Effects of Hypertonic (10%) Saline in Patients With Raised Intracranial Pressure After Stroke

Stefan Schwarz, MD; Dimitrios Georgiadis, MD; Alfred Aschoff, MD; Stefan Schwab, MD

Background and Purpose—The aim of this study was to evaluate the effects of hypertonic saline in stroke patients with increased intracranial pressure (ICP) after conventional therapy with mannitol had failed.

Methods—Twenty-two episodes of ICP crisis occurred in 8 patients in whom the standard treatment of 200 mL of 20% mannitol was not effective. ICP crisis was defined as an increase in ICP of 20 mm Hg (n=18), pupillary abnormality (n=3), or a combination of both (n=1). The patients were treated with 75 mL of 10% saline over the course of 15 minutes. ICP, mean arterial blood pressure, and cerebral perfusion pressure were monitored for 4 hours. Blood gases, hematocrit, hemoglobin, pH, osmolarity, and electrolytes levels were measured before and 15 and 60 minutes after the start of infusion. Treatment was regarded as effective if ICP decreased >10% or the pupillary reaction had normalized.

Results—Treatment was effective in all 22 episodes. The maximum ICP decrease was 9.9 mm Hg 35 minutes after the start of infusion. Thereafter, ICP began to rise again. There was no constant effect on mean arterial blood pressure, whereas cerebral perfusion pressure was consistently increased. Blood osmolarity rose by 9 mmol/L and serum sodium by 5.6 mmol/L. Potassium levels, hemoglobin, hematocrit, and pH were slightly decreased. No unexpected side effects were noted.

Conclusions—Infusion of 75 mL hypertonic (10%) saline decreases elevated ICP and increases cerebral perfusion pressure in stroke patients in whom mannitol had failed. The effect on the ICP and cerebral perfusion pressure reaches its maximum after the end of infusion and is seen for 4 hours. (Stroke. 2002;33:136-140.)

Key Words: brain edema ■ hypertonic solution, saline ■ intracranial pressure ■ stroke

Within the first few days after hemispheric stroke, the extent and location of space-occupying brain edema, which leads to intracranial hypertension, brain tissue shifts, and tentorial herniation, are the main causes of death. Over the years, some of the traditional treatment options such as barbiturates or hyperventilation have lost their shine because it has been recognized that these therapies may critically reduce cerebral perfusion pressure (CPP) and may even cause secondary ischemic damage. In this context, hypertonic solutions offer an attractive alternative because they decrease elevated intracranial pressure (ICP) without negative effects on the CPP. Several hypertonic substances have been used, most extensively mannitol. Although large randomized trials have not yet been undertaken, various clinical and experimental studies demonstrated that single doses of mannitol reduce, at least transiently, elevated ICP. However, there are some aspects that dampen the enthusiasm about mannitol for stroke patients. First, almost all large clinical studies with mannitol have been performed in patients with head injuries; comparable studies in stroke patients have not been undertaken. Second, the long-term beneficial effects of mannitol are unknown. Third, there is some evidence that repeated doses of mannitol may even aggravate brain edema. Furthermore, mannitol fails to be effective in some patients, especially after repeated doses. Therefore, alternative therapies for increased ICP are warranted.

Hypertonic saline solutions were originally used for “small-volume resuscitation” in patients with hemorrhagic shock. Compared with standard shock therapy, small-volume resuscitation produces a more rapid volume expansion; increases cardiac output, systemic blood pressure, and microvascular perfusion; and may improve survival. In the last few years, evidence has accumulated from case series and small randomized trials that hypertonic saline may be an effective treatment for brain edema and elevated ICP after head trauma. In patients with stroke, hypertonic saline preparations have been investigated only anecdotally. In a small prospective case series, Qureshi et al could not detect any beneficial effect of continuous infusion of 3% saline/acetate in 14 patients who had suffered massive stroke. In a previous small randomized study, the effects of bolus infusions of mannitol and hypertonic (7.5%) saline hydroxyethyl starch solution (HS-HES) in stroke patients with acutely raised ICP were compared. Infusion of both substances markedly decreased raised ICP. However, in this study, hydroxyethyl starch was added to the hypertonic saline to
augment the action of hypertonic saline, thus leaving the role of hypertonic saline alone undetermined.

