

ADULT NEUROCRITICAL CARE PROTOCOLS

“Hypertonic Saline”

By Augusto Parra, M.D., M.P.H., F.A.H.A.,

**Director of Neurological Critical Care, Department of Neurosurgery,
UTHSCSA**

(Phone: 210-787-6924 / e-mail: parraa3@uthscsa.edu)

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Introduction:

Two types of osmotic agents remain in current use: mannitol and hypertonic saline solutions. For years, mannitol has been used in the setting of increased intracranial pressure (ICP) due to a variety of diseases, such as stroke and head trauma. Although its mechanism of action has never been fully elucidated, it is widely believed that it creates an osmotic gradient, which mediates its effects on ICP. Other postulated mechanisms of action are radical scavenging effects and increases in cerebral blood flow.

The use of hypertonic solutions (2%, 3% and 23.4% sodium chloride) were initially used for in-the-field resuscitation of patients with multi-system trauma, and later for treatment of increased ICP due to conditions such as brain tumors or isolated traumatic brain injury. Recently, hypertonic solutions have been used as osmotic therapy for brain edema in the neurocritical care arena. Their ICP-reducing effects, in addition to their volume expanding ability, make these solutions extremely attractive in the neurocritical care setting.

Hypertonic Solutions:

Solutions containing 2% and 3% sodium chloride or 2% and 3% sodium chloride/sodium acetate (in a 1:1 ratio by weight) can be used to reach a tailored hypertonic state in this patient population (see patient selection below). The decision to start either solution is made based on baseline serum sodium concentration as well as the overall cardiovascular/fluid status of each specific patient. Further adjustments/interchange between solutions can be made based on the observed initial response to therapy.

The use of hypertonic solutions in the care of this patient population should not alter the standard of care of elevated ICP including hyperventilation, mannitol, and steroid therapy for brain tumor/abscess-induced edema. It is important to keep in mind that acute neurologic deterioration (i.e. transtentorial herniation) can occur in the presence of regional elevations of ICP producing mass effect due to brain edema, even when global ICP values are normal.

This protocol will touch on the use of 23.4% sodium chloride solution for hypertonic therapy induction/rescue in patients with severe brain edema and elevated ICP.

NOTE: The use of hypertonic solutions is not standard treatment for pediatric patients but may be used in select clinical situations (e.g. management of hyperchloremic acidosis).

2% Hypertonic Solutions:

Indications:

- Patients with clinical/radiological evidence of elevated ICP secondary to brain edema, or with ICP values > 15 mmHg as defined by an ICP monitor
- Mild to moderate (more focal) symptomatic brain edema observed
 - After neurosurgical procedures
 - As a result of brain tumors
 - After traumatic brain injury
 - After cerebral infarction or hemorrhage
- During the weaning of 3% or higher strength hypertonic solutions
 - Cases of rebound hyponatremia have been observed with abrupt changes in IV fluid compositions and this could be detrimental in those patients with "brittle" ICP issues
- Volume expansion (flow failure from acute vascular occlusion), dysautonomia, spinal shock from sympathetic injury, hypervolemic-hypertensive-hemodilution (HHH) therapy, etc.
- Syndrome of inappropriate antidiuretic hormone (SIADH)/salt wasting in acute subarachnoid hemorrhage (SAH) patients at risk of vasospasm or patients with important flow failure or shock
- Hypertonic therapy when baseline serum sodium concentrations are close to the upper limit of normal (145 mEq/L)

Administration:

- Can be administered through a peripheral venous line (central line preferred)
- Restricted to ICU and neuro-stepdown unit if the monitoring criteria are followed
- Consider using a 1:1 ratio of sodium chloride/sodium acetate solution if pH ≤ 7.25 and/or serum chloride ≥ 125 mmol/L
- Initiate infusion at 1-2 ml/kg/hr of 2% sodium chloride or 2% sodium chloride/acetate solution (75-150 ml/hr)

