Hypertonic Saline: Simple Therapy to Save Life of Children

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ABSTRACT
Hypertonic saline (HTS) is a solution containing higher molar concentrations of sodium and chloride. HTS has been in clinical use for many decades. Due to its osmotic and volume expanding properties, it is being increasingly used for management of a variety of conditions; most notably raised intracranial pressure (ICP) from multiple etiologies, resuscitation during shock and removal of thick respiratory secretions. Commonly used and easily available in the Western states, few hospitals in Pakistan use HTS owing to a lack of awareness, associated costs and poor availability. The objective of this review is to provide an update on recent knowledge gained on hypertonic saline solution use in clinical settings. In this review, we discuss the historical background, mechanism of action, clinical indications and adverse effects of HTS and discuss trials assessing their clinical utility.

Key word: hypertonic saline, children, Bronchiolitis, cerebral oedema, raised intracranial pressure (ICP).

Introduction
Hypertonic saline (HTS) is a crystalloid solution containing higher concentrations of sodium and chloride. HTS is often used in combination with colloids such as dextran. The reported concentrations of HTS for clinical use range from 2% to 23.5%. Table 1 summarizes the osmolarity and sodium concentrations of the different HTS used in clinical trials.

Table 1: Osmolarity and sodium concentrations of the different HTS Solution

<table>
<thead>
<tr>
<th>Solution</th>
<th>Osmolarity (mOsmol/L)</th>
<th>Sodium concentration (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.7% saline</td>
<td>582</td>
<td>291</td>
</tr>
<tr>
<td>3% saline</td>
<td>1,026</td>
<td>513</td>
</tr>
<tr>
<td>7.5% saline</td>
<td>2,566</td>
<td>1,283</td>
</tr>
<tr>
<td>10% saline</td>
<td>3,424</td>
<td>1,712</td>
</tr>
<tr>
<td>23% saline</td>
<td>8,008</td>
<td>4,004</td>
</tr>
<tr>
<td>30% saline</td>
<td>10,000</td>
<td>5,000</td>
</tr>
</tbody>
</table>

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Historical Background
Hypertonic saline is a relatively old therapy which is enjoying a resurgence. Experimental work on compartmental fluid shifts in animals confirmed HTS produced hemodynamic changes and its use in different clinical settings has followed. The first study in 1919 by Weed and McKibben reported immediate shrinkage of brain parenchyma on gross visualization after intravenous injection of 30% saline solution in brain volume in anesthetized cats. Maximum shrinkage was observed 15 to 30 minutes after completion of injection. In 1951 Wilson et al. reported the effect of various hypertonic salt solutions on cisternal pressures in a group of dogs. The authors evaluated the effect of iso-osmolar doses of 1 M NaCl (5.8%), 1 M Na lactate (11.2%), and 2/3 M Na succinate (18%) on elevated ICP. ICP was increased before administration of HTS by administration of 5% dextrose. ICP decreased by a magnitude of approximately 10 cm H2O after administration of HTS solutions. The cisternal pressure remained depressed for 2.5–4 hrs. Despite these early observations, there was little effort to develop the use of HTS solutions in neurosurgical practice, until nearly 60 years later, when in 1980, de Fillipe reported almost miraculous recovery from near-fatal haemorrhagic shock in 11 patients.
Thought to be due to osmotic fluid shifts, this led to a resurgence of interest in the clinical use of HTS. These concepts were supported by findings in various laboratory settings. Based on findings from clinical and laboratory studies, attention has focused recently on investigating the use of HTS in treatment of cerebral edema and intracranial hypertension and several animal studies and clinical work with humans has been published.

**Mechanism of Potential Therapeutic Effects:**
Several mechanisms of action have been proposed and are presented below.

**Osmotic:** In a traumatic brain injury cerebral edema is caused by leakage from damaged microvasculature resulting from blood brain barrier disruption and vasoregulatory dysfunction. Local cell death and lysis releases osmolytes causing an accumulation of osmotic molecules in the brain interstitium and intracellular spaces of the ischemic brain. HTS has shown a biphasic reduction in ICP, first by way of rheology followed by reducing the osmotic gradient between intracellular and intravascular spaces. The increased serum osmolality with HTS infusion reduces the osmotic gap, thereby limiting osmosis and also reduces CSF production, resulting in improved intracranial compliance. HTS as both bolus and continuous infusions lowers ICP.

