A Randomized Controlled Trial of Hemodilution Therapy in Acute Ischemic Stroke

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SUMMARY Rapid hemodilution in the early phase of ischemic stroke by the combination of venesection (250–650 ml during the first 2 days) and administration of low-molecular weight dextran was evaluated in a prospective controlled trial. Fifty-two patients were randomized to hemodilution therapy and 50 to a control group; the two groups were comparable in important prognostic variables. Mean hematocrit was reduced from 43 to 37% and, in a subsample of patients, whole-blood viscosity at a shear rate of 23 sec⁻¹ from 7.0 to 4.3 cps over the first 2 days. Hemodilution was then maintained by repeated dextran infusions.

Of the hemodiluted patients, 85% improved in neurological scoring over the first 10 days as compared to 64% of the control patients (p < 0.025). The case fatality rate during the first 3 months was little affected by hemodilution. Among the survivors, 8% of the hemodiluted and 31% of the non-hemodiluted patients were unable to walk at 3 months. The proportion of surviving patients still hospitalized at the 3-month follow-up was 13% in the hemodilution group and 39% in the control group (p < 0.01).

The combination of venesection and dextran 40 administration is thus an unsophisticated but effective way to achieve rapid hemodilution in patients with acute cerebral infarction, and it improves the overall clinical outcome over the first 3 months.

PATIENTS WITH POLYCYTHEMIA and other conditions with blood hyperviscosity are prone to vascular complications including cerebrovascular disease. Under normal conditions hematocrit is the main determinant of whole-blood viscosity and epidemiological data suggest that even high hematocrit levels within "normal" limits are associated with an increased risk for ischemic stroke. Cerebral blood flow is inversely correlated with blood viscosity and hematocrit. It has, therefore, been inferred that hemorheological factors play an important role in the development and course of cerebral thromboembolic events.

In focal brain ischemia there is a zone of non-functioning but potentially viable tissue ("penumbra") encircling the infarcted core. Even a marginal improvement in blood supply to this zone would reduce the ultimate extent of the infarct and possibly improve clinical outcome. One of the possible therapeutic interventions in ischemic stroke may therefore be to enhance cerebral blood flow to this border zone by hemodilution.

In experimental focal brain ischemia, hemodilution by exchange transfusions has been shown to increase blood flow and preserve cellular homeostasis. Previous therapeutic studies with hemodilution in patients with brain infarction have involved the administration of a plasma volume expander, usually dextran. Beneficial results have been reported, but not consistently. An alternative approach to hemodilution is bloodletting. In subjects free of cerebrovascular disease, 300–700 ml venesection has been shown to be as effective as 500 ml dextran 40 in promoting cerebral blood flow. Both procedures involve potential circulatory risks. Since autoregulation is impaired in cerebral infarction, a hypovolemia-mediated reduction in blood pressure should probably be avoided. Furthermore, hypovolemic hemodilution by phlebotomy may cause myocardial infarction or cardiovascular collapses. Stroke developing during therapeutic plasmapheresis has been reported. On the other hand, hypervolemic hemodilution by infusion of plasma volume expanders may worsen cardiac failure and precipitate pulmonary edema. In view of the high prevalence of cardiac ailments in the general stroke population, these hazards are not negligible. However, by combining venesection with the administration of a plasma volume expander, rapid and long-lasting hemodilution can be accomplished and the risks of compromising the systemic circulation are reduced. The growing interest in hemodilution in ischemic stroke is reflected in recent reports of positive effects of phlebotomy and concomitant infusion of plasma volume expanders in uncontrolled studies from Germany, the Soviet Union, and the USA.

The present controlled study was initiated to explore if early hemodilution reduces neurological deficits and the need for long-term hospitalization after ischemic stroke. It is the first randomized controlled trial of the combination of venesection and dextran 40 administration in patients with brain infarction.

