Hypertonic Saline in the Treatment of Intracranial Hypertension

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Abstract

Background:

Intracranial hypertension is a life threatening complication affecting the neurological patient. Limited options for treatment can be challenging for healthcare providers. Current research seems to support the effectiveness of hypertonic saline in reducing intracranial pressure.
Objectives:

This article will review the literature to ascertain the safety and efficacy of hypertonic saline in the treatment of intracranial hypertension.
Method:
In order to assess the effect of hypertonic saline administered for the treatment of intracranial hypertension on intracranial pressure, a search of PubMed, Ebsco, Scopus, and the Cochrane Library was performed. Search criteria used for this review included adult human studies using brain edema, neurological injury, intracranial hypertension, brain injury, stroke, subarachnoid hemorrhage, and hypertonic saline as search terms yielded 29 studies which were reviewed. Case reports, letters to the editor, languages other than English, and those which included pediatric participants were excluded. Also excluded were studies that involved use of hypertonic saline intraoperatively, studies that focused on the initial resuscitation of traumatic brain injury, those used for purely elective neurosurgical resuscitation of traumatic brain injury, and those used for purely elective neurosurgical patients. Elective neurosurgical patients were excluded since intracranial hypertension is frequently reversed with surgical evacuation of space occupying lesion and not medical therapy. Of the 29 studies that were obtained, 5 were excluded. Two were case studies. One dealt with the intra-operative use of hypertonic saline, and two other studies has foci related to variables other than effect on intracranial hypertension.
Results:
Whether used as an initial treatment for elevated intracranial pressure or as a rescue therapy for refractory intracranial hypertension, hypertonic saline appears to offer an additional means for lowering intracranial pressure and may provide a bridge to emergent surgical decompression.

BACKGROUND

Intracranial hypertension (IH) resulting from increased intracranial pressure is a common complication of neurological injuries. Research has shown that IH is associated with poor patient outcomes.[1] In an effort to improve morbidity and mortality in these patients, neurologically based research has focused on strategies to reduce IH. Osmotic therapy has long been recognized as a safe and effective treatment for IH.[2] The most researched and commonly used osmotic agent, mannitol, has been associated with untoward side effects. In an effort to find an effective osmotic agent with a safe side effect profile, other osmotic agents have gained some popularity. This article will review studies performed using HS as an osmotic agent for the reduction of intracranial pressure in patients with neurological injury.

INTRACRANIAL HYPERTENSION

The cranial vault, or skull, of an average adult has an approximate volume of 1700 milliliters. Eighty-percent of this volume is comprised of brain tissue and the other twenty

percent is comprised of blood and cerebral spinal fluid.[3] In a healthy individual, compensatory mechanisms keep these contents at a constant volume. When a person suffers from a neurological insult, normal compensatory mechanisms may fail and the delicate balance is disrupted. The Monro-Kellie doctrine states that the total contents of the cranial vault must remain at a constant volume in order to maintain equilibrium. If any one of the contents increases in volume without a corresponding compensatory decrease in another, the pressure in the cranial vault will increase resulting in intracranial hypertension. A normal intracranial pressure (ICP) is considered to be 5-10mmHg.[1] Intracranial hypertension is defined as an intracranial pressure above normal limits. Research has shown that values above 20 mmHg are associated with increased morbidity and mortality.[2] Therefore, most institutions including the Brain Trauma Foundation suggest initiating osmotic treatment for values above 20 mmHg lasting for more than five minutes.[2] The most common cause of IH in patients with neurological insults is related to increased brain volume either from a space occupying lesion or cerebral edema. Space occupying lesions, such as tumors, can be treated with surgical evacuation. In contrast, medical management in the form of osmotic therapy is the cornerstone of treatment for cerebral edema.

