Effects of Hypertonic Saline Hydroxyethyl Starch Solution and Mannitol in Patients With Increased Intracranial Pressure After Stroke

Stefan Schwarz, MD; Stefan Schwab, MD; Markus Bertram, MD; Alfred Aschoff, MD; Werner Hacke, MD

Background and Purpose—The purpose of this study was to prospectively evaluate a protocol with hypertonic saline hydroxyethyl starch (HS-HES) and mannitol in stroke patients with increased intracranial pressure (ICP).

Methods—We studied 30 episodes of ICP crisis in 9 patients. ICP crisis was defined as (1) a rise of ICP of more than 25 mm Hg (n=22), or (2) pupillary abnormality (n=3), or (3) a combination of both (n=5). Baseline treatment was performed according to a standardized protocol. For initial treatment, the patients were randomly assigned to either infusion of 100 mL HS-HES or 40 g mannitol over 15 minutes. For repeated treatments the 2 substances were alternated. ICP, blood pressure, and cerebral perfusion pressure (CPP) were monitored over 4 hours. Blood gases, hematocrit, blood osmolarity, and sodium were measured before and 15 and 60 minutes after the start of infusion. Treatment was regarded as effective if ICP decreased >10% below baseline value or if the pupillary reaction had normalized.

Results—Treatment was effective in all 16 HS-HES–treated and in 10 of 14 mannitol-treated episodes. ICP decreased from baseline values in both groups, P<0.01. The maximum ICP decrease was 11.4 mm Hg (after 25 minutes) in the HS-HES–treated group and 6.4 mm Hg (after 45 minutes) in the mannitol-treated group. There was no constant effect on CPP in the HS-HES–treated group, whereas CPP rose significantly in the mannitol-treated group. Blood osmolarity rose by 6.2 mmol/L in the mannitol-treated group and by 10.5 mmol/L in the HS-HES–treated group; sodium fell by 3.2 mmol/L in the mannitol and rose by 4.1 mmol/L in the HS-HES–treated group.

Conclusions—Infusion of 40 g mannitol and 100 mL HS-HES decreases increased ICP after stroke. The maximum effect occurs after the end of infusion and is visible over 4 hours. HS-HES seems to lower ICP more effectively but does not increase CPP as much as does mannitol. (Stroke. 1998;29:1550-1555.)

Key Words: brain edema ■ hypertonic hydroxyethyl starch ■ mannitol ■ intracranial pressure ■ stroke

Brain edema is the major cause of increased ICP, secondary deterioration, and death in patients after stroke.1 Over the past few years, the use of previously recommended therapies such as barbiturates or hyperventilation has been increasingly questioned since it was recognized that they may critically reduce the CPP through negative effects on the systemic blood pressure or excessive cerebral vasoconstriction with secondary ischemic damage.2,3 From that perspective, treatment with hypertonic fluids is still an attractive means of decreasing the intracranial pressure without having a negative effect on the CPP. Mannitol has been used extensively, and various clinical and experimental studies have demonstrated that single doses of mannitol—at least transiently—reduce increased ICP.4-8 However, several factors limit the indiscriminate use of mannitol in stroke patients. Almost all of the larger clinical studies with mannitol have been performed in patients with head injuries; comparable studies in stroke patients have not been undertaken. The long-term beneficial effects of mannitol are still controversial, and there is some evidence that repeated doses of mannitol may even aggravate brain edema.9,10 Furthermore, mannitol is not effective in some patients. Therefore, alternative therapies for increased ICP are warranted.

Hypertonic saline solutions have been primarily used for “small volume resuscitation” (SVR) in patients with hemorrhagic shock. Compared with standard shock therapy, SVR produces a more rapid volume expansion; increases cardiac output, systemic blood pressure, and microvascular perfusion; and may improve survival.11-14 In particular, the subgroup of patients with severe head injuries seems to have higher survival rates after SVR.13 Various animal experiments of hemorrhagic shock and head trauma have indicated that SVR lowers ICP and improves CPP.15-21 Although SVR has been used primarily in patients with hemorrhagic shock, hypertonic saline with or without dextrans/HES has been successfully used in a few anecdotal reports and in small clinical series of euvoletic head-trauma patients even after the failure of conventional therapy.22-25

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Until now, HS-HES solutions have not been systematically used in stroke patients. We prospectively evaluated a treatment protocol alternating single-dose HS-HES and mannitol in stroke patients with elevated ICP.

