CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2589045

Available online at: http://www.iajps.com *Research Article*

EVALUATION OF HYPONATREMIA IN PATIENTS WITH ISHEMIC STROKE

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Article Received: January 2019 **Accepted:** February 2019 **Published:** March 2019

Abstract:

In the neurocritical care setting, hyponatremia is the commonest electrolyte disorder, which is associated with significant morbimortality. Cerebral salt wasting and syndrome of inappropriate antidiuretic hormone have been classically described as the two most frequent entities responsible of hyponatremia in neurocritical care patients. Nevertheless, to distinguish between both syndromes is usually difficult and useless as volume status is difficult to be determined, underlying pathophysiological mechanisms are still not fully understood, fluid restriction is usually contraindicated in these patients, and the first option in the therapeutic strategy is always the same: 3% hypertonic saline solution.

Keywords: *Hyponatremia; Neurocritically ill patient; Hypertonic saline solution.*

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Please cite this article in press Naurina Noor et al., ***Evaluation Of Hyponatremia In Patients With Ishemic Stroke.,*** *Indo Am. J. P. Sci, 2019; 06(03).*

INTRODUCTION:

Hyponatremia is understood to be a serum sodium concentration of < 0.001). Recently, Sturdik et al. have actually indicated that an age of above sixty-five years, the existence of dilutional hyponatremia, together with its insufficient rectification are a variety of independent hazard considerations corresponding to increasing hospital mortality in hyponatremic patients (Babets, 2017).

Corona et al., within a methodical literature review and meta-analysis incorporating 80 randomized clinical trials (RCTs), demonstrated hyponatremia, even though mild, for being corresponding to an immense escalation in impermanence in the ICU (RR: 2.60; 95%CI: 2.31---2.93, p < 0.0001). Accordingly, inadequate treatment of this electrolyte disorder, failing to observe the required correction range (overcorrection), as well as insufficient treatment, implies added risk that additionally gets worse the forecast of critical patients with hyponatremia. In neurocritical patients, hyponatremia normally the most widespread electrolyte disorder, being previously revealed in approximately 50% of all cases of severe neurological damage. Among the list of acute brain conditions, serious traumatic brain injury (TBI) as well as (SAH) aneurysmal subarachnoid hemorrhage would be those along with the maximum prevalence of hyponatremia (Jovicevic et al., 2015).

In this matter, Sherlock et al. demonstrated hyponatremia to generally be additional continual in patients with hypophyseal disease (5/81; 6.25%), TBI (44/457; 9.6%) and intracranial tumors (56/355; 15.8%). Throughout their research the authors discovered that between 316 patients with SAH, 179 (56.6%) developed hyponatremia, which verified serious natremia between SIADH and CSW is often difficult to establish, and both syndromes moreover have been suggested to be part of one same disease condition, manifesting successively in the same patient (Babets, 2017).

The Mechanisms of Hyponatremia and neuronal adaptation

Hyponatremia is known as a biggest reason behind water entry to the cells, leading to a boost in cell volume (volumetric variance secondary to osmotic change). This transformation in turn stimulates a volume-regulating approach known as regulatory volume decrease, described as an immediate potassium, chloride and sodium effluence phase together with the objective of rapidly ‘‘buffering’’ the osmotic modification, an additional outflow point of organic osmolytes (‘‘non-perturbing’’ osmolytes) that build up through the neurons lacking yielding terrible consequence upon cell structure and function (cyto-protective function) (Babets, 2017).

These compensating systems are imperfect in acute hyponatremia (evolution under 48 h) and comprehensive in chronic hyponatremia (evolution longer than 48 h). Through the existence of cell swelling, an initial phase (called the sudden phase) is discovered, regarding osmolyte outflow, in addition to a second phase (or slow phase) characterized by inhibition of the synthesis of these osmolytes. However, in acute neurological injury these protective mechanisms carried out by the neuroglia in response to plasma hypotonicity are altered. Likewise, the increase in circulating antidiuretic hormone (ADH) levels observed in the two characteristic conditions (CSW and SIADH) results in action upon the V1a receptors of vascular smooth muscle (Jovicevic et al., 2015).

Table 1 Conventional schematic representation of cerebral salt wasting (CSW) and syndrome of inappropriate antidiuretic hormone secretion (SIADH).