HYPERSOMOLAR THERAPY PRINCIPLES

A traditionally held belief is that hyperosmolar therapy effectiveness is a result of brain shrinkage caused from the shifting of water out of the brain. Mannitol has been accepted as treatment for IH, and is considered a safe and effective osmotic diuretic. Considered the drug of choice for IH in Guidelines for the Management of Severe Brain Injury, mannitol is not without its drawbacks.[2] Mannitol, an osmotic diuretic, has been associated with volume depletion and hypotension leading to secondary injury to the brain. Injury to the blood brain barrier (BBB), often found in neurological injuries, can be a confounding factor in the management of IH. One concern is that solutes may escape from the vascular system to the brain tissue. In the presence of an injured BBB, mannitol may escape the intravascular space and accumulate in already edematous tissue, which may lead to an increase in cerebral edema and intracranial hypertension often referred to as rebound phenomenon.

In an attempt to find the “optimal” hyperosmolar agent, the use of other solutions has been explored. An optimal agent should be nontoxic, simple to administer with minimal side effects, have a strong osmotic gradient, and would remain in the intravascular space (reflection coefficient). Reflection coefficient is the measurement of how well a solute crosses a membrane. In regards to treatment of IH, a reflection coefficient of 1 is given to a solute that stays in the intravascular space and is impermeable to an intact BBB (See Table 1).

Figure 1

Table 1. Reflection Coefficients

Agent	Reflection Coefficient
Glycerol	0.56
Mannitol	0.95
Hypertonic Saline	1.00
Urea	0.46

Research has found other agents such as glycerol and urea, with their low reflection coefficients, to be fairly ineffective osmotic agents in the treatment of IH.[4] Hypertonic saline with its low cost, ease of administration, and titratable osmotic gradient (by adjusting its concentration), and its reflection coefficient of 1 has been recognized as an effective osmotic agent.

HYPERTONIC SALINE

The use of hypertonic saline in the treatment of cerebral edema was first proposed in 1919 by Weed and McKibben.[5] Nearly forgotten, more than sixty years later HS reemerged as resuscitation agent for patients in shock. Incidentally found through the resuscitations of patients with multi-organ trauma, use of HS in patients with neurotrauma alone became a focus of research.[6,7] Finding from this early research, in multi-organ trauma, including brain injury, promoted its use in the treatment of intracranial hypertension and herniation syndromes as well.

The proposed mechanism of action of HS is similar to that of mannitol. Through osmosis HS draws water out of the intracellular space, the edematous brain, and back into the intravascular space. In addition, HS has been shown to be effective in resuscitation of patients in shock by the same mechanism. Unlike mannitol which promotes diuresis, HS increases blood volume, decreases viscosity, and increases preload. All of these characteristics lead to an increase in blood pressure, cardiac output, and cerebral perfusion pressure (CPP), thereby improving perfusion to the brain and decreasing secondary injury. Used as a resuscitation agent, HS also has potential to be used as a component of “triple H” therapy (hypervolemia, hemodilution, and hypertension) in the treatment of patients with subarachnoid hemorrhage

(SAH) who are at high risk of severe vasospasm.

FINDINGS

TRAUMATIC BRAIN INJURY

According the Centers for Disease Control, 1.4 million Americans suffer from traumatic brain injury (TBI) annually. Of those, more than 200,000 are hospitalized and 50,000 die. Costs related to TBI, direct and indirect, are figured to be approximately $60 billion.[8] In an effort to improve morbidity and mortality rates in patients with TBI, research to combat and treat IH has been on the forefront of neurological research. Most studies involving TBI, share similar findings that indicate that HS is consistent with a decrease in ICP and an increase in CPP (See Table 2). Maintaining a physiologic normal CPP is as important as decreasing elevated ICP in preventing secondary injury. By increasing blood volume and preload, HS helps to ensure adequate perfusion and oxygenation to at-risk brain tissue.