Subjects and Methods

From March through August 1997, 9 consecutive patients with elevated ICP after acute space-occupying hemispheric stroke (n=8) or hypertensive putaminal hemorrhage with massive perifocal edema (n=1) were included in this study. All patients were treated in the neurointensive care unit at the Department of Neurology of the University of Heidelberg. The patients were treated according to an institutional protocol for stroke patients with elevated ICP. All patients were intubated, artificially ventilated, and anesthetized with analgesics and sedatives. The patients were maintained in a 30° upright position. Ventilation parameters were adjusted to achieve normocapnia and a PaO₂ >90 mm Hg. Serum electrolytes and glucose were kept within normal limits, and hyperthermia was avoided. The ICP was continuously monitored with an epidural (n=2) or intraparenchymatous (n=5) ICP device (Spiegelberg, Hamburg, Germany) ipsilateral to the lesion or via a ventricular catheter (n=2). ICP, oxygen saturation, heart rate, and MAP were monitored continuously. Gelatinous solutions and crystalline fluids were administered to achieve euvolemia (a central venous pressure between 12 and 16 cm H₂O). If volume substitution was not sufficient to reach a CPP of at least 70 mm Hg, the MAP was increased with a continuous infusion of epinephrine and/or dobutamine.

Moderate ICP elevation was tolerated until the ICP reached 25 mm Hg. Indications for intervention were (1) spontaneous ICP increase of more than 25 mm Hg persisting for more than 5 minutes or (2) a newly observed pupillary abnormality (unilateral or bilateral enlargement). If 1 or both of these criteria for intervention were met, the patient was randomly assigned to either HS-HES or mannitol treatment.

The patients assigned to HS-HES therapy were treated with 100 mL of a hypertonic saline solution prepared in low-molecular-weight HES, containing 75 g/L NaCl and 60 g/L HES (average molecular weight 200, degree of substitution 0.6 to 0.66, osmolarity 2570 mOsm/L).

The mannitol-treated patients were treated with 200 mL of a 20% mannitol solution (osmolarity 1100 mOsm/L). With these doses, the osmolar load of the two regimens was approximately identical.

Each drug was administered via a central venous catheter over a period of 15 minutes. Efficacy of treatment was assessed 10 minutes after the end of infusion (ie, 25 minutes after start). Therapy was classified as successful if (1) the ICP fell >10% below the baseline value or (2) pupillary reaction had normalized (in patients with a pupillary abnormality). Patients in whom therapy was not successful were immediately treated with the alternative drug in the same way as described above. These secondary treatments were only analyzed for effectiveness, and otherwise were not included in this study. If this therapy failed anew after 25 minutes, THAM-buffer solution, short-term hyperventilation, and barbiturates were used.

Osmotherapy was repeated in the same patient if the criteria for intervention were met again. Only the initial treatment was random-

