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SPECIAL ARTICLE

Guidelines for the Acute Treatment of Cerebral Edema in Neurocritical Care Patients

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Background: Acute treatment of cerebral edema and elevated intracranial pressure is a common issue in patients with neurological injury. Practical recommendations regarding selection and monitoring of therapies for initial management of cerebral edema for optimal efficacy and safety are generally lacking. This guideline evaluates the role of hyperosmolar agents (mannitol, HTS), corticosteroids, and selected non-pharmacologic therapies in the acute treatment of cerebral edema. Clinicians must be able to select appropriate therapies for initial cerebral edema management based on available evidence while balancing efficacy and safety.

Methods: The Neurocritical Care Society recruited experts in neurocritical care, nursing, and pharmacy to create a panel in 2017. The group generated 16 clinical questions related to initial management of cerebral edema in various neurological insults using the PICO format. A research librarian executed a comprehensive literature search through July 2018. The panel screened the identified articles for inclusion related to each specific PICO question and abstracted necessary information for pertinent publications. The panel used GRADE methodology to categorize the quality of evidence as high, moderate, low, or very low based on their confidence that the findings of each publication approximate the true effect of the therapy.

Results: The panel generated recommendations regarding initial management of cerebral edema in neurocritical care patients with subarachnoid hemorrhage, traumatic brain injury, acute ischemic stroke, intracerebral hemorrhage, bacterial meningitis, and hepatic encephalopathy.

Conclusion: The available evidence suggests hyperosmolar therapy may be helpful in reducing ICP elevations or cerebral edema in patients with SAH, TBI, AIS, ICH, and HE, although neurological outcomes do not appear to be affected. Corticosteroids appear to be helpful in reducing cerebral edema in patients with bacterial meningitis, but not ICH. Differences in therapeutic response and safety may exist between HTS and mannitol. The use of these agents in these critical clinical situations merits close monitoring for adverse effects. There is a dire need for high-quality research to better inform clinicians of the best options for individualized care of patients with cerebral edema.

Keywords: Intracranial pressure, Neurocritical care, Osmotherapy, Hyperventilation, Hypertonic, Mannitol

Introduction

Cerebral edema is a non-specific pathological swelling of the brain that may develop in a focal or diffuse pattern after any type of neurological injury. The underlying cause of this brain swelling is highly variable and relates to multiple physiological cellular changes. The simplest description of cerebral edema is an accumulation of excessive fluid within either brain cells or extracellular

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In one retrospective cohort study of patients with SAH, treatment with HTS was more common in the group of patients who developed AKI. Both increase in mean serum chloride level (OR 7.39 per 10 mEq/L increase) and use of HTS (OR 2.074) were found to be independently associated with AKI. In addition, five independent risk factors for AKI were identified: male gender, hypertension, diabetes mellitus, abnormal baseline creatinine, and degree of increase in mean serum chloride concentration [104]. A separate, propensity-matched retrospective cohort study which included patients with ICH found that those who received continuous infusion 3% NaCl and developed hyperchloremia (Cl > 115 mEq/L) had significantly higher rates of AKI [106]. One retrospective cohort comparison evaluated the effects of bolus dose and continuous infusion 3% NaCl on AKI [98]. Hyperchloremia and AKI were more observed to be more frequent in the continuous infusion cohort.

Three studies have described the effect of HTS on acid–base balance. Two retrospective cohort studies described the use of a sodium acetate and NaCl mix (to equal a 2 to 3% solution) which demonstrated no difference in the rate of metabolic acidosis [101, 107]. Tseng et al. reported on the use of 23.5% NaCl to achieve a goal serum sodium of 145–155 mEq/L in patients with SAH [16]. No significant changes in serum bicarbonate concentration were noted. Despite the relative lack of studies demonstrating substantial acid–base imbalances with HTS use, clinicians should be mindful of the potential for hyperchloremia to induce metabolic acidosis, which may stimulate respiratory drive.