	CSW	SIADH
Extracellular volume	↓	Normal or ↑
Water balance	Negative	Normal or ↑
Sodium balance	Negative	Normal or ↑
Natriuresis	↑↑↑	↑
Body weight	= or ↓	= or ↑
Dehydration	Present	Absent
PCP	↓	= or ↑
CVP	↓	= or ↑
Plasma/urine osmolarity	↓	↑
Hematocrit	↑	= or ↓
Albuminemia	↑	= or ↓
Azotemia/creatininemia	↑	Normal
Uricemia	↓	↓
Serum potassium	= or ↑	= or ↓

CSW: cerebral salt wasting; PCP: pulmonary capillary pressure; CVP: central venous pressure; SIADH: inappropriate antidiuretic hormone secretion syndrome; ↑: increased; ↓: decreased; =: without changes.

Source: (Jovicevic et al., 2015)

Etiology and physiopathology

Cerebral salt wasting and SIADH happen to be considered the most prevalent factors behind hyponatremia in the neurocritical patient. Conversely, there are various other significantly less prevailing aetiologies, such as for instance the hypovolemic presentations and pressure natriuresis, which also must be discarded in order to establish an adequate diagnostic strategy (Kalita and Misra, 2017).

Similarly, even though it has a well known curiosity about both of these syndromes in the last few years, the difference prognosis between CSW and SIADH is generally a genuine struggle, considering the clinical symptoms are not solely absolute, and the laboratory test information is frequently confusing. In this regard, the current tendency is to classify both conditions under one same disease entity. Above mentioned Table 1 shows the main characteristics allowing us to establish a differential diagnosis between CSW and SIADH. Classically, the presence of hypervolemia has been regarded as the distinctive feature of CSW, though it is difficult to diagnose in the neurocritical patient (Lau, Phua and Aw, 2019).

Recently, Gritti et al. have evaluated the cumulative sodium balance with the purpose of diagnosing CSW in 35 neurocritical patients. In these individuals, the authors showed that the risk of developing hypovolemia is increased 7.1-fold ($p < 0.001$) in the presence of a negative sodium balance. Accordingly, the multivariate examination has been revealed that a negative water balance and a negative sodium balance of >2 mEq/kg as independent risk elements for hypovolemia. A negative sodium balance was however revealed as a competitive approach for considering a differential revelation between CSW and SIADH in neurocritical patients (Jovicevic et al., 2015).

SPECIFIC CLINICAL SCENARIOS AND HYPONATREMIA:

Hyponatremia is tremendously predominant in patients with SAH, being characterized in 10-50% of the cases, especially in high grade SAH, through the existence of anterior circulation aneurysms, along with hydrocephalia. In 2005, Kao et al. unveiled 22.9% of the scenario of hyponatremia for being supplementary to CSW, while 35.4% corresponded to SIADH. Within a unique and present research, Hannon et al. prospectively examined the etiology of hyponatremia in an example of one hundred patients with SAH, predicated on clinical evaluation and the dedication of serum cortisol, arginine, vasopressin and brain natriuretic peptide. Throughout their research, the experts recognized SIADH due to the fact prevailing cause (71.4%), whilst hypocortisolism describe for 8.2% of the cases of hyponatremia. The leftover 20.4% of the instances were in turn connected to hypovolemia as well the form of fluid

implemented. Although, the most considerable discovery of the stated research was the absence of cases constant with CSW (Karunanandham, Rajappa and Selvaraju, 2018).

Nakagawa et al. have lately exhibited that the earlier control of fludrocortisone acetate can decrease the risk of hyponatremia (26% versus 16%) and of symptomatic vasospasm (18.5% versus 6.1%) in SAH. These records could suggest the presence of an organization in between hyponatremia and occurance of vasospasm, though further studies are needed to clarify this relationship. Likewise, in SAH, triple H therapy (hypertension, hypervolemia and hemodilution) as an anti-vasospasm strategy promotes pressure natriuresis and the risk of hyponatremia (Kalita and Misra, 2017).

Ischemic stroke

The presence of hyponatremia in ischemic stroke has been proposed as a predictor of poor outcome, though the underlying etiopathogenesis is not fully clear. Huang et al., in 925 patients with a first episode of ischemic stroke, recorded an incidence of hyponatremia of 11.6%, which in turn was associated to a significant increase in mortality after three years (RR: 2.23; 95%CI: 1.30 - 3.82%). Likewise, Rodrigues et al. recently identified the presence of hyponatremia in 16% of 565 stroke patients. In this population, hyponatremia was associated to a significant increase in hospital mortality ($p = 0.039$) and in mortality after three months ($p = 0.001$) and one year ($p = 0.001$). A surprising observation was a greater incidence of urinary infection in the patients with hyponatremia. Lastly, hyponatremia associated to a first episode of ischemic stroke is an independent risk factor for the development of seizures, according to Wang et al. (OR: 2.10) and Roivainen et al. (OR: 3.26; 95%CI: 1.41- 7.57) (Karunanandham, Rajappa and Selvaraju, 2018).

