See the corresponding editorial in this issue, pp 208–209.

J Neurosurg 116:210–221, 2012

Hypertonic saline for treating raised intracranial pressure: literature review with meta-analysis

A review

Martin M. Mortazavi, M.D.,[1] Andrew K. Romeo, M.D.,[1] Aman Deep, M.D.,[2] Christoph J. Griessenauer, M.D.,[1] Mohammadali M. Shoja, M.D.,[2] R. Shane Tubbs, M.S., P.A.-C., Ph.D.,[2] and Winfield Fisher, M.D.[1]

[1]Division of Neurological Surgery, University of Alabama at Birmingham; and [2]Pediatric Neurosurgery, Children's Hospital, Birmingham, Alabama

Object. Currently, mannitol is the recommended first choice for a hyperosmolar agent for use in patients with elevated intracranial pressure (ICP). Some authors have argued that hypertonic saline (HTS) might be a more effective agent; however, there is no consensus as to appropriate indications for use, the best concentration, and the best method of delivery. To answer these questions better, the authors performed a review of the literature regarding the use of HTS for ICP reduction.

Methods. A PubMed search was performed to locate all papers pertaining to HTS use. This search was then narrowed to locate only those clinical studies relating to the use of HTS for ICP reduction.

Results. A total of 36 articles were selected for review. Ten were prospective randomized controlled trials (RCTs), 1 was prospective and nonrandomized, 15 were prospective observational trials, and 10 were retrospective trials. The authors did not distinguish between retrospective observational studies and retrospective comparison trials. Prospective studies were considered observational if the effects of a treatment were evaluated over time but not compared with another treatment.

Conclusions. The available data are limited by low patient numbers, limited RCTs, and inconsistent methods between studies. However, a greater part of the data suggest that HTS given as either a bolus or continuous infusion can be more effective than mannitol in reducing episodes of elevated ICP. A meta-analysis of 8 prospective RCTs showed a higher rate of treatment failure or insufficiency with mannitol or normal saline versus HTS.
(DOI: 10.3171/2011.7.JNS102142)

Key Words • **hypertonic saline** • **mannitol** • **hyperosmolar agent** • **intracranial pressure** • **trauma** • **treatment evaluation** • **traumatic brain injury**

Intracranial hypertension following neurological injury is often associated with poor outcomes.[13] Increased ICP reduces CBF and can lead to brain herniation and death. The Brain Trauma Foundation has recommended that therapy to reduce ICP should begin at pressures > 20 mm Hg. Hyperosmolar therapy is a commonly used treatment for intracranial hypertension. Currently, only 2 agents are used for this purpose: mannitol and HTS. The Brain Trauma Foundation currently recommends mannitol as the mainstay in the management of intracranial hypertension, but HTS represents a potential alternative that is gaining favor.[9] The reported concentrations of HTS for clinical use range from 2% to 23.5%.

Cerebral edema can be classified as either cytotoxic or vasogenic. Cytotoxic edema is the swelling of cells secondary to injury, typically ischemic or toxic. Vasogenic edema is extracellular edema secondary to capillary disruption, leading to breakdown of the BBB. Classically, vasogenic edema has been associated more with traumatic injury, tumors, and abscesses, although recent data suggest that cytotoxic edema predominates in traumatic injuries.[26] Both types of edema probably occur together in most pathological entities. Cytotoxic edema occurs over minutes to hours after injury, compared with vasogenic edema, which occurs over hours to days. The type of edema present is important when considering therapy, because cytotoxic edema is thought to be much more resistant to treatment.[13] The mechanism of action of HTS and other hyperosmolar agents has been classically attributed to the reduction of brain water content through its osmotic effects; however, multiple other mechanisms also

Abbreviations used in this paper: BBB = blood-brain barrier; CBF = cerebral blood flow; CPP = cerebral perfusion pressure; EGOS = Extended Glasgow Outcome Scale; GCS = Glasgow Coma Scale; HES = hydroxyethyl starch; HTS = hypertonic saline; ICP = intracranial pressure; LR = Lactated Ringer; mRS = modified Rankin Scale; NS = normal saline; RCT = randomized controlled trial; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury.

probably contribute. Sodium has a reflection coefficient of nearly 1, meaning that with an intact BBB, very little Na crosses the barrier, thus allowing Na to pull fluid out of the interstitial space.