- A 250 ml bolus over 30 minutes of 2% hypertonic solution may be administered if more aggressive therapy is desired

Monitoring:

- Close supervision by Neurocritical Care Specialist or physician with expertise with hypertonic fluids
- Vital signs every 2 hours
- Continuous pulse oximetry
- Daily weights
- Continuous telemetry monitoring
- If a patient's status deteriorates, dictating a need for more aggressive monitoring and/or treatment with the 3% solution, the patient must be transferred to an intensive care unit
- Rate of 2% solution must be reduced if the goal is mild to moderate hypertonicity/volume expansion
- Serum osmolarities daily
- Chem-7 every 6 hours until Na/surrogate goals are reached then every 12 hours once steady state is reached
 - Goal serum Na of 145 to 150 mEq/L, which closely corresponds to a serum osmolarity of 310 to 315 mOsm/L
 - If serum sodium ≥ 155 mEq/L, check chem-7 and/or serum osmolarity at least every 4 hours until the sodium level stabilizes at the therapeutic goal
- Chem-7 every 12 hours for at least 24 hours following the discontinuation of therapy
 - To assess target serum sodium and/or serum osmolarity
 - To assess possible complications such as hypokalemia and hyperchloremic metabolic acidosis

Cautions or limitations:

- Phlebitis (less than with higher sodium concentrations)
- Hypotension (infusion rate-related)
- Coagulopathy
- Electrolyte abnormalities (hypernatremia, hypokalemia, hyperchloremia, hyperosmolarity)
 - Increase of serum sodium concentration should generally be limited to 8-12 mEq/L over 24 hours or 0.5-1 mEq/L/hr to prevent central pontine myelinolysis (CPM)
- Metabolic acidosis (non-anionic gap)

- Consider switching to 1:1 sodium chloride/sodium acetate
- Pregnancy and lactation category (unknown)
- Renal insufficiency with oliguria or dialysis
- Congestive heart failure and pulmonary edema
 - Hemodynamic monitoring is required if patient develops symptomatic pulmonary edema and/or signs of congestive heart failure
- Avoid abrupt discontinuation of hypertonic fluids
 - Rate of increment or withdrawal of hypertonic fluids will be set by the Neurocritical care team on daily rounds
- Avoid in patients with subacute or chronic hyponatremia ($\text{Na} < 130 \text{ mEq/L}$) to avoid CPM
 - For hypovolemic hyponatremia, consider isotonic fluids or blood products
 - For chronic hyponatremia, serum sodium changes greater than 8-12 meq/L/24h (0.33-0.5 mEq/L/h) are associated with osmotic demyelination syndrome and CPM

3 % Hypertonic Solutions:

Indications:

- Patients with clinical/radiological evidence of elevated ICP secondary to brain edema, or with ICP values $> 15 \text{ mmHg}$ as defined by an ICP monitor
- Severe (more diffuse) brain edema observed
 - After neurosurgical procedures
 - As a result of brain tumors
 - After traumatic brain injury
 - After cerebral infarction or hemorrhage
- Volume expansion (flow failure from acute vascular occlusion), dysautonomia, spinal shock from sympathetic injury, hypervolemic-hypertensive-hemodilution (HHH) therapy, etc.
- Syndrome of inappropriate antidiuretic hormone (SIADH)/salt wasting in acute subarachnoid hemorrhage (SAH) patients at risk of vasospasm or patients with important flow failure or shock if refractory to 2% hypertonic solutions

Administration:

- Can only be administered through central venous access
- Restricted to ICU for the following reasons
 - Closely monitor for evidence of worsening ICP elevation

- Assess and act upon targets of therapy
- Monitor possible risks of rebound hyponatremia after therapy is discontinued
- Consider using a 1:1 ratio of sodium chloride/sodium acetate solution if pH ≤ 7.25 and/or serum chloride ≥ 125 mmol/L
- Initiate infusion at 1-2 ml/kg/hr of 3% sodium chloride or 3% sodium chloride/acetate solution (75-150 ml/hr)
- A 250 ml bolus over 30 minutes of 3% hypertonic solution may be administered if more aggressive therapy is desired

