Hypervolemic Hemodilution Treatment of Acute Stroke

Results of a Randomized Multicenter Trial Using Pentastarch

The Hemodilution in Stroke Study Group

Patients with acute ischemic stroke were randomized <24 hours after onset to standard (S) therapy (n=43) or to hypervolemic hemodilution (HH) with pentastarch (n=45). The therapeutic goal of hypervolemic hemodilution was to rapidly reduce hematocrit to 33%, to raise cardiac output, and to continue hypervolemic hemodilution for 3 days. A graded neurologic examination was scored by a blinded observer at randomization (baseline), at the end of treatment or after 72 hours, and at a 3-month follow-up; each patient was also rated using Barthel's disability scale at the 3-month follow-up. Group demographics and results of the graded neurologic examination were similar at baseline, except that the HH group contained twice the number of patients with severe strokes and fewer patients randomized within 12 hours compared with the S group. The HH group improved an average of 7 points in neurologic score from baseline to the end of treatment (the S group deteriorated 1 point) and 24 points by the 3-month follow-up (the S group improved 16 points; p=0.11). The HH group reached an average Barthel disability scale index of 85 while the S group averaged 70 (p=0.8). Deaths associated with cerebral edema occurred in five patients with severe stroke (four in the HH group vs. one in the S group, p=0.36). The following subgroups of HH patients showed better overall improvement in neurologic scores: patients entered within 12 hours after stroke onset, patients with a 15% decrease in hematocrit, and patients with a 10% increase in cardiac output. Based on these results, we conclude that further evaluation of hypervolemic hemodilution using refined patient selection techniques and improved study design is indicated. (Stroke 1989; 20:317–323)

Hemodilution therapy for acute cerebral ischemia and infarction has been under evaluation for many years, and the theoretical benefit of improving reperfusion of the brain by lowering blood viscosity has even led to the routine use of modified hemodilution protocols in some centers. However, after initial enthusiasm,1,2 two recent large randomized evaluations failed to demonstrate any benefit of hemodilution.3,4 Our study was designed to address some of the criticisms of these recent negative studies and to determine if the neurologic deficit caused by acute stroke can be safely reduced by early, aggressive hemodilution.

Most studies to date have employed relatively isovolemic paradigms combining volume expansion with phlebotomy to lower hematocrit (Hct), whole-blood viscosity, and cerebrovascular resistance and thus improve cerebral perfusion, especially in regions of stagnant blood flow. The rationale for this therapy has been extensively reviewed,5–7 but the chief theoretical concerns are that isovolemic hemodilution would make little difference in the microcirculation, where the factor limiting blood flow is not the relative density of erythrocytes but their ability to squeeze through capillaries. Furthermore, increased cerebral blood flow (CBF) following isovolemic hemodilution may result from compensatory vasodilation caused by lowered oxygen carrying capacity; hence, net oxygen delivery may not be increased.8,9

In an effort to address these concerns, our protocol was designed for hypervolemic hemodilution, which may increase CBF beyond that which can be achieved by isovolemic therapy. Brain tissue distal to an occluded vessel is supplied by maximally dilated vasculature, and blood flow therefore should be passively dependent on cardiac output (CO) and arterial blood pressure. By careful but rapid volume expansion under physiologic monitoring, we attempted to raise CBF not only by lowering viscosity by a reduction of Hct but also by raising CO by a combination of hemodilution and improved left ventricular filling.10
The second major focus of our study was an emphasis on early therapy. Previous studies had allowed entry of patients up to 48 hours after infarction, and hemodilution was achieved over 24–72 hours. Our concern is that impaired cerebral perfusion is an early event in the development of cerebral infarction, and experimental studies demonstrate that even a few minutes of critically reduced blood flow will trigger events (such as calcium entry into neurons) that may lead to irreversible damage. This suggests that reperfusion begun more than 12–24 hours after the onset of symptoms would be futile.

Finally, all patients randomized to hemodilution in our study were hemodiluted with 10% pentastarch in 0.9% saline. Pentastarch is a colloid solution of hydroxyethyl starch with a molar substitution of 0.45 and an osmolarity of 326 mosm/l, expanding plasma volume approximately 1.5 times the volume infused. Pentastarch is actually a polydispersion of macromolecules with an average molecular weight of 250,000 Da but a median molecular weight of 73,000 Da. We used pentastarch because previous studies demonstrated that it expanded plasma volume and reduced Hct comparable to dextran but that plasma viscosity and erythrocyte aggregation, lowered by pentastarch, were actually increased by dextran. Furthermore, pentastarch, unlike a similar commercially available compound (Hespan, American Critical Care, McGaw Park, Illinois) has no known effect on hemostatic function.