Patients and Methods

Patients

Patients were recruited for the study among those admitted acutely to the stroke unit of the Department of Medicine at Umeå University Hospital. The 6-bed non-intensive stroke unit admits unselected patients with presumed acute cerebrovascular disease. The patients are representative of all patients admitted to hospital for acute stroke in the Umeå district. The inclusion criteria were:

a) focal neurological deficits of presumed vascular
origin with acute onset and persisting at the time of inclusion into the study,
b) start of treatment possible within 48 hours of the onset of symptoms,
c) no macroscopically overt hemorrhage in the CSF,
d) hemoglobin levels between 120 and 180 g/l,
e) no myocardial infarction during the last week,
f) absence of severe angina pectoris and overt signs of left ventricular failure (significant pulmonary rales, diastolic filling gallop or roentgenological signs of left ventricular failure),
g) plasma creatinine < 300 \( \mu \text{mol/l} \),
h) absence of concomitant severe disorders in the terminal stage (such as malignancies),
i) absence of coma not responding to pain stimuli, and
k) no ongoing treatment with anticoagulant agents.

Patients were informed orally, whenever possible. When the patient’s condition prohibited meaningful communication, family members were informed. Consent by the patient (or family member) was oral. The patient’s right to withdraw from the trial at any point of time was ascertained. The study was approved by the Ethical Committee of Umeå University.

One hundred and nine patients entered the trial. CT scans obtained early after inclusion showed small intracerebral hemorraghes in four of the patients (two in each of the treatment and control groups). Two additional patients not filling the inclusion criteria were inadvertently randomized; one had hemoglobin below 120 g/l and one overt signs of left ventricular failure on admission. One patient was deaf, blind and aphasic, precluding meaningful neurological scoring. After these seven subjects had been excluded, 52 patients remained for analysis in the treatment group and 50 in the control group.

Hemodilution therapy was interrupted early in two patients who developed anaphylactoid reactions (see Results). Adhering to the intention-to-treat principle, we have included them in the hemodilution group when evaluating the clinical outcome. However, in analyses of the effects of hemodilution on hematological variables and blood pressure, data from these two patients have been omitted.

Some main characteristics of patients included in the study are shown in table 1. Mean age was similar in the two groups, whereas the male preponderance was greater among control patients. A history of cardiovascular disease or diabetes was common in both groups. None of these variables was the difference statistically significant by chi-square test.

As presented in table 2, there were no major differences in the clinical presentation of the acute cerebrovascular accident between hemodiluted and control patients on admission to the stroke unit \((p > 0.05 \text{ in all variables})\). Symptoms strongly indicative of a lesion in the vertebrobasilar vascular territory were present in 9 of the hemodiluted and in 5 of the non-hemodiluted patients.

Intracerebral hemorrhage as a cause of the stroke

**TABLE 1** Age and Sex Distributions and Previous Medical History on Admission in 52 Hemodiluted and 50 Control Patients

<table>
<thead>
<tr>
<th>Age, years (mean; 95% confidence interval)</th>
<th>Hemodilution</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>(range)</td>
<td>73; 71–75</td>
<td>74; 72–76</td>
</tr>
<tr>
<td>Males/females (%)</td>
<td>51–92</td>
<td>54–87</td>
</tr>
<tr>
<td>Pre visceral disorders (%)</td>
<td>58/42</td>
<td>72/26</td>
</tr>
<tr>
<td>TIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed stroke</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>63</td>
<td>48</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>42</td>
<td>34</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>None of the above</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

was excluded in all patients by CT scan performed in the acute phase (see below) or by autopsy. A satisfactory CT scan was obtained during one of the first 5 days in 41 hemodiluted and 36 non-hemodiluted patients. The proportion of visible ischemic lesions of recent origin was 49% and 50%, respectively.

**Procedure**

Following oral consent, patients filling the inclusion criteria were assessed by a neurological score (see below). Using closed envelopes they were then randomly assigned to hemodilution treatment or to a con-
controld group. In patients allotted to hemodilution therapy, a 250 ml venesection was immediately started. During the venesection 150–200 ml of 10% dextran 40-saline (Rheomacrodex®) was infused, making the initial phase of the hemodilution isovolemic. Another 300–350 ml of the dextran solution was given over the next 2–4 hours, the rate being adjusted according to the patient’s cardiac condition. Median interval from the onset of symptoms to the start of treatment was 18 hours.