Monitoring:

- These solutions may be initiated by a Neurocritical Care attending/fellow who has been involved primarily or in a consultative manner in the care of the patient or by an ICU attending (in consultation with the Neuroscience ICU attending/service as needed)
- Vital signs every 2 hours
- Continuous pulse oximetry
- Daily weights
- Continuous telemetry monitoring
- Central venous pressure (CVP) monitoring
- Arterial line
- Serum osmolarities twice a day
- Daily CXR to assess for congestive heart failure or pulmonary edema
- Chem-7 every 4 hours until goal is reached then every 6 hours thereafter
 - Goal serum Na of 150 to 155 mEq/L, which closely corresponds to a serum osmolarity of 320 to 340 mOsm/L
 - An ICU attending/fellow may make this decision (in consultation with the Neurology/Neurosurgery service as needed)
 - If serum sodium ≥ 155 mEq/L, check chem-7 and/or serum osmolarity at least every 4 hours until the sodium level stabilizes at the therapeutic goal
- Improvement of intracranial pressure elevation (clinically or by ICP monitoring) will dictate the duration of the induced hypernatremic state
- Wean no faster than 5-8 mEq/L in Na decrement over 24 hours
- Chem-7 every 12 hours for at least 24 hours following the discontinuation of therapy
 - To assess target serum sodium and/or serum osmolarity
 - To assess possible complications such as hypokalemia and hyperchloremic metabolic acidosis

Cautions or limitations:

- Thrombophlebitis, tissue necrosis if extravasated
- Hypotension (infusion rate-related)
- Coagulopathy
 - There is some laboratory evidence that the use of hypertonic saline could induce platelet dysfunction
 - Assess for clinical evidence of bleeding on a daily basis (CBC, assess stools for blood, arterial or central line entry ports, head CT at 24 hrs of starting the therapy if recent intracranial hemorrhage or neurosurgical procedure)
- Electrolyte abnormalities (hyponatremia, hypokalemia, hyperchloremia, hyperosmolarity)
 - Increase of serum sodium concentration should generally be limited to 8-12 mEq/L over 24hrs or 0.5-1 mEq/L/hr to prevent CPM
- Metabolic acidosis (non-anionic gap)
 - Consider switching to 1:1 sodium chloride/sodium acetate
- Pregnancy and lactation category (unknown)
- Renal insufficiency with oliguria or dialysis
- Congestive heart failure and pulmonary edema
- Avoid in patients with subacute or chronic hyponatremia ($Na < 130$ mEq/L) to avoid CPM
 - For hypovolemic hyponatremia, consider isotonic fluids or blood products
 - For chronic hyponatremia, serum sodium changes greater than 8-12 meq/L/24h (0.33-0.5 mEq/L/h) are associated with osmotic demyelination syndrome and CPM

Use of 23.4 % Sodium Chloride Solution:

Background:

There is clinical evidence that 23.4% sodium chloride can be beneficial in patients with acute intracranial pathology and acute elevation of the intracranial pressure that is refractory to standard guidelines, namely osmotic therapy with IV mannitol and hyperventilation. It may be beneficial as a rescue therapy in those patients with clinical evidence of acute CNS herniation (life threatening ICP elevation) to rapidly induce hyperosmolarity. It is important to keep in mind that acute neurologic deterioration (i.e. transtentorial herniation) can occur in the presence of regional elevations of ICP producing mass effect due to brain edema, even when global ICP values are normal.

