Neurological Deterioration Under Isovolemic Hemodilution With Hydroxyethyl Starch in Acute Cerebral Ischemia

Henning Mast, MD and Peter Marx, MD

In a prospective study, we randomly allocated 70 patients with acute ischemic stroke to two therapy groups. Up to interim analysis, 33 patients underwent bloodletting, with simultaneous infusion of an identical volume of hydroxyethyl starch (10%, 200/0.5). The target hematocrit was 35%. A control group of 37 patients did not receive hemodilution. Apart from an unequal sex distribution, the two groups were comparable with regard to age, cardiovascular risk factors, and medical history. In the hemodilution group, the mean hematocrit fell from 44.4% to 37.7%. After 14 days, improvement on the neurological score scale was 3.5 points in the hemodilution group compared with 6.5 points in the control group (p=0.12). Subgroups with early inclusion (<12 hours) or pronounced lowering of hematocrit (>15% of initial hematocrit) also did not profit from hemodilution. Clinical deterioration observed in eight hemodilution group patients (p<0.01) led to discontinuation of the study for ethical reasons. (Stroke 1991;22:680–683)
we applied the neurological score scale already used (mainly appraising motor performance). Blood hematocrit, but sex distribution still differed significantly. Figure 1 shows the almost equal distribution of initial neurological scores in both groups. There were no relevant differences with regard to age, previous medical history (\%), cardiovascular risk factors, or relevant previous diseases. The male/female ratio was 15/18 and 26/11 in the H and C groups, respectively (\textit{p}<0.05).

There were no statistically significant differences between the two patient groups with regard to age, cardiovascular risk factors, or relevant previous diseases. The male/female ratio was 15/18 and 26/11 in the H and C groups, respectively (\textit{p}<0.05).

A total of 14 patients was excluded for secondary analysis. In three H group patients, hemodilution was terminated because of contraindications, such as gastrointestinal hemorrhage, electrocardiographic signs of ischemia, and renal insufficiency. In two other H group patients, anticoagulation for basilar artery thrombosis was considered necessary and replaced hemodilution. In the C group, one patient with hemispheric hemorrhage and two with basilar artery thrombosis were excluded. One patient in the H group and five in the C group were excluded because their deficits (somatosensory deficit or homonymous hemianopia) could not be evaluated with the scale used. In the remaining 56 patients (Table 1: H group, \textit{n}=27; C group, \textit{n}=29), there were no relevant differences with regard to age, prior diseases, cardiovascular risk factors, time of inclusion, initial neurological score, or initial hematocrit, but sex distribution still differed significantly. Figure 1 shows the almost equal distribution of initial neurological scores in both groups.

On the day of admission and on day 2, 3, 7, and 14, we applied the neurological score scale already used in the Scandinavian multicenter study\textsuperscript{2,4} to evaluate the clinical course. This score (best performance, 48 points) mainly appraises motor performance. Blood pressure and heart rate were measured before and after hemodilution, as well as routinely once a day.

Blood samples for rheological analysis were obtained by venipuncture. Hematocrit was determined by centrifugation at 15,000 \textit{g} over 5 minutes. Additional parameters, such as whole-blood viscosity and plasma viscosity, erythrocyte aggregation, and filterability, will be published separately.

All results are given as mean values with 95% confidence intervals. Statistical significance was tested with Fisher’s exact test, \textit{X}\textsuperscript{2}, and Student’s \textit{t} test. Because it became necessary to exclude patients retrospectively, we carried out both an intention-to-treat and secondary analysis.

### Results

The mean hematocrit on admission was 44.5% (42.7–46.2%) in the C group and 44.4% (42.8–46.0%) in the H group. In the H group, it was lowered to 37.7% (36.3–39.1%) 3–5 hours after the beginning of therapy. Further dilutions were necessary on the second day in 20 patients and on the third day in 16 patients. Hematocrit reduction persisted up to the 14th day.

Mean arterial blood pressure on admission was 109 and 107 mm Hg in the H and C groups, respectively. We found a slight reduction in both groups (103 and 104 mm Hg, respectively) after 3 days; heart rates of 79 and 76 beats/min, respectively, remained essentially unchanged during the treatment period. There were no allergic complications of therapy.