On the following day (“day 1”), patients with hemoglobin levels remaining above 120 g/l underwent a 250–400 ml venesection, the volume being dependant of the hemoglobin level. The equivalent volume of dextran 40 was given during the venesection, followed by dextran to a total volume of 500 ml. In patients with hemoglobin below 120 g/l no bloodletting was performed, but 500 ml of dextran 40 was infused.

Dextran 40 infusions were then given on day 2 (500 ml), day 4 (250 ml) and day 6 (250 ml). No venesections were performed after day 1.

Lumbar punctures were performed in all patients before inclusion into the trial and on day 3 or 4. The CSF was analysed for cells, protein concentration, and hemoglobin degeneration products by spectrophotometry.28 In cooperating patients, two CT scans (EMI Mark One Head Scanner) were performed, the first on day 0–3, the second on day 8–10. In patients unable to cooperate during the early phase, one CT scan was obtained within 3 weeks. Before discharge from the stroke unit, a chest x-ray was obtained; in all those able to stand upright cardiac size was determined.

Both groups were subject to the identical basal therapeutic principles of our stroke team, including modified primary nursing, early detection and aggressive treatment of medical complications, very early onset of rehabilitation, intense family involvement and social support.26

**Evaluation of Treatment**

Neurological assessment was performed by the Frithz & Werner modification27 of the scoring system developed by Mathew.28 Scoring was done by a physician before randomization, on day 3 and on day 9. The ratings were performed blindly, i.e. the examiner did not know to which group the patient had been assigned.

Hemoglobin and hematocrit values were registered daily for the first 10 days. Blood pressure levels were charted at 4-hour intervals during the first 2 days and daily thereafter. Electrocardiograms were obtained daily during the first 3 days in all patients. In a subsample of 7 hemodiluted patients, whole-blood viscosity on day 0, 1, 2 and 7 was determined using a Brookfield viscosimeter.

Deaths, recurrent strokes, other major vascular events and drug therapy was registered during the first three months after the stroke. All surviving patients were seen in our out-patient stroke clinic at 3 months. Examinations at this visit were open, i.e. the examiner knew whether the patient had been hemodiluted or not, and included a crude assessment of the activities of daily life, registration of whether the patient was institutionalized or not, a physical examination and determination of hemoglobin and hematocrit.

**Autopsy Examinations**

Autopsies were performed in 10 out of the 13 hemodiluted patients (77%) and in 12 out of the 14 control patients (86%) who died during the 3-month follow-up period. Permission was not procured from family members in the other instances. The pathologists were unaware of which group the patient had been assigned to.

**Statistical Analyses**

Means were calculated with their 95% confidence intervals (CI). For comparisons of groups of data we used Student’s t-test (for paired data when applicable), chi-square test, Wilcoxon’s rank sum test and log rank test.

**Results**

**Hemoglobin, Hematocrit and Whole-blood Viscosity**

On admission to the stroke unit, mean hemoglobin levels were 147 g/l (95% CI = 144–150 g/l) in patients randomized to hemodilution treatment and 147 g/l (95% CI = 144–151 g/l) in control patients. The corresponding mean hematocrit values were 43.0 (95% CI = 42.0–44.0%) and 43.0 (95% CI = 41.9–44.1%), respectively. As shown in figure 1, the combined venesection and dextran 40 therapy caused a mean reduction of hemoglobin to 128 g/l (95% CI = 124–131 g/l) and of hematocrit to 37.0 (95% CI = 35.9–38.1%) over the first 2 days. The hemodilution effect was then maintained throughout the first 10 days. On follow-up 3 months after the stroke, hemoglobin and hematocrit had returned to levels close to those observed before the onset of treatment.

In control patients there was a slow but statistically significant reduction of the two variables. Thus, 10 days after admission mean hemoglobin had declined by 6 g/l ($p < 0.05$) and mean hematocrit by 2.0% ($p < 0.05$).