Several studies compared mannitol boluses versus HS boluses.[9,10] In one study, Vialet et al. compared 20% mannitol with 7.5% sodium chloride (NaCl) bolus for the treatment of ICP above 25mmHg. This study demonstrated that patients given mannitol have two times more events of elevated ICP compared with HS. In addition, treatment failures were 7 out of 10 for the mannitol group versus those treated with HS. Shackford et al. took a unique approach and compared the use of slightly hypertonic solution of 1.6% NaCl with a slightly hypotonic solution of Lactated Ringers in the TBI population.[11] Intracerebral pressures decreased in the HS group while the patients receiving Lactated Ringers showed an upward trend in ICP. While most of the studies used bolus dosing, a retrospective chart review by Quareshi et al. reviewed the use of HS as a continuous drip with varying infusion rates with the goal of achieving a serum sodium value between 145-155 meq/dl. The investigators found that patients receiving continuous HS had poor long-term outcomes as identified by the Glasgow Outcome Scale (GOS).[12] The GOS ranks patients on five levels based on functional recovery with 1 corresponding with death and 5 corresponding with good recovery. Another unique study design examined the effects of a bolus of 20% NaCl on not only the ICP but the measurable effect on brain tissue using computed tomography.[13] The results of this study revealed that HS may lower ICP by decreasing the overall volume of the healthy brain tissue.

Figure 2

Table 2. Summary of Study Findings for Traumatic Brain Injury

Principle Author	Design	Sample	Osmotic Agent	Amount Administered	Frequency/ Triggers	SOC	Results
Hartl 1997	Prospective	n=6 e=32	7.5%HS	250cc @ 20ml/min	↑ICP		↓ICP by 44% ↑CPP by 38%
Huang 2006	Prospective observational	n=18 e=35	3% HS	300 ml over 20 min	1 daily dose/ ICP>20	x	↓ICP ↑CPP
Ichai 2009	Prospective Randomized	n=34	Hypertonic solution of sodium lactate 20% Mannitol	Equiosmolar~ 1100 mosmo 1.5m/kg over 15 min	ICP>25	x	HS ↓ICP with less treatment failures
Kerwin 2009	Pilot study Prospective	n=22 e=210	23.4% HS 20% mannitol	Varying doses	ICP>20	x	HS ↓ICP by 50% more than mannitol
Lescot 2006	Prospective Observational	n=14	20% HS	40ml over 20 minutes	1 time bolus		↓ volume health brain tissue, ↑ contused tissue
Munar 2000	Prospective	n=14	7.2%HS	1.5ml/kg over 15 minutes	1 time dose/ ICP>15		↓ICP by 30% ↑CPP
Oddo 2009	Retrospective	n=12 e=42	25% mannitol 7.5% HS	0.75g/kg 250ml	ICP>20 ICP>20 if mannitol failed		HS: ↑PbtO2 Effect on ICP not statistically significant
Pasqual 2008	Prospective Observational	n=12	7.5% HS	250ml	Hypotensive and ICP>20		HS: ↓ICP by 40% ↑CPP by 20%
Quareshi 1999	Retrospective	n=82	2 or 3% HS infusion vs. 0.9% saline	Continuous infusion	With or without IH		HS: ↑ in hospital mortality, ↓GOS
Rockswold 2009		n=25	23.4% HS	30ml over 15 min	ICP>20	x	↓ICP↑PbtO2
Schatzmann 1998	Prospective Observational	n=42	10% HS	100ml	↑ICP if mannitol had failed		↓ICP 43%
Shackford 1998	Prospective	n=34	1.6% HS bolus NS maintenance LR bolus ½ NS maintenance	Enough to reverse hypotension and low urine output	Hypotension and low urine output	x	No statistical significant findings
Vialet 2003	Prospective	n=20	20% mannitol 7.5% HS	2ml/kg bolus 2ml/kg bolus	Repeated x1/ ICP>25	x	Mannitol: higher treatment failure Both ↓ICP equally
Ware 2005	Retrospective	n=13 e=22	23.4% HS	30ml bolus	One time		HS: longer duration of effect than mannitol

n=number of participants e=number of IH events NS=normal saline LR= lactated ringers PbtO2=brain tissue oxygenation SOC=standard of care including mechanical ventilation for GCS<8, vasopressors to maintain cerebral perfusion, elevated head of bed, and sedation and analgesia.