Though the quality of the evidence is low, it suggests that severe hypernatremia and hyperchloremia from HTS are associated with AKI. In addition, the impact of HTS on acid–base balance is not well defined in studies including neurocritical care patients. Clinicians should monitor renal function, electrolytes, and acid–base balance closely when using HTS.

Recommendations for the Optimal Administration Method of Hypertonic Sodium Solution

In patients with cerebral edema, how does continuous infusion of hypertonic sodium solutions compare to bolus infusion of hypertonic sodium solutions in improving neurological outcomes?

1. There is insufficient evidence to support use of a continuous infusion of HTS targeting a serum sodium goal for the purpose of improving neurological outcomes.
2. Due to insufficient evidence, we cannot recommend a specific dosing strategy for HTS to improve neurological outcomes in patients with cerebral edema.
3. Clinicians should avoid hyponatremia in patients with severe neurological injury due to the risk of exacerbating cerebral edema (good practice statement).

The panel evaluated whether titrating a continuous infusion of HTS to a target serum sodium concentration compared to the use of bolus/symptom-based dosing resulted in improved neurological outcomes in patients with cerebral edema across a variety of neurocritical care conditions (Table 1, Question 15). Six publications have specifically addressed the issue of how HTS was administered to patients, but the panel only identified one that directly compared continuous infusion versus bolus administration for control of ICP that met the criteria for this PICO. The overall quality of evidence was very low (Table 13).

While the use of a continuous infusion of 3% NaCl is believed to be a common practice in neurocritical care, this strategy is not well studied. Maguigan et al. directly compared continuous versus bolus dose 3% NaCl for control of ICP elevations in a retrospective study of 162 patients with severe TBI to assess which method was the most effective [98]. No significant difference was found in time to the goal osmolarity, although more patients receiving continuous 3% NaCl reached the goal serum osmolarity than patients receiving bolus dosing. There was no difference in ICP or mortality between the two groups.

Given the lack of evidence comparing these dosing strategies, it is not clear whether continuous or bolus dosing is preferable when targeting a goal serum sodium concentration. Additionally, there is a significant gap in the literature regarding the value of targeting a specific serum sodium concentration in patients with cerebral edema, if it is in fact efficacious. While this discussion focuses on increasing sodium concentrations to treat elevated ICP and cerebral edema, clinicians must maintain awareness of the risk and benefits of sudden sodium changes, particularly in patients with chronic hyponatremia) [108].

Non-pharmacologic Treatment of Cerebral Edema and Elevated Intracranial Pressure

In patients with cerebral edema, how do non-pharmacological interventions compare to pharmacological interventions for reduction of cerebral edema?

Recommendations for the Non-pharmacological Treatment of Cerebral Edema

1. We suggest that elevating the head of the bed to 30 degrees (but no greater than 45 degrees) be used as a beneficial adjunct to reduce intracranial pressure

(conditional recommendation, very low-quality evidence).

Rationale: In making this recommendation, the panel rated the quality of available evidence as very low. However, this intervention has been used extensively in the clinical setting and the risk of elevating the head of the bed is generally very low and may be beneficial.

2. We recommend that brief episodes of hyperventilation can be used for patients with acute elevations in intracranial pressure (strong recommendation, very low-quality evidence).

Rationale: In making this recommendation, the panel rated the quality of available evidence was very low. However, a strong recommendation was felt to be appropriate given the extensive amount of practical experience with this therapeutic strategy. Clinicians should be mindful of the limitations of acute hyperventilation related to cerebral blood flow and the extent of $PaCO_2$ reduction. Clinicians should also maintain careful awareness of the duration of therapy to avoid deleterious changes in cerebral perfusion.

3. We suggest that the use of CSF diversion be considered as a beneficial adjunct to reduce intracranial pressure (conditional recommendation, very low-quality evidence).

