3 months were included. After exclusion of patients dying within this interval, scores
were closely similar at entry in the two groups (Figure 5). The recovery during the treatment period (Days 0–5) and thereafter was parallel, and neurologic ratings at 3 months were nearly identical in hemodilution and control subjects (mean 37.5 vs. 37.9 points).

**Major Vascular Events and Medication**

In Table 3, new cerebrovascular and cardiovascular events during the treatment period and the ensuing 3-month follow-up are shown. Among hemodilution patients, 13 cases of clinically verified or suspected myocardial infarction and cardiac failure occurred during treatment, the corresponding number in the control group being 5. After the treatment period, such cardiac events occurred as often in control (13 cases) as in hemodilution (11) patients. Clinically manifest leg vein thrombosis and/or pulmonary embolism seemed to be somewhat more common among control patients (10 vs. 5 events during the 3 months' follow-up). None of the differences in cardiovascular events, whether single or combined, were significant by χ² testing.

As also shown in Table 3, the patterns of drug intake were similar in the two groups in the early as well as the late phase after stroke. In particular, there were no differences in the proportions of patients receiving anticoagulant or antiplatelet therapy. No patient underwent neck vessel surgery or extracranial-intracranial bypass.

**ADL Proficiency, Length of Hospital Stay, and Need for Long-Term Institutional Care**

As shown in Table 4, hemodilution did not improve ADL performance either at the end of treatment (Day 5) or at 3 months after the index event. On the con-
Mortality and Causes of Death

Case fatality rates are shown in Figure 6. Ten hemodilution (5.5%) and 3 control patients (1.6%) died within the first 5 days. Thereafter, mortality curves were closely parallel, and life table product at 3 months was 0.84 in hemodilution and 0.88 in control patients. The relative risk for death within 3 months was calculated to be 1.19:1.00 using the life table technique (p = 0.58).

Table 5 shows the causes of death. During the first 5 days, death was attributed to the presenting stroke in 7 hemodilution and 3 control patients. This difference was not significant. Deaths occurring from Day 6 and onwards were similarly distributed in the two groups.

Discussion

In this study, we were unable to demonstrate any beneficial effects of a simple standardized hemodilution regime applied in a general stroke population. Neither mortality nor the clinical outcome in survivors was improved by the treatment. The results of this study are clearly at variance with those obtained in a previous single-center trial on patients in a stroke intensive care unit, using much the same study protocol. The reason for this discrepancy is not immediately evident. Below, our results will be discussed in relation to the patient population studied (including potential influence of chance), the mode of hemodilution, possible adverse effects of the treatment, and the influence of clinical settings. Finally, lessons from this trial for future research on hemodilution in ischemic stroke will be touched upon.

The two study groups were closely similar at entry. Thus, there were no important differences in sex, age, medical history, neurologic deficits, hematocrit, and blood pressure at entry that could readily explain the lack of positive effect of hemodilution. There was a slight preponderance of patients with low prognostic scores at randomization in the hemodilution group (16 vs. 12%), and this could possibly have influenced the early case fatality rate.

In previous studies of hemodilution, there are no accounts of how the included patients compared with the entire stroke population. In the present trial, 31.5% of all patients considered were entered, and we suspect that similar limitations apply to other studies. If only a minority of stroke patients are included, it is possible that patient populations differ between studies. Reported results must be interpreted in view of this fact.

A large proportion of patients included here had only minor neurologic deficits, and their spontaneous recovery, as observed in the control group, was very good. A large number of such subjects would need to be studied to establish any beneficial effects in this particular subset of patients. However, the proportion of patients with poor neurologic performance at inclusion and poor prognosis (reflected in a combined rate

Table 4. ADL Performance, Length of Stay in Acute-Care Hospital, and Need for Long-Term Institutional Care in 161 Hemodilution and 172 Control Patients Surviving 3 Months

<table>
<thead>
<tr>
<th>ADL performance points (median; Q1–Q3)</th>
<th>Hemodilution</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>Day 5</td>
<td>65; 20–100</td>
<td>80; 30–100</td>
</tr>
<tr>
<td>3 Months</td>
<td>90; 60–100</td>
<td>95; 70–100</td>
</tr>
</tbody>
</table>

Length of stay in acute-care hospital (median; Q1–Q3) | Hemodilution | Control |
<table>
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<tr>
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<th></th>
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<tbody>
<tr>
<td>18; 10–39</td>
<td>15; 9–35</td>
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Surviving patients treated in hospital or nursing home at 3 months (%) | Hemodilution | Control |
<table>
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<tr>
<td>35</td>
<td>31</td>
<td></td>
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ADL, activities of daily living assessed by Maryland Disability Index. Q1 and Q3 denote 25th and 75th percentiles, respectively.