MIXED NEUROLOGICAL INSULTS

Samples with mixed neurological injuries were examined in six studies (See Table 3). Battison et al. examined the effect of equiosmolar does of mannitol versus HS. Findings supported that both agents decreased ICP. Mannitol decreased ICP on average by 7.5 mmHg, whereas, HS decreased by 13.5 mmHg. The investigators also suggested that patients who received HS appeared to have a longer duration of effect than those who received mannitol.[14] Francony et al. also compared equiosmolar doses of mannitol with HS.[15] Findings contrasted the research by Battison et al. showing that mannitol decreased ICP better than HS, though none of the findings were statistically significant. Becoming more popular as a rescue therapy for malignant IH (i.e., ICPs refractory to traditional treatments), Koenig et al. reviewed the effect of 23.4 % bolus in patients with signs of impending herniation syndromes. Concentrated HS was successful at reversing herniation syndromes in 57 of the 76 events.[16]

Figure 3

Table 3. Summary of Study Findings for Mixed Neurological Injuries

Principle Author	Design	Sample	Osmotic Agent	Amount Administered	Frequency/ Triggers	SOC	Results
Battison 2005	Prospective Randomized	n=9	7.5% HS 20% mannitol	100ml over 5 minutes 200 ml	2 treatments alternating between HS and mannitol	x	HS: > ↓ICP >↑CPP HS had longer durations
Francony 2008	Randomized Control	n=20	231 ml 20% mannitol over 20 min 7.45% HS	231ml over 20 min 100ml	ICP>20 Ix dose only	x	Results not statistically significant
Hartunyan 2005	Prospective randomized	n=32	7.2% HS 15% mannitol	Varying amounts. Stopped once ICP <15	ICP>15	x	HS>↓ICP
Horn 1999	Prospective	n=10 e=48	7.2% HS	2ml/kg at 20ml/min	ICP>25		HS>↓ICP >↓CPP
Koenig 2008	Retrospective	n=68 e=76	23.4% HS	30ml or 60ml	Clinical herniation syndrome	x	Herniation reversal occurred 57/76
Quareshi 1998	Retrospective	n=27 e=30	3% HS	Continuous	To achieve serum sodium goal of 145-155		↓ICP
Suarez 1998	Retrospective	n=8 e=20	23.4% HS	30cc over 15-20min	One time		↓ICP by 50% ↑CPP

n=number of participants e=number of IH events SOC=standard of care including mechanical ventilation for GCS<8, vasopressors to maintain cerebral perfusion, elevated head of bed, and sedation and analgesia.

SUBARACHNOID HEMORRHAGE

Only four studies were found that evaluated the use of HS in the SAH population (See Table 4). Bentsen et al. evaluated the use of 7.5% HS combined with 6% hydroxyethyl starch 2ml/kg bolus dose in two different studies.[17] One study was performed in patients with elevated ICP. [17] In the other study the same concentration and dose was given to patients with stable ICP between 10-20mmHg.[18] Both studies had similar findings of decreased ICP and increasing CPP. Tseng et al. also studies patients with SAH patients in two separate studies.[19, 20] In contrast, these studies used 23.5% NaCl boluses. The goal of both studies by Tseng et al. was not focused on ICP reduction but on increased cerebral blood flow. By increasing cerebral blood flow, arteries may be "splinted" open during periods of vasospam thereby preventing ischemic events. In both studies, cerebral blood flow increased, with reduction in intracranial pressure, and increase in CPP after administration of HS.[19,20]

STROKE

Only two published studies involving the use of HS for the treatment of IH in stroke patients were found. Two different concentrations of HS were used for these two studies with similar findings. Both studies revealed a decrease in ICP and an increase in CPP.[21,22]

PATIENT OUTCOMES

While the majority of the studies showed decreases in ICP values and an improvement in CPP, a decrease in morbidity and mortality has yet to be proven. The studies that examined the Glasgow Outcome Scale (GOS) found that those patients treated with HS were more likely to survive but without significant improvement in quality of life. When assessed the majority of patients treated with HS had outcomes that correlates with severe disability or death.[12, 16, 23,24] One reason for this finding may be related to use of HS in higher acuity patients. As seen in the studies reviewed, HS is often used as a second line therapy or as a rescue therapy in the face of refractory IH.