Other mechanisms of action have also been suggested based on clinical data. For example, Lescot et al.[24] compared edema on CT scans obtained before and after HTS treatment and found an equal decrease in ICP in those with no decrease in brain volume and in those with decreased brain volume. Also, a sustained decrease in ICP has been noted in several studies, even after serum Na levels were such that the osmotic effect should not be active.[20,46] Several theories have been proposed. Early after administration, HTS reduces blood viscosity, increasing the rheological properties, which improves CBF and cerebral oxygenation, causing autoregulatory vasoconstriction, thereby reducing ICP. Hypertonic saline is also thought to induce endothelial cell shrinkage, which also improves circulation.[20,45] A variety of other beneficial effects have been attributed to HTS therapy, including an immunomodulatory role and reduction of CSF production.[13]

In 1988 Worthley et al.[47] first reported the use of HTS to reduce ICP in 2 patients who were unresponsive to mannitol. Since then, more recent studies have suggested that HTS is possibly more effective than mannitol for the reduction of ICP.[3,7,11,16,19,20,29,31,35,38,44,45,48] Also, the side effect profile of HTS appears to be more favorable than that of mannitol; the latter notoriously causes delayed hypovolemia secondary to its diuretic effect, which can be undesirable in trauma patients. Hypertonic saline improves mean arterial pressure and increases circulating blood volume without the delayed hypotensive effect observed with mannitol use. Unfortunately, appropriate guidelines for the use of HTS have not been developed; indications for use, dosing, and timing of use still vary widely among institutions. Clinical studies vary widely in design, making them difficult to compare, and most suffer from small numbers of patients. Therefore, the present review was undertaken for a better understanding of the efficacy of these 2 treatments of raised ICP.

Methods

Literature Search

A PubMed literature search was performed to identify all clinical studies in which HTS has been used for the treatment of intracranial hypertension. The following search terms were used: "hypertonic saline and intracranial pressure," "hypertonic saline and intracranial hypertension," "hypertonic saline and traumatic brain injury," "hypertonic saline and subarachnoid hemorrhage," and "hypertonic saline and neurosurgery." Table 1 summarizes these results. Studies that were either not related to neurosurgical problems or that did not directly involve either HTS's effects on cerebral hemodynamics or the treatment with HTS of patients with clinical or radiographic evidence of cerebral swelling were eliminated. Seven studies were excluded that used HTS for resuscitation in hypotensive or hemodynamically unstable patients. Four studies were excluded because there was no ICP monitoring. One retrospective study also had no ICP monitoring, but it was not excluded because it reported relevant secondary outcomes.[48] All animal studies and review articles were excluded as well.

TABLE 1: Literature search for articles about HTS treatment for ICP

key words used in online PubMed literature search
hypertonic saline and intracranial pressure
hypertonic saline and intracranial hypertension
hypertonic saline and traumatic brain injury
hypertonic saline and subarachnoid hemorrhage
hypertonic saline and neurosurgery
results of search
787 articles located initially*
281 duplicates eliminated
38 excluded due to foreign language
127 excluded because unrelated to neurosurgery
134 excluded because unrelated to HTS's effects on cerebral hemodynamics
7 excluded because blood pressure used as primary therapy goal
4 excluded because of lack of ICP monitoring
67 animal studies excluded
88 review/opinion articles excluded
41 studies remained for inclusion

* Includes 1 additional study located from review article.

Data Extraction

We extracted the following data from each study: its design, objective, number of patients, concentration of HTS used, method of delivery, timing of measurements, main results of the study, and follow-up results. The outcomes assessed included ICP, CBF, brain tissue oxygen, brain water content, and GOS score. Each trial was grouped according to study design as shown in Table 2.

Meta-Analysis Method

Eight prospective randomized controlled studies reported treatment failure or insufficiency. The overall rates of treatment failure or insufficiency with HTS versus mannitol or NS for intracranial hypertension were compared. A homogeneity-based method of meta-analysis was performed using Review Manager for Windows (version 5, Cochrane Collaboration and Update Software) for prospective RCTs. Homogeneity between studies was assessed by means of the standard Cochran Q statistic and I^2 statistic. A fixed-effect model was used to merge odds ratio values and to estimate the overall effect size. Overall effect, odds ratio, and confidence interval were presented.

Results

In total, 787 articles were initially identified, of which 746 were excluded, leaving 41 clinical studies for analysis. Table 1 summarizes the results. Of the 41 studies included, 10 were prospective RCTs, 1 was a prospec-