Subjects and Methods

The study was carried out at 13 centers in the United States (Appendix 1) between September 1985 and February 1987. It was designed as a randomized comparison of hypervolemic hemodilution using pentastarch (HH) with standard therapy (S). Patients in both groups were admitted to the intensive care unit (ICU) for the first 72 hours, but only the HH group received hemodynamic monitoring with a Swan-Ganz (SG) catheter, so neither the managing physician nor the patient were blinded to treatment. In all instances, an independent neurologist unaware of the patient’s treatment measured all outcome throughout the patient’s study course; baseline examinations were carried out at enrollment or before SG catheter placement, and end-of-treatment examinations were performed 72 hours later. After hypervolemic hemodilution had been terminated and the SG catheter had been removed, subclavian bandages were applied to all patients to blind the neurologist. A central unblinded safety committee periodically reviewed outcome in the two treatment groups and was instructed to terminate the study before the anticipated enrollment of 100 patients if excess morbidity or mortality were observed in either group.

We included patients who had acute ischemic infarction in the distribution of one carotid artery. In all instances, treatment had to start within 24 hours after the onset of symptoms, and a computed tomogram (contrast optional) at enrollment (baseline CT scan) had to be normal or compatible with acute nonhemorrhagic infarction.

In an effort to eliminate patients with minimal potentials for recovery and high probabilities of acute deterioration due to cerebral edema, we excluded patients who met any of the following criteria: 1) all of complete hemiplegia, hemianesthesia, hemianopsia, global aphasia if on the dominant side, and hypodensity on baseline CT scan; 2) reduced level of consciousness, with Glasgow Coma Scale score of <9; or 3) baseline CT scan showing a mass effect with ventricular compression and midline shift. Because we began treatment within 24 hours after the onset of symptoms, we tried to detect and eliminate patients with transient ischemic attacks; therefore, we also excluded patients if they demonstrated significant improvement by history or between two neurologic examinations separated by 2–4 hours performed during the period of screening evaluation or had a minimal neurologic deficit with a score on a graded neurologic examination (GNE) of <20. Since the HH group received volume expansion and pulmonary artery catheterization, we also excluded patients with the following characteristics (which might confer a high risk for complications of SG catheter placement or volume expansion): acute myocardial infarction (MI), clinical congestive heart failure (CHF), uncontrollable cardiac arrhythmia, severe hypertension, or acute therapy with heparin. Finally, since the physiologic goals of hypervolemic hemodilution were to administer pentastarch until pulmonary wedge pressure (PWP) reached 15 mm Hg or until Hct fell to 30–35% (or until the maximum amount of pentastarch allowable had been given), we also excluded patients who at their baseline examination already had a high PWP (>20 mm Hg) or a low Hct (<36%).

After the screening evaluation consisting of baseline neurologic assessment, baseline CT scan, evaluation of inclusion and exclusion criteria, signature of informed consent, and repeat neurologic assessment, all patients were admitted to the ICU and then randomized to HH or S.

All HH patients underwent placement of a SG catheter, and pentastarch was administered until Hct was reduced to 30–33%, PWP rose to 15 mm Hg, or the maximum amount of pentastarch allowable had been given. Up to 1,500 ml pentastarch could be administered during the first 24 hours (500 ml/30 min×3). If PWP reached 15 mm Hg before Hct fell to 38%, then 250 ml whole blood could be withdrawn, coupled with infusion of 200 ml pentastarch to further lower Hct without raising PWP above 15 mm Hg. Pentastarch infusion was continued for 72 hours in an attempt to maintain PWP and Hct with a maximum pentastarch volume of 1,000 ml/day on Days 2 and 3. If neurologic status deteriorated upon tapering the pentastarch infusion after 72 hours, further treatment for 24 hours was allowed.
TABLE 1. Group Characteristics at Randomization Into Multicenter Trial of Hypervolemic Hemodilution Treatment of Acute Stroke Using Pentastarch

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hypervolemic hemodilution (n=45)</th>
<th>Standard therapy (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>Mean 63</td>
<td>Mean 64</td>
</tr>
<tr>
<td></td>
<td>Range 28-89</td>
<td>Range 35-85</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>29:16</td>
<td>28:15</td>
</tr>
<tr>
<td>Graded neurologic examination score</td>
<td>49±3</td>
<td>45±3</td>
</tr>
<tr>
<td>Severe strokes (score of &gt;60)</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>42±2</td>
<td>43±2</td>
</tr>
<tr>
<td>Time after stroke onset</td>
<td>15±1</td>
<td>12±1</td>
</tr>
<tr>
<td>&lt;12 hr</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>12-24 hr</td>
<td>29</td>
<td>21</td>
</tr>
</tbody>
</table>

Data are mean±SEM for graded neurologic examination score, hematocrit, and time after stroke onset; number of patients for sex, severe strokes, and categories of time.

