Evaluation of Long-Term Outcome and Safety After Hemodilution Therapy in Acute Ischemic Stroke

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Background and Purpose: In a previous single-center, randomized controlled trial including 102 patients treated in a stroke unit, we showed that rapid, modest hemodilution improved short-term clinical outcome in ischemic stroke patients. I now evaluate the long-term outcome and potential risks of this combined venesection/dextran 40 therapy in the same 52 treated and 50 control patients.

Methods: Mortality, need for institutional care, and recurrent strokes were registered during 1 year following inclusion in the trial, and a final evaluation of functional outcome was performed at 12 months after the stroke. Cerebrospinal fluid was analyzed for protein content and hemorrhagic admixture at two occasions during the acute phase.

Results: Thirty-six hemodiluted and 30 control patients survived the first year following the stroke (difference not significant). One year after the stroke, persistent neurological deficits were less frequent among the hemodiluted patients and a larger proportion of hemodiluted survivors was independent in walking (92% versus 73%, p<0.05). Two hemodiluted patients (6%) and nine control patients (30%) were totally dependent in the activities of daily living (p<0.05). Three hemodiluted patients (8%) and eight control patients (27%) remained hospitalized 1 year after the stroke (p<0.05). With the possible exception of patients with a medical history of congestive heart failure, subset analyses revealed a tendency toward improved outcome for hemodiluted patients in all clinically important subgroups compared with the controls. When analyzing cerebrospinal fluid, signs of blood–brain barrier breakdown and hemorrhagic admixture to the cerebrospinal fluid during the acute phase were less frequent in the hemodiluted subjects.

Conclusions: These results suggest that, when applied in a stroke unit, the combination of venesection and dextran 40 administration is a clinically safe, therapeutic regimen in the treatment of acute cerebral infarction that improves long-term clinical outcome.

KEY WORDS • cerebral ischemia • hemodilution • stroke outcome

In a randomized, controlled study including 102 patients we showed that the combination of venesection and infusion of dextran 40 during the acute phase of cerebral infarction significantly improved the clinical outcome up to 3 months after stroke. The moderately hypervolemic hemodilution regimen applied induced a rapid and persistent reduction in hematocrit and whole blood viscosity without overt adverse hemodynamic effects.1 All patients were treated in a stroke unit and received equal amounts of rehabilitation procedures.2

In the majority of stroke patients, functional gains seem to be primarily a spontaneous event over time,3 with the full potential for spontaneous recovery reached 6–12 months after the stroke.4 Thus, evaluations of acute therapeutic regimens designed to reduce the ultimate extent of brain damage necessitate assessment of the long-term outcome, that beyond 6 months after the initial stroke. Other randomized studies of the same size5–7 or larger than ours8–9 have failed to show significant long-term effects5–6 or did not study long-term outcome.6–8

The aims of this extension of the prior study are, first, to evaluate the effects of hemodilution on long-term neurological and functional outcome and, second, to evaluate the safety of the applied hemodilution regimen.

Subjects and Methods

During a 2 year period, we included 102 patients with acute cerebral infarction in a randomized study of early hemodilution therapy. All patients recruited for the study were initially treated in the stroke unit of the Department of Medicine at Umeå University Hospital.1

Anemic patients (hemoglobin concentration of <120 g/l), patients with overt signs of acute left ventricular failure (significant pulmonary rales), and patients with acute myocardial infarction or unstable angina pectoris were excluded from randomization. Patients in a condition that could hamper proper evaluation of therapeutic effects, including patients in a coma, patients with neurological deficits lasting >48 hours, patients in the
terminal stage of concomitant severe disorders, and patients with ongoing anticoagulant treatment, were also excluded. Patients with a plasma creatinine concentration of >300 μmol/l were also excluded because of possible adverse effects of dextran in patients with renal failure. All other patients with neurological deficits persisting at randomization and without macroscopically overt hemorrhage in the cerebrospinal fluid (CSF) at acute lumbar puncture were included. Fifty-two patients were randomized to hemodilution treatment and 50 to a control group. The patients were comparable in prognostic indicators. Mean age was 73 years in both groups (range 51–92 years).

