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Is Hypertonic Saline Superior to Mannitol in Reducing Cerebral Edema?

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Cerebral edema is a potentially life threatening complication that can arise from any acute neurological insult. The brain is encased in a closed skull and relies on fluid level to maintain a “balance”. Alexander Monro hypothesized that the blood circulating in the cranium was of constant volume at all times and his hypothesis was supported by experiments performed by Kelli. This became known as the Monro-Kelli doctrine, or hypothesis. An increase in one should cause a decrease in one or both of the remaining two. Specifically, the Monro-Kelie hypothesis says that “the total bulk of three elements (inside the skull) the brain 1400 ml, cerebral spinal fluid (CSF) 150 ml and blood 150 ml must remain constant” (Jha, S. 2003). When the brain experiences a traumatic injury, rupture of aneurysm, mass or stroke, the skull cannot allow for the additional volume. If the brain, blood volume or CSF continues to rise, this will increase intercranial pressure (ICP) and reduce CSF from circulating. This will cause the brain to lose the capability to compensate leading to cerebral edema and the complications that develop. Urgent intervention is required to stop the cascade of events to prevent herniation and death. Surgical intervention is typically required to alleviate intercranial pressure; however medical management is still a very important component in controlling cytotoxic and/or vasogenic edema.

Cytotoxic edema results from apoptosis and/or cellular injury. Intracellular trapping of sodium causes engorgement of the cell leading to apoptosis and release of sodium into the parenchyma. Vasogenic edema may be a secondary insult as it results from the breakdown of endothelial junctions of the blood-brain barrier (BBB). This breakdown allows proteins and intravascular fluids to enter the extracellular space. Both cytotoxic and vasogenic edema may result from traumatic brain injury, stroke, aneurysm rupture or brain tumors.

Traumatic brain injury (TBI) occurs in over 1.7 million people annually and is a contributing factor in 30.5% of all injury related deaths in the nation. Adults aged 75 years and older have the highest rates of TBI-related hospitalization and death. Unfortunately, 77.2% of those will die as a result of their injury. Non traumatic strokes are a close second affecting roughly 795,000 people annually. Broken down that means every 40 seconds in the United States someone will have a stroke (www.cdc.gov/traumaticbraininjury). Spontaneous intracerebral hemorrhage (ICH) is a neurologic emergency that accounts for about 10-20% of all strokes and has a 30 day mortality rate of 35-52%. Only 21% of ICH patients are expected to recover at 6 months (Fernando D. Testai, Venkatesh, 2008). Finally, brain tumors are diagnosed in roughly 200,000 people annually; 40,000 of those diagnosed have a primary brain tumor while the remaining result from metastasis to the brain. Brain tumors are the second leading cause of cancer death in males ages 20-29 and the fifth leading cause in females ages 20-39. There are over 120 different types of brain tumors; however, medical management is essentially the same for all (www.cancer.gov). Therefore, the patient's outcome from a cerebral insult is directly related to the degree of injury and extent of edema that ensues.

Mannitol, a sugar alcohol has been the gold standard for the treatment of cerebral edema for several decades; however hypertonic saline (HS) is quickly gaining momentum as an equal or perhaps superior alternative to mannitol. The underlying principles of the medications are to reduce cerebral edema with a diuretic affect as well as renal vasodilation.

The purpose of this study is to evaluate the effectiveness of each drug and attempt to answer the question "Is Hypertonic Saline Superior to Mannitol in Reducing Cerebral Edema?"

A systematic review of literature was conducted to evaluate if hypertonic saline (HS) is superior to mannitol in reducing cerebral edema. Based on The Campbell Collaboration the purpose of a systematic review is to summarize the best available research to answer a specific question. This requires integration of the results of numerous studies. The object is to evaluate the outcomes of pertinent research that can be duplicated by other facilities under the same circumstances. “A systematic review must have: Clear inclusion/ exclusion criteria, an explicit search strategy, systematic coding and analysis of included studies, and meta-analysis” when available (<http://www.campbellcollaboration.org>).