<table>
<thead>
<tr>
<th>Baseline Characteristics of Patients</th>
<th>All Events (n=30)</th>
<th>HS-HES-Treated (n=16)</th>
<th>Mannitol-Treated (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successfully treated</td>
<td>26</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Age, y (n=9 patients)</td>
<td>56.6±3.6</td>
<td>54.7±3.6</td>
<td>60.3±8.7</td>
</tr>
<tr>
<td>ICP, mm Hg</td>
<td>27.4±0.7</td>
<td>28.6±1.2</td>
<td>26.1±0.4</td>
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<tr>
<td>MAP, mm Hg</td>
<td>98.0±2.8</td>
<td>97.6±4.4</td>
<td>98.5±3.2</td>
</tr>
<tr>
<td>CPP, mm Hg</td>
<td>70.6±2.8</td>
<td>69.0±4.4</td>
<td>72.4±3.4</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>34.8±1.0</td>
<td>35.5±1.3</td>
<td>34.0±1.7</td>
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<tr>
<td>Sodium, mmol/L</td>
<td>139.9±1.1</td>
<td>140.2±1.3</td>
<td>139.5±1.6</td>
</tr>
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<td>Oxygen saturation, %</td>
<td>98.8±0.2</td>
<td>98.8±0.3</td>
<td>98.3±0.3</td>
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<td>FiO₂</td>
<td>0.51±0.02</td>
<td>0.50±0.03</td>
<td>0.52±0.03</td>
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<tr>
<td>PacO₂, mm Hg</td>
<td>103.1±2.6</td>
<td>102.3±3.2</td>
<td>107.7±5.0</td>
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<tr>
<td>PacO₂, mm Hg</td>
<td>37.5±0.5</td>
<td>37.1±0.6</td>
<td>37.8±0.8</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>80.0±2.9</td>
<td>78.9±3.8</td>
<td>81.2±4.7</td>
</tr>
<tr>
<td>Osmolarity, mOsm/L</td>
<td>311.0±3.4</td>
<td>310.1±5.1</td>
<td>311.9±4.7</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

Differences between the HS-HES–treated and mannitol-treated events were not significant (P>0.05 for all parameters).

Results

In all, 30 ICP episodes were treated in 9 patients (6 men, 3 women; mean age, 56.6 years [range, 43 to 75 years]). The Table shows baseline characteristics. HS-HES was used in 16 episodes and mannitol in 14 episodes. Indications for intervention were (1) a rise in ICP >25 mm Hg in 22 episodes, (2) a newly observed pupillary abnormality in 3 episodes, and (3) both, ICP crisis in combination with pupillary abnormality, in
Effects of Mannitol

Therapy was classified as successful 10 minutes after the end of infusion in 10 of 14 mannitol-treated episodes. In 3 of 4 episodes in which mannitol failed, a subsequent infusion of osmotherapy was not more effectively and faster compared with mannitol. (After 25 minutes, mannitol treatment of 4 ICP episodes was terminated because of ineffectiveness.)

the remaining 5 events. The mean interval between stroke onset and initial osmotherapy was 57 hours (range, 33 to 85 hours). Concomitant therapy included continuous infusion of vasopressors (most frequently norepinephrine) during the observation period in 18 episodes.

By the end of the study, 3 patients had died of uncontrollable intracranial hypertension (GOS 5). The remaining 6 patients remained severely disabled (GOS 3).

Effects of Mannitol

Therapy was classified as successful 10 minutes after the end of infusion in 10 of 14 mannitol-treated episodes. In 3 of 4 episodes in which mannitol failed, a subsequent infusion of HS-HES was effective. In 1 patient, osmotherapy was not continued because blood osmolarity had already reached 350 mOsm/L.

Mean baseline ICP in the mannitol group was 26.1±0.4 mm Hg. Immediately after the start of mannitol infusion, the ICP decreased significantly (P<0.01 for all time points). After 15 minutes, the end of infusion, ICP had decreased by 17% to 21.5±1.2 mm Hg. The greatest decrease in the ICP from baseline level occurred after 45 minutes, by 24% (to 19.7±1.1 mm Hg, P<0.001) in the 10 events in which the observation period was continued beyond 25 minutes (in the other 4 events, patients were switched to HS-HES therapy) (Figure 1). The initial MAP was 98.5±3.2 mm Hg and remained unchanged except for the time after 25 minutes (mean increase, by 6.5%, to 104.9±2.2 mm Hg, P<0.05).

CPP was significantly higher than at baseline after 15, 25, 35, and 60 minutes primarily as an effect of the changes in the ICP. The increase in CPP was most marked after 35 minutes (mean increase, by 19.2%, to 84.9±3.9 mm Hg; P<0.01) (Figure 2).