The aim of this prospective case series was to evaluate the effects of bolus infusions of hypertonic saline without the addition of any augmentative substance in patients with acutely raised ICP after conventional therapy with mannitol failed.

**Materials and Methods**

From January to July 2001, 8 consecutive patients with elevated ICP after acute space-occupying hemispheric stroke (n=6) or supratentorial hemorrhage with massive perifocal edema (n=2) were included in this study. All patients were treated in the neurocritical care unit according to an institutional protocol for stroke patients with elevated ICP. All patients were intubated, ventilated, and anesthetized with analgesics and sedatives. The patients were nursed in a 30° upright position. Ventilation parameters were adjusted to achieve normocapnia and a PaO₂ >90 mm Hg. The ICP was continuously monitored with an intraparenchymatous (n=6) ICP device (Spiegelberg) ipsilateral to the lesion or via a ventricular catheter (n=2). ICP, pulse oxygenation, heart rate, and mean arterial blood pressure (MAP) were continuously monitored. Crystalline fluids and colloidal (hydroxyethyl starch) solutions were administered to achieve a central venous pressure of 12 to 16 cm H2O. If volume substitution was not sufficient to reach a CPP of ≥70 mm Hg, we administered norepinephrine and/or dobutamine as a continuous infusion via a central line. Patients with large space-occupying hemispheric infarctions were treated with decompressive hemicraniectomy or therapeutic measures were not used until the ICP reached 20 mm Hg or persistent for 5 minutes or (2) a newly observed pupillary abnormality in 3 episodes, and (3) ICP increase of 20.2% to 79.0% at baseline level, 38%, occurred after 35 minutes (to 16.8 mm Hg, P <0.001).

The initial ICP was 92.4 ±19.3 mm Hg and remained unchanged except for the time point at the end of infusion (mean increase of 8.0% to 99.8 ±16.2 mm Hg, P <0.05). Mainly as an effect of the changes in ICP, CPP was significantly higher than at baseline at all time points. The initial CPP was 65.7 ±17.4 mm Hg. The increase in CPP was most marked after 15 minutes at the end of infusion (mean increase of 20.2% to 79.0 ±14.2 mm Hg, P <0.001).

Arterial blood gases, pH, osmolality, serum electrolytes, and hematocrit/hemoglobin are given in the Table. At the end of infusion, hematocrit levels and hemoglobin had decreased. Subsequently, hemoglobin levels rose again but were still below baseline after 60 minutes. Both serum sodium and chloride levels increased by 5.6 mmol/L after 15 minutes. Serum sodium and chloride decreased thereafter but still remained elevated after 60 minutes.

This study was conducted according to local ethics committee standards. Informed consent was obtained from the patient’s relatives. All data analysis was performed without patient identification. Statistical analysis was performed with the Wilcoxon signed-rank test to detect differences between each time point and baseline values. Differences were considered significant at values of P <0.05. Data are presented as mean ±SD. Statistical analysis was performed for values obtained within the first 60 minutes only, because we could not maintain possible influencing factors such as nursing procedures, ventilation parameters, or other medication for a longer period of time.

Results

In all, 22 events were treated in 8 patients (4 women; mean age, 59.8 ±8.8 years). Of the 6 patients with large hemispheric infarcts, 2 underwent decompressive surgery; the remaining 4 patients with large hemispheric infarcts were treated with therapeutic mild to moderate hypothermia. The mean interval between stroke onset and the first administration of hypertonic saline was 69 hours (range, 38 to 109 hours). In those patients treated with hypothermia, ICP crises occurred almost exclusively during or shortly after rewarming.

Indications for therapy with hypertonic saline were (1) a rise in the ICP >20 mm Hg in 18 episodes, (2) newly observed pupillary abnormality in 3 episodes, and (3) ICP crisis plus pupillary abnormality in the remaining 1 episode. Precedent standard therapy with mannitol had no effect at all in 1 patient and yielded only insufficient and short-lasting effects in the other 7 patients. Concomitant therapy included continuous infusion of vasopressor drugs during the observation period in 18 episodes.

