Hypervolemic Hemodilution in Acute Ischemic Stroke
The Multicenter Austrian Hemodilution Stroke Trial (MAHST)

Franz T. Aichner, MD; Franz Fazekas, MD; Michael Brainin, MD; Werner Pölz, PhD; Bruno Mamoli, MD; Karl Zeiler, MD

**Background and Purpose**—Experimental studies suggest a beneficial effect of hemodilution on acute ischemic stroke. This was not proven by previous multicenter trials in the clinical setting. Various reasons have been suggested for the failure of these studies, which we attempted to consider in the Multicenter Austrian Hemodilution Stroke Trial (MAHST).

**Methods**—MAHST is a randomized, double-blind, placebo-controlled study of hypervolemic hemodilution (HHD) within 6 hours of a clinically first ischemic stroke localized in the middle cerebral artery territory. The treatment consisted of 10% hydroxyethyl starch 200/0.5 (HES) and was tested against pure rehydration with Ringer’s lactate over a period of 5 days. Our primary outcome measure was clinical improvement within 7 days as measured by the Graded Neurologic Scale (GNS). We performed an adaptive interim analysis to reevaluate the study goal after entering half of the projected number of patients (n=200). At least 600 patients per group would have been required for significant results, and therefore we decided to terminate the trial.

**Results**—Ninety-eight patients received HHD and 102 patients placebo. The baseline characteristics were comparable between both groups. In the HHD group the absolute reduction of the hematocrit was 2.5% on day 2 with a maximum of 3.7% on day 5, which compares with a reduction in the placebo group of 1% and 1.9%, respectively. Intention-to-treat analysis showed no significant difference of the change of the GNS scores between HHD-treated (median, −8.5; 95% confidence interval, −14.2 to −4.0) and placebo-treated patients (median, −6.0; 95% confidence interval, −11.0 to 0.0) on day 7, and GNS scores remained similar in both treatment groups throughout the trial. At 3 months, slightly more HHD patients showed complete independence on the Barthel Index (28 versus 24), and fewer HHD than placebo patients had died (13 versus 17), but these differences were not statistically significant. HHD treatment was not associated with any specific adverse event.

**Conclusions**—Mild HHD is safe but failed to demonstrate a significant beneficial effect over the pure rehydration regimen in patients with acute ischemic stroke. (*Stroke*. 1998;29:743-749.)

**Key Words:** clinical trials • hemodilution • hydroxyethyl starch • stroke, ischemic

Experimental studies have shown hemodilution to increase cerebral blood flow in areas of ischemic brain. This may translate into a reduction of the size of infarction and improve neurological outcome.1–8 These beneficial results were accomplished by a maximum interval between ischemia and hemodilution of less than 3 hours, a low target hematocrit of 32%, and the use of low-molecular-weight HES. However, a number of controlled clinical trials and a subsequent meta-analysis failed to confirm the clinical benefit of hemodilution therapy.9–21 This discrepancy may be explained by various differences between experimental and clinical conditions.

In part, negative and discordant clinical results may have resulted from too long and variable intervals between ischemic stroke and the onset of hemodilution therapy. The Scandinavian, North American, and Italian hemodilution trials used entry times of 48, 24, and 12 hours, respectively.11,13,14 The proportion of patients in whom hemodilution was started within 6 hours was only 6% in the Scandinavian trial and 55% in the Italian trial and has not been indicated in the North American study.

Hypovolemia may have counteracted any beneficial rheological effect of hemodilution even more seriously in some trials.11–18 Intermittent reduction of the circulatory volume is a consequence of phlebotomy before the adequate substitution of fluids and may be even more dangerous in stroke victims who are prone to dehydration. Data from the North American trial and the experience of others strongly argue for
an increase of cardiac output in order to benefit from hemodilution. However, vigorous fluid therapy may have the drawback of invasive monitoring and could increase the risk of cardiopulmonary complications. Experience has also accumulated in regard to the choice of the hemodiluting agent. Albumin and LMWD have been used in the majority of previous trials. LMWD is associated with an increase of viscosity when given for more than 3 days because of the accumulation of large dextran molecules. Furthermore, LMWD may exacerbate the formation of brain edema and conveys a potential risk of anaphylactic side effects. Recently, the complex polymer HES has been introduced, which seems to lack these negative properties and also decreases thrombocyte and erythrocyte aggregation.