Figure 4

Table 4. Summary of Study Findings for Non-Traumatic Injuries

Principle Author	Design	Sample	Osmotic Agent	Amount Administered	Frequency/ Triggers	SOC	Results
Bentsen 2004	Prospective Observational	SAH n=7	7.2% HS	2ml/kg over 20 min	ICP >20	x	↓ICP ↑CPP
Bentsen 2006	Prospective Randomized	SAH n=22	7.2% HS 0.9% NS	2ml/kg over 30 minutes	Stable ICP10-20		HS >↓ICP >↓CPP
Tseng 2007	Prospective	SAH n=10 e=17	23.5% HS	2ml/kg	↓CBF by TCD or Xenon CT		↑CPP ↑MCA velocity
Tseng 2007	Prospective	SAH n=35 e=50	23.5% HS	2ml/kg	↑ICP		↓ICP by 93% ↑CPP by 21%
Schwarz 1998	Prospective Observational	Stroke n=9 e=30	7.5% HS 20% mannitol	100ml over 15 min 40grams over 15 min	ICP> 25 1st time randomized 2nd occurrence alternate		HS>↓ICP
Schwarz 2002	Prospective Observational	Stroke n=8 e=22	10% HS	75ml over 15 min	Given after mannitol failed		↓ICP ↑CPP

n=number of participants, e=number of IH events, NS=normal saline, CBF=cerebral blood flow, TCD=transcranial Doppler, MCA= middle cerebral artery SOC=standard of care including mechanical ventilation for GCS<8, vasopressors to maintain cerebral perfusion, elevated head of bed, and sedation and analgesia.

LIMITATIONS

All studies reviewed included small sample sizes and a few studies revealed some selection bias. Often the use of HS was used as a rescue therapy or after the standard of care had already failed to control intracranial pressure in the most critically ill patients. Using HS earlier in the course of the patients' treatment, instead of as a last resort may provide better success. Another potential limitation to the studies as a group was that saline concentrations varied greatly among investigators. Concentrations ranged from 2-20% sodium chloride. Not all studies that compared mannitol with HS used equiosmolar dosing (See Table 5).

Figure 5

Table 5. Comparing Osmolarity of IV Agents

Agent	Osmolarity (mOsm/L)	Sodium Concentration (mEq/L)
Lactated Ringers	275	130
0.9& NaCl	308	154
1.7% NaCl	582	291
3.0% NaCl	1026	513
7.5% NaCl	2566	1283
10.0% NaCl	3424	1713
20% NaCl	6848	3426
23.4% NaCl	8008	4004
Mannitol 20%	1098	n/a

Agents with a stronger osmotic action may affect the ICP values. Therefore, comparing two agents of unequal osmolar activity may be considered unjust. Varying doses among the study groups as a whole, as well as in individual studies, occurred throughout many of the studies. This lack of consistency make findings difficult to generalized the entire neurological population.

POTENTIAL ADVERSE EFFECTS

Like other osmotic agents, side effects from the administration of HS are potential risks that must be balanced with the potential benefits of its use. In the studies reviewed, no significant complications were mentioned. Most studies listed exclusion criteria, to minimize harm to patients who may be a highest risk for untoward effects. Patients commonly excluded were those with heart failure, pulmonary edema, and kidney failure who may be harmed from an increase in intravascular volume. In one study, lung water was evaluated and unchanged over three hours post HS administration.[17] In a retrospective chart review, three patients that received HS developed pulmonary edema. Of the three patients, one of them had underlying cardiomyopathy.[12] In a study, that specifically looked at complication in patients with neurological injury receiving continuous infusion of HS, the incidence of renal failure was not found to correlate with HS use.[12] Hypernatremia, serum sodium levels greater than 155, did correlate with a small yet statistically significant increase in BUN and creatinine levels.[25]

Central pontine myelinolysis (CPM), a demyelination of the pons is a concern during administration of any concentrated sodium solution. First described in 1958, CPM is associated with chronically hyponatremic patients who undergo rapid correction hyponatremia with a concentrated saline solution. No evidence exists to support the fear of CPM in patients with acute cerebral salt wasting, excessive renal secretion of sodium in the face of neurological injury, or traumatic brain injury. Since CPM is an irreversible and devastating condition, practitioners should continue to be cautious when administrating HS until significant research proves whether or not this population is at risk.