**Hemodynamic:** Increases in mean arterial pressure (MAP) by HTS infusion have been documented in human models of cardiogenic, septic and hemorrhagic shock. The proposed mechanism of action is that HTS increases intravascular volume by causing fluid to enter the intravascular compartment through osmosis. The increased serum osmolality with HTS infusion reduces the osmotic gap, thereby limiting osmosis and also reduces CSF production, resulting in improved intracranial compliance. HTS as both bolus and continuous infusions lowers ICP.

**Vasoregulatory:** Secondary brain injury may result from vasomotor dysfunction resulting in cerebral ischemia. Studies have also documented ischemia due to cerebral edema and vasospasm, as well as hyperperfusion in the first 2 weeks after injury. HTS therapy increases capillary vessel inner diameter and plasma volume, effectively countering vasospasm and hypoperfusion by changing the rheological properties of RBCs. This action may be by dehydration of endothelium and erythrocytes, increasing the internal diameter of vessels, and improving movement of red blood cells through cerebral capillaries. HTS simultaneously prevents increased ICP with hyperperfusion. The net effect increases cerebral oxygen delivery and improves PaO by improved cerebral blood flow and decreased pulmonary edema. These effects are noted in the peripheral vasculature as well. HTS has direct influences upon the endothelium. It may reduce leukocyte adherence to endothelial cells. The increased Na+ concentration may also induce the endothelium to release endothelium-derived relaxing factor and endothelins. It has been shown to release PGI2 (a prostacyclin) from human umbilical vein endothelial cells in vitro, which leads to vasodilation and inhibition of platelet aggregation. However, not all studies showed increased CBF with decreased ICP.

**Neurochemical:** Primary brain injury during trauma causes extensive neuronal depolarization, increasing extracellular glutamate then, secondary ischemia reduces the amount of ATP production, preventing the homeostatic function of active transport transmembrane (Na+/K+) exchange pumps. The resulting lower extracellular Na+ reverses the direction of the Na+/glutamate passive cotransporter, increasing extracellular glutamate. Increased phospholipase activity and increased membrane permeability allow leakage of additional glutamate from the cell. The higher intracellular sodium concentration binds to cell surface receptors and opens Ca2+ channels, increasing the diffusion of water into the cell, opening stretch-sensitive channels that allow further release of glutamate. This leads to a positive feedback loop and can cause cell death. HTS can prevent pathologic glutamate release, since increased extracellular Na+ returns the Na+/glutamate pump to its normal function of glutamate reuptake. The intracellular concentrations of Na+, Cl−, and resting membrane potential are also restored. The Na+/Ca2+ pump is activated to reduce intracellular Ca2+, thereby limiting neuronal excitation.

**Immunologic:** Severe trauma activates the inflammatory response. Leukocytes migrate to areas of injured microvasculature and cause secondary injury through peroxidase and protease mediated cell death. Vasospasm and interstitial edema may
be caused by release of inflammatory molecules, such as eicosanoids from activated leukocytes. HTS therapy has multiple immunomodulatory effects. Alterations in prostaglandin production and increases in cortisol and adrenocorticotropic hormone (ACTH) levels have been noted. It has also been shown to decrease leukocyte adherence and migration, as well as decreased CD11b expression on neutrophils (unactivated and activated) in vitro and in vivo in healthy humans. Activation of p38 MAPK (mitogen-activated protein kinase) promotes superoxide release by activated PMNs. Inhibition of p38 MAPK activation reduces infarct size and immediate diffusion-weighted imaging (DWI) intensity in a model of permanent focal stroke. HTS inhibits cytoskeletal reorganization in vitro at clinically relevant doses, but primes PMNs at higher doses, or with previous formyl-methionyl-leucyl-phenylalanine (fMLP) stimulation. Inflammatory complications of other organ systems are also prevented by HTS therapy. Reduced lung injury after hemorrhagic shock was noted with HTS infusion. Despite these suppressive effects on the inflammatory system, infusion of HTS reduces the rate of infectious complications. Inflammatory complications of other organ systems are also prevented by HTS therapy. Reduced lung injury after hemorrhagic shock was noted with HTS infusion. Despite these suppressive effects on the inflammatory system, infusion of HTS reduces the rate of infectious complications. It reduces CD4+ suppression and normalizes natural killer (NK) cell activity in the rat model. HTS infusion in hemorrhagic shock models also limits the amount of bacterial translocation, reducing the risk of bacterial seeding and sepsis. Thus, HTS acts through multiple parallel complementary and interacting pathways to produce complex effects on multiple systems. The net effect is to reduce ICP and improve cardiovascular function to reduce secondary brain injury and improve outcomes.

