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A review of therapies for elevated intracranial pressure following traumatic brain injury

Emily Stephens, PharmD Candidate 2023[1]
[1]University of Findlay College of Pharmacy

Abstract

Increases in intracranial pressure (ICP) secondary to cerebral edema or hemorrhage is a notable complication that may arise following a traumatic brain injury (TBI). The main goal in the management of elevated ICP is prevention of secondary brain injury. The 2016 Brain Trauma Foundation Guidelines for the Management of Severe Traumatic Brain Injury recommend hyperosmolar therapy in the treatment algorithm for reducing ICP, with the previous guideline edition suggesting that mannitol is an effective hyperosmolar agent. The guidelines acknowledge that hypertonic saline has become increasingly popular as an alternative agent to mannitol, possibly due to a longer duration of action and a reduced likelihood of inducing electrolyte abnormalities. The guidelines indicate that there is a lack of sufficient evidence required to make a formal recommendation supporting the use of one particular hyperosmolar agent. Since osmotherapy fluid selection is left to clinician preference, these healthcare providers should be informed about differences in mechanisms which may influence perceived benefits, potential off-target effects, as well as patient groups in which one agent may be favored.

Traumatic brain injury (TBI) most commonly occurs as a result of a fall, motor vehicle accident, firearm-related suicide or assault. In 2019, there were 60,611 TBI-reated deaths in the United States and in 2018, approximately 223, 050 hospitalizations occurred secondary to TBI.[1] While adults of advanced age are at an increased likelihood of hospitalization and death due to TBI, such injuries may be misdiagnosed or missed entirely due to overlapping symptoms with other disease states commonly seen in this age group, such as dementia.[2]

Following a TBI, an increase in intracranial pressure (ICP) may occur.[3] In other words, the pressure within the craniospinal compartment, which is comprised of brain tissue, blood, and cerebrospinal fluid (CSF) increases.[3] This increase in ICP may be the result of cerebral edema or hemorrhage causing the collection of fluid at the site of injury.[3] Left untreated, elevated ICP may ultimately result in seizures, coma, stroke, or death. Prompt treatment is critical in order to prevent long term complications and mortality. Further brain injury that may occur following the initial offense is caused by CSF exiting the ventricular system and entering the spinal subarachnoid space, causing a reduction in blood volume as blood exits the veins and arteries. Consequently, fluid accumulates in the brainn and this is referred to as cerebral edema.[4] This depletion of blood volume jeopardizes cerebral perfusion pressure (CPP), which may be calculated as the difference of mean arterial pressure (MAP) and ICP. As the blood volume decreases, the body maintains cerebral perfusion by inducing systemic hypertension as a compensatory mechanism to preserve an adequate MAP.[4] Eventually this accommodation is exhausted and ICP will continue to rise exponentially to the point of diminished cerebral blood flow if interventions are not made.[3]

A mainstay in the pharmacologic approach in reducing ICP is hyperosmolar therapy, with mannitol and hypertonic saline being the most common agents.[3,5] The 2016 Brain Trauma Foundation Guidelines for the Management of Severe Traumatic Brain Injury do not indicate a preferred osmotherapy agent.[5] Trials to date have been small and primarily retrospective or observational, thereby limiting the number of comparative studies to assist a clinician in selecting an osmotic agent.[5] Given the nature of this treatment selection, it is imperative that clinicians are made aware of advantages and limitations alike for the osmotherapy agents available. The mechanistic goal of hyperosmolar therapy is to promote the movement of fluid from the intracellular and interstitial spaces and into the intravascular space by increasing plasma osmolarity.[4] This results in a net expansion of blood volume to increase blood perfusion, neuronal dehydration to alleviate cerebral edema, and endothelial dehydration to reduce capillary wall thickness, further promoting blood flow and brain oxygenation.[4]

Hyperosmolar Agents

Mannitol

Mannitol has been the recommended agent for use in hyperosmolar therapy since the 1960s and the guidelines still recommend its use.[3] The initial mechanism by which mannitol reduces ICP is by enhancing the flow of blood. Lowering blood viscosity allows blood to flow more easily through the vasculature and promote oxygen delivery to the brain.[3,4] Assuming compensatory pathways are intact, the body recognizes an improvement in blood viscosity and increase in intravascular volume and subsequently induces cerebral vasoconstriction.[3] This constriction of arterioles will lower the total blood volume in the brain tissue, thereby decreasing ICP. If this autoregulation is not functional, the decrease in ICP seen by this mechanism will be minimal.[3] This is one explanation for potential ineffectiveness of mannitol in the management of intracranial hypertension. An additional mechanism by which mannitol reduces ICP is through the formation of an osmotic gradient.[3] Mannitol extracts water from intracellular and interstitial spaces in the brain and returns it to the intravascular space to increase total blood volume and reduce cerebral swelling.[3] An obstacle to hyperosmolar therapy, regardless of the selected agent, is that it requires an intact blood-brain barrier in order to support the movement of fluid across the osmotic membrane.[3] In instances where the blood-brain barrier is compromised, osmotic substances such as fluid and electrolytes will accumulate in the brain tissue and subsequently draw fluid into the area, resulting in cerebral edema.[9] These molecules may alter the osmotic equilibrium between blood and interstitial fluid on either side of the blood brain barrier and cause an inability of fluid to shift out of the brain via osmotic gradient.[7] Studies have shown that if the blood-brain brain is impaired, fluid loss may still occur in regions of both injured and uninjured brain tissue, although the vast majority of water extraction will occur from sites of uninjured tissue.[3]