An internet search was conducted utilizing MD Consult, MEDLINE, CINAHL and Google scholar search engines. Initially, studies pertaining to *mannitol* were completed. The second search included *hypertonic saline* and other research articles pertaining to other modalities of *medical therapy for cerebral edema*. Studies were searched based on levels of evidence as established by the U.S. Preventative Services Task Force (USPSTF). The USPSTF has two methods for grading levels of confidence. This particular study employed the following evidence categories:

I: Evidence obtained from a single randomised [sic - British spelling from the original] controlled trial or a meta-analysis of randomised controlled trials

IIa: Evidence obtained from at least one well-designed controlled study without randomisation

IIb: Evidence obtained from at least one well-designed quasi-experimental study [i.e., no randomization and use of existing groups]

III: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities (http://sophia.smith.edu/~jdrisko/rating_the_evidence.htm)

Over one hundred articles were assessed in regards to mannitol alone or in comparison to other medical therapies. Inclusion criteria for the articles was based on clinical and laboratory studies, credibility, sufficient quality, credentials of authors, and ability to replicate the study. Studies were not excluded based on surgical intervention along with conservative treatment methods. Since evidence based practice is dependent on remarkable research, certain standards must be acknowledged. The highest level of review includes systematic, double blind studies and cohort studies. Weaker papers include case studies and opinion articles. Therefore articles that failed to meet the criteria were excluded, which included foreign language, insufficient data, opinion based without evidence and/or the age of the paper. Although a few older articles were included based on results or offered pertinent information for the review. After careful analysis, fifty one articles were selected for examination. Based on USPSTF guidelines, twenty six of the articles were evidence category I, fourteen were category II, seven level III and four were level IV. While the goal was to obtain level I or II, the lesser qualifying papers were kept for significant findings in the conclusion. This paper will compare the findings between the “gold standard” mannitol to hypertonic saline based on criteria documented previously.

Despite mannitol being the standard treatment of ICP for the last few decades in reducing cerebral edema, optimal dosing for the medication nor the affects of the medication based on other factors such as age, sex, location of insult have been established. Mannitol is a cell impermeable non-toxic alcohol and its purpose is to drive water out of cells to decrease volume (Zolta, 2007).The mechanism of mannitol is poorly defined, but effects are proposed to be mediated by the reduction in CSF by reducing water volume, and viscosity by vasoconstriction that leads to reducing blood volume within the brain (Rabinstein, 2008). Reduction of volume prevents further infarct to brain tissue, which is vital to decrease morbidity and mortality.

Findings in the mannitol group were included in all studies reviewed, with or without HS for comparison. The dosage of mannitol most studied was 20% concentration; however 15% concentrations were also noted in two of the studies. Human and animal models were included. The studies concentrated on intercranial hemorrhage, stroke and traumatic brain injury. However a few studies were included whereby intercerebral edema was secondary to another medical problem. The articles evaluated mannitol dosing and protocols versus superiority to other agents such as HS. The effects of mannitol manifests within 30 minutes of administration and is generally sustained for several hours. Continuous infusion or scheduled boluses are standard for treatment; however repeated boluses have shown to have a direct correlation with rebound increases of ICP (Damek, 2010). Early responses to mannitol were all favorable. The smallest study included a single case study and the largest involved multi-center with 1572 patients in China. Most notable in the Chinese study it was documented that patients had a 3x higher mortality/disability that underwent neurosurgery in conjunction with medical therapy (Wei & Huang, 2011). One study found that reduction in ICP with mannitol was greater in patients with supratentorial ICH compared to infratentorial ICH (Meyer, 2010). Others described significant differences in dosing and outcomes after initial ICP reduction, but not after ICP reached a fixed level. Mannitol saturation was noted to be the cause of patient receiving no further benefit from treatment. Based on analysis of studies, more than thirty medications have been tested in the treatment of ICP with mannitol demonstrating the greatest benefit (Annals of Emergency Medicine, 2010); however higher doses were documented to lead to volume depletion, severe electrolyte abnormalities such as rebound cerebral HTN, hypernatremia, hyperkalemia, metabolic acidosis and renal failure. Electrolyte disturbances were most significant after three days of mannitol therapy, most notably sodium levels (Sushree, 2008).