The hemodilution procedure has been described in detail previously. In short, a 250 ml venesection was performed immediately after randomization and followed by another hemoglobin level–dependent venesection of maximally 400 ml the next day. During the venesections, equivalent volumes of 10% dextran 40 in saline were simultaneously infused cautiously avoiding transient hypovolemia, followed by dextran to a total volume of 500 ml over the next 2–4 hours. On days 3, 5, and 7, 500, 250, and 250 ml, respectively, of dextran 40 were given without concomitant venesection. The initial phase of the hemodilution procedure thus was approximately isovolemic, followed by a second phase of moderate plasma volume expansion. There was a slight, but not significant, reduction in blood pressure during the first week after admission in the hemodiluted group compared with the control group. The median delay from symptom onset until the hemodilution procedure started was 18 hours. The hemodiluted and control patients were subjected to identical basal therapeutic principles of our stroke team.

Deaths, recurrent strokes, and other major vascular events were registered during the first 12 months after the stroke. All surviving patients were seen in our outpatient stroke clinic at 3 and 12 months after the stroke. Examinations at these visits included an evaluation of the activities of daily living (ADL) by a simplified version of the ADL scale according to Barthel, registration of whether the patient was institutionalized, and a physical examination.

In cooperating patients, two computed tomograms (CT scans) were performed, the first on day 0–3 after hospital admission, the second on day 8–10. In patients unable to cooperate during the early phase, one CT scan was obtained within 3 weeks.

Lumbar puncture was performed in the lateral recumbent position in all patients before inclusion in the trial and repeated on day 3 or 4. Two consecutive CSF samples, approximately the 1–3 and 6–7 ml fractions, were collected at each lumbar puncture and centrifuged as soon as possible to minimize the possible influence of red blood cell admixture at traumatic lumbar punctures. The CSF was analyzed for hemoglobin degradation products by spectrophotometry according to Kjellin and Söderström. The CSF absorbance at 415 nm was defined as the most appropriate in detecting hemorrhagic admixture from a cerebrovascular lesion. A peak oxyhemoglobin absorbance at 415 nm of <0.0015 was considered as a normal pattern or a pattern of infarction. A bleeding pattern was defined as a peak oxyhemoglobin absorbance of >0.0030, and values between 0.0015 and 0.003 were defined as indicating possible hemorrhagic infarcts. The CSF total protein content was determined according to Lowry et al. In our laboratory, a CSF protein concentration of <450 mg/ml (250–450 mg/dl) is considered normal. Because of grossly traumatic lumbar punctures, missing analyses, clinical deterioration, and early deaths, CSF spectrophotometry and CSF protein analysis were not performed in all patients included in the study.

Subsets and the groups hemodiluted versus control were compared using the χ² test; for comparing the means of CSF parameters Student's t test was used.

Results

Survival curves revealed no significant difference in mortality rates (Figure 1). Early mortality was not affected by hemodilution therapy as reported previously. One year after the stroke, 16 of the 52 patients randomized to hemodilution therapy (31%) and 20 of the 50 patients randomized to the control group (40%) were dead. Between 3 and 12 months after the stroke, nine patients (three in the hemodiluted group and six in the control group) died. Late mortality was of cardiac etiology in the majority of patients. Among the 19 severely disabled patients who were hospitalized 3 months after the stroke, six (two in the hemodiluted group and four in the control group) died during the remainder of the year.

Persisting neurological deficits, detectable at routine clinical examination, were less frequent in the hemodiluted group than in the control patients (Figure 2). One year after the stroke, disturbances of orientation, speech, and motor function were less frequent among the survivors who had been hemodiluted. Four of 36 hemodiluted patients surviving the 1-year follow-up suffered a recurrent stroke; corresponding figures for the control patients were two of 30.