By the end of the study, 4 patients had died of uncontrollable intracranial hypertension (GOS 5). The remaining 4 patients remained severely disabled (GOS 3).

Therapy was classified as successful 10 minutes after end of infusion in all episodes.

ICP, MAP, and CPP are presented in the Figure. Mean baseline ICP was 26.7 ±6.8 mm Hg. Immediately after the start of mannitol infusion, ICP fell significantly (P <0.001 for all time points). After 15 minutes, at the end of infusion, ICP dropped by 22% to 20.8 ±6.1 mm Hg. The highest drop in ICP from baseline level, 38%, occurred after 35 minutes (to 16.8 ±6.5 mm Hg, P <0.0001).

The initial MAP was 19.3 ±19.3 mm Hg and remained unchanged except for the time point at the end of infusion (mean increase of 8.0% to 99.8 ±16.2 mm Hg, P <0.05).
ICP, CPP, and MAP of 22 episodes of increased ICP after stroke. After the start of infusion of 75 mL of 10% saline, ICP fell significantly and CPP increased, mainly because of the decrease in ICP. Except for 1 time point at the end of infusion after 15 minutes, MAP remained unchanged. Maximum reduction in ICP occurred after 35 minutes, 20 minutes after the end of infusion. Thereafter, ICP rose again but did not reach baseline values throughout the observation period. Statistical analysis was performed for values obtained within the first 60 minutes only, because possible influencing factors such as nursing procedures, ventilation parameters, or other medication could not be maintained unchanged for a longer period of time. All data are presented as mean±SE.

Blood osmolality rose by 9 mOsm/L at the end of infusion. After that time point, osmolality fell again; however, after 60 minutes, osmolality was still higher than at baseline.

The pH fell slightly as a result of hyperchloremic acidosis. In addition, there was a slight decrease in potassium levels. PaO₂ and PaCO₂ remained unchanged during the observation period. We did not notice any side effect or, in particular, any sign of cardiovascular or pulmonary decompensation.

Repeated interventions became necessary in all but 1 patient (mean, 2.8 events per patient; range, 1 to 4). Because of the small number of repeated events, further analysis of the effects of repeated interventions was not performed.

# Discussion

In this study, bolus infusion of hypertonic saline consistently led to an almost immediate and substantial decrease in an acutely raised ICP and to a marked rise in CPP, mirroring the effects on ICP. In all patients, previous treatment with mannitol was not effective. It is particularly remarkable that the infusion of hypertonic saline was highly effective, although the osmolality was markedly increased already before the start of treatment with hypertonic saline by previous therapy with mannitol. The osmolar load of 75 mL of 10% saline (3422 mOsm/L) is comparable to that of 200 mL of 20% mannitol (1100 mOsm/L). One may speculate that the repeated administration of mannitol could have evoked the same effects, but in this emergency situation with acutely elevated ICP, we did not consider it reasonable to repeat a treatment that initially was not successful. The osmotic effect of hypertonic saline may be more pronounced than with equiosmolar amounts of mannitol, because, despite the much higher molecular weight of sodium, the blood-brain barrier permeability is lower for sodium. The volume of hypertonic saline is smaller than that of mannitol; however, the total volume of both preparations is so small that this difference probably has no clinical relevance. Mannitol acts as a potent diuretic drug. Hypertonic saline also has a 2-fold diuretic effect: directly as a consequence of natriuresis and indirectly via the release of atrial natriuretic hormone. A further advantage of hypertonic saline over mannitol is its very low price. Infusion of hypertonic saline may also carry some risks, however. Rapid changes in serum sodium concentrations may result in seizures and are associated with central pontine myelinolysis, although this seems to occur predominantly in chronic states of hyponatremia. Until now, there have been no reports of central pontine myelinolysis after administration of hypertonic saline. Other possible complications of treatment with hypertonic solutions in general such as heart failure, lung edema, hemolysis, and coagulation abnormalities were not noted in our patients. After prolonged use of hypertonic solutions, hyperchloremic acidosis will develop. In our patients, pH fell significantly after administration of hypertonic saline, but the degree of change was quite small and probably clinically not relevant. To prevent hyperchloremic acidosis, hypertonic saline/acetate solutions have been

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<td>Na⁺, mmol/L</td>
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<td>Hemoglobin, g/dL</td>
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used in patients continuously treated with hypertonic saline.14 This is probably not necessary if hypertonic saline is administered as a bolus infusion. However, repeated use of hypertonic saline will be limited by hypernatremia, which inevitably occurs after multiple treatments. In contrast, mannitol leads to hyponatremia. Because of its complementary effects on sodium levels, which may limit the repeated use of either drug, mannitol and hypertonic saline could be used in alternation if repeated treatments are needed.