A retrospective random cohort study conducted on traumatic brain injury included 171 patients that were given mannitol as part of treatment plan. Patients were given mannitol and/or furosemide. Results of acute kidney injury was documented in both group based on accumulative dosing. It was shown that mannitol was an independent risk factor for acute kidney injury in head trauma patients (Fang, 2010).

A study published in the Neurologic Clinics documented the osmotic effect of mannitol was found to increase serum tonicity, which draws edema from cerebral parenchyma. This process takes 15 to 30 minutes, until gradients are established. Serum osmolality should be at or around 320 mOsm to avoid adverse effects from treatment, which included hypovolemia, hyperosmolality, and renal failure. If mannitol opens the BBB it can leak to surrounding tissues and augment vasogenic edema. Therefore mannitol should be tapered to prevent a rebound in edema and ICP. Adverse effects were most pronounced when mannitol was utilized for extended periods.

Finally, mannitol and HS were compared in patients that had experienced traumatic brain injuries to reduce the inflammation associated with injury. Neutrophils and monocytes have been proven to exacerbate cerebral edema as they are toxic to delicate cerebral tissues. The body's own response to send neutrophils and increased production of chemokines lead to further insult by inflammatory cells. Under microscopic evaluation of tissues, neutrophils traveled across the choroidal epithelial directly into the CSF. In TBI a combination of cytotoxic as well as vasogenic edema typically are seen. Studies demonstrated reactive oxygen species (ROS), inflammatory cytokines, endothelial growth factor and matrix metalloproteinases have all been identified as cause of BBB leakage after trauma. This dysfunction of the BBB progresses through a positive feedback loop, leading to further damage of the brain. Mannitol and HS were compared in the

treatment of cerebral edema that is a result of neuroinflammatory response to trauma. It was this author's opinion mannitol was superior in the reducing ICP in patients with TBI. Hypertonic saline was theorized to reduce water and potentially edema; however there was evidence of worsening effect on endothelial cells (Zink, 2010).

In contrast studies demonstrate HS administered in concentrations from 3% to 23.4%, also creates an osmotic force to pull fluid from the interstitial space of the brain parenchyma into the intravascular compartment thereby reducing intracerebral volume and ICP. This study found in researching the topic that hypertonic saline was shown to be more effective than mannitol in reducing ICP. Hypertonic saline was documented to have advantage over mannitol in hypovolemic and hypotensive patients. Furthermore, mannitol is contraindicated in hypovolemic patients because of its diuretic effects, whereas HS enhanced intravascular volume and potentially increase blood pressure, along with decreasing ICP. However, hypertonic saline was not associated with improved neurologic outcomes. Adverse effects of hypertonic saline administration included hypokalemia. In addition hyponatremia needs to be excluded before administration of HS to reduce the risk for central pontine myelinolysis. The outcomes were not significantly different in final results (Infanti, 2008).

Hypertonic saline has not been shown to improve mortality benefits, yet another study with 65 subjects noted different results in patients with traumatic brain injury. HS was initiated pre-hospital and significant changes were documented in inflammatory and coagulation markers on every patient in the study. *Relative to control, NS patients showed up to a 2-fold higher surface expression of CD62L, CD11b and CD66b on polymorphonuclear neutrophils (PMNs) and monocytes that persisted for 48-h. HSD blunted the expression of these cell-surface activation/adhesion molecules at all time-points to levels approaching control values. Admission*

concentrations of endothelial-derived sVCAM-1 and sE-selectin were generally reduced in HSD patients. Circulating sL-selectin levels were significantly elevated at 12 and 48, but not 24 h post-resuscitation with HSD. TNF- α and IL-10 levels were elevated above control throughout the study period in all patients, but were reduced in HSD patients. Plasma sTF and D-D levels were also significantly lower in HSD patients, whereas sTM levels remained at control levels (Rhind & Crnko, 2010). The results support an important role utilizing HS for resuscitation in easing upregulation of leukocyte and endothelial cell inflammatory mediators, which may help alleviate secondary brain injury.