![Figure 1. Hemoglobin and hematocrit levels in 50 hemodiluted (●●●●●) and 50 control (O-O-O) patients with acute ischemic stroke. Mean and 95% CI. Data from two patients in the hemodilution group have been omitted; in both the hemodilution was interrupted early because of anaphylactoid reactions (see text).](image-url)
HEMODILUTION IN ISCHEMIC STROKE/Strand et al

BLOOD VISCOSITY
cps

15 10 5 0 2.3 5.75 11 23 46 115

DAYS AFTER ONSET OF HEMODILUTION

Figure 2. Mean whole-blood viscosity at six different shear rates (2.3–115 sec⁻¹) in 7 hemodiluted patients.

Blood Pressure Changes, Cardiac and Circulatory Events During Treatment

As shown in figure 3, initial blood pressure recordings were closely similar in hemodiluted and non-hemodiluted patients. A decline in blood pressure during the first days after admission to hospital after ischemic stroke was observed in both groups. Mean blood pressure did not differ between the groups at 3 months' follow-up.

As shown in table 3, the hemodilution patients appeared to have a lower occurrence of cardiac and other circulatory events during treatment period (day 0–9). In the 52 treated patients there were 4 major cardiac events (definite or suspected myocardial infarction, and cardiac failure) as compared to 10 such events in the control group. Clinically manifest venous thromboembolic events were observed in 2 of the hemodiluted and 5 of the non-hemodiluted patients during the acute phase. No corresponding differences were apparent during the follow-up period (day 10 to 3 months).

The frequency of atrial fibrillation/flutter (permanent or intermittent) was similar in the two groups of patients during the first 10 days (table 4). As also shown in table 4, chest x-rays obtained within 4 weeks of the stroke revealed no difference in relative cardiac size or signs of cardiac decompensation between treated and control patients.

Neurological Deficits

On inclusion, median neurological score was 64 points in patients subsequently allotted to the treatment group and 69.5 points in control patients. The changes in rating over the first 10 days are illustrated in figure 4. Using paired data, Wilcoxon’s rank sum test showed the improvement to be statistically greater in the hemodiluted patients from inclusion to day 3 (p < 0.05) as well as to day 9 (p < 0.002).
TABLE 3  Vascular Events Occurring during the First Three Months after Stroke in 52 Hemodiluted and 50 Control Patients

<table>
<thead>
<tr>
<th>Day 0–9</th>
<th>Day 10 to 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hemedilution</td>
</tr>
<tr>
<td>Patients under observation at start of the interval</td>
<td>52</td>
</tr>
<tr>
<td>No. of events</td>
<td></td>
</tr>
<tr>
<td>Definite myocardial infarction</td>
<td>2</td>
</tr>
<tr>
<td>Suspected myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Clinical signs of left ventricular failure*</td>
<td>2</td>
</tr>
<tr>
<td>Definite pulmonary embolism†</td>
<td>1</td>
</tr>
<tr>
<td>Suspected pulmonary embolism</td>
<td>0</td>
</tr>
<tr>
<td>Leg vein‡ thrombosis</td>
<td>1</td>
</tr>
</tbody>
</table>

*Orthopnea, significant pulmonary rales and/or gallop rhythm and in need of treatment with diuretics.
†Verified by pulmonary-artery cineangiography, lung scintigraphy or autopsy.
‡Overt clinical signs and verified by phlebography, fibrinogen uptake test or autopsy. Patients with concurrent pulmonary embolism are not included here.

One additional patient allotted to the hemodilution group had pulmonary embolism; the treatment was, however, interrupted early on the first day after the development of an anaphylactoid reaction to dextran (see text).

The proportion of patients improving in neurological score was also significantly greater in the treatment group. Hence, 44 of the 52 hemodiluted patients (85%), but only 32 of the 50 non-hemodiluted patients (64%) improved in neurological scoring over the first 10 days ($p < 0.025$ by chi-square test). As shown in figure 5, the improvement seemed to encompass all the neurological variables assessed in the score. A deterioration in neurological score over the first 10 days (including deaths) was observed in 4 hemodiluted patients (8%) and 13 non-hemodiluted patients (26%) ($p < 0.02$). Rapidly progressing symptoms, causing heparin therapy to be initiated, occurred in 2 control subjects; none of the hemodiluted patients received anticoagulants because of progressing stroke.