Table 5. Causes of Death in 29 Hemodilution and 24 Control Patients Dying Within the First 3 Months After Stroke

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Days 0–5 Hemodilution</th>
<th>Days 0–5 Control</th>
<th>Days 6–90 Hemodilution</th>
<th>Days 6–90 Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting stroke</td>
<td>7</td>
<td>3</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>3*</td>
<td>4</td>
</tr>
</tbody>
</table>

*1 case each of progressive heart failure, gastrointestinal bleeding, and infection of unknown origin.

In 4 hemodilution and 3 control patients more than 1 immediate cause of death was registered. In 1 hemodilution subject, cause of death could not be classified because of lack of clinical data.
of death and long-term institutional care of 43% in control patients) was large enough to permit marked therapeutic effects to be demonstrated in a patient population as large as this. The risks for a Type II (δ) error, missing an important overall clinical effect in the present trial, seem small. Previous randomized trials of hemodilution and plasma volume expanders in acute stroke have included considerably fewer patients and, therefore, the risks of obtaining false-positive or false-negative results have probably been greater.

The method of hemodilution applied here differs somewhat from that used in the previous single-center trial by Strand et al. In that study the rate of hematocrit reduction during hemodilution was slower than we thought optimal. Therefore, the present protocol involved a more aggressive hemodilution regimen, more blood being taken, and more dextran given. This strategy could have uncovered deleterious effects of the treatment that counterbalanced any positive effects. Indeed, there was a tendency for more patients to die and more cardiovascular events to occur during the 5 days of treatment in the hemodilution compared with the control group. These observations are contrary to those of Strand et al. The risks for myocardial infarction and circulatory collapse during blood-letting have previously been pointed out, but since the present regimen was not hypovolemic such risks were probably reduced. The possible higher incidence of cardiac failure during hemodilution (7 vs. 2 cases) could be the result of volume overload, poor capacity to increase cardiac output, or reduced oxygen supply to the myocardium. It could perhaps also reflect better surveillance for cardiac failure in patients receiving dextran infusions. It must be emphasized, however, that the number of early deaths and complications was low even in hemodilution patients and cannot be regarded as unreasonably high. Long-term mortality and neurologic outcome apparently was not adversely affected by hemodilution.

The type and volume of plasma substitute to use during hemodilution treatment is a matter of debate. In most previous studies of hypervolemic therapy, low-molecular-weight dextran has been used. Dextran was also used in combination with venesection by Strand et al as proposed by Gottstein. Other investigators have used albumin and synthetic starch. The advantages of dextran 40 are that it is less expensive than albumin and that it has the potential to desaggregate erythrocytes, which may improve microcirculatory flow. The blood–brain barrier permeability to dextran 40 is negligible. It does not seem to cause brain edema or other indirect effects on microvascular flow by accumulation in the brain tissue. Dextran 40 also has a number of other effects on hemostatic mechanisms of putative value in the treatment of thromboembolic events (see discussion in Ref. ). A major disadvantage of dextran has been the risk for anaphylactic reactions in patients with antibodies to dextran. By pretreatment with hapten-dextran, as performed in this study, the risk is reduced. Nevertheless, in 1 instance a suspected anaphylactic reaction that was readily reversible occurred. It has also been demonstrated that during repeated daily infusions of low-molecular-weight dextran, dextran moieties of higher molecular weight may accumulate, and that this increases plasma viscosity. Whether this is of any clinical importance is uncertain. Prolonged reductions of whole-blood viscosity even during repeated dextran 40 infusions in stroke patients have been observed.

Dextran 40 confers short-term volume expansion in excess of the volume of dextran infused. Since blood withdrawal was accompanied by the infusion of the same volume of dextran, the present hemodilution regime was slightly hypovolemic. This is probably rational since many patients with acute stroke may have some degree of hypovolemia when they arrive at a hospital. Hemodynamic monitoring may help to determine whether the stroke patient is hypovolemic.

What would be the optimal reduction in hematocrit during the hemodilution treatment of ischemic stroke? Theoretical considerations and experimental data suggest that the net delivery of oxygen to most tissues is maximal at hematocrit levels of 32–33% in the systemic circulation. Such a relation between hematocrit and oxygen delivery does not, however, apply to the normal brain, where tissue oxygenation seems to be constant over the entire normal range of hematocrit or only slightly increased after venesection. In cerebral ischemia with compromised regulatory mechanisms, however, it is possible that oxygen supply depends more directly on hematocrit. Whether the reduction in mean hematocrit from 44.3 to 37.1% in the present study approaches the optimum can only be a matter of speculation. It is at least as large as the reduction we observed in our previous hemodilution study with a positive outcome and would involve a 30% reduction in whole-blood viscosity at low shear rates. It should be noted, however, that the effects of hematocrit reductions in the systemic circulation on hemorrheology at the microcirculatory level of the ischemic brain have not been explored. It has been argued that a more aggressive hematocrit reduction than that employed in this study should be attempted. The present observations of a possible increase in cardiovascular complications even with our moderate hemodilution regime underline the importance of precautions like hemodynamic monitoring if the aim is to reduce the hematocrit faster and further. In forthcoming subgroup analyses, the outcome will be related to hematocrit at entry and the relative decrease in hematocrit during hemodilution.