Based on these data, we designed a hemodilution trial that incorporated the aspects of early treatment, ease of application, minimal risk for the patient, and a well-defined patient population.

### Subjects and Methods

This double-blind study was performed at 15 hospitals in Austria between October 1992 and December 1996. It tested whether mild HHD with low substituted HES is safe and conveys any benefit over pure rehydration with crystalloid fluid regarding neurological recovery from acute ischemic stroke.

#### Selection of Patients

Consecutive stroke patients were considered for inclusion if they had sudden onset of focal neurological symptoms and signs characteristic of middle cerebral artery infarction such as hemiparesis, sensory impairment, and aphasia; if they scored <70 points on the Mathew Scale; and if therapy could be initiated within 6 hours after the onset of stroke. Patients were required to give informed consent and to be available for a follow-up period of 3 months. The study design was approved by the local ethical committees.

Diagnostic Work-up

All patients underwent ECG and sonographic examination of the carotid arteries within 3 days of stroke onset. Hemodynamically significant carotid artery obstruction was defined as a stenosis >80% or occlusion. CT was not available within 6 hours after the onset of stroke in some of the participating centers, and therefore we allowed CT or MRI of the brain to be performed within the first week. Infarcts were classified as lacunar or nonlacunar. Each scan was reviewed centrally by a neuroradiologist blinded to all clinical information, including treatment group.

#### Outcome Measures

Stroke severity was determined according to the GNS (inverted Glasgow Coma Scale, language and other cortical functions, cranial nerves, motor function, sensory function), which ranged from 0 to 100 points, immediately at the start of therapy. The GNS was repeatedly performed after 24 ±4 hours, on day 7, 3 weeks ±2 days, and 3 months ±5 days after the acute event. Improvement in the GNS scores over the treatment period, ie, between the start of HHD and day 7, was the primary outcome variable. Domains that could not be properly assessed by the GNS were given the worst rating, ie, death was 100 points on the GNS. Stroke severity was additionally rated according to the Mathew Scale on day 7 and during the follow-up visits. The patients’ ability to perform activities of daily living was measured by means of the Barthel Index. Care was taken to have these evaluations consistently performed by the same investigator. To homogenize the interpretation of stroke severity between centers, a training video was rated by every participating physician before the start of the trial. Recurrent stroke and death of any cause were pretermination study end points. Adverse events were monitored by a Safety Committee.

#### Treatment and Randomization

A loading dose of 250 mL 10% HES in physiological saline (Expahes 10%, Laevosan Gesellschaft) was given within 1 hour. This infusion was followed by another 250 mL of HES and 250 mL of Ringer’s lactate administered over a period of 4 hours. After an interval of at least 3 hours, patients received 250 mL HES parallel with or prior to 250 mL Ringer’s lactate (over 3 to 4 hours) twice daily for a total of 10 doses. Placebo treatment consisted of equivalent volumes of Ringer’s lactate. During the treatment phase patients were allowed to receive a maximum daily dose of 5000 IU of low-molecular-weight heparin or of 15 000 IU of unfractionated heparin for the prevention of deep venous thrombosis. Acetylsalicylic acid (in an initial dose of 250 to 300 mg and subsequent daily doses of 100 mg) was recommended for secondary stroke prevention. This comedication was at the discretion of the treating physician. Any further concomitant use of drugs with a potential effect on cerebrovascular ischemic diseases was prohibited.

The randomization scheme was generated by permutation of random numbers (Software Randomsys, University of Linz) in 150 blocks with a length of four patients each by an external biometrics consultant. This block formation should guarantee an even distribution between HES- and placebo-treated patients within every center. In practice, Laevosan Gesellschaft provided a numbered box containing active or placebo treatment in identical bottles for every patient. These bottles were stained transparently yellow to mask slight differences in color between HES and Ringer’s lactate. The difference between both solutions was too discrete to become apparent in a regular infusion set. Every medication box contained a scaled envelope with the randomization code, which was allowed to be broken only in case of emergency.
Sample Size and Interim Analysis

The North American Hemodilution in Stroke Study Group reported a difference of 40% on the GNS over 3 days of treatment in favor of the hemodiluted group. In view of the possible therapeutic efficacy of the rehydration therapy of controls and our moderate hemodilution regimen, we estimated a smaller difference of 15% to 20% in the change of the GNS during an interval of 7 days. This was also in agreement with other clinical data. With α = 5% (two-tailed), β = 10%, the required sample size was 200 patients per group (intention-to-treat). The determination of the sample size was made by the blinded control committee in accordance with the study protocol before the codes were broken.