Mortality and Causes of Death

Hemodilution had no apparent long-term effect on survival (figure 6). During the first 10 days, one patient in the treatment group and 5 in the control group died. Thereafter, the survival curves were closely similar throughout the 3-month follow-up period. Case fatality rate by 3 months was 25% in hemodiluted and 28% in control subjects.

As emerges from table 5, the proportion of patients where cardiac or cerebrovascular disorders were the immediate cause of death was smaller in the hemodiluted patients (5 of 13) than in control patients (10 out of 14). On the other hand, more hemodiluted patients died from bronchopneumonia or bronchitis during the follow-up period. The 6 hemodiluted patients with bronchopneumonia listed as the major cause of death were all very old (82–92 years) and difficult to mobilize after the stroke; they all died more than 10 days after the last dose of dextran was given.

Functional Outcome and Need for Long-term Hospitalization

The need for long-term hospitalization was less in hemodiluted patients, as shown in figure 7a. If calculations are based on survivors only, 13% of the hemodiluted and 39% of the control patients remained in hospital at three months after the stroke ($p < 0.05$ by chi-square test). A log rank test of the difference in hospitalization in surviving patients over the entire 3-months period yielded a $p$-value of 0.05.

Among survivors, there was no great difference be-

TABLE 4  Cardiac Size, Chest X-ray Findings and Heart Rhythm in Hemodiluted and Control Patients

<table>
<thead>
<tr>
<th>Cardiac variable</th>
<th>Hemodilution</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative cardiac size, m/m$^2$ body surface, mean; 95% confidence interval</td>
<td>542; 490–594 (31)</td>
<td>578; 521–635 (27)</td>
</tr>
<tr>
<td>Roentgenological signs of possible cardiac decompensation,* no. of patients</td>
<td>8 (48)</td>
<td>9 (46)</td>
</tr>
<tr>
<td>Presence of atrial fibrillation or flutter,† no. of patients</td>
<td>10 (48)</td>
<td>12 (39)</td>
</tr>
<tr>
<td>At 3 months</td>
<td>7 (39)</td>
<td>7 (39)</td>
</tr>
</tbody>
</table>

*Dilatation of central pulmonary veins and/or pleural effusions.
†Intermittent as well as permanent fibrillation or flutter. Diagnosis by at least one (usually 3) ECG recordings during the first 10 days. Diagnosis by physical examination at 3 months and confirmed by ECG only if physical examination revealed obvious change in cardiac status.

Figures within parentheses denote number of patients in whom observations were made.

FIGURE 4. Changes in neurological score from inclusion into the study (day 0 to day 3 and day 9). A 0–100 scoring system (22) was used and ratings were performed blindly. Results are presented as median change in neurological score in each quintile. Columns in broken lines represent control patients and columns in unbroken lines hemodiluted patients.
between the two groups in the proportion of patients walking unaided at 3 months after the stroke. Thus, 62% of the surviving patients in the hemodilution group and 53% of the surviving control patients were able to walk without technical aid (fig. 7a). However, the proportion of surviving control patients not able to walk at all by 3 months was significantly larger than the corresponding proportion of hemodiluted patients (31% vs 8%; \( p < 0.005 \) by chi-square test).

**CASE FATALITY RATE**

![Figure 6](image)

*Case fatality rates during the 3-month follow-up period after admission in 52 hemodiluted and 50 control patients with acute ischemic stroke.

