Cerebral salt wasting after traumatic brain injury: an important critical care treatment issue

Traumatic brain injury is an important public health issue that requires the expertise of informed neurosurgeons, neurointensivists, and other critical care practitioners. The treatment of patients with traumatic brain injury (TBI) using established guidelines and less well-established novel treatment strategies, including invasive brain monitoring, has led to a silent albeit robust improvement in the outcome after TBI. Rather than adopting a nihilistic posture about TBI, physicians are being called upon to once again champion the care of the patient and to use available treatment measures to facilitate a good outcome. It is truly an exciting time to be caring for patients with TBI in the intensive care unit, and real treatment options do exist.

One of the most profound treatment developments in the intensive care of patients with brain trauma has been the focus on identifying and treating hyponatremia as well as inducing a state of hypernatremia among TBI patients with malignant brain edema. For purposes of our current discussion, hyponatremia is operationally defined as a low serum sodium concentration. The actual nominal value of sodium for which hyponatremia is said to exist is not well agreed upon, with various threshold levels of 130, 132, or 135 mmol/L being used in various articles. Using one of more of the threshold values, the incidence of hyponatremia among patients with TBI has ranged from 5% to 10% of patients. However, one must recognize that most patients with TBI will have sodium levels of less than 140 mmol/L.

The etiology of the hyponatremia among TBI patients appears to be due primarily to cerebral salt wasting (CSW). Cerebral salt wasting is a condition in which there is an elevation of brain natriuretic peptide (BNP) levels, which results in a reduction in the efficacy of aldosterone and hence a reduction in the ability to reabsorb sodium in the kidney [3]. Brain natriuretic peptide results in an osmotic diuresis in which large amounts of sodium is excreted from the kidney along with free water. The clinical expression of this syndrome is a high urine output of sodium-rich, isotonic, or slightly hypertonic urine, with an elevated specific gravity. Typically the patient will make in excess of 2.5 mL/(kg·h) of urine, with a resultant reduction in total blood volume. If left untreated, CSW can result in hypovolemia, brain ischemia, and death under experimental conditions [8].

Cerebral salt wasting has been most well studied and most frequently reported in aneurysmal subarachnoid hemorrhage [1,2,14]. Cerebral salt wasting occurs temporarily in conjunction with cerebral vasospasm and can result in the precipitation of delayed ischemic stroke lesions when occurring in conjunction with vasospasm. Indeed, CSW, fever, and vasospasm often occur together as a clinical triad. However, CSW commonly occurs in TBI and many other forms of central nervous system trauma, with or without vasospasm. Cerebral salt wasting is thought to be mediated by elevated levels of BNP, and the source of this BNP has been in debate for several years. Because CSW occurs in conjunction with postsubarachnoid hemorrhage vasospasm, it has been thought that BNP originates in the brain and represents one form of neuron-endocrine response to brain ischemia. The treatment of CSW under conditions of vasospasm has consisted of providing supplemental hypertonic saline in the form of continuous infusions of 3% NaCl and the administration of replacement doses of a mineralocorticoid, similar to aldosterone, used in the form of fludrocortisone [7]. This combined treatment has been used with success to reverse hyponatremia and usually is required for several days until the neuroendocrine response to vasospasm resolves. Several articles have documented the existence of this syndrome, yet some debate remains about the role of BNP in this process.

It is in this context that we consider the current article by Lu and colleagues [6] on cerebral salt wasting and elevated intracranial pressure (ICP). These authors report malignant brain edema in association with hyponatremia related to CSW. The hyponatremia is associated with elevated levels of BNP. Measures of elevated BNP levels and resultant CSW have previously been carried out in patients with TBI. A recent study of CSW in patients with TBI was conducted by Kirchhoff and colleagues [5]. These authors reported cerebrospinal fluid and serum levels of BNP measured at the time of admission, and at 12, 24, 48, and 72 hours after TBI. Kirchhoff et al further reported that patients with elevated ICP had sustained levels of BNP for 72 hours after TBI compared with TBI patients without elevated ICP and...
control of ICP than previous treatment strategies. Although the Lund therapy is controversial, the tenet of maintaining a high oncotic pressure and high serum osmolarity appears to be supported by the above-mentioned sodium control studies. Hence, many lines of thought appear to be converging on the concept that the prevention of hyponatremia and/or the maintenance of hypernatremia plays a crucial role for the treatment of the patient with TBI.