At the end of infusion, hematocrit had decreased from a baseline level of 34.0%±1.7% to 32.0%±1.5% (P<0.01). After 15 minutes, the hematocrit rose again and did not differ from baseline after 60 minutes. The serum sodium levels fell from 139.5±1.6 to 136.3±1.8 mOsm/L after 15 minutes (P<0.01), and were still below baseline levels at 60 minutes (135.6±2.0 mOsm/L, P<0.01) (Figure 3).

Blood osmolarity was analyzed in 12 of 14 mannitol-treated episodes. Osmolarity rose from a baseline level of 311.9±4.7 to 318.1±4.5 mOsm/L after 15 minutes (P<0.01). Thereafter, osmolarity fell again. After 60 minutes, osmolarity was still higher than at baseline (313.4±3.7 mOsm/L, P<0.01) (Figure 4).

Inspiratory PaO₂ (baseline 107.7±5.0 mm Hg), FiO₂ (baseline 0.5±0.1 mm Hg), arterial oxygen saturation (baseline 98.9%±0.3%), and heart rate (baseline 81.2±4.7 bpm) remained unchanged during the observation period.

Effects of HS-HES Treatment

Therapy was successful in all 16 HS-HES–treated episodes. Baseline ICP in the HS-HES group was 28.6±1.2 mm Hg. Immediately after the start of mannitol infusion, the ICP fell significantly (P<0.001 for all time points). After 15 minutes, the end of infusion, ICP had decreased by 34% to 18.9±1.3 mm Hg. The greatest decrease in the ICP from baseline level occurred after 25 minutes, by 38% to 17.6±1.3 mm Hg (P<0.001) (Figure 1).

Initial MAP was 97.6±4.4 mm Hg and remained unchanged during the observation period. CPP (baseline 69.0 mm Hg) was significantly higher than at baseline after 25 and 35 minutes (P<0.05). The increase of CPP was most marked after 35 minutes (mean increase, by 7.5%, to 78.2±5.3 mm Hg) (Figure 2).

At the end of infusion, hematocrit levels had decreased from baseline 35.5%±1.3% to 33.7%±1.3% (P<0.001). After 15 minutes, the hematocrit rose again, but was still below baseline after 60 minutes (34.4%±1.2%, P<0.01). Serum sodium levels increased from 140.2±1.6 to 144.3±1.3 mOsm/L after 15 minutes (P<0.001). Serum sodium decreased thereafter and did not differ from baseline after 60 minutes (Figure 3).

Blood osmolarity was analyzed in 11 of 16 HS-HES–treated episodes. Osmolarity rose from a baseline level of 310.1±5.1 to 320.5±4.6 mOsm/L after 15 minutes (P<0.001). After 15 minutes, osmolarity fell again. After 60 minutes osmolarity was still higher than at baseline (316.6±4.8 mOsm/L, P<0.001) (Figure 4).

Inspiratory PaO₂ (baseline 102.3 mm Hg±3.2), FiO₂ (baseline 0.5±0.01), arterial oxygen saturation (baseline
Comparison Between the 2 Groups  
Baseline values were not different between the 2 groups (Table). As mentioned above, a statistical comparison was not possible. However, after HS-HES treatment, the drop in the ICP seemed to be greater and faster (Figure 1). After 25 minutes, the mean decrease of the ICP from baseline was 11.0 mm Hg in the HS-HES–treated ICP episodes, but only 5.3 mm Hg in the mannitol-treated events. After 25 minutes the difference became smaller probably because after 25 minutes, 4 mannitol-treated patients were switched to HS-HES treatment. HS-HES–treated patients had higher serum sodium levels after 15 and 60 minutes (Figure 3). The mean increase of osmolarity after 15 minutes was greater for HS-HES–treated events (10.5 versus 6.2 mOsm/L) (Figure 4).

Effects in Subsequent Events  
Repeated interventions became necessary in all but 1 patient (mean, 3.3 events per patient; range, 1 to 7 events). Because of the small number of repeated events, further analysis was not performed.