Hypertonic saline compounds may be more effective than mannitol because the hypertonicity expands intravascular volume and cardiac performance. Based on an older study from Qureshi and Suarez (2000) hypertonic saline was first documented in medical literature around 1919 by Weed and McKibben after injecting 30% saline solution in cats. Shrinkage was noted in the parenchyma in 15-30 minutes after administration. Further studies were completed in the 1950's most frequently on animal models; however HS was not widely accepted or used for the purpose of reducing cerebral edema. Even though this study is old, it was included because it covered 34 years of research and the lack of response from the medical community over this time span in utilizing HS as a valid treatment option. Hypertonic saline was shown in the older study to have positive outcomes in animal models to prevent or reduce ICP when used in the initial resuscitation phase of treatment instead of standard fluid resuscitation such as normal saline as well. HS was proven to have a favorable effect on systemic and intercranial pressures. The caveat in this study was mannitol was shown to have longer duration of benefit than HS. Even though HS has been utilized in the treatment of cerebral edema for almost 100 years, the outcome was more research is still needed to be done to establish HS as a superior

treatment to mannitol in human subjects with specific dosing guidelines including bolus versus continuous infusion.

Hypertonic saline (HS) dosing ranges from 3-23.4% in studies reviewed. As with mannitol, no definitive dosing has been established to prove greater efficacy over the other. However studies suggest even the lowest concentration of 3% HS was shown to be sufficient to reduce water in the brain, elevate mean arterial pressure, reduce ICP and improve cerebral perfusion by reducing edema (Liu, 2011).

Solution	Sodium mmol/l	Osmolality
0.9 NS	154	308
Mannitol	—	1373
3% Saline	513	1026
7.5%	1283	2565
23.4%	4004	8008

Twenty six articles were reviewed with the objective to evaluate HS efficacy versus mannitol and other medications for the treatment of increased ICP. One article initially described a valuable study. Research literature was obtained on HS, mannitol and nine other treatment options for ICP over a 28 year period; however the design was not well documented and results were vague. The study was therefore not included in the review of literature. Studies include animal and human trials. Interestingly several of the HS studies did not list number of patients in the trial. The most significant study was a multicenter, randomized clinical trial with 5848 patients over a three year period. A large pre-hospital intervention was initiated in the treatment of hypovolemic shock and traumatic brain injury. Resuscitation efforts began in the field with 7.5% HS treatment. The results displayed a favorable outcome with pre-hospital treatment as well set a standard of care for the community.

Due to the lack of standardization with most appropriate treatment for ICP one study addressed the issue by asking neurointensivists choice of agent and dosing protocols. Interestingly 295 practitioners responded with an almost even split. HS was preferred by 54% & the remaining preferred mannitol. Some respondents did say they reserved HS for patients with refractory intracranial HTN. Results were not surprising; variations in opinions will make standardization difficult at best (Hays, 2011). Many articles found no significant difference between mannitol and HS, but one that stood out with significant results was HS in reversal of transtentorial herniation. Sixty eight patients were included in the study and the results were quite significant. Seventy-six TTH events occurred in 68 patients admitted with intracerebral hemorrhage (n = 29), subarachnoid hemorrhage (n = 16), stroke (n = 8), brain tumor (n = 8), subdural hematoma (n = 5), epidural hematoma (n = 1), and meningitis (n = 1). In addition to 23.4% saline, TTH management included hyperventilation (70% of events), mannitol (57%), propofol (62%), pentobarbital (15%), ventriculostomy drainage (27%), and decompressive hemicraniectomy (18%). Reversal of TTH occurred in 57/76 events (75%). Intracranial pressure decreased from 23 ± 16 mm Hg at the time of TTH to 14 ± 10 mm Hg at 1 hour ($p = 0.002$), and 11 ± 12 mm Hg at 24 hours ($p = 0.001$) among 22 patients with intracranial pressure monitors. Reversal of TTH was predicted by a ≥ 5 mmol/L rise in serum sodium concentration ($p = 0.001$) or an absolute serum sodium of ≥ 145 mmol/L ($p = 0.007$) 1 hour after 23.4% saline. Adverse effects included transient hypotension in 13 events (17%); no evidence of central pontine myelinolysis was detected on post-herniation MRI (n = 18). Twenty-two patients (32%) survived to discharge, with severe disability in 17 and mild to moderate disability in 5. Treatment with 23.4% saline was associated with rapid reversal of transtentorial herniation (TTH) and reduced intracranial pressure, and had few adverse effects. Outcomes of TTH were poor, but medical

