Pediatric Critical Care Protocol for the Use of Hypertonic Saline

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Introduction:

Sodium homeostasis is of importance in the pediatric population. Metabolic disturbances in children can present as emergencies. Hyponatremia is one of the most common electrolyte abnormalities in hospitalized children, and is typically defined as serum sodium ≤125 to 130 mEq/L. [1,2] Signs and symptoms of hyponatremia include altered mental status, lethargy, vomiting, diarrhea, seizures, and circulatory collapse.

Another situation in which osmolar changes affect the pediatric patient emergently is in the case of cerebral edema in diabetic ketoacidosis (DKA). Symptomatic cerebral edema occurs in 0.5% to 1% of pediatric DKA episodes and has a high mortality rate (21%-24%) with a substantial proportion of survivors (15%-26%) left with permanent neurologic sequelae. [3,4] This is one of the most dreaded complications of DKA.

A third role in which sodium plays an important role in pediatric critical care is in the management of traumatic brain injury (TBI). Whether due to non-accidental trauma, motor vehicle accidents or falls, children are at high risk for TBI. In recent decades ongoing research in the management of intracranial hypertension after TBI has introduced many recommendations. Among the "first tier" therapies is hyperosmolar therapy which includes the use of hypertonic saline. [5-10]

HYPERTONIC SALINE

The common thread of treatment in all these emergent situations is the recommendation for treatment with hypertonic saline to raise sodium levels. While the 3% sodium chloride formulation is the most common in the literature, 2% and 3% sodium chloride or 2% and 3% sodium chloride/sodium acetate solutions (in a 1:1 ratio by weight) should be considered based on the patient's baseline sodium level, acid-base status, and cardiovascular/fluid status.

In cerebral edema whether due to DKA or TBI, the main mechanism of action of hypertonic saline is an osmotic effect similar to mannitol but the advantage is that hypertonic saline is believed to preserve intravascular volume status. In addition, hypertonic saline theoretically (1) restores normal cellular resting membrane potential and cell volume, (2) inhibits inflammation, (3) stimulates atrial natriuretic peptide release and (4) enhances cardiac output. [5-8]

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
    - After fluid resuscitation of patients with Diabetic Ketoacidosis
- Acute symptomatic hyponatremia (e.g. seizures or altered mental status).
- 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 Pediatric Intensive Care Unit
- Consider using a 1:1 ratio of sodium chloride/sodium acetate solution if pH $\leq$ 7.25 and/or serum chloride $\geq$ 125 mmol/L
- A 3-5 ml/kg bolus over 30-60 minutes of 2% hypertonic solution may be administered if more aggressive therapy is desired
- A 2% hypertonic solution may be initiated at a rate of 0.1-1 ml/kg/hr IV continuous infusion.

Monitoring:

- These solutions must be initiated by or on behalf of a Pediatric Critical Care attending or a Neurosurgery attending who has been involved primarily or in a consultative manner in the care of the patient.
- Vital signs every 2 hours
- Continuous pulse oximetry
- Daily weights

- Continuous telemetry monitoring
- 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
    - For symptomatic cerebral edema/elevated ICP:
        - 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
    - For symptomatic hyponatremia (AMS/seizures):
        - Goal is cessation of seizure and/or return to baseline neurologic status; generally can safely raise serum Na initially by 5 mEq/L or at least to get serum Na >125 mEq/L
- 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 titrated by the Pediatric Critical Care team and/or Neurosurgery team
- Avoid in patients with chronic hyponatremia (Na<130 mEg/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 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
  - After fluid resuscitation of patients with Diabetic Ketoacidosis
- Acute symptomatic hyponatremia (e.g. seizures or altered mental status).
- 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:

- Continuous infusion can only be administered through central venous access
- In emergent situations before central access is available, may administer initial bolus dose over 30-60 minutes peripherally at the discretion of attending physician
  - Use largest vein possible to avoid phlebitis
  - Emergent situations may include refractory intracranial hypertension with impending herniation, acute symptomatic hyponatremia, or altered mental status secondary to cerebral edema
- Restricted to Pediatric 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 $\leq$ 7.25 and/or serum chloride $\geq$ 125 mmol/L
- A 3-5 ml/kg bolus over 30-60 minutes of 3% hypertonic solution may be administered if more aggressive therapy is desired
- A 3% hypertonic solution may be initiated at a rate of 0.1-1 ml/kg/hr IV continuous infusion.

Monitoring:

- These solutions must be initiated by or on behalf of a PICU attending or Neurosurgery attending who has been involved primarily or in a consultative manner in the care of the patient
- 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
    - For symptomatic cerebral edema/elevated ICP:
        - 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
    - For symptomatic hyponatremia (AMS/seizures):
        - Goal is cessation of seizure and/or return to baseline neurologic status; generally can safely raise serum Na initially by 5 mEq/L or at least to get serum Na >125 mEq/L
- 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 (hypernatremia, 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 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
- Avoid abrupt discontinuation of hypertonic fluids
    - Rate of increment or withdrawal of hypertonic fluids will be titrated by the Pediatric Critical Care team and/or Neurosurgery team

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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. Place a “High Alert” sticker on label.

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. Place a “High Alert” sticker on label.

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. Place a “High Alert” sticker on label.

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. Place a “High Alert” sticker on label.

General Treatment Algorithms for Pediatric 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 Pediatric Critical Care and/or Neurosurgery attending and administered in the ICU setting. 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 TBI, inflammatory cytotoxic edema component of tumor, anoxic injury, ICH, stroke, etc…)

GCS>7: Clinical and imaging monitoring of edema.

- Consider 2 or 3% hypertonic saline IV bolus of 3-5 ml/kg to be given over at least 30 minutes
- Consider using 2% or 3% hypertonic saline solution according to the degree of edema at 0.1-1 ml/kg/hr IV continuous infusion
- Keep patient normovolemic and normotensive.
- Monitor Chem7 & serum osmolarity 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<=7: Clinical, imaging monitoring of edema and ICP monitor.

- Consider 3% hypertonic saline IV bolus of 3-5 ml/kg to be given over at least 30 minutes
- Consider starting maintenance infusion of 3% hypertonic saline solution according to the degree of edema at 0.1-1 ml/kg/hr IV infusion
- Keep patient normovolemic and normotensive.
- Monitor Chem7 & serum osmolarity 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

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 osmolarity q 4 hours during taper and keep monitoring for 24 hours after discontinuation of the hypertonic solution.