Mannitol 20% is more commonly used for reduction of elevated ICP, although 25% concentrations may be used as well.[7] The guideline recommended dose of mannitol for management of elevated ICP is 0.25 g/kg to 1 g/kg,[5] with more recent data demonstrating that doses <0.5 g/kg are considered to be less effective.[7] Mannitol will reduce ICP and increase cerebral blood flow in a dose-dependent manner and will not decrease ICP if it is not elevated at baseline.[8]

One disadvantage to using mannitol is that approximately 45 minutes after administration of mannitol IV bolus, osmotic diuresis occurs.[4] As mannitol continues through the promixal convoluted tubule and loop of Henle, free water is unable to be reabsorbed into systemic circulation as the hyperosmolar solution progresses through the nephron.[4] This causes a suppression of antidiuretic hormone and activation of atrial natriuretic peptide, leading to further urine dilution.[4] Consequences of diuresis are a reduction in blood volume, resulting in systemic hypotension and jeopardized cerebral perfusion pressure,[4] thus mannitol may not

be a favorable agent in patients with increased ICP and systemic hypotension.[8] Due to the risk of osmotic nephrosis secondary to mannitol administration, this agent is contraindicated in patients with renal failure.[7] Additionally, a concept known as "rebound phenomonen" has been observed with mannitol administration in patients with intracranial hypertension secondary to cerebral edema.[3] This complication may be caused by the central nervous system compensating for the sudden loss of fluid in the brain secondary to mannitol administration. This compensatory mechanism involves the promotion of an increase in electrolyte concentration in the brain to restore the edematous state.[3] This rebound activity is identified by the return to elevated ICP levels, sometimes even exceeding those present before hyperosmotic therapy.

Hypertonic saline

Hypertonic saline (HTS) is another commonly used agent for the reduction of elevated ICP in traumatic brain-injured patients. As with mannitol, HTS exerts its ICP reducing effects through various mechanisms. HTS demonstrates modifications in rheology to reduce blood viscosity and promote initial increases in blood flow reaching cerebral tissue.[3] HTS produces a similar osmotic gradient to that of mannitol, drawing free water from the brain tissue environment and into the intravascular space for an immediate effect on cerebral edema.[9] Not only have studies been published that report more prominent and longer durations of reduction of ICP occur following HTS therapy, but HTS is devoid of the rebound phenomenon as seen with mannitol.[3] Crystalloids, such as HTS, are typically preferred agents for fluid therapy in comparison to colloids, like mannitol.[9] This preference is rooted in the composition of crystalloids being most similar with the normal constituents of the intracellular and extracellular spaces within the body.[9] Such a similarity allows for the osmotic substances within the exogenous fluid to be redistributed in the body more easily.[9] This redistribution minimizes the central nervous system compensation as seen with mannitol treatment, thereby avoiding rebound pressure.[9]

HTS has also been identified as having immunomodulatory effects which may regulate the immune system to promote favorable conditions for reductions in intracranial hypertension.[9] HTS can function to alter vasomotor tone and induce nitric oxide and endothelin release, in addition to reversing macrophage proinflammatory effects.[9] The net result with such anti-inflammatory activity is a reversal of endothelial cell swelling, increase in capillary lumen, and subsequent improvement in cerebral blood flow and perfusion.[9]

The current HTS dose used in the management of intracranial hypertension is sodium chloride 23.4% 30 mL IV bolus over 2 to 10 minutes as needed to reduce elevations in ICP, to be administered via central venous access only.[10] An alternative which would permit peripheral venous administration, thereby being more practical for prehospital administration, as well as emergent cases in the ED when central

venous access is not readily available is sodium chloride 3% 30 to 50 mL/hour IV continuous infusion to be titrated to a serum sodium concentration between 145 to 155 mEq/L.[10] This variability in dosing recommendations reinforces the need for high quality comparative studies in order to establish optimal dosing.