Traumatic brain injury

Hyponatremia is highly prevalent in patients with severe TBI, where dysfunction of the hypothalamic, hypophyseal, adrenal axis is common, having been described in 15 - 68% of the cases, with an incidence of hypopituitarism of 50% in the course of the disorder. In severe TBI, hypopituitarism is more frequent in younger patients, as well as in those administered etomidate, propofol or fenobarbital. The clinical manifestations include hypocortisolism, hyponatremia, hypoglycemia and arterial hypotension (Lau, Phua and Aw, 2019).

In clinical rehearse the organized evaluation of hypophyseal function remains advisable in patients with skull base fractures, permeate axonal destruction, as well as in instances of extended admittance to the ICU. Although, the happening of hypocortisolism, the existing research contraindicates the scientific utilization of corticosteroids as particular treatment for intracranial hypertension in TBI. The review of other causes of hyponatremia in TBI shows SIADH to account for 33% of the cases, presenting a particular association to subdural hematoma and focal contusions (Patiño and Torres, 2018).

Similarly, SIADH frequently exhibits all through the 2nd week of admittance towards the ICU as well as during the development of main or neurogenic diabetes insipidus, this being revealed by the production of ADH stored in the axons of the neurohypophysis. Finally, it needs to be pointed out that in patients with dangerous TBI, hyponatremia may be secondary to the use of certain drugs such as 20% mannitol administered as an osmotically active agent for the control of intracranial pressure (hypovolemic stimulus secondary to osmotic diuresis) carbamazepine and desmopressin (iatrogenic hyponatremia), used for the treatment of the central diabetes insipidus (Lau, Phua and Aw, 2019).

Severe and symptomatic hyponatremia: hyponatremic encephalopathy

In the case of severe and symptomatic hyponatremia (hyponatremic encephalopathy), these guides recommend the intravenous infusion of 150 ml of 3% hypertonic saline solution (HSS) over 20 min. This 3% HSS bolus is to be repeated in the next 20 min as long as the symptoms persist or if natremia fails to increase significantly. In this regard, dosing can be repeat up to two times or until a natremia increment of 5 mmol/l is achieved. The infusion of 3% HSS is able to increase natremia by 1 - 2 mmol/h---reversion of the symptoms of hyponatremic encephalopathy (seizures, altered consciousness) requiring an increase of 4 - 6 mmol (see Fig. 1).