At University of California, Los Angeles we have used an aggressive sodium correction treatment regimen as a component of our TBI protocol [12]. The mean target goal is a serum sodium level of 138 mmol/L or higher if ICP is 15 to 20 mm Hg, and 145 to 155 mmol/L. We mainly use 3% NaCl to control serum sodium levels and prevent hyponatremia. Using this protocol, we report a 12% incidence of serum sodium levels of less than 137 mol/L and a 1% incidence rate of serum sodium levels of less than 132 mol/L. We have no documented cases of central pontine myelinolysis using this protocol. The effects of serum sodium levels on ICP are presently under study, but by comparison to other study cohorts, our percent time of elevated ICP of higher than 20 mm Hg has been low in our reported studies (21% of all values). Hence, our data are in agreement with that of Khanna and colleagues [4]. Our protocol for sodium regulation in TBI is illustrated in Table 1.

1. Conclusion

In summary, hyponatremia after TBI appears to be most frequently related to CSW. Brain natriuretic peptide plays a central role in the development and maintenance of CSW. The origin of BNP appears to be difficult to identify but may be the brain in a substantial percentage of cases. The control of serum sodium levels through the prevention and/or treatment of CSW appears to be a readily available treatment strategy that may be crucial for ICP control. Finally, the concept of CSW and the influence of sodium dysregulation needs to be well known among neurosurgeons and neurointensivists who care for patients with TBI.

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References


Control subjects. Moreover, the authors concluded that there was a substantial synthesis and release of BNP from the central nervous system that was facilitated by an earlier yet temporary disruption of the blood-brain barrier. The time course of elevation was long (72 hours) in the article by Kirchhoff et al, but the study did not report serum sodium levels nor relate the time course of BNP to serum sodium levels. One can conclude that prolonged elevations of BNP levels will lead to hyponatremia, brain swelling, and elevated ICP.

Given that ICP is the main treatment target for patients with TBI, it is crucial that we address changes in serum sodium levels and osmolality. There is a wealth of observational data in both adult and pediatric patients with TBI that the prevention of any degree of hyponatremia and/or the induction of moderate hypernatremia are associated with less elevation in ICP [11,13]. The induction of moderate hypernatremia with serum sodium concentrations ranging from 145 to 155 mmol/L has been routinely achieved by continuous infusion of hypertonic saline. This treatment appears to be well tolerated with minimal adverse effects. Under conditions of moderate hypernatremia, ICP is lower, and the percent time of elevated ICP of more than 20 mm Hg is less [4,10]. These results have led some to consider that the threshold for diagnosis of hyponatremia should be higher, perhaps as high as less than 140 mmol/L. If one were to consider values of less than 140 mmol/L to be hyponatremia, then the incidence of hyponatremia would be quite a bit higher than that reported by Lu et al [6]. Hence, one needs to carefully consider the sodium threshold of 130 mmol/L, that was used in the current article and be cognizant of the possibility that the reduction in sodium created by CSW may be a very common phenomenon that requires treatment.

As a corollary to the above discussion, there has been a great deal of discussion and debate over the proposed “Lund therapy” for TBI [9]. The Lund therapy consists of a central tenet of controlling the ill effects of hydrostatic pressure through the use of a combination of osmotic agents and manipulation of cerebral blood volume. Using strict control of osmotic therapy, the Lund group has reported better

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| Table 1 |
| Treatment protocol for sodium regulation in TBI |
| 1. Measure serum sodium level twice daily for initial 96 hours after TBI. |
| 2. Establish serum goal of ≥138 mmol/L. |
| 3. Start continuous infusion of 3% NaCl at 25 mL/h for Na of ≤138 mmol/L. |
| 4. Maintain 3% NaCl at 25-50 mL/h if ICP is 15-20 mm Hg. |
| 5. Add fluocortisone 0.1 mg bid (ora) if Na is ≥138 mmol/L. |
| 6. Increase 3% NaCl to 50-100 mL/h to achieve Na of ≥145-155 mmol/L if ICP is >20 mm Hg despite the use cerebrospinal fluid drainage using ventriculostomy. |