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Review Article

When do our patients need a pinch of salt!

Sanjith Saseedharan

Abstract

Hyponatremia is a well known occurrence in traumatic and non traumatic brain injury which is known to complicate the management, affect the prognosis and increase hospital length of stay. Hypertonic saline is one of the drugs among the clinician's armamentarium in order to combat this complication. However its use is marked with many controversies and myths due to lack of robust evidence and non uniformity of trial protocols. In this review the author attempts to review the use of hypertonic saline in brain injury touching on practical use, indications, limitations and goes on to suggest a practical protocol for hypertonic saline in brain injury with raised intracranial pressure. Data Sources: MEDLINE, MICROMEDEX, The Cochrane database of Systematic Reviews from 1967 through May 2012.

Keywords: *hypertonic saline, brain injury*

Introduction

Moses once proclaimed "With all thine offerings thou shall offer salt". When, how much, in what way and at what time the salt has to be given is the big question. There are three primary indications for the use of hypertonic saline in critical care: hyponatremia, brain injury and volume resuscitation. In this review the author intends to touch on practical aspects of the use of hypertonic saline in brain injury emphasizing on clinical dogmas, implications and evidence in an easy to understand plain language question answer format ending with suggestion of a protocol for the use of hypertonic saline

How is sodium homeostasis maintained in the body?

Sodium, being the most abundant extracellular cation, exerts significant osmotic pressure thus linking it closely to blood volume and pressure.[1] A close interplay between the neural and hormonal systems are responsible for the tight control of sodium. Table I gives an overview of mechanisms of sodium homeostasis in the body.

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Table-I : Mechanisms of maintenance of sodium homeostasis.

system	stimulus	mechanism
Renin angiotensin aldosterone system	Decreased blood pressure Increased renal filtrate osmolarity Sympathetic nervous system stimulation	Release of aldosterone[2,3]
Aldosterone	Decrease in blood volume Decrease in blood pressure Decrease in serum sodium High levels of serum potassium	Reabsorption of sodium in distal convoluted tubules and collecting ducts[4,5]
Antidiuretic hormone	Brain injury, sepsis, cancer, drugs, hypothyroidism, guillian barre syndrome	Dilutional effect as a result of water reabsorption[6]
Atrial natriuretic peptide	Atrial stretch from any cause	Inhibiton of renal tubules from reabsorbing sodium, hence helping to excrete sodium (and thus water) Inhibitons of renin angiotensin and aldosterone.[1,7]
Glucocorticoids	Stress Exogenous use	Increased tubular reabsorption[4]
Female sex hormones	High levels of estrogens Progesterone	Enhances reabsortion of sodium by renal tubules retention of water Blocking effect of aldosterone sodium and water loss via diuresis.[8]
Aortic and carotid artery baroreceptors of the cardiovascular system	Blood pressure alterations	Stimulation of the Renin angiotensin aldosterone system.[9]

What is the significance of sodium in brain injury ?

Critically ill brain injured patients develop hyponatremia in 2 to 7 days post injury with almost a 60% attributable mortality.[10,11] Post brain injury hyponatremia usually develops due to Syndrome of inappropriate antidiuretic hormone (SIADH) or Cerebral salt wasting (CSW). This drop in sodium (even small drop) has profound impact on the injured brain forming one of the most dreaded complication in brain injury patients.[12-14] In addition, hyponatremia in the neurologic intensive care unit (NICU) can frequently be produced, worsened, or perpetuated by iatrogenic causes, such as inappropriate or excessive supply of free water and use of mannitol, corticosteroids, or diuretics to treat cerebral edema. Due to the movement of free water into the intracerebral fluid presence of hyponatremia can exacerbate cerebral edema in a brain injured patient where the intracranial compliance is already precarious.[15,16] Animal studies have also shown that acute hyponatremia acts as one of the secondary insults following severe traumatic brain injury (TBI). This secondary insult may not be attributable to further disruption of BBB permeability, but rather to the ischemia resulting from the swelling of perivascular astrocytic foot processes impeding microcirculation laying stress on the already compromised perfusion.[17] Hyponatremia is known to increase hospital stay and increase the incidence of poor neurological outcome in brain injured patients.[18,19] Arieff et al found that the acute onset of severe hyponatremia following TBI was associated with a poor neurological outcome or death after a sudden onset of seizures, followed by coma, apnea, and brainstem compression.[20]

Which subsets of brain injury patients are more prone to hyponatremia?