Electrolyte and acid base imbalances are frequent occurrence in the critical care patient population. Several studies included potassium levels as dependent variables.[23, 26] These studies collectively revealed a mild decrease in potassium immediately following administration with a rebound in potassium near baseline levels after a few hours. While these studies suggest that hypokalemia may not be a concern for patients receiving HS therapy, it may be wise to monitor potassium levels in patients who are receiving frequent boluses of HS especially patients who are at risk of arrhythmias. Hyperchloremic metabolic acidosis may result from continuous or frequent bolus doses of HS. In the above studies, some institutions alternated sodium chloride concentrations with sodium acetate concentrations to decrease its incidence.

In hemorrhagic neurological insults, an injured BBB may result in the translocation of hyperosmolar solutions which have the potential to cause rebound IH. Animal studies have found mannitol and HS to cross an injured BBB, but no studies have been done in humans to evaluate post mortem effects of HS in the brain. Impaired platelet aggregation and coagulopathy is a concern in hemorrhagic neurologic injuries. Animal studies have suggested that hypertonic saline may be responsible for increased bleeding. In one human study, clotting factors diminished when 10% of plasma was replaced with HS versus normal saline.[27] In another study, HS/dextran was similarly mixed with human plasma at 1:5 and 1:10 concentrations, with only minimal increase in PT.[28] While none of the above studies mentioned bleeding complications, no study has specifically looked at bleeding complications in neurological patients receiving HS. Therefore, the clinician should consider this possible complication in any patient receiving HS until research in this area is completed.

RESEARCH IMPLICATIONS

The above studies provide a foundation for future research.

In order to strengthen the current foundation, future studies should strive for larger sample size. Noted in the above studies were the varying concentrations and doses of HS. These variations make assessment of the overall effectiveness of this solution difficult. Further research is needed to strengthen the evidence for a standard therapy or to assess the effectiveness of one concentration compared with another. Research is also needed in the SAH with vasospasm population, who may benefit from the intravascular volume expansion that HS offers. At this time, HS has not been shown to improve long-term outcomes, which may be due to its use in refractory IH. Studies are needed in which HS is used as a treatment of cerebral edema prior to other treatments. Finally, studies that focus on HS use in other than severe traumatic brain injury should be considered for future research.

CONCLUSIONS

Hypertonic saline offers promise as a treatment for IH. Current research seems to support its effectiveness in reducing intracranial pressures. Each patient's co-morbidities and expected results before choosing an osmotic therapy is an important consideration. Whether used as an initial treatment for elevated intracranial pressure or as a rescue therapy for refractory IH, HS appears to offer an additional means for lowering ICP and may provide a bridge to surgical decompression.