Rationale: In making this recommendation, the panel felt that the quality of evidence was very low. Clinicians should assess the risks and benefits of CSF diversion using patient-specific factors.

4. While non-pharmacological interventions may be effective for acute elevations in intracranial pressure, there is insufficient evidence that non-pharmacological interventions are effective for the treatment of any specific physiological changes that produce brain swelling related to cerebral edema.

The panel evaluated whether non-pharmacologic therapies such as hyperventilation, head of the bed elevation, and CSF diversion can be used to reduce ICP and cerebral edema in neurocritical care patients (Table 1, Question 16). It must be noted that these non-pharmacological interventions decrease ICP through mechanical or structural changes without actually having any impact on cerebral edema and brain swelling. Other non-pharmacologic therapies such as surgical decompression and therapeutic hypothermia were not included, as they are adequately addressed by other guidelines [3]. The overall quality of evidence was very low (Table 14).

The panel identified nine studies which assessed ICP in relation to elevation of the head of the bed [109–117]. Compared to supine positioning, ICP was consistently lower in patients at angles of 15° to as high as 90 °. The effect of head of bed elevation may be attributable to cardiovascular physiology and cerebral blood volume, which can at times manifest as alterations in CPP. In fact, several studies suggest that CPP is slightly reduced as the extent of head of bed elevation increases, though not to a clinically significant degree. One prospective observational study of patients with TBI suggested that ICP was reduced and CPP was stable when elevating the patients' head of the bed from supine to 30° [113]. However, further increases in the angle of head elevation above 45° may increase ICP and/or reduce CPP [109, 113, 116].

The panel identified four studies evaluating the use of transient hyperventilation for reducing ICP; studies of prophylactic and/or prolonged hyperventilation were not considered for the final recommendations. Three heterogeneous studies evaluated the effect of transient hyperventilation on ICP with variable results. Oertel et al. completed 57 trials of hyperventilation in 27 patients with TBI and noted a significant reduction in ICP in 96.5% of the patients [118]. Fortune et al. performed transient hyperventilation in 16 episodes of elevated ICP occurring in 22 patients with TBI and noted a significant reduction in ICP in 88% of the episodes [119]. In contrast, Soustiel et al. found no significant change in ICP in response to transient hyperventilation [120]. Muizelaar et al. evaluated the impact of prophylactic hyperventilation on ICP and neurological outcomes in 113 patients with TBI and found that prophylactic hyperventilation ($PaCO_2$ of 25 mmHg) was associated with a more stable ICP course compared to the normal ventilation group ($PaCO_2$ of 35 mmHg) [121]. There was no difference in long-term outcomes, and a subgroup analysis suggested that prophylactic hyperventilation may be harmful in patients with a motor subscore of 4–5 on the GCS. While the quality of the literature for transient hyperventilation is graded as very low, clinical experience with this practice as a temporizing treatment for elevated ICP is extensive. The use of transient hyperventilation in patients with symptoms suggesting acute cerebral edema or herniation has been a standard practice in multiple clinical settings (pre-hospital, emergency department, ICU and operating room), and clinicians have seen improvement in pupil diameter, physical examination, or ICP measurements in response to this intervention. In addition,

the harm associated with hyperventilation is generally related to the risk for cerebral ischemia with prolonged vasoconstriction. Given the potential life-threatening nature of elevated ICP, lack of apparent associated harm, and possible short-term benefit with transient hyperventilation, we felt that virtually all clinicians would choose hyperventilation as an adjunctive treatment strategy given the possibility that it may decrease ICP. Thus, the panel felt that a strong recommendation was warranted.

The panel identified four studies evaluating the efficacy of CSF diversion in reducing ICP [122–125]. Physiologically, it may be reasonable to assume that CSF drainage can lower ICP by decreasing the volume of the intracranial compartment by shunting CSF from the ventricles (as opposed to decreasing cerebral edema). Overall, CSF diversion appeared to be effective at reducing the ICP in two separate prospective, observational cohort studies [122, 123]. There was a significant change in ICP immediately after drainage without a measurable improvement in other indices of cerebral perfusion. In addition, Nwachuku et al. found that continuous CSF drainage results in a lower mean ICP and overall ICP burden compared to intermittent drainage [125].