Comparison

The guidelines recognize a rise in popularity of HTS as an alternative agent to mannitol, but emphasize the absence of sufficient evidence comparing both agents to make a reliable recommendation.[3] Case series have been conducted demonstrating a clinical role for HTS use as both an alternative and as adjunct therapy to mannitol.[3] A patient's electrolyte status on presentation may have an impact on agent selection as well. Several studies have reported data regarding serum osmolarity and electrolytes following mannitol or HTS administration.[3,7,11,12] Target osmolarity for the indication of intracranial hypertension is between 310 and 320 mOsm/L and the increase in serum osmolality towards this goal is significantly greater in the HTS treatment groups.[7] With regard to sodium levels, mannitol may induce hyponatremia via inhibition of sodium resorption across the renal tubule, leading to excretion.[3] Given the possibility of hyponatremia, mannitol is not an ideal hyperosmotic agent to treat a patient presenting with a low sodium level. However, mannitol may be better suited for normotensive patients with hypernatremia in order to prevent worsening of sodium serum levels.[12] Additional electrolyte abnormalities associated with mannitol include hyperkalemia, hypokalemia, hypomagnesemia, and hypophosphatemia.[7] Studies have reported consistently elevated serum sodium levels associated with treatment of HTS, although levels remained within normal limits.[11] Since concentrations of HTS used ranges from 3% to 23.4%, solutions can vary widely in sodium content suggesting that the degree of risk for hypernatremia may vary as well.[7,12]

The reflection coefficient of HTS is 1.0, suggesting that solutes are entirely impermeable to an intact membrane.[11] Theorectically this will lead to a greater extent of fluid withdrawing from the brain tissue in comparison with mannitol, which has a reflection coefficient of 0.9 and though mostly impermeable to solutes, may have a lessened effect on reducing ICP.[3] Mannitol has shown to be progressively less effective with subsequent administration, therefore HTS plays an important role in the management of elevated ICP refractory to mannitol.[3]

Another possible advantage to using HTS as an alternative to mannitol is HTS has a prolonged effect on the reduction of ICP as it does not undergo the diuresis mechanism like mannitol. In the absence of diuresis, the volume expansion within the vasculature will be sustained for a longer duration.[11] This may prove to be beneficial in patients presenting with hypotension and/or hypovolemia. HTS has repeatedly shown to have a more rapid onset and a greater duration of ICP reduction.[9] Given this rapid ICP reduction, HTS may be superior in the way of minimizing secondary brain damage to preventing neurologic

deterioration.[9,12] However, as far as all-cause mortality effects, there is no significant difference between the two agents.[12] Despite this perceived benefit over mannitol, several studies have indicated that there are minimal clinical outcome differences regarding neurologic outcomes.[7,8] Larger studies may be needed in order to demonstrate significance of the clinical benefits of the onset and sustained ICP reduction of HTS on neurologic outcomes.

HTS seems to be advantageous over mannitol relative to cardiac output performance.[11] HTS offers a sustained effect on increasing blood volume, whereas mannitol readily undergoes diuresis resulting in depleted blood volume.[11] Therefore, it is suggested that HTS provides a better stroke volume and cardiac output profile compared to mannitol.[11] For this reason, HTS may be a more appealing agent for patients with hypovolemia or hypotension.[11] This desired impact on cardiac output will also increase mean arterial pressure, thereby increasing cerebral perfusion pressure, especially as intracranial pressure is inversely decreased through osmotherapy.

Limitations

As emphasized by the 2017 Guidelines for the Management of Severe Traumatic Brain Injury, a lack of comparative studies poses a challenge in recognizing either mannitol or HTS as the superior agent for the management of intracranial hypertension following TBI. The challenges faced by researchers conducting comparative analyses on mannitol and HTS use is the degree of heterogeneity of the individual trials. Differing comparators, dosing regimens, small sample sizes, and differences in clinical settings at the time of administration are all factors that may contribute to heterogeneity among studies, if they are not first deemed ineligible per systematic review or meta-analysis exclusion criteria.[12] Many studies are conducted in the ICU, which may pose difficulties when extrapolating the data to apply to unstable patients presenting to the ED or in prehospital settings.[12]

Conclusion

The guidelines recogonize hyperosmolar therapy as the initial treatment in the medical management of elevated ICP. The recommendation for the use of mannitol in hyperosmolar therapy has been carried forward from previous guideline editions.[5] Despite off-label use of HTS for this same indication, the guidelines are unable to make a formal recommendation between HTS and mannitol due to current data being insufficient to permit changes in standards of care.[5] The data that is available influences clinicians' decisions regarding hyperosmolar therapy in an area where further research is yet to be conducted. Large studies are needed to compare clinical improvements and differences in all-cause mortality as none are currently available, leaving conclusions to be drawn from heterogenous studies with small sample sizes.

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