References

1. Frank J, Rosengart A: Intracranial pressure: monitoring and management. In Principles of critical care. NewYork: McGraw Hill; 2005 Retrieved on March 20, 2010 from http://online.statref.com/document.aspx?fxid=70&docid=606
2. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons: Guidelines for the management of severe traumatic brain injury. J Neurotrauma; 2007; 24(S): S14-S20.
3. Hickey JV: The clinical practice of neurological and neurosurgical nursing (6th ed.). Philadelphia: Lippincott Williams & Wilkins; 2009.
4. Qureshi AI, Suarez JI: Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. Crit Care Med; 2000; 28(9): 3301-3313.
5. Weed L, McKibben P: Experimental alteration of brain bulk. Am J Physiol; 1919; 48: 531-555.
6. Vassar MJ, Perry CA, Gannaway WL, Holcroft JW: 7.5% sodium chloride/dextran for resuscitation of trauma patients undergoing helicopter transport. Arch Surg; 1991; 126(9): 1065-1072.
7. Vassar MJ, Fischer RP, O'Brien PE, Bachulis BL, Chambers JA, Hoyt DB, Holcroft, J: A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride. The effect of added dextran 70. The multicenter group for the study of hypertonic saline in trauma patients. Arch Surg; 1993; 128(9): 1003-1011.
8. Centers for Disease Control. What is traumatic brain injury? Retrieved April 10, 2009 from http://www.cdc.gov/ncipc/tbi/TBI.htm.
9. Oddo M, Levine JM, Frangos S, Carrera E, Maloney-Wilensky E, Pascual JL, Kofke WA, Mayer SA, LeRoux, P: Effect of mannitol and hypertonic saline on cerebral oxygenation in patients with severe traumatic brain injury and refractory intracranial hypertension. J Neurol Neurosurg Psychiatry; 2009; 80 (8): 916-920.
10. Vialet R, Albanese J, Thomachot L, Antonini F, Bourgouin A, Alliez B, Martin, C: Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. Crit Care Med; 2003; 31(6): 1683-1687.
11. Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM, Clark DE: Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. J Trauma; 1998; 44(1): 50-58.
12. Qureshi AI, Suarez JI, Castro A, Bhardwaj A: Use of hypertonic saline/acetate infusion in treatment of cerebral edema in patients with head trauma: experience at a single center. J Trauma; 1999; 47(4): 659-665.
13. Lescot T, Degos V, Zouaoui A, Preteux F, Coriat P, Puybasset L: Opposed effects of hypertonic saline on contusions and noncontused brain tissue in patients with severe traumatic brain injury. Crit Care Med; 2006; 34(12): 3029-3033.
14. Battison C, Andrews PJ, Graham C, Petty T: Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. Critical Care Medicine; 2005; 33(1): 196-202.
15. Francony G, Fauvage B, Falcon D, Canet C, Dilou H, Lavagne P, Jacquot C, Payen J: Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. Crit Care Med; 2008;36(3): 795-800.
16. Koenig MA, Bryan M, Lewin JL, Mirski MA, Geocadin RG, Stevens RD: Reversal of transtentorial herniation with hypertonic saline. Neurology; 2008; 70(13): 1023-1029.
17. Bentsen G, Breivik H, Lundar T, Stubhaug A: Predictable reduction of intracranial hypertension with hypertonic saline hydroxyethyl starch: a prospective clinical trial in critically ill patients with subarachnoid haemorrhage. Acta Anaesthesiol Scand; 2004; 48(9): 1089-1095.
18. Bentsen G, Breivik H, Lundar T, Stubhaug A: Hypertonic saline (7.2%) in 6% hydroxyethyl starch reduces intracranial pressure and improves hemodynamics in a placebo-controlled study involving stable patients with subarachnoid hemorrhage. Crit Care Med: 2006; 34(12): 2912-2917.
19. Tseng MY, Al-Rawi PG, Czosnyka M, Hutchinson PJ, Richards H, Pickard JD. Kirkpatrick PJ: Enhancement of cerebral blood flow using systemic hypertonic saline therapy improves outcome in patients with poor-grade spontaneous subarachnoid hemorrhage. J Neurosurg; 2007; 107(2): 274-282.
20. Tseng MY, Al-Rawi PG, Pickard JD, Rasulo FA, Kirkpatrick PJ: Effect of hypertonic saline on cerebral blood flow in poor-grade patients with subarachnoid hemorrhage. Stroke; 2003; 34(6): 1389-1396.
21. Schwarz S, Schwab S, Bertram M, Aschoff A, Hacke W: Effects of hypertonic saline hydroxyethyl starch solution and mannitol in patients with increased intracranial pressure after stroke. Stroke; 1998; 29(8): 1550-1555.
22. Schwarz S, Georgiadis D, Aschoff A, Schwab S: Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. Stroke; 2002; 33(1): 136-140.