Statistical Analysis

After termination of the trial, all 200 patients were included in the intention-to-treat analysis. The per-protocol analysis comprised 158 patients. In addition to a descriptive analysis, a confirmatory analysis was performed on both the basis of the intention-to-treat and per-protocol principles. Decisions concerning valid cases or dropouts were made by the blinded control committee in accordance with the study protocol before the codes were broken.

The statistical tests performed on all baseline variables comprised the Mann-Whitney U test for ordinal or interval variables and Fisher’s exact test or χ² test for nominal variables in the form of frequency tables. The Mann-Whitney U test was used to test the group differences of the GNS scores between onset of therapy and day 7 (primary outcome variable). The Mann-Whitney U test and Fisher’s exact test were also used for testing secondary outcome variables, as appropriate.

For the neurological scores, the worst-case principle was used with respect to missing subcores. In case of a missing score at a certain time point, the respective score of the last visit was carried forward. In cases of death, the worst possible scores were assigned.

Results

At the termination of the study 98 patients had been randomized to HHD and 102 patients to placebo treatment. Both groups were comparable in regard to age, sex, hematocrit, type of stroke and pathogenetic factors, interval to treatment, and severity of stroke symptoms as measured by the GNS and the Mathew Scale (Table 1). There was a tendency toward a lower median systolic blood pressure and a higher blood glucose level in the HHD group, but these differences did not reach statistical significance (Table 1). Acetylsalicylic acid and subcutaneous heparin were given to almost all patients, except for one patient in the HHD group and one in the placebo group. Seventy-seven patients in the HHD group and 81 patients in the placebo group completed the study per protocol. The baseline characteristics of these subsets were distributed to the intention-to-treat population in a similar manner, and there were no significant differences between the HHD and the placebo groups except for a lower median systolic blood pressure in HHD-treated individuals (150 versus 160 mm Hg; P = .04). Forty-two patients were not considered for the per-protocol analysis for the following reasons: cerebral hematomas (n = 11), brain stem and cerebellar infarcts (n = 3), protocol violations such as Mathew score > 70, low hematocrit, elevated creatine, cardiac complications, and others.

After HHD there was an immediate drop of the hematocrit from 44.0% to 41.9% on day 2 (relative reduction, 4.7%). However, pure rehydration was also associated with a reduction of hematocrit from 43.8% to 42.8% (relative reduction, 2.3%) on day 2. In the following days, the hematocrit of HHD-treated patients continued to decline, with a maximum relative reduction of 10% on day 5 (difference from hematocrit reduction by rehydration, 7.6%), while the hematocrit of placebo-treated patients remained rather stable. A significantly lower hematocrit in HHD- than in placebo-treated patients was reached on day 4 of the trial, but the absolute differences remained small. Table 2 illustrates the time course of the hematocrit in both treatment groups according to intention-to-treat analysis.

<table>
<thead>
<tr>
<th>TABLE 1. Group Characteristics at Randomization into MAHST (Intention-to-Treat)</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Age, y*</td>
</tr>
<tr>
<td>Sex (M/F)†</td>
</tr>
<tr>
<td>GNS*</td>
</tr>
<tr>
<td>Mathew Scale*</td>
</tr>
<tr>
<td>Hematocrit*</td>
</tr>
<tr>
<td>Systolic blood pressure*</td>
</tr>
<tr>
<td>Diastolic blood pressure*</td>
</tr>
<tr>
<td>Blood glucose*</td>
</tr>
<tr>
<td>Interval to treatment, h*</td>
</tr>
<tr>
<td>Atrial fibrillation†</td>
</tr>
<tr>
<td>High-grade carotid stenosis†</td>
</tr>
<tr>
<td>Nonlacunar infarction†</td>
</tr>
</tbody>
</table>

Values are median (95% confidence intervals).

* Mann-Whitney U test.
† Fisher’s exact test.
Neurological recovery as described by the GNS score was similar in both HHD and placebo treated patients. The Figure shows clinical improvement to have been greatest within the first 7 days of the trial, with a parallel course of the median of the GNS scores of both treatment groups throughout the trial. Accordingly, there was no significant difference in the absolute increase in the GNS scores over time between HHD- and placebo-treated patients. This was true for intention-to-treat as well as for per-protocol analysis (Table 3). Similar results were obtained when we analyzed patients’ improvement by means of the Mathew Scale. In the HHD group, the median of the Mathew score (intention-to-treat) improved from 57 (95% CI, 55 to 60.2) before treatment to 65 (57 to 69) after 3 months (P = .32) in the placebo group.

