Hypertonic saline for cerebral edema and elevated intracranial pressure

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Cerebral edema and elevated intracranial pressure (ICP) are important and frequent problems in the neurocritically ill patient. They can both result from various insults to the brain. Improving cerebral edema and decreasing ICP has been associated with improved outcome.[1] However, all current treatment modalities are far from perfect and are associated with serious adverse events:[1–4] indiscriminate hyperventilation can lead to brain ischemia; mannitol can cause intravascular volume depletion, renal insufficiency, and rebound ICP elevation; barbiturates are associated with cardiovascular and respiratory depression and prolonged coma; and cerebrospinal fluid (CSF) drainage via intraventricular catheter insertion may result in intracranial bleeding and infection.

Other treatment modalities have been explored, and hypertonic saline (HS) solutions particularly appear to be an appealing addition to the current therapeutic avenues for cerebral edema. This article succinctly reviews some of the basic concepts and mechanisms of action of HS and discusses some of its possible clinical applications.

PHYSIOLOGIC CONTEXT

The blood-brain barrier

The blood-brain barrier (BBB) represents both an anatomic and a physiologic structure. The BBB is made up of tight junctions between the endothelial cells of the cerebral capillaries.[5] Various mechanisms exist for compounds to cross the BBB, including active transport, diffusion, and carrier-mediated movements. Because transport through the BBB is a selective process, the osmotic gradient that a particle can create is also dependent on how restricted its permeability through the barrier is. This restriction is expressed in the *osmotic reflection coefficient*, which ranges from 0 (for particles that can diffuse freely) to 1.0 (for particles that are excluded the most effectively and therefore are osmotically the most active).

The reflection coefficient for sodium chloride is 1.0 (mannitol's is 0.9), and under normal conditions sodium (Na^+) has to be transported actively into the CSF.[5,6] Animal studies have shown that in conditions of an intact BBB, CSF Na^+ concentrations increase when an osmotic gradient exists but lag behind plasma concentrations for 1 to 4 hours.[5] Thus, elevations in serum Na^+ will create an effective osmotic gradient and draw water from brain into the intravascular space.

Cerebral edema and intracranial dynamics

Cerebral edema is defined as an increase in brain water leading to an increase in total brain mass.[7] There are three major categories of brain edema:

- **Vasogenic edema**, which is caused by increased permeability of the endothelial cells of brain capillaries and is seen in patients with brain neoplasms
- **Cytotoxic edema**, which results from the influx of water into cells. This type of edema may be caused by energy depletion with failure of the ATP-dependent Na^+-K^+ pump (ie, cerebral infarction) or low extracellular Na^+ content (ie, hyponatremia).
- **Interstitial edema**, in which CSF diffuses through the ependymal lining of the ventricles into the periventricular white matter. This type of edema is seen with hydrocephalus.

It is important to point out that different types of edema can coexist in the same patient. For instance, brain ischemia is associated with both cytotoxic and vasogenic edema.

The presence of cerebral edema, with the subse-

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quent increase in brain mass, alters the intracranial contents (brain, blood, and CSF). Small increases in brain volume can be compensated by changes in CSF volume and venous blood volume. Beyond that, changes in intracranial volume (ΔICV) will result in changes in ICP (ΔICP), which has been termed compliance (ΔICV/ΔICP). When brain compliance decreases, such as when intracranial volume rises, ICP rises.[8] However, it is important to realize that focal cerebral edema can create ICP gradients and cause tissue shifts in the absence of a global increase in ICP.[1]

■ HYPERTONIC SALINE: MECHANISMS OF ACTION

HS solutions can possibly affect the volume of the intracranial structures through various mechanisms. All or several of them are likely to be interacting to achieve the end result of HS therapy: reduction of cerebral edema and elevated ICP. These mechanisms are summarized below:

- **Dehydration of brain tissue** by creation of an osmotic gradient, thus drawing water from the parenchyma into the intravascular space. As mentioned above, this would require an intact BBB. Experimental evidence suggests that the brain water–reducing properties of HS are accomplished at the expense of the normal hemisphere.
- **Reduced viscosity.** HS solutions enhance intravascular volume and reduce viscosity.[9] The autoregulatory mechanisms of the brain vasculature have been shown to respond not only to changes in blood pressure but also to changes in viscosity.[10] Thus, a decrease in blood viscosity results in vasoconstriction in order to maintain a stable cerebral blood flow (CBF).
- **Increased plasma tonicity.** It has been postulated, based on experimental animal data, that increased plasma tonicity, such as that seen after HS administration, favors more rapid absorption of CSF.[11]
- **Increased regional brain tissue perfusion**, possibly secondary to dehydration of cerebral endothelial cells and erythrocytes, facilitating flow through capillaries.[12]
- **Increased cardiac output and mean arterial blood pressure**, with resultant augmentation of cerebral perfusion pressure, most likely due to improvement of plasma volume and a positive inotropic effect.[9,13]
- **Diminished inflammatory response to brain injury**, which has been demonstrated with HS administration.[14]
- **Restoration of normal membrane potentials** through normalization of intracellular sodium and chloride concentrations.[13]
- **Reduction of extravascular lung volume**, leading to improved gas exchange and improved PaO_2.[15]

■ EXPERIMENTAL SUPPORT FOR THE EFFICACY OF HYPERTONIC SALINE

Animal studies

HS solutions have been studied extensively in a variety of animal models, as thoroughly detailed in a recent review.[13] The literature suggests that fluid resuscitation with an HS bolus after hemorrhagic shock prevents the ICP increase that follows resuscitation with standard colloid and crystalloid fluids for 2 hours or less. This effect can be maintained for longer periods by using a continuous HS infusion. HS may be superior to colloid solutions with regard to ICP response during the initial period of resuscitation.[16,17] In animal models of cerebral injury, the maximal ICP-reducing effect of HS is appreciated with focal lesions, such as cryogenic injury or intracerebral hemorrhage. Again, the ICP reduction may be caused by reduction in water content in areas of the brain with the BBB intact, such as the nonlesioned hemisphere and the cerebellum. HS has also been compared with mannitol and was found to have equal efficacy in reducing ICP but to have a longer duration of action and to yield greater improvement in cerebral perfusion pressure.[13]

Human studies

Despite the numerous studies in animal models, most of the evidence in humans is based on the publication of case series and a few randomized studies. Some of the published studies are briefly reviewed here. Readers are referred to a recent review[13] for a more detailed description.

Acute ischemic stroke. HS in two different concentrations, 7.5% and 10%, has been used to reduce ICP in patients after large cerebral infarcts.[18,19] Schwarz et al[18] compared the effect of 100 mL of 7.5% HS hydroxyethyl starch (osmolarity 2,570 mosm/L) and 200 mL of 20% mannitol (osmolarity 1,100 mosm/L) in 9 patients with stroke randomized to one of the two treatments. HS hydroxyethyl starch caused a greater and earlier peak reduction in ICP, although mannitol caused more improvement in cerebral perfusion pressure. These same researchers studied the effect of 10% saline bolus

infusions in 8 patients in whom mannitol had failed.[19] HS reduced ICP by at least 10% in all the instances it was used, and the maximal effect was noted at 20 minutes after the end of the infusion. Even though ICP rose subsequently, it did not reach pretreatment values during the 4 hours of data recording.

Intracranial hemorrhage. There has been one report of 2 patients with nontraumatic (presumably hypertensive) intracranial hemorrhage who were treated with continuous HS infusion.[20] Both patients improved clinically after 24 hours of treatment but deteriorated at 48 and 96 hours despite continued HS infusion. Repeat CT scanning showed extension of edema. These findings were attributed to a rebound effect similar to that described with mannitol.

Subarachnoid hemorrhage. Two studies have been published on the effect of HS on clinical improvement and CBF in patients with subarachnoid hemorrhage.[9,21] Suarez et al[21] retrospectively studied 29 patients with symptomatic vasospasm and hyponatremia who received continuous infusions of 3% saline. They found that a positive fluid balance was achieved, and there was short-term clinical improvement without adverse effects. Tseng et al[9] studied the effect of 23.5% saline bolus infusions on CBF, ICP, and cerebral perfusion pressure in 10 patients with poor-grade subarachnoid hemorrhage. They found that HS caused a significant decrease in ICP and a significant rise in blood pressure with a subsequent increase in cerebral perfusion pressure. These effects were accompanied by a significant elevation in CBF as determined by transcranial Doppler ultrasonography and xenon CT. The ICP-lowering effect occurred immediately after the infusion and continued for more than 200 minutes. The increase in blood flow velocities lasted 175 to 450 minutes.