During pentastarch infusion, intravenous crystalloid fluid management therapy could also be given as needed to help maintain physiologic parameters at desired levels.

Patients randomized to the S group were also admitted to the ICU for 72 hours but did not receive SG catheterization or pentastarch infusion. No attempt was made to establish uniform fluid management in S patients. However, our protocol called for standard crystalloid fluid management therapy without intentional volume expansion unless clinically indicated for dehydration.

In addition to the two GNEs before randomization, GNEs were carried out at 72 hours (or at the end of treatment in the HH group), 1 and 2 weeks, and 1, 2, and 3 months after the onset of symptoms. A Barthel disability scale (DBS) index was also calculated at the 3-month follow-up. Outcome was measured by an independent observer blinded to the patient’s treatment. The GNE we used has been described in detail and validated for patients meeting the entry criteria of this study.14

Statistical analysis was performed using SAS Version 5.16. SAS was also used to prepare data listings and tables of summary statistics. Changes and percent changes from baseline values were used in the analyses of the GNE, while actual scores were used in the analysis of the BDS; both variables were analyzed using analysis of variance. Categorical data were analyzed using Fisher’s exact test.

**Results**

Forty-five patients were randomized to HH and 43 to S. The groups were comparable in age, sex, and mean GNE score at baseline (Table 1). However, almost twice as many patients with severe strokes (GNE score of >60) were randomized to HH (15 vs. 8) (Figure 1). Mean time from onset to randomization was 15±1 hour in the HH group and 12±1 hour in the S group, and fewer patients were randomized to HH within 12 hours of stroke onset than to S (16 vs. 22). Baseline Hct was comparable in the two groups (Table 1). Baseline CT scan was abnormal, suggesting acute infarction on the appropriate side in 58% of the patients in both groups; the baseline CT scan appeared normal in the remaining 42%. Only two patients in the HH and six in the S group demonstrated evidence of early cerebral edema. Associated cardiac disease (clinical or radiographic CHF or previous MI on electrocardiogram) was present in 22 HH and 22 S patients, and cardiomegaly was present on the admission chest x-ray film in nine HH and seven S patients.

Twenty-one randomized patients did not complete the entire 3-month follow-up (Table 2); 12 of these patients died. Five deaths occurred <7 days (early) and seven deaths occurred >7 days (late) after the stroke onset. Three-month mortality was 20% in the HH and 7% in the S group, and although this difference did not reach significance, it caused the study to be terminated by the safety committee before its intended completion (Figure 2).

All five early deaths were due to cerebral edema, four in the HH and one in the S group. Of the seven late deaths, five occurred in the HH group and were randomized to HH.

![Figure 1. Distribution of patients in hypervolemic hemodilution (filled bars) and standard therapy (open bars) groups according to baseline graded neurologic examination score.](http://stroke.ahajournals.org/)

**TABLE 2. Patients Randomized Into Multicenter Trial of Hypervolemic Hemodilution Treatment of Acute Stroke Using Pentastarch Not Completing 3-Month Follow-up**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Hypervolemic hemodilution (n=45)</th>
<th>Standard therapy (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dropped before completing treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Low hematocrit</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Malingering</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lost to follow-up &gt;discharge but</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Confined to distant nursing home</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Had not reached 3-month follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>when study terminated</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Died</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>6</td>
</tr>
</tbody>
</table>

Data are number of patients.
due to new stroke, renal failure, and MI; the two late deaths in the S group were due to pulmonary embolus and pneumonia. The excess mortality in the HH group, especially the early deaths due to cerebral edema, occurred almost entirely in patients with severe strokes (GNE score of >60) (Figure 3).

Sixty-seven patients completed the study (30 in the HH and 37 in the S group). In the HH group, the average dose of pentastarch on Day 1 was 1390±61 ml, during which time Hct declined 6% (by 14% of baseline); 830±57 and 820±59 ml were the average doses of pentastarch on Days 2 and 3, and average Hct at the end of treatment was 7% below baseline (a mean reduction of 17%). In the S group, average Hct 72 hours after stroke onset was 42% (a mean reduction of 2% from baseline). In the HH group, average PWP rose from 10 mm Hg at baseline to a maximum of 17 mm Hg at the end of treatment. In the 43 HH patients completing treatment, a mean of 8.3±2.2 hours was required to reach one of the physiologic end points: PWP of 15 mm Hg, Hct reduced to 80-100% of lowest value during treatment, or 1,500 ml pentastarch administered.