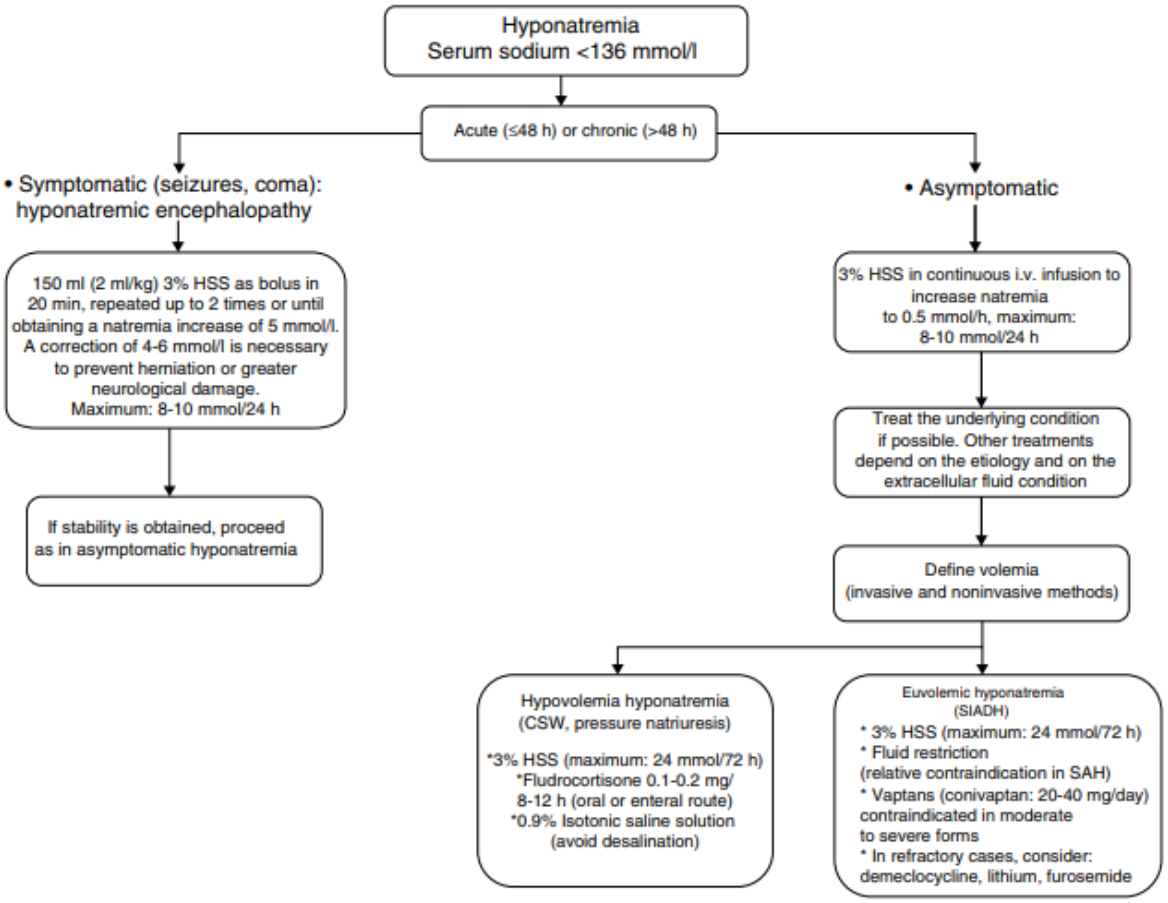

Figure 1 Therapeutic algorithm for hyponatremia in the neurocritical patient.

Source: (Patiño and Torres, 2018)

TREATMENT:

The hyponatremia administration approach in neurocritical patients indicates remedy for the fundamental trigger in parallel to handling of hyponatremia per se. As part of current clinical exercise in neurological ICUs, developing a derived function analysis in between CSW and SIADH must not necessarily be regarded as a essential step for directing therapy. It has typically been regarded about the remedy for CSW demands vigorous sodium administration in the shape of 3% HSS, together with the objective of compensating natriuresis. On the other hand, SIADH concerns fluid restriction due to the fact basis of treatment, considering the renal reabsorption of free water is increased in SIADH. However, this strategy is relatively contraindicated in patients with SAH, due to the high risk of vasospasm (level of evidence ii). Likewise, other management measures that can be adopted in SIADH are the use of lithium, demeclocycline and furosemide (according to above mentioned Fig. 1) (Patiño and Torres, 2018).

In 2008, Sterns and Silver launched the very idea of cerebral salt wasting, which supposes that in patients with serious brain injury, the inclusion of hyponatremia requires the administration of 3% HSS independently of the cause underlying the sodium disorder. On the other hand, in neurocritical patients with high ADH and natriuretic peptide levels, the administration of isotonic saline solution generates the so-called desalination phenomenon, which can worsen hyponatremia secondary to natriuresis, with the renal production of electrolyte-free water (Paunkovic, Vlajic and Paunkovic, 2015).

CONCLUSION:

Hyponatremia is the most frequent electrolytic disturbance in neurocritical patients, and is a leading cause of morbidity, mortality if adequate and immediate treatment is not provided. The syndrome of inappropriate antidiuretic hormone secretion and CSW have been described as the two syndromes that most often explain the presence of hyponatremia associated to increased natriuresis in neurocritical

patients. In these cases the evaluation of volemia allows us to establish a differential diagnosis between the two disease conditions, though in many patients such differentiation is a genuine challenge.

However, recent evidence has questioned the existence of CSW as a cause of hyponatremia in aneurysmal SAH. Conceptually, the diagnosis of cerebral salt wasting seems more appropriate for defining hyponatremia in the neurocritical patient, since the reference treatment is always the same, regardless on the underlying cause: the administration of hypertonic saline solution. Likewise, in the neurocritical ICU, the treatment of hyponatremia depends on a number of factors such as the underlying disease process, the speed with which the condition develops, and patient volemia. Lastly, some alternative treatments have been studied, such as fludrocortisone and the vaptans, though conclusive evidence regarding their use is still lacking, and no definitive agreement has been reached regarding their indications.

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