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UNDERSTANDING THE DISEASE

Understanding the renal response to brain injury

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Introduction

Acute brain injury induces changes to remote organs, including the kidney. We briefly review acute brain injury-associated changes in renal function and how they impact treatments.

1. Water and sodium handling.

Hyponatremia

Rapid development of hypo-osmolar hyponatremia (natremia < 135 mmol/L) can generate cerebral edema, seizures, increase intracranial pressure (ICP), and increase the risk of cerebral ischemia [1].

Hyponatremia is the consequence of increased renal free-water reabsorption after antidiuretic hormone (ADH) secretion [2]. Two mechanisms of excessive ADH secretion have classically been proposed in neuro-ICU patients: the syndrome of inappropriate ADH secretion (SIADH) and the cerebral salt-wasting syndrome (CSWS) (online supplemental material, Table 1). Under normal physiological circumstances, ADH secretion is inhibited when plasma osmolarity drops. In the so-called SIADH, ADH secretion will increase despite hyponatremia [3]. In CSWS, decreased vascular volume resulting from high natriuresis and negative sodium balance is the trigger for ADH secretion. Potential mechanisms of CSWS include release of natriuretic peptides [4] and "pressure-induced natriuresis" secondary to increased systemic arterial pressure after sympathetic system activation or vasopressors' infusion. Pressure-induced natriuresis is aimed at lowering intravascular blood volume and blood pressure through natriuresis when arterial pressure rises [5]. Since it represents a physiological response to systemic hemodynamic changes, a more appropriate term of "renal salt wasting" was proposed [6].

What are the therapeutic implications?

Both in SIADH and CSWS, fluid management should be adjusted based on urine osmolarity [2]. Infusing hypo- or isotonic solutes (i.e., with osmolarity lower than urine) leads to free-water retention and promotes hyponatremia (Fig. 1). This phenomenon is described as desalination [7], where infused sodium and chloride are excreted as osmoles while sodium-free water is reabsorbed due to the action of ADH at the collector tube level (Fig. 1). Infusion of normal saline will result in positive free-water balance, despite having slightly higher osmolarity compared to plasma, and promote hyponatremia in the context of high ADH and high urine osmolarity. Restriction of sodium-free water administration and administration of hypertonic saline is expected to prevent or correct hyponatremia both in SIADH and CSWS, and should be considered as the first-line strategy. Oral urea administration (15–30 g daily) is an alternative effective strategy to correct hyponatremia in SIADH that can be considered in less-severe patients or as a second-line treament [8]. Urea only partially crosses the brain capillaries, maintaining a plasma-to-brain concentration gradient, decreasing brain-water content and ICP. However, osmotic diuresis secondly occurs with loss of electrolyte-free water leading to a rise of serum sodium concentration (i.e., the lower the urine osmolarity, the higher the loss of electrolyte-free water and rise of serum sodium) making it inappropriate in CSWS.

Correction of hypovolemia is required in CSWS, making hypertonic saline the best choice, for the

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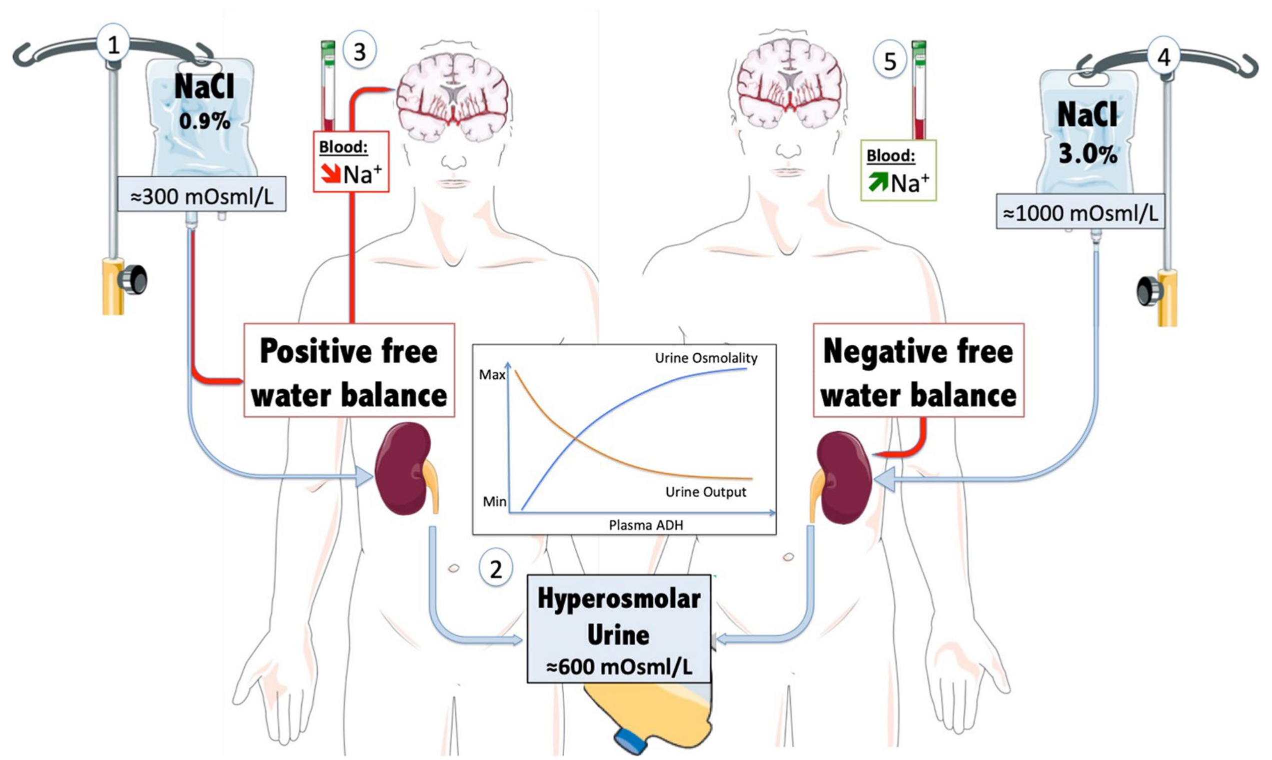