TABLE 2: Literature grouped by study design*

Case Reports	Retro Studies†	Prospective Observational Studies	Prospective RCTs	Prospective Nonrandomized Study
Worthley et al., 1988	Qureshi et al., 1998[32]	Härtl et al., 1997	Fisher et al., 1992	Oddo et al., 2009
Qureshi et al., 1998[31]	Suarez et al., 1998	Schatzmann et al., 1998	Simma et al., 1998	
Berger et al., 2002	Qureshi et al., 1999	Horn et al., 1999	Schwarz et al., 1998	
Saltarini et al., 2002	Peterson et al., 2000	Khanna et al., 2000	De Vivo et al., 2001	
Einhaus et al., 1996	Larive et al., 2004	Munar et al., 2000	Vialet et al., 2003	
	Ware et al., 2005	Schwarz et al., 2002	Harutjunyan et al., 2005	
	Yildizdas et al., 2006	Tseng et al., 2003	Battison et al., 2005	
	Bentsen et al., 2008	Bentsen et al., 2004	Bentsen et al., 2006	
	Koenig et al., 2008	Al-Rawi et al., 2005	Francony et al., 2008	
	Kerwin et al., 2009	Huang et al., 2006	Ichai et al., 2009	
		Lescot et al., 2006		
		Tseng et al., 2007		
		Rockswold et al., 2009		
		Al-Rawi et al., 2010		
		Bourdeaux & Brown, 2010		

* Retro = retrospective.

† No distinction was made between retrospective observational studies and retrospective comparison trials. Prospective studies were considered observational if effects of a treatment were evaluated over time but not compared with another treatment.

tive nonrandomized controlled trial, 15 were prospective observational studies, 10 were retrospective, and 5 were case studies (Table 2). For the purpose of this meta-analysis, the 5 case reports will not be considered, leaving 36 articles for the bulk of the review.

The concentration and volume of HTS used varied significantly, ranging from 1.5% to 23.5% in concentration and 10 to 30 ml/kg in volume. In 7 studies, HTS was administered with an oncotic agent such as dextran or HES.[3–6,15,16,38] In 5 others, HTS was administered with a basic anion such as acetate, lactate, or bicarbonate.[8,19,23,32,33]

Experimental Trials: HTS Versus Mannitol

Twelve of the 36 studies compared HTS with mannitol.[3,10,14,16,19,20,23,29,38,44,45,48] These are summarized in Table 3. Seven were RCTs, 1 was a prospective nonrandomized study, and 4 were retrospective. Six of the 12 were crossover studies in which both mannitol and HTS were used in the same patients.[3,20,23,29,38,45] In the other 6, patients receiving HTS or mannitol, but not both, were compared.[10,14,16,19,44,48] Ichai et al.[19] and Yildizdas et al.[48] both had crossover and noncrossover groups. Five of 6 RCTs were noncrossover. One retrospective study was also noncrossover.[48] Two studies compared equimolar doses of HTS and mannitol,[3,14] and 1 study compared equal volumes of mannitol and HTS.[44]

Of the 12 comparisons between HTS and mannitol, 3 did not find HTS to be clinically superior to mannitol for ICP control or clinical outcome.[10,14,23] The first was an RCT that used HTS for intraoperative brain relaxation and postoperative ICP control. No significant difference in ICP was found between the 2 study groups at any point during the 72-hour postoperative period.[10] In the second trial, Francony et al.[14] randomized patients to receive either equimolar doses of mannitol or 7.45% saline to treat an episode of ICP > 20 mm Hg that lasted > 10 minutes. An equal reduction in ICP was found throughout the 2-hour study period, and CPP only increased in the mannitol group. Last, in a retrospective study, only the incidence of adverse effects between one cohort that received mannitol and another that received HTS was compared, and no difference was found; however, HTS was effective at reducing ICP below the target level of 20 mm Hg in that study.[23]

Thus 9 of the 12 comparisons between HTS and mannitol, including 7 RCTs, suggested that HTS provides superior control of ICP over mannitol. A greater reduction in ICP after addition of HTS than after mannitol in the minutes to hours after fluid administration was found in 6 trials. A longer duration of effect was found in 2 trials. In 1 RCT, the number of episodes of intracranial hypertension per day was lower in patients who received HTS than in those who received mannitol. Outcomes were not consistent among trials. In 1 RCT consisting of 34 patients, better 1-year GOS scores were seen in the HTS group.[19] Better outcomes were also seen in a retrospective study consisting of 67 patients. The HTS group had a lower mortality rate and shorter duration of comatose state than patients who received mannitol.[48] However, another RCT consisting of 20 patients did not demonstrate any difference in mortality rate or 90-day neurological outcome between the HTS group and the mannitol group, despite showing a better ICP control with HTS.[44] Changes in mean arterial pressure varied between studies after both mannitol and HTS; however, no significant risk of hypotension was seen in any study after either mannitol or HTS.