Mucociliary Clearance
Pathological findings in acute bronchiolitis include a peribronchial infiltration of white blood cell types, mostly mononuclear cells and edema of the sub mucosa and adventitia, necrosis and desquamation of ciliated epithelial cells, proliferation of cuboidal cells and excess mucus secretion. The combination of airway wall swelling, sloughing of necrotic debris, increased mucus production and impaired secretion clearance eventually leads to airway obstruction, gas trapping, atelectasis and impaired gas exchange. The postulated mechanisms of HTS benefit are as follows:

1) HTS breaks the ionic bonds within the mucus gel, thereby reducing the degree of cross-linking and entanglements and lowering the viscosity and elasticity of the mucus secretion. 2) HTS induces an osmotic flow of water into the mucus layer, rehydrating secretions and improving mucus rheology. 3) It stimulates ciliary beat via the release of prostaglandin E2. Thus, by absorbing water from the mucosa and submucosa, hypertonic saline solution can theoretically reduce edema of the airway wall in acute bronchiolitis. The pathogenesis of lung disease in cystic fibrosis is characterised by decreased airway surface liquid volume and subsequent failure of normal mucociliary clearance. Mucus within the cystic fibrosis airways is enriched in negatively charged matrices composed of DNA released from colonizing bacteria or inflammatory cells, as well as F-actin and elevated concentrations of anionic glycosaminoglycans. Therapies acting against airway mucus in cystic fibrosis include aerosolized HTS. It has been shown that HTS possesses mucolytic properties and aids mucociliary clearance by restoring the liquid layer lining the airways, also causing sputum induction and cough, which can help to clear the sputum outside of the bronchi and thus improve airway obstruction. Recent clinical and bench studies are beginning to broaden our view on the beneficial effects of HTS, which now extend to include anti-infective as well as anti-inflammatory properties.

Clinical Indications
1. Role of HTS in traumatic and nontraumatic Intracranial Hypertension: Raised ICP is an independent prognostic factor in patients with brain injury from a variety of causes and reducing ICP is a cornerstone of management for the brain injury. Many pediatric studies that used HTS in traumatic & non traumatic brain injury were identified. These are summarized in Table 2. A clinical benefit in ICP control or patient outcome was seen in all. One retrospective study demonstrated a better outcome in terms of the mortality rate in patients treated with HTS.
<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Study Design</th>
<th># of Pts</th>
<th>Concentration of HTS</th>
<th>Bolus Vs Continuous Infusion</th>
<th>Indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mangat 2015</td>
<td>Prospective study</td>
<td>35 pts of HTS group</td>
<td>3% HTS Vs mannitol</td>
<td>Bolus</td>
<td>Severe TBI</td>
<td>HTS is more effective</td>
</tr>
<tr>
<td>Angela 2014</td>
<td>prospective, double-blind, RCT</td>
<td>44</td>
<td>3% HTS Vs NS</td>
<td>Bolus</td>
<td>TBI</td>
<td>3% HTS is more effective than NS in acutely reducing concussion pain in children.</td>
</tr>
<tr>
<td>Upadhyay 2010</td>
<td>Prospective randomized study</td>
<td>200</td>
<td>3% HTS Vs mannitol</td>
<td>Bolus</td>
<td>TBI &amp; NTBI</td>
<td>HTS is Safe and effective</td>
</tr>
<tr>
<td>Khanna et al 2000</td>
<td>prospective observational</td>
<td>10</td>
<td>3% HTS</td>
<td>Continuous infusion</td>
<td>TBI</td>
<td>Decrease in ICP and increases CPP</td>
</tr>
<tr>
<td>Peterson et al 2000</td>
<td>Retrospective</td>
<td>68</td>
<td>3% HTS</td>
<td>Continuous infusion</td>
<td>Head trauma</td>
<td>Decrease in ICP</td>
</tr>
<tr>
<td>Kumar 2015</td>
<td>Prospective open label RCT</td>
<td>29 in each group</td>
<td>3% HTS Vs 20% Mannitol</td>
<td>Bolus followed by continuous infusion.</td>
<td>Acute CNS infections</td>
<td>3% HTS was superior to 20%-Mannitol for controlling raised ICP</td>
</tr>
</tbody>
</table>