reversal may extend the window for adjunctive treatments. Herniation has a significant mortality rate and the results show promise for the use of HS in this subgroup of patients (Neurology, 2008). Mannitol and HS were evaluated along with hypothermia and hyperventilation in the treatment of traumatic brain injury. Mannitol was deemed satisfactory except for patients with compromised intravascular volume. The treatment of choice was the administration of hypertonic saline. Recent data suggest that an intravenous bolus of 23.4% saline, 30 mL, given over 10 to 15 minutes, may effectively reverse herniation and decrease ICP, with only transient hemodynamic repercussions (Neurologic Clinics, 2008).

Another comparison between the two diuretics documented better outcomes with HS alone. Four randomized clinical trials have evaluated efficacy and safety of mannitol and side effects of same. It was shown that HS did not create life threatening side effects or rebound cerebral hypertension. It was proven to be a safer alternative to mannitol; however the number of patients in the study were not included (Infanti, 2008). Hypertonic saline was deemed to be a safe alternative in all but one study. No scientific documentation was offered to prove theory in this study that mannitol was a safer alternative to HS.

Results of this study suggest there was no significance in onset of action between mannitol and HS. Mannitol while effective showed rebound increases in ICP and saturation. Meaning effectiveness stopped after a certain level of infusion. There were no statistically significant mortality differences between the two medications despite decreasing ICP. Hypertonic saline was shown to be superior in reducing short term morbidity especially in patients with herniation. HS actually reversed herniation in this study allowing the physician more time to intervene and potentially reduce mortality risk in this subgroup of patients. Hypertonic saline demonstrated specific physiological responses: *HSD blunted the expression of these cell-surface*

activation/adhesion molecules at all time-points to levels approaching control values. Admission concentrations of endothelial-derived sVCAM-1 and sE-selectin were generally reduced in HSD patients. Circulating sL-selectin levels were significantly elevated at 12 and 48, but not 24 h post-resuscitation with HSD. TNF- α and IL-10 levels were elevated above control throughout the study period in all patients, but were reduced in HSD patients. Plasma sTF and D-D levels were also significantly lower in HSD patients, whereas sTM levels remained at control levels. No adverse effects noted with HS with exception to one study; however the study did not offer adequate documentation to back up the generalized statement. Mannitol however was associated with sometimes severe electrolyte disturbances, and rebound intracranial hypertension. Articles specific to electrolyte disturbances saw these changes within 96 hours of initiation of treatment.

Mannitol has long been the standard of care in the treatment of cerebral edema and ICP despite nearly one hundred years of documentation that hypertonic saline is a safe alternative treatment option. Each article reviewed made very pertinent arguments, but HS was proven to be equally effective as mannitol without the life threatening side effects. Hypertonic saline is contraindicated in heart failure; however this subset of patients would still have the benefit of mannitol. Hypertonic saline was documented to reverse herniation, which has significant morbidity and mortality. By reversing herniation, it will afford the patient more time for potential recovery that would not otherwise be an option.

In summary, a large multi-center study would be recommended to support HS superiority to mannitol in these very complex patients. Guidelines should be established in regards to standardizing treatment protocols for both medications; specifically dosage, continuous infusion versus bolus and length of time medications will be administered for preeminent outcomes. Finally, continue research at a cellular level to promote evidence based research outcomes.

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