Four more patients of the HHD group gained full independence in activities of daily living over the 3-month follow-up period compared with placebo-treated patients. However, the median score of the Barthel Index was not significantly different between the HHD group (median, 45; 95% CI, 25 to 65) and placebo-treated patients (50; 95% CI, 25.75 to 64.25) at the end of the study (P = .31), and 65 (61.6 to 69) after 3 months (P = .32) in the placebo group.

The time window beyond which the evolution of damage prohibits any possible impact of hemodilution is not known. In previous trials, patients were enrolled as long as 72 hours after stroke. The Scandinavian Stroke Study investigated 363 patients with an inclusion time of 48 hours. Treatment was started within less than 12 hours in 28% of patients, but this subgroup did not show a more favorable effect of hemodilution than the remainder of the study population. The American hemodilution trial studied 88 patients within 24 hours and found a slight benefit for those patients treated no later than 12 hours after stroke. The Italian hemodilution trialists included all their patients within 12 hours after onset of symptoms. They found a treatment effect neither for the entire study population in regard to case fatalities and disability at 6 months nor for the 55% of patients in whom treatment was started within 6 hours. MAHST is the first study that required hemodilution to be initiated within 6 hours in all patients; however, in the Italian study, 702 (55%) of the 1267 patients were already randomized within 6 hours after their first symptoms. A maximal delay of 6 hours has been considered a reasonable interval both on pathophysiological and practical grounds. However, this may still be too long for hemodilution to become effective, especially when a mild hemodilution regimen is used. Some support for this assumption has recently come from a study by Yanaka et al. These investigators found that hemodilution in an animal model significantly reduced the size of infarction and improved the neurological outcome when initiated within 3 hours after onset of ischemia. Hemodilution was ineffective when delayed for 6 hours.

Experimental studies suggest a hematocrit of 30% as the limit below which oxygen delivery becomes compromised because increased transportation from augmentation of cerebral blood flow no longer compensates for the reduction of oxygen-carrying capacity. These results cannot be directly transferred to stroke victims, who tend to suffer from more widespread vascular disease and in whom compensatory mechanisms may be already exhausted to some extent. It is therefore assumed that the level of hematocrit at which oxygen delivery begins to decline in ischemic brain tissue is much higher, but the exact threshold is not yet known.

Previous controlled hemodilution trials targeted a hematocrit...
of 33% to 38% with an absolute reduction by 4% to 7%. This was usually achieved by phlebotomy and corresponded to a decrease of 9% to 16% in relative terms. MAHST aimed at a more gradual reduction of the hematocrit. We chose not to include venesection in our treatment regimen because we wanted to avoid any possibility of hypovolemia and because many patients dislike the procedure. We also decided not to infuse larger amounts of fluid because we were concerned about the need for more extensive monitoring and an increased risk of brain edema or cardiac failure. Therefore, on day 2 the hematocrit of our HHD patients had dropped by 2% (relative reduction, 4.7%), and maximal reduction by 4% (relative reduction, 10%) was not obtained before day 5. This mild hemodilution regimen might certainly be a further explanation for the failure of MAHST. Otherwise, our treatment scheme was well tolerated, and there has been no evidence of a better outcome of patients with >15% relative reduction of hematocrit in the Scandinavian and Italian trials.

In the HHD group there was a tendency toward a lower median systolic blood pressure and a higher blood glucose level at entry. Since these differences did not reach statistical significance, their impact on the outcome of HHD treated patients cannot be defined.

Differences between HHD- and placebo-treated patients in MAHST may have been minimized by a positive treatment effect of rehydration therapy alone. Changes in physical activity such as bed rest and placebo treatment with crystalloids also exert some hemodiluting effect, as noted previously and confirmed by MAHST. In the Amsterdam study, Goslinga et al observed a significant reduction in mortality and a higher rate of independence at home after hemodilution of patients with a baseline hematocrit <45%. In patients with a higher hematocrit, however, pure rehydration with crystalloids was superior to hemodilution, and rehydrated patients with high hematocrit (≥45%) fared significantly better than their counterparts in the normal to low hematocrit range. In this context it seems important to note that MAHST was the first study to test hemodilution against a predetermined treatment regimen of the placebo group. Moreover, because we avoided phlebotomy, MAHST could be performed in a truly blinded fashion.