**Concomitant Drug Therapy**

In the acute phase after the stroke (day 0–9) there were no important differences in the drug consumption profile between the two groups (table 6). During the follow-up period (day 10 to 3 months) 33% of the hemodiluted and 22% of the non-hemodiluted patients were on anticoagulant therapy at any point in time. The most common reason for anticoagulant therapy in the follow-up phase was a presumed embolic cause of the brain infarction; these patients were started on anticoagulants on day 10–14 and received this treatment throughout the follow-up period. The second-most common indication for anticoagulants was leg vein thrombosis with or without pulmonary embolism. Sa-

**TABLE 5 Immediate and Contributing Causes of Death in 13 Hemodiluted and 14 Control Patients Dying during the 3-months Follow-up Period**

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Immediate Hemo-acidation</th>
<th>Contributing Hemo-acidation</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present stroke</td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Bronchopneumonia or bronchitis</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*In 2 control patients two concurrent immediate causes of death were registered.
†In 3 hemodiluted and 6 control patients two or more contributing causes of death were registered.
‡Hyperosmolar non-ketotic coma.
A. NEED FOR HOSPITAL CARE AT 3 MONTHS

![Diagram showing need for hospital care and walking ability in hemodiluted and control patients at 3-months' follow-up.]

**TABLE 6**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Day 0-9 Hemo-</th>
<th>Day 0-9 Control</th>
<th>Day 10 to 3 months Hemo-</th>
<th>Day 10 to 3 months Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients under</td>
<td>52</td>
<td>50</td>
<td>51</td>
<td>45</td>
</tr>
<tr>
<td>observations at the start of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>the interval</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients on treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>2</td>
<td>3</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Salicylates</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Other non-steroid anti-</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>inflammatory drugs</td>
<td>26</td>
<td>25</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium blocking agents</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other antihypertensive drugs</td>
<td>7</td>
<td>11</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

Salicylates were used less commonly in the hemodiluted (6%) than in the non-hemodiluted (16%) patients during the follow-up period. The most common causes for salicylate treatment were minor strokes or embolic strokes where anticoagulant therapy was considered inappropriate because of high age or expected poor compliance.

**Adverse Reactions to the Hemodilution Therapy**

Two patients developed anaphylactoid reactions with nausea, pallor, markedly decreased blood pressure and impaired consciousness within the first few minutes after the first dextran 40 infusion was started. In one patient (a 67 year-old male) the reaction reversed rapidly after the infusion was stopped. In the other patient, a 77 year-old woman, with more severe symptoms epinephrine and corticosteroids were injected and this reversed the reaction. Otherwise, no other side effects were observed.

**Discussion**

It appears that hemodiluted and control patients were reasonably comparable in several important
prognostic indicators. Mean age was nearly identical in the two groups. Cardiovascular diseases\textsuperscript{22, 30} and diabetes\textsuperscript{31} adversely affects the outcome of stroke, and the great majority of subjects in both groups had either of these disorders, although several concomitant manifestations of heart disease appeared to be slightly more frequent in patients allotted to hemodilution treatment. The greater proportion of males in the control group was probably of less significance, because gender in itself is of little prognostic value in acute stroke.\textsuperscript{32}

Hemodiluted patients may have been somewhat more affected by the stroke on admission; the proportion of patients with lowered consciousness, conjugate ocular deviation and inability to walk was greater in hemodiluted than in control patients. This was reflected in a difference in neurological score on inclusion which, however, did not reach statistical significance. In all, it seems highly unlikely that differences in clinical outcome between the two groups resulted from an unequal distribution of prognostic variabes in favour of the hemodilution group on inclusion into the study.

The case fatality rate over the first 10 days after the stroke was 10% in the control group. Therefore, the 102 patients included in the present study constitute too small a sample to permit any effect of hemodilution on mortality during the acute phase to be assessed accurately. The close parallelity of the survival curves from day 10 to 3 months after the stroke makes it less probable that early hemodilution will have any lasting effects on survival. Possible beneficial effects on early mortality (first 10 days) or on the proportion of vascular deaths during the first months after the stroke — as hinted by our results — can be estimated reliably only in a larger trial.

When compared with control patients 3 months after the ischemic stroke, hemodiluted subjects were left with less impairment of walking and their need for long-term hospitalization was reduced. The magnitude of these differences was somewhat surprising in view of the modest difference in neurological scorings by day 9 between the two groups. It appears that the more rapid neurological recovery among hemodiluted patients during the first day after stroke facilitated further rehabilitative efforts and that hemodilution perhaps reduced the ultimate extent of brain infarction.