Discussion  
In this study, HS-HES and mannitol were both effective in reducing elevated ICP. HS-HES seemed to lower the ICP more effectively, but comparison between the 2 treatments has its limitations, since the optimum dose and infusion rate are largely unknown for both substances. Because of the lack of exact experimental or clinical data, dose, and mode of application, the end point of 10 minutes after the end of infusion for determining efficacy and the definition of treatment “success” in our clinical study are based primarily on personal experiences and general recommendations. Although mannitol is used in many patients with intracranial hypertension, larger dose-finding studies in humans have not been performed. Single doses of mannitol from 0.25 up to 2.27 g/kg body wt have been used.5,27–29 Marshall et al5 studied the effect of different mannitol doses in 8 patients and concluded that small doses (0.25 g/kg) were as effective as larger doses. Our dose of 40 g mannitol equals approximately 0.4 to 0.6 g/kg.

For SVR of patients with hemorrhagic shock, a dose of 4 mL/kg 7.5% saline with or without dextran/HES has been used.11 For treatment of refractory, highly elevated intracranial hypertension without hemorrhagic shock, Härtl et al22 administered HS-HES at a rate of 20 mL/min until the ICP significantly decreased (average 171 mL). In our patient group with an overall only moderately elevated ICP, only 100 mL HS-HES was effective in all events.

In a sheep model, an identical volume of either 20% mannitol or 7.5% saline yielded similar responses.36 We chose the dose of 100 mL HS-HES (257 mOsm) to achieve a osmolar load similar to the standard dose of 200 mL 20% mannitol (220 mOsm). Although osmolality was similar, blood osmolality rose faster and remained elevated for a longer time after HS-HES, indicating that the osmolar load is not the only relevant parameter of hypertonic solutions (Figure 4).

The mechanisms by which hypertonic fluids act are still a matter of controversy. The traditional and still most widely accepted theory, advocated since 1919, postulates that hypertonic fluids create an osmotic gradient between the intracerebral intravascular compartment and the cerebral parenchyma, resulting in dehydration and shrinkage of endothelial cells and brain tissue. For mannitol, this effect has been repeatedly demonstrated in radiological studies in humans and in animal experiments.7,28,31–35 A reduced brain water content has been also demonstrated after the infusion of hypertonic saline.16–19,36,37 An intact blood-brain barrier is the prerequisite for establishing an osmotic gradient. It has been assumed that dehydration of brain tissue is more pronounced on the side contralateral to the lesion where the brain tissue is preserved. Studies with hypertonic saline and most studies with mannitol support this hypothesis.16,17,19,28,31,33,37

It has been proposed that the almost immediate decrease in ICP after mannitol infusion cannot be explained solely by dehydration of brain tissue.31 A variety of alternate mechanisms of mannitol effects have been subjected to extensive experimental studies. These postulated effects include improvement of cerebral blood flow and CPP via reactive cerebral vasodilatation, a decrease in cerebral spinal fluid formation and resorption, increased cardiac output and blood pressure, effects on blood viscosity, brain oxygenation and microcirculation, and neuroprotective properties.7,16,27,29,31,32,38–46 Several authors have assumed that the effects of mannitol on the cerebral hemodynamics depend on the autoregulatory capacities. If the vascular autoregulation is intact, mannitol may lead to a reactive vasodilatation either through increased systemic blood pressure or hemodilution with improved red cell deformability and decreased blood
HS-HES and Mannitol for Raised ICP

viscosity.\textsuperscript{5,7,39,40} Rosner and Coley\textsuperscript{40} concluded that the effect of mannitol would be small if the CPP $>70$ mm Hg because in this situation vasoconstriction is already maximal.

In our euvolemic patients, SABP did not consistently change after the infusion of HS-HES or mannitol. This finding is in agreement with the results of several clinical and animal studies in which the SABP remained unaffected or even decreased after mannitol, probably due to a reactive decrease in the peripheral resistance.\textsuperscript{6,7,27,31,41} Similarly, in contrast to patients with hemorrhagic shock, HS-HES does not increase SABP in euvolemic patients.\textsuperscript{22,42,43}