Fig. 1 Impact of perfusion of normal saline versus hypertonic saline on free-water balance and natremia changes in the setting of high antidiuretic hormone (ADH) secretion. Left panel: ADH is a stress hormone secreted by hypothalamic neurons in response to brain injury and low intravascular volume. In the context of brain injury, excessive ADH secretion due to SIADH or CSWS will result in high urine osmolarity and renal electrolyte-free water reabsorption while the kidney excretes osmoles (i.e., electrolytes). Infusion of NaCl 0.9% despite having slighter higher osmolarity compared to plasma, will result in positive free-water balance and promote hyponatremia in this context (1). In the example depicted with urine osmolarity ≈ 600 mOsmol/L due to high ADH secretion, administration of osmoles in normal saline (NaCl 0.9%, solute osmolarity ≈ 300 mosml/L) will be eliminated in hyperosmolar urines (2), resulting in a net free-water positive balance, promoting hyponatremia (3). Right B: infusion of hypertonic saline (4) (i.e., with osmolarity being superior to urine osmolarity) will result in increase of natremia, due to a negative free-water balance (5)

above-mentioned reasons. Adjusting arterial pressure on cerebral blood flow autoregulation might further help tailoring arterial pressure level and avoid unnecessary and potentially harmful systemic hypertension [9]. Finally, administration of hydrocortisone was shown to effectively decrease renal sodium excretion in patients with subarachnoid hemorrhage and CSWS [10]. In a randomized trial conducted in patients with CSWS complicating meningitis, fludrocortisone, in addition to normal saline and oral salt supplementation, resulted in earlier correction of hyponatremia but did not affect outcomes [11].

Hypernatremia

Main causes of hypernatremia include infusion of hypertonic sodium solutions, free-water renal losses due to osmotic diuresis after mannitol infusion, loop diuretics administration, insufficient water intake, and extrarenal losses. Excessive renal free-water loss may be the consequence of decreased ADH secretion (i.e., diabetes insipidus after pituitary surgery and in brain-dead patients) [12].

What are the therapeutic implications?

Acute hypernatremia is sometimes induced as a therapeutic target to reduce the ICP. Whether such prophylactic hypertonic saline infusions are an effective and safe strategy to reduce ICP and improve outcomes is uncertain, and is currently being tested in a randomized controlled trial (NCT03143751). Hypernatremia induced by mannitol might be less predictable due to variable renal free-water losses. Titration of mannitol adjusted on renal response (i.e., diuresis) and plasma osmol gap is warranted to limit the risk of secondary hypovolemia. The best strategy to prevent or correct excessive hypernatremia associated with mannitol is probably to monitor the osmol gap and decrease or stop mannitol if necessary. Excessive hypernatremia can also be corrected slowly by the administration of free water [13]; although this strategy has a risk on rebound intracranial hypertension. In patients with diabetes insipidus, hypo-osmolar urine output (i.e., < 100 mosmol/L) guides free-water (e.g., glucose 2.5% solution) volume supplementation adjusted on urine volume, and trigger recombinant antidiuretic hormone supplementation.

2. Changes in renal glomerular function.

Glomerular hyperfiltration

Hyperfiltration is diagnosed after identification of high creatinine clearance (i.e., CreatCl > 120 ml/min) using the following equation: CreatCl = [urine creatinine × (urine volume/serum creatinine)/minutes of urine collection]. Increased cardiac output and high arterial pressure are associated with augmented renal clearance at the early phase of acute brain injury [14].

What are the therapeutic implications?

Renal hyperfiltration exposes to therapeutic underdosing of drugs with renal elimination (i.e., antibiotics, anti-epileptic drugs) and drug-level monitoring and adjustment should be considered [15].

Acute kidney injury

Acute kidney injury (AKI) occurs in up to 20% of acute brain injury patients and is associated with higher mortality. Chronic kidney disease, use of nephrotoxic agents, hyperchloremia, rhabdomyolysis, and sepsis were identified as risk factors. Brain death induces systemic immune response, neurohormonal activation, endothelial activation and hemodynamic instability, all potential contributing factors to kidney injury and delayed allograft function [16].

What are the therapeutic implications?

The risk of AKI should be assessed when using potential nephrotoxic drugs and requires creatinine and urine output monitoring. Fluid balance should be carefully adjusted, as both hypovolemia and venous congestion were identified as risk factors for brain and kidney injuries [17, 18]. Specifically, prevention and correction of hypovolemia (e.g., after mannitol infusion) are expected to limit the risk of AKI [19].

To conclude, monitoring of free-water handling and glomerular filtration allows therapeutic adjustments through understanding of the renal physiology after acute brain injury.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05685-z) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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