The reduced incidence of permanent neurological deficits in the hemodiluted subjects was reflected in a sustained difference in functional outcome between survivors in the two groups 1 year after the stroke. As shown in Figure 3, independence in walking (needs no assistance) was noted in 33 of the 36 hemodiluted patients (92%) but in only 22 of the 30 control patients (73%) (p <0.05). Two hemodiluted and six control patients were totally dependent in the performance of personal hygiene (0.1 >p >0.05). As shown in Figure 4A, independence in ADL performance (walking, dressing, feeding, and hygiene) was noted in 25 hemodiluted (69%) and 17 control (57%) survivors. Another nine
hemodiluted and four control patients were partly dependent in dressing and personal hygiene, leaving two hemodiluted (6%) and nine control (30%) survivors severely disabled and needing assistance with most ADL (p<0.05).

The better ADL performance in the hemodiluted group reduced the need for long-term hospitalization (Figure 4B). One year after the stroke three hemodiluted and eight control patients remained hospitalized in geriatric clinics, which corresponds to 8% and 27% of the survivors, respectively (p<0.05).

As shown in Figure 5, in all subsets but one a greater proportion of hemodiluted patients were living in their homes 3 months and 1 year after the stroke compared with the controls. However, in patients with a medical history of congestive heart failure (22 hemodiluted and 17 control patients) this tendency was not evident, and mortality and hospitalization rates appeared quite similar. Because of the small number of patients in each subgroup, statistical testing is not meaningful.

Fourteen patients had a stepwise or progressing onset of neurological deficits before arrival at the hospital and randomization. Of these, seven were randomized to hemodilution therapy and seven to the control group. Three months after the stroke five of the hemodiluted patients were discharged to their homes, one was in a long-stay hospital, and one was dead. Corresponding figures for the control patients were two, two, and three.

One satisfactory CT scan was obtained in 45 of the 52 hemodiluted patients and in 42 of the 50 control patients some time during the first 3 weeks after symptom onset. Of these 87 satisfactory CT scans, 50 revealed a hypodense area in the brain parenchyma. Six hemodiluted and eight control patients showed deep cerebral infarcts in the region of the capsula interna, thalamus, or putamen. All six hemodiluted patients were discharged to their homes 3 months after the stroke compared with three of the eight control patients. Of the remaining control patients with deep infarcts two were hospitalized at 3 months and the other three were dead. Large infarcts, including those in both deep and superficial hemispheric regions, were revealed in 10 hemodiluted and six control patients. One hemodiluted patient was discharged to home 3 months after the stroke, and the 15 remaining patients were either hospitalized or dead. Pure superficial hemispheric infarcts were visualized in 14 hemodiluted and six control patients. Nine of the hemodiluted patients were at home and the other five were hospitalized or dead 3 months after the stroke. Corresponding figures in the

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**Figure 2.** Bar graph of neurological deficits in survivors 12 months after stroke. Filled bars, hemodiluted patients (n=36); hatched bars, control patients (n=30); n.s., difference not significant.

**Figure 3.** Bar graph of performance of activities of daily living in survivors 12 months after stroke. Filled bars, hemodiluted patients (n=36); hatched bars, control patients (n=30); n.s., difference between hemodiluted and control groups not significant. *Cooking not included.
A. FUNCTIONAL CAPACITY IN SURVIVORS AT 12 MONTHS

36 PATIENTS

57%

30% 

5%

INDEPENDENT

PARTLY DEPENDENT

TOTALLY DEPENDENT

30 PATIENTS

69%

23%

18%

INDEPENDENT

PARTLY DEPENDENT

TOTALLY DEPENDENT

FIGURE 4. Pie charts of functional capacity in survivors (panel A) and mortality and need for hospital care 12 months after stroke (panel B). H, hemodiluted patients; C, control patients.