It has been proposed that 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.9 It seems unlikely that a damaged blood-brain barrier would maintain its selective permeability; therefore, this presumed negative effect would probably occur with hypertonic saline also. Furthermore, osmotic agents predominantly lead to dehydration and shrinkage of normal brain tissue and may facilitate displacement of brain tissue and even increase the risk of herniation.26 However, to date, these largely theoretical considerations could not be convincingly substantiated in clinical studies. In 2 single patients, edema formation late in the course of intracerebral hemorrhage has been linked to prolonged administration of hypertonic saline,22 but it must be noted that late edema formation frequently occurs in this patient group regardless of therapeutic measures.

In our euvolemic patients, arterial blood pressure did not persistently change after infusion of hypertonic saline. This result is in agreement with other clinical and experimental studies that have shown that in contrast to patients with hemorrhagic shock, the blood pressure remains unaffected or even decreases after hypertonic saline, probably because of a reactive decrease in the peripheral resistance.21,27,28

In a previous study, we evaluated the effects of hypertonic saline combined with HS-HES compared with standard treatment with mannitol.8 Although the results of the 2 studies can be compared only with great caution, inclusion criteria and treatment modalities were nearly identical (7.5 g sodium chloride was infused over 15 minutes in both studies). The previously described effects of HS-HES on laboratory parameters, ICP, and MAP were nearly identical to those obtained in the present study using hypertonic saline alone. The effect mechanisms of HS-HES are complex, because it consists of 2 components: sodium chloride, which is responsible primarily for the osmotic gradient, and HES, which is added to maintain the short-living volume effect of hypertonic saline. To improve the cerebral microcirculation, HES or dextrans have been used for many years in stroke but have failed to improve patient outcome.29 To date, a clear advantage of the augmentative addition of colloids to hypertonic saline over hypertonic saline alone has not been demonstrated in various animal or clinical studies (for a review, see reference 13). We recommend that colloids not be used in addition to hypertonic saline until more evidence has been collected supporting this treatment strategy.

In this study, we assessed the early effects of hypertonic saline. It appears to be indisputable that hypertonic saline can, at least transiently, decrease an elevated ICP and therefore may be beneficial in emergency situations in an acutely deteriorating patient before therapies such as hematoma evacuation or decompressive surgery can be initiated. The long-term effects of repeated or continuous treatments with hypertonic saline in stroke patients remain unclear. In a mixed patient population with various intracranial pathological conditions leading to brain edema, continuous hypertonic (3%) saline/acetate failed to show any beneficial effect on lateral displacement of the brain and other outcome measures in those patients with ischemic and hemorrhagic stroke.14

Our results strongly indicate that hypertonic saline can be successfully used in patients with acutely raised ICP after stroke, even after conventional treatment with mannitol has failed. The optimal concentration and dosage, duration and mode of therapy, and in particular long-term safety and efficacy of this treatment need to be evaluated further. However, although hypertonic saline certainly is no magic bullet for the treatment of brain edema, our results suggest that hypertonic saline is at least a useful alternative to current therapies of brain edema after stroke.

Conclusions

Single doses of 75 mL hypertonic (10%) saline reduce elevated ICP and augment CPP in patients with brain edema after stroke after standard therapy with mannitol has failed, even if the osmolarity is already increased by previous treatments with mannitol. Hypertonic saline has no major effect on MAP. The effects on ICP and CPP are most prominent shortly after administration but are seen over 4 hours. Unexpected side effects were not noted. Hypertonic saline can be successfully used after mannitol has failed.

References


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