After 2 weeks, the average improvement in neurological score was 3.3±0.4 in the H group and 6.5±7.7 points in the C group (\textit{p}=0.12). The neurological score of six hemodiluted patients (eight patients in the intention-to-treat analysis) had deteriorated as compared with the finding on admission. By contrast, clinical deteriorations were not registered in the C group (Table 2). This result was significant for both the

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**Table 1. Patient Data at Randomization in Secondary Analysis Groups (\textit{n}=56)**

<table>
<thead>
<tr>
<th></th>
<th>Hemodilution group (\textit{n}=27)</th>
<th>Control group (\textit{n}=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>67 (62–72)</td>
<td>65 (58–72)</td>
</tr>
<tr>
<td>Range (yrs)</td>
<td>36–92</td>
<td>18–89</td>
</tr>
<tr>
<td>Male/female*</td>
<td>11/16</td>
<td>20/9</td>
</tr>
<tr>
<td>Time after stroke onset (hrs)</td>
<td>23 (18–28)</td>
<td>20 (16–24)</td>
</tr>
<tr>
<td>Early inclusion (&lt;12 hrs)</td>
<td>8/27</td>
<td>9/29</td>
</tr>
<tr>
<td>Neurological score (points)</td>
<td>29.7</td>
<td>31.5</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>44.4 (42.8–46.0)</td>
<td>44.5 (42.7–46.2)</td>
</tr>
</tbody>
</table>

Previous medical history (\%\[])

- Transient ischemic attack: 0 (0) vs 3 (10)
- Stroke: 4 (15) vs 6 (21)
- Myocardial infarction: 6 (22) vs 4 (14)
- Myocardial insufficiency: 5 (19) vs 2 (7)
- Atrial fibrillation: 3 (11) vs 3 (10)
- Angina pectoris: 4 (15) vs 2 (7)
- Hypertension: 7 (26) vs 11 (38)
- Diabetes mellitus: 9 (33) vs 9 (31)
- Hyperlipidemia: 3 (11) vs 4 (14)

Values are mean and 95% confidence interval (in parentheses) where applicable.

*Significant difference (\textit{p}<0.05) between hemodilution and control groups.
The disappointing results of most clinical studies are in contrast to experiments showing smaller infarct areas in hemodiluted animals compared with controls.8-10 One difference between these experiments and the clinical situation is that hemodilution in animal models was carried out either during or immediately after vessel ligation, whereas under clinical conditions, hemodilution usually starts after a delay of several hours when irreversible tissue damage is likely to have already occurred.

Table 3. Data From Secondary Analysis of Six Deteriorating Patients in Hemodilution Group

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Score (day 1/14)</th>
<th>Hematocrit (%)</th>
<th>Inclusion time (hrs)</th>
<th>CCT</th>
<th>Cardiovascular risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>70/F</td>
<td>10/8</td>
<td>45/35</td>
<td>24</td>
<td>Deep infarct MCA</td>
<td>None</td>
</tr>
<tr>
<td>62/F</td>
<td>30/24</td>
<td>50/37</td>
<td>7</td>
<td>Deep infarct MCA</td>
<td>None</td>
</tr>
<tr>
<td>72/F</td>
<td>41/27</td>
<td>40/33</td>
<td>20</td>
<td>Lacune MCA</td>
<td>None</td>
</tr>
<tr>
<td>67/F</td>
<td>22/9</td>
<td>46/38</td>
<td>4</td>
<td>Deep infarct MCA</td>
<td>None</td>
</tr>
<tr>
<td>60/F</td>
<td>27/22</td>
<td>47/40</td>
<td>47</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>92/F</td>
<td>35/20</td>
<td>43/36</td>
<td>12</td>
<td>Cortical infarct MCA</td>
<td>MI, AF, MI-INSUF</td>
</tr>
<tr>
<td>Mean</td>
<td>28/18</td>
<td>46/37</td>
<td>19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CCT, cranial computerized tomography; MCA, middle cerebral artery; MI, myocardial infarction; AF, atrial fibrillation; MI-INSUF, myocardial insufficiency.
In addition, hemodilution in animal experiments usually is carried out under constant orthostatic conditions and with maintenance of a constant blood pressure, which cannot be ensured in the clinical situation. This may explain why cerebral oxygen deficiency does not develop even at very low hematocrit values, whereas reduction of the autoregulation reserve caused by hemodilution might not be compensated by patients.

The increase of cerebral blood flow during hemodilution merely compensates for the reduction in oxygen capacity. It does not allow inferences to be made with regard to clinical efficacy. An optimal hematocrit of approximately 42% was calculated from cerebral blood flow measurements at various hematocrit values in humans and is likely to be even higher for ischemic tissue because the vasodilation reserve is already reduced, if not exhausted. This compares well with the results of the Scandinavian multicenter study, in which the mortality of ischemic stroke was lowest for patients with a hematocrit of approximately 45%.

We conclude that both isovolemic and hypervolemic hemodilution below a hematocrit of approximately 45% is a potentially dangerous stroke therapy for which a clear clinical advantage has not been documented up to now. Hypervolemic hemodilution in particular carries a high risk in multimorbid patients.

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References


KEY WORDS • cerebral ischemia • hematocrit • hemodilution
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