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Hypertonic Saline for Cerebral Edema and Elevated Intracranial Pressure

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ABSTRACT *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. However, all current treatment modalities are far from perfect and are associated with serious adverse events.. 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. Various mechanisms exist for compounds to cross the BBB, including active transport, diffusion, and carrier-mediated 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.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. 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. 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-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. 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

■ *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.

• *Reduced viscosity.* HS solutions enhance intravascular volume and reduce viscosity. 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. 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.

• *Increased regional brain tissue perfusion*, possibly secondary to dehydration of cerebral endothelial cells and erythrocytes, facilitating flow through capillaries.

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• *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.

• *Diminished inflammatory response to brain injury*, which has been demonstrated with HS administration

• *Restoration of normal membrane potentials* through normalization of intracellular sodium and chloride concentrations.

• *Reduction of extravascular lung volume*, leading to improved gas exchange and improved PaO2.

■ *ADVERSE EFFECTS*
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.

• The possibility of excess neuronal death has been postulated after continuous infusion of 7.5% saline in a rat model of transient ischemia.

• Alterations in the level of consciousness associated with hypernatremia.

. 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.

• *Systemic complications*

• Congestive heart failure can be precipitated secondary to volume expansion.

• Transient hypotension is possible after rapid intravenous infusions, but it is followed by an elevation in blood pressure and cardiac contractility.

• Decreased platelet aggregation and prolonged prothrombin times and partial thromboplastin times have been reported with large-volume infusion of HS.

• 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.

Hypertonic saline has a clear advantage over mannitol in children who are hypovolemic or hypotensive. Other situations where it may be preferred are renal failure or serum osmolality >320 mosmol/Kg. It has been found effective in patients with serum osmolality of up to 360 mosmol/Kg .

Concerns with its use are bleeding, rebound rise in ICP, hypokalemia, and hyperchloremic acidosis, central pontine myelinolysis, acute volume overload, renal failure, cardiac failure or pulmonary edema.

It would be reasonable to administer hypertonic saline as a continuous infusion at 0.1 to 1.0 mL/kg/hr, to target a serum sodium level of 145–155 meq/L.

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