Previous controlled clinical trials of dextran administration — without concomitant phlebotomy — in ischemic stroke have given conflicting results. In retrospective studies, Gottstein et al\textsuperscript{13, 14} reported the clinical outcome in 202 patients receiving dextran and compared this to the outcome in 226 patients on a vasodilating regimen employed in previous years. A highly significant reduction in mortality during “the acute phase” and a greater proportion of patients with a total recovery were observed after dextran therapy was introduced. Gifroy et al\textsuperscript{15} performed a randomized controlled trial of dextran 40 in 46 treated and 54 nontreated patients with acute stroke and found a statistically significant difference in neurological outcome over the first 10 days in favour of the dextran therapy. No later follow-up was made. Another randomized trial of dextran 40 involving 100 patients with ischemic stroke showed reduced early mortality (first 3 weeks), but at 6 months after the stroke no difference in mortality could be detected.\textsuperscript{17} In survivors, no overall effect of dextran was found,\textsuperscript{17} although, in subset analyses, a beneficial effect on strokes affecting the carotid — as opposed to the vertebrobasilar — territory could possibly be discerned.\textsuperscript{8} In a smaller randomized study, Spudis et al\textsuperscript{16} were unable to demonstrate any difference in clinical outcome over the first 3 weeks in stroke patients treated with and without dextran 40, respectively, in a community hospital setting. Finally, Kaste et al\textsuperscript{18} treated 20 stroke patients with a combination of dextran and dexamethasone. No favourable effect of this therapy was observed during a 30-day follow-up period, when compared with a control group.

The reasons for these contradictory results in clinical trials of dextran treatment in stroke patients are not immediately evident. The use of historical controls\textsuperscript{13, 14} makes it difficult to exclude an interference of other secular changes, particularly in view of the very high mortality rate (54%) during the control period. The fact that the use of dextran without venesection gives not only hemodilution but also a considerable hypervolemia may, per se, be detrimental to any beneficial effects of hemodilution in stroke patients. It may precipitate cardiac failure. In addition, hypervolemic hemodilution has been shown to raise intracranial pressure in experimental brain infarction.\textsuperscript{33} Therefore, a less pronounced hypervolemia by the combination of venesection and dextran administration may have unravelled the positive effects of hemodilution. Since data on hemoglobin, hematocrit or blood viscosity are not given, the hemodiluting effect is difficult to assess in the previous trials. Direct comparisons with our present results are therefore not possible.

As shown by animal studies, intravascular volume expansion (by whole blood transfusions) without concomitant reduction in hematocrit does not enhance cerebral blood flow or reduce the size of experimental brain infarction.\textsuperscript{34} It seems logical to assume that the hemodiluting rather than the volume expanding aspects of the present regime were of significance for the positive results.

When compared with the control group, blood pressure levels were little affected by the hemodilution regimen. This seems to confirm that the volume expansion was balanced by other changes, e.g. peripheral vasodilation, during hemodilution treatment. In laboratory experiments, intentional hemodilution is accompanied by a reduction in peripheral vascular resistance.\textsuperscript{35, 36} In view of the impaired cerebral vascular autoregulation in acute stroke,\textsuperscript{19} a reduction of systemic blood pressure should probably be avoided in most patients. It therefore seems appropriate to keep the hemodilution somewhat hypervolemic, as in the present trial.

Although dextran was employed in the present study mainly as a plasma substitute and a hemodiluting agent, it cannot be ruled out that it also had other beneficial effects. Effects of dextran infusions on
erythrocytes, platelets, vessel walls and coagulation have been documented. Thus, dextran reduces platelet adhesiveness and aggregation and this could counteract a possible activation of platelets induced by bleeding. Low-molecular dextran (as opposed to high-molecular dextran) promotes erythrocyte disaggregation, which may benefit microcirculatory flow. Coating of the vascular endothelium and blood corpuscles by dextran, diminution of factor VIII related antigen, and reduction of fibrinolytic inhibitory activity (α2-antiplasmin) have also been implicated in the antithrombotic effects of the agent. It was beyond the scope of our trial to explore the relative contribution of each of these elements to the clinical outcome. But when we selected a plasma substitute to use in combination with venesection in the hemodilution regimen, it seemed appropriate to use low-molecular dextran in view of these other putatively advantageous effects on thromboembolic processes.