Meta-analysis of previous trials has clearly shown that even optimal hemodilution may not be expected to provide dramatic benefits. Hemodilution could help to salvage the ischemic penumbra but may not be able to reduce the core of infarction. Recently, much more aggressive treatment strategies such as intravenous thrombolysis resulted in only modest treatment benefits at best. Although we made every effort to reduce the heterogeneity of our study population, the calculation of group sizes needed for obtaining statistically significant results was still flawed by expectations that were too high. This became evident from the interim analysis that we performed after 200 patients were entered. In contrast to the American Hemodilution in Stroke Study Group, MAHST showed only a 7% difference regarding the primary end point, ie, the neurological deficit before treatment versus day 7. Both a conservative and a nonconservative calculation showed that a sample size of 600 to 800 patients per group would be necessary for the results to become statistically significant.

At present, no proven treatment strategies exist for acute ischemic stroke except the intravenous application of recombinant tissue plasminogen activator, as suggested by the National Institute of Neurological Disorders and Stroke trial. This medication is associated with potentially serious complications and may be given only to a well-defined patient population that seems to be relatively small. In this context and in view of some previous hemodilution trials that were terminated prematurely, the low rate of adverse events in MAHST is noteworthy. Overall, the total number of deaths

### TABLE 3. Improvement of the GNS in MAHST

<table>
<thead>
<tr>
<th></th>
<th>10% HES</th>
<th>Ringer’s Lactate</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat (n=98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of treatment (day 7)</td>
<td>-8.5 (-14.2 to -4.0)</td>
<td>-6.0 (-11.0 to 0.0)</td>
<td>.24</td>
</tr>
<tr>
<td>Follow-up at 3 wk</td>
<td>-11.0 (-18.0 to -6.8)</td>
<td>-9.5 (-16.0 to -4.6)</td>
<td></td>
</tr>
<tr>
<td>Follow-up at 3 mo</td>
<td>-15.0 (-22.0 to -9.0)</td>
<td>-16.0 (-21.4 to -6.6)</td>
<td></td>
</tr>
<tr>
<td>Per protocol/completers</td>
<td>(n=77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of treatment (day 7)</td>
<td>-12.0 (-17.0 to -7.0)</td>
<td>-9.0 (-13.8 to -3.2)</td>
<td>.27</td>
</tr>
<tr>
<td>Follow-up at 3 wk</td>
<td>-16.0 (-24.0 to -9.0)</td>
<td>-14.0 (-21.0 to -9.0)</td>
<td></td>
</tr>
<tr>
<td>Follow-up at 3 mo</td>
<td>-20.0 (-25.0 to -13.4)</td>
<td>-21.0 (-25.0 to -14.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are median (95% confidence intervals). Mann-Whitney U test.

### TABLE 4. Serious Adverse Events and Deaths

<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>10% HES</th>
<th>Ringer’s Lactate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>with serious adverse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>7 (6)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Brain edema</td>
<td>1 (1)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>3 (2)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1 (0)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Total No. of deaths</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Deaths during medication</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Deaths during follow-up</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate serious adverse events associated with death.
was smaller in HHD- than in placebo-treated patients, and we observed no association of treatment with any specific adverse event. Our mild HHD regimen and the choice of the hemodiluting agent are likely to have been major contributing factors.

HES is characterized by the average molecular weight (200 kD), the degree of molar substitution (0.5 = ratio of substitut-ed/total of anhydroglucose residues on the polymer chain), and the pattern of substitution (ie, the ratio of substitution on residues C2/C6).22,23 The latter two parameters control the degradation of HES to smaller molecules by serum amylase and its subsequent renal excretion. In addition to being well tolerated, HES also decreases thrombocyte and erythrocyte aggregation.23 Certain other trials have used LMWD.11,13,17 This substance causes an increase in viscosity when administered for more than 3 days because of the accumulation of large dextran molecules. More importantly, LMWD may exacerbate edema formation in cerebral ischemia and conveys a potential risk of anaphylactic side effects; however, the pharmacological evidence that HES may be superior to LMWD is not substantiated by the findings of this clinical study.

In conclusion, mild HHD after the MAHST treatment protocol did not show a statistically significant treatment effect. Consequently, there is still no scientific support for the use of hemodilution in clinical practice.

Appendix

MAHST Participants

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References

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