RCT: Randomized control trial

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Study Design</th>
<th># of Pts</th>
<th>Concentration of HTS</th>
<th>Bolus Vs Continuous Infusion</th>
<th>Indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malik 2014</td>
<td>prospective, double-blind, RCT</td>
<td>114</td>
<td>3% HTS VS Mannitol</td>
<td>Bolus</td>
<td>NTBI</td>
<td>HTS provided better brain relaxation than mannitol</td>
</tr>
<tr>
<td>Decourcey 2013</td>
<td>Retrospective cohort study.</td>
<td>43,107</td>
<td>3%HTS Vs Mannitol</td>
<td>Bolus</td>
<td>DKA</td>
<td>Increased risk of mortality with HTS</td>
</tr>
<tr>
<td>Kamat P et al 2003’6</td>
<td>Case series</td>
<td>04</td>
<td>3% HTS</td>
<td>5-10 ml/kg bolus</td>
<td>DKA</td>
<td>Safe and Effective</td>
</tr>
<tr>
<td>Crutis et al 2001</td>
<td>Case report</td>
<td>01</td>
<td>3% HTS</td>
<td>Bolus</td>
<td>DKA</td>
<td>Decrease in ICP.</td>
</tr>
<tr>
<td>Singh RK 2011</td>
<td>Case report</td>
<td>01</td>
<td>3% HTS</td>
<td>Continuous infusion</td>
<td></td>
<td>Acute liver failure</td>
</tr>
<tr>
<td>Murphy et al 2004</td>
<td>Prospective RCT</td>
<td>30</td>
<td>30% HTS</td>
<td>continuous infusion</td>
<td>Acute liver failure</td>
<td>Reduce ICP and incidence of clinically significant intracranial hypertension.</td>
</tr>
<tr>
<td>Yildizdas et al 2006</td>
<td>Retrospective</td>
<td>67</td>
<td>3% HTS Vs Mannitol</td>
<td>1ml/kg and continuous infusion</td>
<td>Refractory ICP</td>
<td>Lower mortality rate &amp; duration of comatose state in HTS group</td>
</tr>
<tr>
<td>Bentsen et al 2004</td>
<td>Prospective clinical study</td>
<td>07</td>
<td>7.2% saline in 6% hydroxyethyl starch</td>
<td>2 ml kg during 20 min</td>
<td>SAH</td>
<td>Decrease in ICP and elevation of CPP.</td>
</tr>
<tr>
<td>Schwarz et al 2002</td>
<td>Prospective case series</td>
<td>08</td>
<td>10% HTS</td>
<td>Bolus of 75 mL over a period of 15 minutes.</td>
<td>Stroke</td>
<td>Decrease in ICP and elevation of CPP.</td>
</tr>
</tbody>
</table>

RCT: Randomized control trial
Current treatment guidelines for the management of pediatric patients with traumatic brain injury reflect that HTS is becoming widely accepted as a therapy for intracranial hypertension. Guidelines recommend a continuous infusion of 3% NaCl ranging between 0.1 and 1.0 mL/kg/h administered on a sliding scale, serum osmolarity should be maintained below 360mOsm/L required.

2. HTS for Resuscitation: Only few studies have shown effectiveness of HTS as a resuscitative fluid for septic shock and burn. A prospective, randomized trial was reported by Chopra et al. They studied 60 pediatric septic shock patients, randomized to 3% HTS or Normal saline as initial resuscitative fluid. Both normal saline and hypertonic saline were equally effective as resuscitation fluid with respect to restoration of hemodynamic stability, average duration of ICU stay and mortality but the amount of 3% saline required was approximately half the amount of 0.9% saline. Hypertonic saline appears to be a promising fluid for resuscitation of septic shock but additional clinical trials of 3% HTS as a resuscitative fluid are warranted.