Almost all neuro-ICU patients are prone to hyponatremia. However among the neuro-ICU patients aneurysmal subarachnoid hemorrhage,[21] traumatic brain injury[22] and basilar meningitis[23] are more prone to hyponatremia commonly due to SIADH, CSW or iatrogenic administration of hypotonic fluid to these vulnerable group of patients[24].

Which patients need urgent treatment with hypertonic saline?

All patients with severe life threatening manifestations of hyponatremia like seizures, coma and life threatening arrhythmia warrant treatment with hypertonic saline to start with for the initial couple of hours with close monitoring of electrolytes irrespective of the chronicity of the hyponatremia.[25]

As per new emerging evidence it seems reasonable to use hypertonic saline in controlling episodes of raised intracranial pressure. In this regards the balance of evidence indicates that hypertonic saline is more effective than mannitol for the treatment of intracranial hypertension.[26-31]

How does hypertonic saline work?

1. Hypertonic saline causes marked osmotic shift of fluid from the intracellular to the interstitial and intravascular space with predominant mobilization from the intravascular space than the interstitial space as a result of the favorable reflection coefficient of sodium.[32-34]
2. Hypertonic saline causes improvement of regional microcirculatory blood flow thus improving perfusion in ischemia and vasospasm.[35]
3. If autoregulation is intact then hypertonic saline induced increased vascular volume helps in reducing intracranial pressure via vasoconstriction.[36,37]
4. Hypertonic saline alters the balance between pro inflammatory and anti-inflammatory cytokines reducing incidences of lung injury which is seen very frequently in severe brain injured patients thus contributing to reduced mortality.[38-40]
5. Hypertonic saline causes rapid restoration of membrane potential helping to offset raised ICP.[41]
6. Hypertonic saline may have beneficial effect on the initial low blood pressure in bleeding brain injured patients due to its volume expansion effects and thus improves mean arterial pressure and thus cerebral perfusion pressure.[42]

What is the dose of hypertonic saline in a brain injury emergency?

There are myriad of doses in various studies as mentioned below (table II).

Table II-various dose reported in literature.

solution	administration	indication	studies
23.4% NS	30 ml over 20 mins.	Refractory intracranial hypertension	Suarez et al [43]
23.4% NS	30 ml bolus	Imminent herniation	Koenig et al [44]
10% NS	100 ml	Raised ICP*	Schatzmann et al [45]
7.5 % NS	2 ml/kg bolus	Raised intracranial pressure in traumatic SAH**	Horn et al [46]
7.5% NS	2 ml/kg	Traumatic brain injury with raised intracranial pressure	Vailet et al [47]
7.2 % NS	2 ml/kg	Poor grade SAH**	Bentsen g et al [48]
7.2% NS	1.5 ml/kg	Traumatic brain injury with raised ICP*	Munar et al [49]
3% NS	Continuous infusion based on serum sodium	Traumatic brain injury with Glasgow Coma Scale<8	Khanna et al [50]
3% NS	75-150 ml/hr titrated to Na of 145- 155 meq/l	Brain injury	Qureshi et al [51]
3% NS	Continuous infusion	ICP *>20 mm of Hg	Petersen et al [52]*

*ICP-Intracranial pressure; **SAH-sub arachnoid hemorrhage,

In the author's opinion, based on the above observations and an in depth review of the above studies, in cases of severe brain injury with refractory intracranial pressure or imminent herniation, it seems reasonable to prescribe a bolus of around 4 - 4.5 ml/kg of 3% saline which is equivalent to a 2 ml/kg of 7.5% hypertonic saline bolus or a 30 ml of 23.4% hypertonic saline bolus over 45 minutes to 1 hour which would be sufficient to reduce the intracranial pressure significantly and improve the cerebral perfusion in severe brain injury patients and patients with poor grade subarachnoid hemorrhage with imminent herniation. This bolus therapy would raise the sodium by approximately 5 - 6 meq/L and thus help to buy time for other measures to become effective. Generally further doses may not be required.

Is a central line required for administration of 3 % saline?