Indications:

- Conditions that have the potential to lead to this clinical neurological emergency (ie acute herniation) are brain edema observed
 - After neurosurgical procedures
 - As a result of brain tumors
 - After traumatic brain injury
 - After cerebral infarction or hemorrhage

Administration:

- Restricted to ICU for the following reasons
 - Closely monitor for evidence of worsening ICP elevation
 - Assess and act upon targets of therapy
 - Monitor possible risks of rebound hyponatremia after therapy is discontinued
 - Invasive monitoring of blood pressure is required secondary to its ability to induce transient hypotension
- Can only be administered through central venous access
- Dose is 30 ml of 23.4% sodium chloride over 20 to 30 minutes
 - Dose may be given via IV piggyback OR as an IV PUSH over 30 minutes by an expert ICU care attending or fellow
 - A PA may administer the dose IV push, but ONLY if the expert ICU attending or fellow is present at the bedside
- May repeat in 6 hours, if target Na not meet with clinical indication

Monitoring:

- Vital signs every 2 hours
- Continuous pulse oximetry
- Daily weights
- Continuous telemetry monitoring
- CVP monitoring
- Arterial line
- Chem-7 every 4 hours until goal is reached then every 6 hours thereafter
 - Goal serum Na of 150 to 155 mEq/L, which closely corresponds to a serum osmolality of 320 to 340 mOsm/L
 - An ICU attending/fellow may make this decision (in consultation with the Neurology/Neurosurgery service as needed)
 - If serum sodium ≥ 155 mEq/L, check chem-7 and/or serum osmolality at least every 4 hours until the sodium level stabilizes at the therapeutic goal

- Patients must have an ICP monitor to assess and guide response to therapies, before the administration of 23.4% sodium chloride or immediately after
 - On a case-by-case basis, the clinical response to 23.4% sodium chloride may be enough to assess the positive response to the treatment
- Standing orders should not be used (i.e. 23.4% sodium chloride 30 ml every 4 or 6 hours)
 - The primary endpoint is the acute treatment of the neurological emergency while other measures are rapidly instituted
 - Rapid achievement of a hyperosmolar state is not to be considered a secondary endpoint, since there is evidence that a favorable acute clinical response may occur even in the absence of induced hypernatremia
 - Additional doses of 23.4% sodium chloride may be administered on as needed basis following the initial ICP response to therapy
- Therapy with 2% or 3% hypertonic solutions should be initiated for prolonged ICP control (as indicated in a previous section)
- Hypertonic saline has a diuretic effect therefore the volume status of the patient should be carefully monitored to prevent intravascular volume depletion and rebound intracranial pressure elevation
- Chem-7 every 12 hours for at least 24 hours following discontinuation of therapy
 - To assess target serum sodium and/or serum osmolarity
 - To assess possible complications such as hypokalemia and hyperchloremic metabolic acidosis

Cautions or limitations:

- Thrombophlebitis, tissue necrosis if extravasated
- Hypotension (infusion rate-related)
- Coagulopathy
 - There is some laboratory evidence that the use of hypertonic saline could induce platelet dysfunction
 - Assess for clinical evidence of bleeding on a daily basis (CBC, assess stools for blood, arterial or central line entry ports, head CT at 24 hrs of starting the therapy if recent intracranial hemorrhage or neurosurgical procedure)
- Electrolyte abnormalities (hypernatremia, hypokalemia, hyperchloremia, hyperosmolarity)

- Increase of serum sodium concentration should generally be limited to 12-24 mEq/L (0.5-1 meq/L/hr) over 24hrs to prevent CPM
- Metabolic acidosis (non-anionic gap)
- Pregnancy and lactation category (unknown)
- Renal insufficiency with oliguria or dialysis
- Congestive heart failure and pulmonary edema
- Avoid in patients with subacute or chronic hyponatremia (Na<130 mEq/L) to avoid CPM
 - For hypovolemic hyponatremia, consider isotonic fluids or blood products
 - For chronic hyponatremia, serum sodium changes greater than 8-12 mmol/L/24h (0.33-0.5 mEq/L/h) are associated with osmotic demyelination syndrome and CPM

References:

1. Bhardwaj A, Ulatowski JA. Cerebral edema: Hypertonic saline solutions. *Current Treatment Options in Neurology* 1999; 1:179-87.
2. Khanna S, Davis D, Peterson B et al. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. *Critical Care Medicine* 2000;28:1144-1151.
3. Peterson B, Khanna S, Fisher B, Marshall L. Prolonged hypernatremia controls elevated intracranial pressure in head-injured pediatric patients. *Critical Care Medicine* 2000;28:1136-1143.
4. Qureshi AI, Suarez JI, Bhardwaj A, et al. Use of hypertonic (3%) saline/acetate infusion in the treatment of cerebral edema; Effect on intracranial pressure and lateral displacement of the brain. *Critical Care Medicine* 1998;26:440-446.
5. Qureshi AI & Suarez JI. Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. Review. *Critical Care Medicine* 2000;28:3301-3313.
6. Suarez JI, Qureshi AI, Bhardwaj A, et al. Treatment of refractory intracranial hypertension with 23.4% saline. *Critical Care Medicine* 1998;26:1118-1122.
7. Mayer, SA. Columbia University Neurocritical Care Hypertonic Fluid Protocol.

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Pharmacy Instructions:

NOTE #1: Remember, the sodium chloride/acetate is a 1:1 ratio by weight

NOTE #2: The source of concentrated sodium chloride to compound these solutions should ALWAYS be 23.4%

2% Hypertonic Solutions:

2% Sodium Chloride/Sodium Acetate (total 292.8 mEq of sodium/liter)

Ingredients:

Sterile Water

Sodium Chloride 23.4% = 4 mEq/ml = 234 mg/mL

Sodium acetate 32.8% = 4 mEq/ml = 328 mg/mL

Composition for a total volume of 1000 ml:

1. Sterile Water = 927 ml
2. Sodium chloride 23.4% (4 mEq/ml) = 170 mEq = 42.5 ml. This is equivalent to 10 grams of sodium chloride per liter
3. Sodium acetate (4 mEq/ml) = 122 mEq= 30.5 ml. This is equivalent to 10 grams of sodium acetate per liter
4. Total 1% sodium chloride/1% sodium acetate = 73 ml. Add 927 ml of Sterile Water to make 1000 ml
5. Indicate the expiration time/date on the label (expires in 24 hours) and label the bag

2% Sodium Chloride (total 342.2 meq of sodium/liter)

Ingredients:

Sterile Water

Sodium Chloride 23.4% = 4 mEq/ml = 234 mg/mL

Composition for a total volume of 1000 ml:

1. Sterile Water = 914.5 ml
2. Sodium chloride 23.4% (4 mEq/ml) = 342 mEq = 85.5 ml. This is equivalent to 20 grams of sodium chloride per liter
3. Total 2% sodium chloride = 85.5 ml. Add 914.5 ml of Sterile Water to make 1000 mL
4. Indicate the expiration time/date on the label (expires in 24 hours) and label the bag

3% Hypertonic Solutions:**3% Sodium Chloride/Sodium Acetate (total 513 meq of sodium/liter)**

Ingredients:

Sterile Water

Sodium Chloride 23.4% = 4 mEq/ml = 234 mg/mL

Sodium acetate 32.8% = 4 mEq/ml = 328 mg/mL

Composition for a total volume of 1000 ml:

1. Sterile Water = 890.25 ml
2. Sodium chloride 23.4% (4 mEq/ml) = 256 mEq = 64 ml. This is equivalent to 15 grams of sodium chloride per liter
3. Sodium acetate (4 mEq/ml) = 183 mEq= 45.75 ml. This is equivalent to 15 grams of sodium acetate per liter
4. Total 1.5% sodium chloride / 1.5% sodium acetate = 109.75 ml. Add 890.25 ml of Sterile Water to make 1000 mL
5. Indicate the expiration time/date on the label (expires in 24 hours) and label the bag

3% Sodium Chloride (total 513 meq of sodium/liter)

Ingredients:

Sterile Water

Sodium Chloride 23.4% = 4 mEq/ml = 234 mg/mL

Composition for a total volume of 1000 ml:

1. Sterile Water = 871.8 ml
2. Sodium chloride 23.4% (4 mEq/ml) 128.2 ml = 30 grams = 512 mEq. This is equivalent to 30 grams of sodium chloride per liter
3. Total 3% sodium chloride =128.2 ml. Add 871.8 ml of Sterile Water to make 1000 ml
4. Indicate the expiration time/date on the label (expires in 24 hours) and label the bag

General Treatment Algorithms for Adult Patients with Neurological Injury:

Hypertonic Saline Solutions Protocol for Increased Intracranial Pressure:

Note: Hypertonic saline solutions can be used in combination with other therapies directed to alleviate increased ICP (e.g., hyperventilation, IV Mannitol, diuretics, sedation, temperature control etc...). These are generalized recommendations for the neurological patient with increased ICP. The selection of the hypertonic saline strength and /or type of alternative therapies for this process must be individualized to the physiological characteristics of each patient. This therapy must be approved and supervised by the Neurocritical Care attending. This therapy must be administered in the ICU setting with the exception of 2% sodium chloride which could be administered in an intermediate care setting with an adequate monitoring protocol. Central venous access is required for hypertonic saline solutions with a concentration $\geq 3\%$. Caution if patient has prolonged hyponatremia of not to increase the serum Na $> 10-12$ mEq over 24 hrs.

Evidence of symptomatic cerebral edema or Increased ICP by brain imaging and /or ICP monitor
(Edema caused by ICH, stroke, TBI, inflammatory cytotoxic edema component of tumor, anoxic injury, etc...)

GCS>7: Clinical and imaging monitoring of edema.

- Start IVD of 2% or 3% hypertonic saline solution according to the degree of edema at 1-2 ml/kg/hr IVD
- Keep patient normovolemic and normotensive.
- Monitor Chem7 & serum osmolality q4 hrs during the first 24 hrs and once Na /osmolar goal is reached q6hrs.
- Serum Na /serum Osmolar goal for mild to moderate symptomatic edema 145-150 mEq/L / 290-320 mOsm/L.
- Serum Na /serum Osmolar goal for moderate to severe symptomatic edema 150-155 mEq/L / 320-340 mOsm/L

GCS \leq 7: Clinical, imaging monitoring of edema and ICP monitor.

- Start IVD of 3% hypertonic saline solution according to the degree of edema at 1-2 ml/kg/hr IVD
- Keep patient normovolemic and normotensive.
- Monitor Chem7 & serum osmolality q4 hrs during the first 24 hrs and once Na /osmolar goal is reached q6hrs.
- Serum Na /serum Osmolar goal for moderate to severe symptomatic edema 150-155 mEq/L / 300- 340 mOsm/L

Imminent Brain Herniation

- Start IVB of 23.4% over 30 min x 1. May repeat in 4-6 hrs if needed.
- Keep CPP \geq 60-70 depending on the type of patient. Continuous ICP monitoring.
- Monitor Chem7 & serum osmolality q4 hrs during the first 24 hrs and once Na /osmolar goal is reached q6hrs.
- Serum Na /serum Osmolar goal for moderate to severe symptomatic edema 150-155 mEq/L / 300 - 340 mOsm/L

**ADULT NEURO –CRITICAL CARE PROTOCOLS
“Hypertonic Saline”**

General Treatment Algorithms for Adult Patients with Neurological Injury:

Evidence of symptomatic improvement of cerebral edema by clinical assessment, brain imaging and /or ICP monitor.

- Recommended weaning no faster than 5-8 mEq/L in Na decrement over 24 hours.
- Resume prior rate of hypertonic saline if evidence of edema and / or ICP deterioration.
- Monitor Chem7/ serum osmolality q 4 hours during taper and keep monitoring for 24 hours after discontinuation of the hypertonic solution.