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Continuous Hyperosmolar Therapy for Traumatic Brain Injury-Associated Cerebral Edema: As Good as It Gets, or an Iatrogenic Secondary Insult?

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Abstract

Cerebral edema is a heterogeneous condition that is present in almost every type of neurological disease process – ranging from tumor, to cerebrovascular disease, to infection, to trauma, among others. It is associated with a high rate of morbidity and mortality. The pathophysiologic mechanisms of edema formation are distinct for the different conditions, thereby defining the various classifications. A relatively new treatment practice for cerebral edema is known as induced, sustained hyponatremia. This practice is highly controversial, is in widespread use, and lacks robust evidence for efficacy. Herein, we review details of the controversy regarding this practice.

Keywords

Edema; Hyponatremia; Hyperosmolar; Hypertonic; Trauma; Tumor; Vasogenic

The recent article by Ropper in the *New England Journal of Medicine* highlights the increasing popularity of medical therapies for traumatic brain injury (TBI)-associated cerebral edema.¹ In general, treatment options are sparse, and are aimed at curtailing the secondary insults that occur downstream of the original trauma, like cerebral ischemia. A major source of morbidity and mortality associated with TBI is cerebral edema, resulting in local or generalized increases in intracranial pressure (ICP). When ICP becomes elevated, hyperosmolar therapy is often initiated in bolus form and is often maintained with continuous infusions to target a goal of sustained hyponatremia.¹ As studies such as the recent Decompressive Craniectomy in Diffuse Traumatic Brain Injury (DECRA) trial bring into question the utility of decompressive hemicraniectomy for TBI-associated edema², interest in alternative medical therapies, such as pharmacologic induction of a *sustained* hyperosmolar/hyponatremic state (herein abbreviated as “sustained hyponatremia”), as described in the article by Ropper¹, are likely to gain popularity.

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Conflicts of Interest / Disclosure

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However, despite enthusiastic recommendations by Ropper¹, there is no robust evidence that sustained hyponatremia influences mortality, improves functional outcomes, or even lowers ICP following TBI. Sustained hypertonic treatments may be *deleterious* to a patient's health, either by inducing an additional secondary metabolic insult and/or exacerbating cerebral edema directly. While bolus therapy with hyperosmolar solutions is generally considered efficacious for the acute lowering of ICP during times of crisis, it cannot be extrapolated that continuous therapy will be beneficial. Therefore, a clear distinction must be made between the use of bolus and continuous hyperosmolar therapy. Could the present adoption of induced, sustained hyponatremia for the treatment of TBI-associated cerebral edema be reminiscent of obsolete protocols such as "sustained hyperventilation for intracranial hypertension"³, which after inclusion in dogmatic neurointensive care protocols has been shown to worsen outcomes?⁴

Several other issues need to be more adequately addressed in any discussion of hyperosmolar therapy. First, TBI-associated cerebral edema is not uniform; there is a variety of injury patterns and a similar diversity of edema mechanisms that result from focal contusion injury, diffuse injury (seen in the context of axonal injury from rapid angular acceleration), blast-associated injury, missile injury, and penetrating trauma injury. Permutations of these exist, commonly along with concurrent ischemic insults as a result of hypovolemic shock and hypoxemia from systemic injury. Many of these edema subtypes have a common "radiographic phenotype" using conventional techniques, but are driven by different pathophysiological antecedents and therefore might require different treatment strategies.

Second, it is known (now on molecular scale) that TBI-associated cerebral edema is a *dynamic* process; which means that a patient's injury is different at day 2 compared to day 5 after trauma. The successive failure of the blood–brain barrier as a result of endovascular dysfunction and capillary fragility often leads to a transition from cytotoxic edema (from ATP paucity) to vasogenic edema and secondary progressive hemorrhage; paradoxically, the literature is filled with remarks of how an intact blood–brain barrier is a *sine qua non* for hyperosmolar agents to work.⁵ These observations lead us to question a basic tenet of sustained hyponatremia: what is its mechanism of action? Certainly, the potential effects of any hyperosmolar treatment are not solely due to an intracranial osmotic diuresis. Other effects, like alterations in intravascular volume status, cerebral blood flow, or immune function also are likely to be significant. Also, with sustained hyponatremia, one cannot discount the brain's capacity to homeostatically counter the iatrogenically-introduced osmolar load with the cellular inclusion of so-called "idiogenic osmoles", whether produced *de novo* in cells or transported into cells from the extracellular space. Such idiogenic osmoles (often amino acids) not only put constraints on cell volume, but may pathologically alter intracellular ion homeostasis, with ramifications for both neuronal structure and neurotransmission.⁶

Third, TBI-associated edema in children can be very different from adults, even with similar primary injuries. The edema in newborns and young infants is often more brisk for reasons that are unclear, although increased cerebral blood flow during this developmental time and an incompletely developed autoregulatory mechanism in the cerebral vasculature have been postulated.^{7,8} Should these patients also be treated with sustained hyponatremia? Obviously, more data is needed to make these decisions.

Last, inadequately addressed in Ropper's article are recent studies highlighting novel insights into disease pathogenesis and potential molecular-based therapies for TBI-associated cerebral edema.^{9,10} The current practice of sustained hyponatremia, although performed with good intentions and in the context of few real options, is largely unsupported

by any existing data and should be considered empiric and not based on a cellular and/or molecular understanding of the disease. More research is needed, not only on novel therapies, but also on the effects and mechanisms of current therapies.

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JMS is the holder of several patents related to cerebral edema and ion channels, including “Novel Non-Selective Cation Channel in Neuronal Cells and Methods for Treating Brain Swelling” (U.S. Patent No. 2006/0276411 A1), “Therapeutic Agents Targeting the NCCa-ATP Channel and Methods of Use Thereof” (U.S. Patent No. 2009/0130083 A1), and “Targeting NCCA-ATP Channel for Organ Protection following Ischemic Episode” (U.S. Patent No. 2010/0143347 A1). He also is a member of the scientific advisory board and holds shares in Remedy Pharmaceuticals.

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