Summary

The pharmacologic treatment of cerebral edema should be guided whenever possible by the underlying pathology. The available evidence suggests hyperosmolar therapy may be helpful in reducing ICP elevations or cerebral edema in patients with SAH, TBI, AIS, ICH, and HE, although neurological outcomes do not appear to be affected. This finding is consistent with many other interventions used in the acute care of patients with neurological conditions in that treatments may affect an immediate abnormality, but outcomes are often influenced by multiple factors that may be beyond the awareness or control of the treating team (e.g., comorbidities, associated injuries, rehabilitation availability, etc.). Corticosteroids appear to be helpful in reducing cerebral edema in patients with bacterial meningitis, but not ICH. Differences in therapeutic response and safety may exist between HTS and mannitol. The use of these agents in these critical clinical situations merits close monitoring for adverse effects.

The various treatments for ICP or cerebral edema reviewed in this guideline are used in patients with critical intracranial pathologies worldwide. Despite their ubiquity, the overall quality of the literature in this area is low and there is a paucity of rigorous prospective trials. The strength of the panel's recommendations was frequently downgraded due to the limited evidence available comparing the different treatments. The concepts of hyperosmotic therapy have been entrenched in the critical care management of patients with neurological injuries for years, yet there is limited evidence to guide clinicians on the optimal practical use of mannitol or hypertonic saline. There is a dire need for high-quality research to better inform clinicians of the best options for the individualized care of patients with cerebral edema. The goals of research activities in this area should address specific questions, adequately reflect the scope of planned patient enrollment, and select reasonable outcome measures. Basic criteria of research efforts should include a definition of how cerebral edema is being measured, the specific purpose of any intervention (e.g., resuscitation, management of ICP, effect on physiological parameters), and what outcome measures will be assessed. In addition, research efforts should consider and report on the osmolar equivalents of agents used in the management of cerebral edema, assess the effects of specific ranges of sodium levels on markers of edema, evaluate the best duration of therapy, standardize and report basic care protocols, and consider the impact of all pharmacological and non-pharmacological interventions on designated outcomes. Finally, while the goal of all interventions in the management of neurological injuries is to improve survival and minimize disability, it must be acknowledged that a single intervention to address a specific physiological variable may have limited impact on the multiple factors that contribute to both short- and long-term outcomes.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-020-00959-7) contains supplementary material, which is available to authorized users.

Abbreviations
AIS: Acute ischemic stroke; AKI: Acute kidney injury; APACHE: Acute physiology, age, and chronic health evaluation; CE: Cerebral edema; CNS: Central nervous system; CPP: Cerebral perfusion pressure; CSF: Cerebrospinal fluid; CT: Computerized tomography; GCS: Glasgow coma score; GOS: Glasgow outcome scale; GOSE: Glasgow outcome scale extended; HE: Hepatic encephalopathy; HES: Hydroxyethyl starch; HTS: Hypertonic sodium solution (usually referring to sodium chloride 3%, 7.5%, or 23.4%, but also inclusive of solutions ranging from 1.5 to 23.5% and various other sodium salts including lactate and bicarbonate); ICH: Intracerebral hemorrhage; ICP: Intracranial pressure; mRS: Modified Rankin scale; NaCl: Sodium chloride; NIHSS: National Institutes of Health Stroke Scale; PICO: Population, intervention, comparison, outcome; RCT: Randomized controlled trial; SAH: Subarachnoid hemorrhage; TB: Tuberculosis; TBI: Traumatic brain injury; TTH: Transtentorial herniation.

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Compliance with Ethical Standards

Conflict of interest
The authors declare that they have no conflicts of interest.

Informed Consent
Not applicable.

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