There is no robust evidence based recommendation in this regards. A study done by Hands et al comparing peripheral and central infusions of 7.5% NaCl/6% dextran 70 revealed no damage when infused into a peripheral vein.[53] Studies done to evaluate incidence of thrombophlebitis after infusing high osmolar parenteral nutrition solutions (upto 1200 mosmol/L) into a peripheral vein for short durations (around 7 days) indicate no significant increase in thrombophlebitis when used for short duration.[54-56] Taking cue from these studies the authors conclude that in an emergency it would be safe to administer a 250 ml bolus of 3% saline solution, which has an osmolarity of 1026 mosm/kg (osmolarities comparable to those of solutions of sodium bicarbonate and 50% dextrose in water), via peripheral vein. It would be reasonable to insert a central venous catheter if a more hypertonic saline is required or if the solution is required for a prolonged period of time. Alternatively, if a peripheral vein used for infusion then good care should be taken to prevent extravasation.This can be done by infusing the solutions into a large vein with good blood flow or infusing the solution concomitantly with isotonic solutions to dilute it at the catheter insertion site.

Is there a role of hypertonic saline in severe life threatening hyponatremia few days after the brain injury?What would be the dose of hypertonic saline?

In patients actively seizing 3% saline can be given initially at a higher rate of about 2 to 3 ml/kg/hour(to raise sodium at 1.5 – 2 meq/L/hr for 1st 3-4 hours) over the first few hours. An alternative approach is an initial 50-ml bolus of 3% saline and an additional 200 ml given over the subsequent 4 to 6 hours.[57] Patients with serious signs or symptoms should receive hypertonic (3%) saline at a rate of about 1 ml/kg/hour for the first several hours.[58] The safety and efficacy of these approaches are not beyond doubt and the clinician is thus advised to monitor extracellular fluid volume status, neurologic status, and serum sodium levels closely. Hypertonic saline should be promptly discontinued once serious signs and symptoms have resolved. Hypertonic saline should be stopped well before the sodium has risen beyond 8-10 meq/L in the 1st 24 hours to avoid overshoot of sodium levels. It is also important to avoid attempting to normalize sodium levels, as this would be unnecessary. It is often seen that the frequently cited Adrogue-Madias formula underestimates increase in sodium concentration after hypertonic saline therapy.[59] To date, no data are available to determine reliable adjustments in infusion of hypertonic saline to achieve desirable serum sodium concentrations and often iatrogenic hypernatremia occurs during the course of treatment with hypertonic saline. As per an elegant review and seconded by the author it is advisable to check serum sodium every 1-2 hours when hypertonic saline is on flow.[60]

What are the risks with hypertonic saline therapy?

Correcting chronically elevated hyponatremia beyond 10- 12 meq/L in the 1st 24 hours or beyond 18 meq/L in the first 48 hours are definitely associated with the serious consequences of osmotic demyelination syndrome which is characterized by gradual irreversible neurological deterioration occurring one to several days after after correction of hyponatremia.[61,62] At this stage it is important to note that hypertonic saline administration in patients with normal sodium levels is not associated with osmotic demyelination and treatment of elevated intracranial pressure in patients with brain injury and normal sodium levels are safe.[63-65]

Exceeding a serum osmolarity of 320 mosm/L with mannitol use is known to be associated with renal failure. Unlike mannitol, an osmolarity up to 365 mosm/L (up to a serum sodium of 160 meq/L) is known to be well tolerated while using hypertonic saline.[65,66] Mechanical shearing of the bridging vessels causing subarachnoid hemorrhage as a result of brain shrinkage due to hypertonic solutions are theoretical concerns and not seen clinically with modest elevations of sodium levels.[65]

Summary

Managing sodium levels in brain injury can be a very difficult proposition and most cases of hyponatremia can be managed without the use of hypertonic saline. The available evidence is very promising in for the use of saline in severe hyponatremia associated with brain injury. However its use in less severe indications needs additional research to better define optimal dosing regimens.

Suggested protocol-

In severe brain injury adult with raised intracranial pressure, or suspicion of raised intracranial pressure administer a 150-250 ml bolus of 3% hypertonic saline over 30 minutes to 1 hour through a peripheral line. Cannulate a central vein (preferably femoral in order to avoid the supine position needed for jugular and subclavian vein cannulations and consequences of raised intracranial pressure). Rebolus every 6 hours till intracranial pressure is controlled or serum sodium of 145- 155 meq/L is achieved. Monitor sodium levels every 4-6 hours. If intracranial pressure is still a problem then administer a 10- 20 mg bolus of frusemide with close watch on cerebral perfusion pressure in an effort to mobilize tissue sodium. However it is very important to note that osmotherapy is only one of the facets of the multifaceted approach to brain injury.

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