Substantial improvement in GNE score occurred during treatment in the HH group, while no improvement occurred in the S group during 72 hours. At 3 months, the HH group had improved 24 points in GNE score compared with 16 points for the S group (Figure 4); this represents a 50% better recovery in the HH group than in the S group, but this difference was not significant (p=0.11). The HH group also showed a better BDS index than the S group at 3 months (85 vs. 70), but while this difference clearly favored the HH group, it did not quite reach significance (p=0.08).

We analyzed the following subgroups: patients entering the study <12 hours after the onset of stroke symptoms versus those entering after 12-24 hours, HH patients with a Hct reduction of >15% versus those with a reduction of <15%, and HH patients with an improvement in CO of >10% versus those whose improvement was <10%. Among patients entered within 12 hours, by the 3-month follow-up the HH subgroup improved 32 points on the GNE compared with 16 points for the S subgroup (p=0.11). The HH subgroup entered after 12-24 hours improved by 20 points (Figure 5). This represents an 88% better recovery in HH patients entered <12 hours after the onset compared with S (p=0.15). Substantial improvement occurred during treatment in those HH patients in whom treatment was begun early. A Hct reduction of >15% was achieved in only one third of the HH patients, but they tended to have better GNE scores than the subgroup of HH patients with a Hct reduction of <15% at the 3-month follow-up (Figure 6). By the 3-month follow-up, the subgroup of HH patients

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**Figure 2.** Mortality at 1 week (p=0.36) and 3 months (p=0.12) after stroke onset in hypervolemic hemodilution (HH) and standard therapy (S) groups.

**Figure 3.** Mortality in patients with severe strokes (graded neurologic examination score of >60) (filled portion of bars) and in all patients (entire bars) in hypervolemic hemodilution (HH) and standard therapy (S) groups.

**Figure 4.** Comparison of graded neurologic examination (GNE) scores in all patients remaining in hypervolemic hemodilution (HH) and standard therapy (S) groups. Baseline, before randomization; End Treatment, 72 hours after randomization; Month Three, 3 months after onset of stroke.
FIGURE 5. Comparison of graded neurologic examination (GNE) scores in patients randomized within 12 hours of stroke onset to standard therapy (●) or hypervolemic hemodilution (□) and patients randomized to hypervolemic hemodilution 12–24 hours after stroke onset (▲).

with a CO increase of >10% (mean increase for 18 patients was 26%) improved 25 points on the GNE compared with a 21-point improvement in the subgroup of HH patients with a CO increase of <10% and a 16-point improvement in the S group (differences not significant) (Figure 7). This represents a 56% better recovery in the high-CO subgroup of HH patients compared with the S group. A significant improvement in GNE score from baseline occurred during treatment in the high-CO HH subgroup compared with the S group (p=0.02).

Discussion

Our study suggests but does not prove that, in patients successfully completing hypervolemic hemodilution, improved outcome measured by GNE score and BDS index occurs. Problems with the study arose, however, because of an excess number of patients with severe strokes randomized to this treatment and because some HH patients did not achieve a satisfactory physiologic response and others developed cerebral edema and died. We believe that most of these problems can be obviated in future studies by better patient selection and by improved study design.

Several of our findings support the efficacy of hypervolemic hemodilution. While the HH group did not improve significantly compared with the S group, consistent trends toward improved outcome were seen in the HH group and in all optimally hemodiluted HH subgroups. Because our study was terminated prematurely, only 30 HH patients and 37 S patients completed the study. If the number of patients completing the study were doubled and the same differences between HH and S groups' GNE scores occurred, these differences would probably reach significance. Such a sample size would be consistent with other therapeutic trials showing a benefit of hemodilution in patients with acute stroke.

In the HH group and in all optimally treated HH subgroups, notable improvement occurred during treatment while the S patients showed slight worsening during the first 72 hours, again suggesting a positive biologic effect of hypervolemic hemodilution. For the most part, these initial gains were maintained during the 3-month follow-up.

Our data suggest that hypervolemic hemodilution should optimally begin within 12 hours after stroke onset, should lower Hct by >15%, and should raise CO by >10% above baseline. Early treatment is logical for any reperfusion therapy, although in a recent negative study of hemodilution only 28% of patients were entered within 12 hours after stroke onset and optimal hemodilution was not achieved for 72 hours. In our study, no difference was detectable between the subgroup of HH patients treated 12–24 hours after stroke onset and the S controls. Therefore, any improvement in HH compared with S patients occurred in those HH patients...
treated within 12 hours after stroke onset, emphasizing the need for early entry of patients in future studies.