The time available for the reversal of an ischemic insult is not known. Median interval from the onset of symptoms to the arrival at a hospital has been reported to be 5 hours in a representative Scandinavian stroke population. Considering the diagnostic procedures needed to exclude intracerebral hemorrhage, a delay of much less than 12 hours to the start of treatment is difficult to achieve if the aim is to treat a majority of stroke patients. In the present study, hemodilution was started within 12 hours in only 28% of the patients. Even in the patients entered into the study within this...
interval no positive effects of hemodilution were observed (to be published).

Since experimental\textsuperscript{19} and clinical\textsuperscript{20,41} experiences suggest that hyperglycemia may aggravate ischemic brain lesions, a saline-dextran preparation was used in this study. The daily amount of sodium supplied by this route was modest (77 mmol). However, severe cardiac disease is often present in stroke patients, and it cannot be excluded that the additional salt load may have contributed to cardiac failure in a few vulnerable patients.

A prerequisite for an increase in CBF is that cardiac output increases adequately during hemodilution. The importance of cardiac output augmentation has recently been demonstrated in experimental brain infarction.\textsuperscript{42} The results of Grotta et al\textsuperscript{27} indicate that many patients with ischemic stroke indeed increase their cardiac output during hemodilution involving volume expansion. The tendency to a more pronounced decline in blood pressure during the first few days in our hemodilution patients could perhaps reflect a limited ability to increase cardiac output. On the other hand, the outcome in hemodilution patients relative to controls was not worse if there was a history of heart disorders, cardiac failure in particular (to be published). Therefore, the overall negative results cannot be attributed merely to an obtunded cardiac response to hemodilution in a subset of patients with heart disease.

Previous therapeutic studies in stroke patients have usually been confined to university hospital settings. The beneficial results of hemodilution reported by Strand et al\textsuperscript{20} were obtained in a research-oriented stroke unit. In some of the small hospitals participating in this trial, no CT scan was available, and hemorrhage was excluded by CSF spectrophotometry. Early after the onset of symptoms, a few small, deeply situated hematomas may be missed by this procedure.\textsuperscript{43} Therefore, if a CT scan was not performed, the CSF analysis was repeated after 4–7 days, which considerably enhances the sensitivity of the method.\textsuperscript{43}

The clinical outcome in stroke patients has been shown to depend profoundly on the general strategy for basic medical care, nursing, and early activation.\textsuperscript{44,45} Even if patients were stratified by participating center in the present trial, it is possible that large variations in basic care of stroke patients may have made it more difficult to demonstrate a modest effect of hemodilution. Such “background noise” seems to be an inherent characteristic of multicenter trials, making them, in general, less sensitive in detecting small clinical differences.\textsuperscript{46} Nevertheless, it must be emphasized that one of the major aims of this trial was to study hemodilution treatment in its “natural habitat” and that we failed to show beneficial effects in these settings. Certainly, logistics of this multicenter trial were not adversely affected by the inclusion of nonuniversity hospitals; the data quality of protocols kept in these centers was, in general, as good as that in university centers.

The present results may be regarded as a challenge to the concept of hemorheologic therapy in brain infarction. Our approach has been very pragmatic, and we have used a standardized and very simple hemodilution regime. Patients with various types of ischemic stroke were included. Exploration of cerebral function in patients with brain infarction employing new sophisticated techniques have highlighted how multifaceted the pathophysiologic events are. There is a great variability in the flow pattern in the area adjacent to a brain infarction, and not only hyperperfusion but also hyperperfusion occurs.\textsuperscript{47,48} According to the penumbra concept,\textsuperscript{49} only patients with low flow in the borderline zone would benefit from hemodilution. It is not known if the different flow patterns have any correlates in the clinical presentation of a stroke patient. Using repeated CBF measurements during hemodilution in 12 patients with stroke (included in the present multicenter trial), Vorstrup et al\textsuperscript{50} observed a selective improvement of local flow in the area surrounding the infarct and concomitant relief of neurologic deficits in only 2 patients. This suggests that there may, after all, be a minority of stroke victims who benefit from the present standardized hemodilution regime. Further analyses of our data will show if it is feasible to apply clinical criteria for the selection of a subset of patients in whom hemodilution is effective.

Our results do not, of course, exclude that other variations of the hemodilution theme may be of benefit. In other ongoing controlled trials, modifications such as very early intervention, more aggressive hemodilution, individualized hemodilution protocols based on hemodynamic monitoring, plasma substitutes other than dextran, etc., are used. The outcome of these studies will help to determine if this therapy is a viable strategy in acute brain infarction. Awaiting these results, we conclude that the present standardized hemodilution regime has no overall beneficial effects on the clinical outcome in a general stroke population with acute ischemic stroke.

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References

Hemodilution in Ischemic Stroke


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