3. Nebulized HTS for Bronchiolitis and Cystic fibrosis: Several studies reported on the use of nebulized 3% saline solution for infants with bronchiolitis and Cystic fibrosis with the majority reporting substantial benefits. It has been shown to increase mucociliary transit time in various situations: in vitro, in normal subjects, in patients with cystic fibrosis (CF), and in patients with sinonasal diseases. Evidence from multiple clinical settings suggest that HTS favorably alters mucociliary clearance in both normal and diseased lungs, shown in Table 3. A recent Cochrane

Table 3: Clinical trials of HTS in Bronchiolitis and Cystic fibrosis

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Study Design</th>
<th># of Patients</th>
<th>Interventions</th>
<th>Indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faber 2015</td>
<td>Observational study</td>
<td>27</td>
<td>3% HTS</td>
<td>Acute viral Bronchiolitis</td>
<td>No improvement</td>
</tr>
<tr>
<td>Everard 2014</td>
<td>RCT</td>
<td>317</td>
<td>3% HTS Vs Standard care</td>
<td>Acute viral Bronchiolitis</td>
<td>No improvement</td>
</tr>
<tr>
<td>Zhao 2014</td>
<td>RCT</td>
<td>129</td>
<td>3%HTS, 5% HTS vs NS</td>
<td>Acute viral Bronchiolitis</td>
<td>Decreases clinical symptoms.</td>
</tr>
<tr>
<td>Susan W 2014</td>
<td>double-blind, RCT</td>
<td>197 in NS group &amp; 211 in HTS group</td>
<td>Nebs 3% HTS vs 0.9% NS</td>
<td>Acute viral Bronchiolitis</td>
<td>Decreases hospital admissions with HTS</td>
</tr>
<tr>
<td>Florin T 2014</td>
<td>RCT</td>
<td>31 in each group</td>
<td>Nebs 3% HTS vs 0.9% NS</td>
<td>Acute viral Bronchiolitis</td>
<td>Less improvement with HTS as compare to NS</td>
</tr>
<tr>
<td>SHARMA 2013</td>
<td>double-blind, RCT</td>
<td>250 infants</td>
<td>Ns 3% HTS vs 0.9% NS, along with 2.5 mg salbutamol,</td>
<td>Acute viral Bronchiolitis</td>
<td>No difference</td>
</tr>
<tr>
<td>Zhang 2013</td>
<td>Cochrane Database of Systematic Reviews 2013</td>
<td>11 trials involving 1090 infants</td>
<td>nebulized 3%HTS vs 0.9%NS</td>
<td>Acute viral Bronchiolitis</td>
<td>HTS is Effective and Safe</td>
</tr>
<tr>
<td>Margaret 2012</td>
<td>multicenter, randomized, double-blind, placebo-controlled trial</td>
<td>344</td>
<td>7% HTS vs 0.9% NS, nebulized twice daily for 48 weeks</td>
<td>Cystic fibrosis</td>
<td>No improvement</td>
</tr>
<tr>
<td>Wark et al 2009</td>
<td>Cochrane Database Syst Rev. 2009</td>
<td>12 trials involving 442 participants with an age range of 6 years to 46 years</td>
<td>7% HTS vs placebo other mucolytic therapy</td>
<td>Cystic fibrosis</td>
<td>HTS is effective and safe with no increased infection risk.</td>
</tr>
</tbody>
</table>
Database Systemic Review of 11 trials ($n=1090$) examined the role of HTS in acute bronchiolitis. The authors concluded that nebulized 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis. Though shown to be an effective treatment for viral bronchiolitis, further evidence needs to be generated to determine optimum dosage and identify benefits from co-administration of bronchodilators.

Despite relatively safe and efficacious use of HTS in clinical settings, there can be adverse effects related to use of HTS, though infrequently reported.