B. NEED FOR HOSPITAL CARE AT 12 MONTHS

52 PATIENTS

45%

15%

43%

31%

AT HOME

IN HOSPITAL

DEAD

50 PATIENTS

16%

57%

30%

AT HOME

IN HOSPITAL

DEAD

control patients were two and four. Fifteen hemodiluted and 22 control patients showed no lesion on CT scan. Of these patients, all 15 randomized to hemodilution therapy were in their homes 3 months after the stroke. In the control group, 16 patients were at home and six were hospitalized or dead.

The first lumbar puncture, before randomization, showed a bleeding pattern or one of possible hemorrhagic infarction in 10 patients randomized to hemodilution therapy and 11 patients randomized to the control group (Table 1). At the second lumbar puncture (day 3 or 4), corresponding patterns were shown in 15 hemodiluted and 18 control subjects. From the first to the second lumbar puncture 17 of 40 hemodiluted and 18 of 30 control patients showed an increase in peak hemoglobin absorbance. Mean hemoglobin absorbance increased from the first to the second lumbar puncture in both groups. This increase was larger in the control group than in the hemodiluted group (difference not significant). As shown in Table 2, 17 of 45 hemodiluted patients (38%) showed increasing levels of CSF total protein from the first to the second lumbar puncture; the corresponding figures for control patients were 26 of 41 (63%) (p<0.02). Mean CSF protein concentration increased from the first to the second lumbar puncture in the control group while it decreased slightly in the hemodiluted group (difference not significant).

Discussion

Compared with control patients hemodiluted patients were less disabled and showed significantly better ADL performance 1 year after the stroke. The proportion of patients still hospitalized 1 year after the stroke was significantly reduced in the hemodiluted group. Long-term mortality was slightly lower among the hemodiluted patients.

Long-term evaluations of stroke recovery are easily hampered by extracerebral deaths, recurrent strokes, and insufficient rehabilitation procedures following the initial stroke event. If only severely disabled patients die during follow-up in one therapeutic group and all severely disabled patients survive in the other, the evaluation of neurological outcome in survivors will unfairly favor the former group. This problem is seldom discussed in studies of stroke therapy. In the present study evaluation of neurological outcome in 1-year survivors was not disturbed by unequal distributions of patients suffering recurrent strokes or by high mortality rates among the severe cases that could possibly favor the hemodiluted group. Neither did the prognostic indicators registered at randomization (age, medical history, and neurological symptoms) or the findings at CT scan indicate that the hemodiluted subjects should have a more favorable spontaneous prognosis. The multifaceted stroke unit regimen and the Swedish health care system guaranteed equal amounts of appropriate rehabilitation efforts for all included patients during the acute phase and the first year after the stroke.

It is not immediately evident why our positive results from hemodilution therapy were not reproduced in other

<table>
<thead>
<tr>
<th>Peak absorbance at 415 nm</th>
<th>Hemodiluted First (n=43)</th>
<th>Second (n=40)</th>
<th>Controls First (n=43)</th>
<th>Second (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>≥0.0030</td>
<td>5</td>
<td>12</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>0.0015–0.0029</td>
<td>5</td>
<td>12</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>&lt;0.0015</td>
<td>33</td>
<td>77</td>
<td>25</td>
<td>63</td>
</tr>
<tr>
<td>Mean absorbance (mean±SD)</td>
<td>0.0012±0.0011</td>
<td>0.0018±0.0033</td>
<td>0.0010±0.0009</td>
<td>0.0022±0.0025</td>
</tr>
</tbody>
</table>

Patients with increasing absorbance from first to second lumbar puncture

First lumbar puncture was performed before randomization and second on average day 4 after symptom onset.
Hemodilution therapy is aimed at increasing blood flow, and benefit is expected only if parts of the infarcted area are ischemic at the time of therapy and if the neurons are neurophysiologically silent but still viable. Ischemic brain regions supplied by collaterals are more likely to benefit from hemodilution than infarcts supplied by occluded end-arteries. In the present study, outcome was better in hemodiluted patients with cortical as well as deep CT-verified infarcts than in controls.