Traumatic brain injury. Most of the human studies have been in patients with traumatic brain injury. Although there is no agreement on the appropriate concentration, dose, or duration of treatment, HS has been reported to have a beneficial effect on elevated ICP in patients after traumatic brain injury.[22–33] Most of the reported studies are limited by small sample size and the use of various concentrations of HS. The use of HS in patients with traumatic brain injury deserves more attention, and well-designed studies are needed.

Miscellaneous conditions. Other investigators have reported on the use of HS in patients with various intracranial pathologies.[34–37]

Gemma et al[34] performed a prospective, randomized comparison of 2.5 mL/kg of 20% mannitol and 7.5% saline in patients undergoing elective supratentorial procedures. They found that the two treatments had similar effects on CSF pressure and on clinical assessment of brain bulk. However, the administered solutions used were not equiosmolar.

In a retrospective study, Qureshi et al[35] determined the effect of continuous 3% saline/acetate infusion on ICP and lateral displacement of the brain in patients with cerebral edema and a variety of underlying cerebral lesions. The authors found a reduction in mean ICP within the first 12 hours, correlating with an increase in serum sodium concentration, in patients with traumatic brain injury and postoperative edema, but not in patients with nontraumatic intracranial hemorrhage or cerebral infarction. This beneficial effect was not apparent at later intervals.

In a retrospective review of 8 patients with intracranial hypertension refractory to hyperventilation, mannitol, and furosemide, Suarez et al[36] showed that bolus administration of 23.4% saline was effective in reducing ICP and raising cerebral perfusion pressure. The effect was still present at 3 hours after administration of the HS solution.

Horn et al[37] reported on the administration of 7.5% saline boluses in patients with subarachnoid hemorrhage or traumatic brain injury and refractory intracranial hypertension. The authors demonstrated an increase in cerebral perfusion pressure and a decrease in ICP. The maximal drop in ICP was observed at a mean of 100 minutes after the bolus was given.

■ ADVERSE EFFECTS

The administration of HS has been associated with potential adverse effects, both theoretical and real, as summarized below.

Intracranial complications

- Rebound edema can occur as a result of continuous infusion.
- Disruption of the BBB ("osmotic opening") may be due to the shrinking of endothelial cells and a loosening of the tight junctions that form the BBB,[38] or to an increase in pinocytotic activity and possibly an opening of transendothelial channels.[39]
- The possibility of excess neuronal death has been postulated after continuous infusion of 7.5%

saline in a rat model of transient ischemia.[40] This has not been proven.

- Alterations in the level of consciousness associated with hypernatremia.[6] Also, other intracranial alterations have been reported in children with fatal hypernatremia, including capillary and venous congestion; intracerebral, subdural, and subarachnoid bleeding; and sagittal sinus and cortical vein thrombosis with hemorrhagic infarction. Severe hypernatremia (> 375 mosm/L) has been found to cause similar changes in animal models.[6]
- Central pontine myelinolysis is a syndrome typically associated with too-rapid correction of (in most cases chronic) hyponatremia.[41] Such grave complications have not been reported in association with the use of HS in humans.

Systemic complications

- Congestive heart failure can be precipitated secondary to volume expansion.[35]
- Transient hypotension is possible after rapid intravenous infusions, but it is followed by an elevation in blood pressure and cardiac contractility.[42]
- Decreased platelet aggregation and prolonged prothrombin times and partial thromboplastin times have been reported with large-volume infusion of HS.[43]
- Hypokalemia and hyperchloremic metabolic acidosis can be seen with infusion of large quantities of HS solutions but can be avoided by adding potassium and acetate, respectively, to the infusion.[36]
- Phlebitis can be avoided by infusing HS solutions through a central venous catheter
- Renal failure was reported to occur with increased incidence in a single study.[44]

■ SUMMARY

The use of HS solutions has been shown to reduce ICP both in animal models and in human studies in a variety of underlying disorders, even in cases refractory to treatment with hyperventilation and mannitol. There are several possible mechanisms of action, and important complications such as central pontine myelinolysis and intracranial hemorrhage have not been reported in the human studies. Different types of HS solutions with different methods of infusion (bolus and continuous) have been used in the past, and so far there are not enough data to recommend one concentration over another. Many issues remain to be clarified, including the exact mechanism of action of HS, the best mode of administration and HS concentration to be given, and the relative efficacy of HS vis-à-vis available treatments, particularly mannitol.

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