In any regimen involving such a spectacular procedure as bloodletting, a considerable "placebo" effect should probably be expected. If so, it may hamper a proper evaluation of the effect of hemodilution on the cerebral lesion per se. Nevertheless, we found it inappropriate from an ethical perspective to apply a sham procedure involving bloodletting in the control group. It follows that the design of the trial does not permit an estimation of the relative contribution of venesection and dextran 40 administration, respectively, to the positive effect on clinical outcome.

The potentially most hazardous adverse reaction to the combined venesection/dextran 40 therapy is the development of dextran hypersensitivity with serious anaphylaxis. The incidence of severe reactions is estimated to be 0.04–0.5% per patient given dextran 40 or dextran 70. The higher risk figures seem to apply to elderly subjects, in particular those with cardiac disorders. The general stroke patient population would therefore be at specific risk. Indeed, 2 out of 52 patients in our treatment group developed anaphylactoid reactions. This risk is greatly reduced by hapten inhibition of dextran-antidextran precipitation which has recently been introduced for clinical use. This pretreatment should probably be given all stroke patients receiving dextran.

Dextran administration also involves a potential risk for volume overload and ensuing heart decompensation in patients with cardiovascular disorders. Also in this respect, stroke patients seem to be at particular risk, since concomitant cardiac ailments are prevalent in this population (table 1). However, in none of the aspects we analyzed did the hemodiluted patients appear less compensated than the control patients—the proportion needing diuretic therapy was not greater, their cardiac sizes were not larger by X-ray, roentgenological signs of decomposition were not observed more frequently, and most importantly, clinically overt heart failure was not more common.

By combining venesection and administration of dextran the risks of compromising the systemic circulation are diminished. In addition, intentional hemodilution is known to reduce peripheral vascular resistance and to increase cardiac output under normal conditions. In elderly patients, undergoing hip surgery, isovolemic hemodilution seems to have less effect on cardiac output but it increases systemic arterial oxygen tension. It is possible that hemodilution, albeit moderately hypervolemic in our version, has beneficial rather than detrimental effects on the heart and the systemic circulation in stroke patients.

In other clinical situations, hemodilution may also reduce the risk of venous thrombotic events. Stroke patients are prone to get leg vein thrombosis and pulmonary embolism. As will be reported separately, it may be that the present hemodilution regimen reduced the extent of venous thrombus formation in the lower extremities of our stroke patients, although the effects were modest (Mellbring et al, in preparation).

What is optimal hemodilution in cerebral infarction? There are no solid data on the interactions between the degree of hemodilution and the clinical effect in other circulatory disorders where hemodilution therapy has been applied. It is not known whether a hematocrit reduction in relative or in absolute terms is preferable and, alternatively, if a lowering of the hematocrit to a fixed level should be strived for. Data obtained in normal individuals indicate that oxygen delivery to peripheral organs is, in general, enhanced as hematocrit is reduced down to 30–33%; below this watershed the oxygen supply declines rapidly. Such a biphasic relationship does probably not exist for the normal brain. Instead, the oxygen delivery seems to be constant over the entire normal hematocrit range.

However, the interrelations between hematocrit and oxygen supply in acute cerebrovascular disease with compromised nutritive flow and impaired autoregulation can only be a matter of speculation: It appears likely that hemorheological factors are more important determinants of cerebral blood flow as normal regulatory mechanisms do not operate. Our present data and the observation that the hematocrit level on admission to hospital for acute stroke is a prognostic factor for the clinical outcome lend support to this contention.

It must be emphasized that the present results were obtained in patients admitted to a stroke unit. In Sweden, most stroke patients are treated in general medical wards. Some uncertainty therefore remains whether or not our findings are applicable to these more common hospital settings. A Scandinavian multicenter trial of hemodilution in acute ischemic stroke, involving large as well as small hospitals in four countries, is now under way.

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