Combining bloodletting and infusion of a plasma volume expander affects both the oxygen carrying capacity and the total blood volume. Chronic arterial hypertension, prior strokes or transient ischemic attacks, cardiac disorders, diabetes mellitus, and old age were considered as conditions with a possible reduced tolerance against rapid fluctuations in plasma volume or hematocrit. Subset analyses showed that mortality rates were similar or lower in all hemodiluted subsets than in the control subsets. Compared with controls, a greater proportion of hemodiluted patients was able to live in their homes during the first year after the stroke in almost all subsets. The only exception was patients with a history of congestive heart failure, in whom long-term outcome appeared quite similar in hemodiluted and control patients. In those patients, the modest hypervolemia induced by hemodilution may impair cardiac function, decrease cardiac output, and thus counteract the presumed beneficial effects of hemodilution on cerebral blood flow and oxygenation. Nevertheless, in patients fulfilling the inclusion criteria of this study, nothing indicates that the modality of hemodilution therapy applied adversely affected short- or long-term mortality or disability. This is in accordance with results from the Scandinavian Multicenter Study. Furthermore, Grotta and coworkers performed hemodynamic monitoring during hypervolemic hemodilution in nine acute stroke patients in stable cardiac conditions and showed that large fluctuations of pulmonary wedge pressure and reductions of hematocrit could be tolerated without apparent adverse effects.

A progressing deterioration of neurological deficits after symptom onset in ischemic stroke patients may indicate that labile thromboembolic processes are operating. In the subset of patients with a stepwise or gradual course of symptom onset who received early hemodilution therapy, both mortality and functional disability were reduced compared with controls. This is a possible indication that hemodilution may also positively influence the outcome in progressing ischemic stroke.

Therapeutic regimens directed toward reperfusion may convert an ischemic lesion to a hemorrhagic one. This risk increases with the size of the cerebral infarct and when the infarction is caused by cerebral embolization. A hemorrhagic component in cerebral tissue, if small, may not be visualized on a CT scan but will probably increase the concentration of hemoglobin degradation products in the CSF. Compared with control patients, the hemorrhagic admixture to CSF appeared less in the hemodiluted group according to the spectrophotometric analysis performed about the fourth day after symptom onset. The risk of converting an ischemic infarct to a hemorrhage by early hemodilution therapy therefore seems unlikely.

Another problem, partly related to reperfusion, is the development of cerebral edema. Improved blood flow to regions with an ischemically injured microvasculature may increase the leakage of water and plasma proteins into an infarcted area and increase the ultimate extent of brain edema. Signs of aggravated blood-brain barrier permeability, detected as an increase in the CSF total protein content from the first to the second lumbar

### Table 2. Cerebrospinal Fluid Protein Concentrations at First and Second Lumbar Punctures in Hemodiluted and Control Patients

<table>
<thead>
<tr>
<th>Hemodiluted</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>First (n=48)</td>
<td>Second (n=45)</td>
</tr>
<tr>
<td>Concentration (mean±SD mg/ml)</td>
<td>538±188</td>
</tr>
</tbody>
</table>

Patients with increasing concentrations from first to second lumbar puncture:
- Hemodiluted: 17/45 (38%) *p<0.02 different from hemodiluted by χ^2 test.
- Control: 26/41 (63%)
puncture, were significantly less frequent in hemodiluted subjects than in the controls. Thus, the risk of aggravating the so-called vasogenic component of cerebral edema by our modality of slightly hypervolemic hemodilution seems unlikely.

This study was aimed at evaluating the ultimate effect on neurological recovery of hemodilution therapy at the time maximal spontaneous recovery of neurological function is expected. The study was also aimed at evaluating potential hazards with the hemodilution regimen applied. Although this is a small, single-center study, its strength is that the comparability in important clinical variables was sustained during the 1-year follow-up. The conclusion is that modest hypervolemic hemodilution is a safe acute therapeutic regimen for the majority of ischemic stroke patients. This therapy improves long-term functional outcome, particularly when applied in a stroke unit that also is directed toward early rehabilitation.

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