Experimental studies indicate that Hct should be lowered by at least 15% of baseline to achieve a significant reduction of viscosity and an improvement of CBF. Surprisingly, successful reduction of Hct to this level occurred in only one third of our HH patients, and during Day 1 mean Hct declined by only 6%. This 14% reduction was probably due to an inadequate volume of pentastarch administered or to the investigators' reluctance to employ isovolemic hemodilution with phlebotomy to lower Hct to <36% once PWP reached 15 mm Hg.

Because it contains a large proportion of smaller molecules that can be readily filtered by the kidney and rapidly excreted, 40% of a pentastarch solution has a serum half-life of only 4 hours, necessitating frequent dosing to maintain hemodilution. Therefore, in many patients the permitted doses of pentastarch may not have been sufficient to reduce Hct by >15% and maintain the reduction. Another impediment to reducing Hct may be that phlebotomy is a cumbersome procedure and many physicians are uncomfortable lowering Hct to <36% by removing blood since there has still been no accurate determination of the Hct at which oxygen delivery begins to decline in ischemic brain tissue. Future studies should be based on a better understanding of the physiologic relation of Hct to oxygen delivery in the brain and should employ a more effective hemodiluting agent that will reduce Hct by volume expansion without requiring phlebotomy.

HH patients whose CO rose by >10% showed significantly improved GNE scores during treatment. In this HH subgroup, there was an immediate response of cardiac function to volume expansion, with a mean CO increase of 26%. Experimental studies have demonstrated increased CBF after raising CO by intravascular volume expansion without hemodilution. In our patients in whom CBF was measured before and after treatment, CBF increases were seen more consistently in the HH than in the S group. Six of seven HH patients had increased CBF in the symptomatic hemisphere (38–50 ml/100 g/min) compared with three of six S patients (33–36 ml/100 g/min) similarly studied. Sample sizes were too small to determine if the CBF increases correlated better with increased CO than with decreased Hct, but our results strongly suggest that raising CO is crucial to the success of hypervolemic hemodilution since patients in whom CO did not improve demonstrated recovery not different from that of S patients.

The excess deaths in the HH group were largely due to cerebral edema during the first week of treatment in patients with severe strokes. It is possible that these excess deaths were merely due to more patients with severe strokes randomized to the HH than the S group. However, it is also possible that hypervolemic hemodilution aggravates cerebral edema in patients with acute stroke. Cerebral edema and/or hemorrhage are unwanted side effects of attempts to increase the perfusion of acutely infarcted brain regions by a number of therapies including surgery, hypertension, or thrombolysis. All these treatments may cause a sudden increase in hydrostatic pressure, but this should not occur with hypervolemic hemodilution. Furthermore, pentastarch administration did not exacerbate cerebral edema in a recent animal study.

Another explanation for the increased cerebral edema might be excess intravenous saline administered to the HH patients. Although an accurate record of the amount of saline eliminated by each patient was not maintained, pentastarch was formulated in 0.9% saline so that during the first 24 hours of therapy the average HH patient received approximately 215 meq NaCl plus additional saline in other intravenous fluids to maintain PWP at 15 mm Hg, totaling 265 meq NaCl, while S patients usually received only daily infusions of 1–2.1 5% dextrose in half-normal saline, totaling 100–150 meq NaCl. The excess saline administered to HH patients would expand the interstitial volume and could collect in the injured brain tissue, thereby aggravating cerebral edema.

Although there was no significant difference in mortality between the HH and S groups, we believed that it was necessary to terminate the study when possible excess early mortality in the HH patients was detected. Of course, patient safety was our primary concern and we felt that further analysis was required to eliminate the possible high-risk patient subgroups. In addition, selection of a better colloid and vehicle appeared necessary. Furthermore, excess deaths in one group would introduce a bias into the analysis of surviving patients by a “harvesting” effect, that is, patients doing poorly would not survive to be included in the 3-month follow-up analysis.

In conclusion, hypervolemic hemodilution may be beneficial in the treatment of acute cerebral infarction, especially in patients in whom treatment is begun within 12 hours and in whom a satisfactory reduction of Hct and an increase in CO are achieved. Our study is inconclusive because of premature termination to analyze possible excess mortality due to cerebral edema in HH patients. This excess mortality can probably be obviated in future studies by randomizing comparable numbers of patients with severe strokes to the two treatment groups and by refining the colloid solution.

Appendix I. Hemodilution in Stroke Study Group Investigators

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References


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