1. Neurologic complications
   a) Osmotic demyelination syndrome
   The most serious theoretical complication of HTS therapy is the development of neurologic complications due to osmotic demyelination syndrome (ODS) or central pontine myelinolysis (CPM). This is the destruction of myelinated fibers after a rapid rise in serum sodium, most commonly affecting deep white matter, with the pons being most susceptible. Human trials with HTS have not documented rapid increases in Na+, and no development of ODS. Despite mean peak serum Na+ concentration of 171 mEq/l (single highest 187 mEq/l) seen with continuous infusion of 3% HTS, no ODS was visible on Magnetic Resonance Imaging (MRI)$^{15}$. Subdural and intracerebral hemorrhages with rapid changes in serum Na+, causing denovo neurologic deficits have been reported in animal studies$^{77}$. However, this has not been observed in human studies from various age groups$^{23}$. 

   b) Rebound Increases in ICP
   Continuous osmotherapy may lead to a rebound phenomenon and increased ICP when serum Na returns toward normal$^{78}$. This may be due to the intrinsic half-life of HTS effects. Prough et al. demonstrated a progressive increase in ICP after HTS administration in a dog model of traumatic brain injury$^{79}$. Qureshi et al. described two patients who developed intractable intracranial hypertension after HTS administration$^{80}$. Most other studies have failed to confirm these findings. Nau suggested that the risk of developing rebound ICP increases with repeated administration of HTS, the degree of damage to the BBB, and the position of the patient on the ICP-volume curve. Whether or not this phenomenon exists is still a matter of debate$^{78}$. 

2. Systemic complication
   a) Renal Failure
   The link between the use of HTS and the development of renal failure is not clearly established. In a study of children with head injuries who received HTS, Khanna et al. reported development of Acute Renal Failure (ARF) after administration of HTS$^{15}$. Peterson et al. performed a retrospective chart review to determine the benefits and complications of continuous HTS infusion to obtain ICP control in 68 children, no child develop renal failure during HTS treatment$^{52}$. Though documented, cases of renal insufficiency and failure after HTS therapy is less common than with the use of other osmotic diuretics used to control cerebral edema$^{23}$. Studies of hemorrhagic or septic shock showed improved hemodynamics and increased renal blood flow with HTS compared to isotonic fluid$^{32}$. 

   b) Electrolyte abnormalities
   HTS-induced hypernatremia has been associated with other noncerebral adverse effects including coagulopathies, excessive intravascular volume and electrolyte abnormalities. Electrolyte abnormalities are common-hyperkalemia may develop after intravascular fluid administration and natriuresis, requiring judicious monitoring.

   c) Coagulopathy
   Hemorrhage secondary to excessive fluid resuscitation has been reported with both HTS and isotonic fluids. This is usually associated with uncontrolled primary hemorrhage. One proposed explanation for the observed coagulopathy is the dilution of plasma constituents with rapid intravascular volume expansion. Decreased platelet aggregation with increased prothrombin time/partialthromboplastin time (PT/PTT) with ≥ 10% plasma replacement has also been observed. However, animal and human studies have not shown these effects. Theoretically, the smaller volumes used in HTS resuscitation should actually reduce the rate of coagulopathies$^{23}$. 


d) Fluid overload
Aggressive fluid resuscitation for hemorrhagic shock has been associated with fluid overload, particularly with the use of isotonic fluids in patients with pre-existing/predisposed to heart failure. No cases of congestive heart failure or pulmonary edema were found in a retrospective study of 29 patients with subarachnoid hemorrhage and hyponatremia on continuous 3% HTS infusions.

3. Adverse effect of nebulized hypertonic saline
The only significant adverse effect of nebulized hypertonic saline solution is the risk of bronchospasm. There is a fairly clear dose response relationship with use of HTS therapy and bronchospasm in individuals with asthma. Typical concentrations used in studies of individuals with asthma range from 4.5% to 7%, with widely varying volumes being required to induce bronchospasm. No evidence has established that 3% saline solution induces bronchospasm in infants with bronchiolitis, but its safety when used without adjunctive bronchodilators has not been established.

Conclusion
HTS is effective in the control of elevated ICP, from a variety of causes and appears to occur through a variety of mechanisms, including optimization of systemic and cerebral hemodynamics, reduction of cerebral edema, modulation of cerebral vasospasm and alterations in cerebral immunology and neurochemistry. Nebulized 3% saline produces reduction in the mean length of hospital stay and also significantly reduces clinical severity score, principally among outpatients with viral bronchiolitis. Intravenous HTS therapy have a high safety profile with minimal adverse effects.

Conflict of Interest: None  Source of Funding: None

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