23. Munar F, Ferrer AM, de Nadal M, Poca MA, Pedraza S, Sahuquillo J, Garnacho A: Cerebral hemodynamic effects of 7.2% hypertonic saline in patients with head injury and raised intracranial pressure. J Neurotrauma; 2000; 17(1): 41-51.
24. Suarez JI, Qureshi AI, Bhardwaj A, Williams MA, Schnitzer MS, Mirski M, Hanely DF, Ulatowski, J: Treatment of refractory intracranial hypertension with 23.4% saline. Crit Care Med: 1998; 26(6): 1118-1122.
25. Froelich M, Ni Q, Wess C, Ougorets I, Hartl R: Continuous hypertonic saline therapy and the occurrence of complications in neurocritically ill patients. Crit Care Med: 2009; 37(4): 1433-1441.
26. Huang SJ, Chang L, Han YY, Lee YC, Tu YK: Efficacy and safety of hypertonic saline solutions in the treatment of severe head injury. Surg Neurol; 2006; 65(6): 539-546.
27. Reed RL, Johnston TD, Chen Y, Fischer RP: Hypertonic saline alters plasma clotting times and platelet aggregation. J Trauma; 1991; 31(1): 8-14.
28. Hess JR, Dubick MA, Summary JJ, Bangal NR, Wade CE: The effects of 7.5% NaCl/6% dextran 70 on coagulation and platelet aggregation in humans. J Trauma; 1992; 32(1): 40-44.
29. Horn P, Munch E, Vajkoczy P, Herrmann P, Quintel M, Schilling L, Schmledek P, Shurer L: Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. Neurol Res; 1999; 21(8): 758-764.
30. Ichai C, Armando G, Orban J, Berthier F, Rami L, Samat-Long C, Grimaud D, Leverve X: Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. Intensive Care Med: 2009; 35: 471-479.
31. Kerwin A, Schinco M, Tepas J, Renfro W, Vitarbo E, Muehlberger M: The use of 23.4% hypertonic slaine for the management of elevated intracranial pressure in patients with severe traumatic brain injury: a pilot study. J Trauma; 2009; 67: 277-282.
32. Pascual JL, Maloney-Wilensky E, Reilly PM, Sicoutris C, Keutmann MK, Stein SC, LeRoux PD, Gracias, VH: Resuscitation of hypotensive head-injured patients: is hypertonic saline the answer? Am Surg; 2008; 74(3): 253-259.
33. Hartl R, Ghajar J, Hochleuthner H, Mauritz W: Hypertonic/hyperoncotic saline reliably reduces ICP in severely head-injured patients with intracranial hypertension. Acta Neurochir Suppl; 1997; 70: 126-129.
34. Hartl R, Ghajar J, Hochleuthner H, Mauritz W: Treatment of refractory intracranial hypertension in severe traumatic brain injury with repetitive hypertonic/hyperoncotic infusions. Zentralbl Chir; 1997; 122(3): 181-185.
35. Harutjunyan L, Holz C, Rieger A, Menzel M, Grond S, Soukup J: Efficiency of 7.2% hypertonic saline hydroxyethyl starch 200/0.5 versus mannitol 15% in the treatment of increased intracranial pressure in neurosurgical patients - a randomized clinical trial. Crit Care; 2005; 9(5): R530-40.
36. Qureshi AI, Suarez JI, Bhardwaj A: Malignant cerebral edema in patients with hypertensive intracerebral hemorrhage associated with hypertonic saline infusion: A rebound phenomenon? Journal of Neurosurg Anesthesiol; 1998; 10(3): 188-192.
37. Qureshi AI, Suarez JI, Bhardwaj A, Mirski M, Schnitzer MS, Hanley DF, Ulatowski, J: Use of hypertonic (3%) saline/acetate infusion in the treatment of cerebral edema: Effect on intracranial pressure and lateral displacement of the brain. Crit Care Med; 1998; 26(3): 440-446.
38. Rockswold G, Solid C, Paredes-Andrade E, Rockswold S, Jancik J, Quickel R: Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure and brain tissue oxygenation. Neurosurgery; 2009; 65: 1035-1042.
39. Schatzmann C, Heissler HE, Konig K, Klinge-Xhemajli P, Rickels E, Muhling M, Borschel M, Samil, M: Treatment of elevated intracranial pressure by infusions of 10% saline in severely head injured patients. Acta Neurochir Suppl; 1998; 71: 31-33.
40. Ware ML, Nemani VM, Meeker M, Lee C, Morabito D J, Manley GT: Effects of 23.4% sodium chloride solution in reducing intracranial pressure in patients with traumatic brain injury: a preliminary study. Neurosurgery; 2005; 57(4): 727-736.
41. Worthley LI, Cooper DJ, Jones N: Treatment of resistant intracranial hypertension with hypertonic saline. J Neurosurg; 1988; 68(3): 478-481.

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