Mechanisms of HS-HES are complex, because HS-HES consists of 2 components; sodium chloride, which is mainly responsible for the osmotic gradient, and HES, which is added to maintain the short-lived volume effect of hypertonic saline. Similar to mannitol, the postulated mechanisms of HS-HES, aside from osmotic dehydration of brain tissue, include improved cerebral blood flow, increased oxygen delivery and rhesology, and clearance of toxic metabolites from the brain.\textsuperscript{14,16,21,36,42,44,45} To improve cerebral microcirculation, HES or dextrans have been used for many years in stroke, but have failed to improve patient outcome.\textsuperscript{46,47} A major effect on brain edema and ICP cannot be expected from colloid solutions, since the main determinant of water exchange in the brain is mediated by the osmotic pressure, whereas the oncotic pressure has no or only limited effect.\textsuperscript{48} HS without dextrans or HES has been reported anecdotally to be successful in patients with intracranial hypertension\textsuperscript{19} and is effective in animals.\textsuperscript{15,17–19,21,30,48} HS may possibly be as effective as HS-HES in reducing elevated ICP, in particular because HS-HES does not increase the SABP in euvolemic patients. However, with HS, more sodium chloride may be necessary to achieve the same effects as HS-HES, which could limit repeated use of HS-HES.\textsuperscript{18}

In this study, we assessed the early effects of mannitol and HS-HES. It appears to be indisputable that hypertonic solutions can at least transiently decrease an elevated ICP and, therefore, that they may be beneficial in emergency situations in an acutely deteriorating patient before therapies such as hematoma evacuation or decompressive surgery can be initiated. For that indication, HS-HES apparently acts more rapidly and effectively. The long-term effects of repeated treatments with hypertonic solutions remain unclear. Repeated infusions of mannitol could aggravate cerebral edema if the osmotic substances migrate through a damaged blood–brain barrier into the brain tissue, reversing the osmotic gradient.\textsuperscript{9} It seems unlikely that a damaged blood–brain barrier would maintain its selective permeability, and, therefore, this presumed negative effect would probably occur with HS-HES as well. In contrast to most other body tissues, sodium ions cannot cross an intact blood–brain barrier, because the intercellular junctions between the cerebral capillary endothelial cells are extremely tight.\textsuperscript{46} Furthermore, osmotic agents lead predominantly to dehydration and shrinkage of normal brain tissue and may facilitate displacement of brain tissue and even increase the risk of herniation.\textsuperscript{50} However, these largely theoretical considerations have not been substantiated in clinical studies to date. In 3 of 4 episodes in which mannitol had failed to reduce ICP, infusion of HS-HES was still effective. Of course, the repeated administration of mannitol could have evoked the same effect, but in this emergency situation with acutely elevated ICP, we believed it was not reasonable to repeat a treatment that was initially unsuccessful.

In our series, we did not observe any negative systemic effects after treatment with either drug. In 1 patient, we discontinued osmotherapy after blood osmolarity reached 350 mOsm/L. To date, relevant systemic side effects have not been reported after a single dose of HS-HES.\textsuperscript{13,51,52} However, the effects of repeated infusion of HS-HES are still to be evaluated. Its repeated use may lead to an excessive increase in sodium levels and osmolarity, resulting in volume overload with heart failure and lung edema, or may induce hyperchloremic metabolic acidosis and coagulation disorders.\textsuperscript{53,54} Similar side effects have been attributed to mannitol, except for sodium levels that decrease after mannitol. Therefore, the use of hypertonic solutions in patients with a compromised cardiac function should be restricted to a minimum under close cardiac monitoring. The use of hypertonic solutions may be hazardous, particularly for elderly stroke patients who already receive volume load or vasopressor drugs. Because of its complementary effects on sodium levels that may limit the repeated use of either drug, we suggest that the 2 drugs be alternated if repeated treatments are needed.

Conclusions

Single doses of 100 mL HS-HES and 40 g mannitol are effective in reducing elevated ICP in patients with brain edema after stroke without a negative effect on MAP or CPP. HS-HES seems to lower elevated ICP more rapidly and effectively. HS-HES can still be successfully used after mannitol has failed. HS-HES has no major effect on the CPP, whereas mannitol increases CPP.

References


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