TABLE 3: Studies of HTS versus mannitol*

Authors & Year	Study Design	No. of Pts	Neuro/Mortality Outcome
Ichai et al., 2009	RCT	34	better 1-yr GOS scores in HTS group
Francony et al., 2008	RCT	20	unspecified
Harutjunyan et al., 2005	RCT	32	59% survival in HTS/HES group, 40% survival in mannitol group
Battison et al., 2005	RCT, crossover	9	GOS Score 5 in 3 pts & Score 3 in 6 pts at discharge
Vialet et al., 2003	RCT	20	no difference in mortality rate or 90-day neuro outcome
De Vivo et al., 2001	RCT	30	GOS Score 1 in 22 pts & Score 2 in 8 pts at discharge
Schwarz et al., 1998	RCT, crossover	9	3 pts w/ 2-wk GOS Score 5, other 6 pts w/ GOS Score 3
Oddo et al., 2009	prospective nonrandomized crossover	12	4 pts died
Kerwin et al., 2009	retro crossover	22	unspecified
Yildizdas et al., 2006	retro crossover	67	lower mortality rate & duration of comatose state in HTS group compared w/ mannitol group
Ware et al., 2005	retro	13	upper mod disability in 31%; lower mod disability in 8%; 31% died; 31% lost to FU (by 6-mo EGOS score)
Larive et al., 2004	retro crossover	28	21% died; median hospital stay 14 days

* FU = follow-up; mod = moderate; Neuro = neurological; pts = patients.

Continuous Infusion Versus Bolus

Hypertonic saline was administered as a continuous infusion in 11 studies, which are summarized in Table 4.[10,15,16,21,23,30,32–34,40,48] Only 3 of these 11 studies were RCTs, 3 were prospective observational trials, and 5 were retrospective. In 6 trials the infusion was titrated to maintain a target serum Na range,[23,32–34,40,48] in 4 it was titrated to a target ICP level,[15,16,21,30] and in the last a continuous infusion via a 3-day taper was used for postoperative patients.[10] Infusions lasted from several minutes to several days.

Two RCTs demonstrated better ICP control with HTS compared with control fluid.[16,40] Harutjunyan et al.[16] titrated an infusion of HTS/HES to maintain an ICP < 20 mm Hg. Infusion times lasted only several minutes. The average infusion time was shorter in the HTS/HES group, and the average ICP was lower 1 hour postinfusion. In the other RCT, Simma et al.[40] compared an infusion of HTS with LR solution given over 72 hours. Fewer ICP spikes were found in the HTS group, and a correlation between serum Na and ICP was found.

There were 6 observational studies in which HTS was administered as a continuous infusion.[15,21,23,30,32,34] The mean maximum serum Na ranged from 144 to 170 mmol/L. A correlation between serum Na and ICP was found in 3 of those trials.[21,30,32] In 2 observational studies short infusions were administered lasting from a few minutes to several hours.[15,34] In the other 4 observational studies long infusions were administered over several days.[21,23,30,32] One retrospective observational trial discussed above only found a favorable trend in ICP reduction in patients with TBI and postoperative patients. Rebound ICP was seen in this study after the first 24 hours of the infusion;[32] rebound ICP was not seen in any of the other studies.

A clinical benefit in ICP control from HTS infusion was not seen in 4 of the 11 studies.[10,32,33,48] One of the 4 studies had no ICP monitoring, but patients treated with HTS demonstrated a lower mortality rate than those treated with mannitol alone.[48] Another study only demonstrated a favorable trend in ICP reduction after HTS in the TBI and postoperative patient subgroups, but not in the intracranial hemorrhage or infarction subgroups. Higher serum Na levels were also seen in the TBI and postoperative groups.[32] In 1 RCT, De Vivo et al.[10] demonstrated no significant difference in ICP during the 3-day HTS infusion in postoperative patients than in those treated with mannitol. Last, a retrospective case-control study found no significant difference in ICP between patients with TBI who received a 72-hour HTS infusion and those who received NS. The in-hospital mortality rate was higher in the HTS group.[33]

In summary, multiple studies, including 2 of 3 RCTs, suggest that HTS administered as a continuous infusion is an effective method of reducing ICP. However, 1 retrospective study demonstrated a worse mortality rate than in patients who received NS, as described above.[33] Worse outcome after HTS was not seen in any bolus study. Also, only 2 of 3 RCTs support its use as a continuous infusion, compared with 6 of 7 RCTs in which HTS was used as a bolus.

Twenty-six studies in which HTS was administered in boluses of defined doses are shown in Table 5. Of these, 7 studies were RCTs, 1 was a prospective nonrandomized trial, 13 were prospective observational trials, and 5 were retrospective. The number of patients ranged from 6 to 68. Nine studies used 23% HTS, 3% HTS was used in 3 studies,[12,18,19] 7.5% HTS/6% HES or dextran was used in 5,[3–6,38] and 7.5% HTS was used in 5.[14,17,28,29,44] The remaining studies used various concentrations of HTS ranging from 8.5% to 20%. Doses ranged from 30 to 300 ml by volume and 1.5 to 10 ml/kg by weight, with 2 ml/kg being the most common.

Among the 7 RCTs, only 1 did not demonstrate better ICP outcome than with control fluid.[14] Francony et al.[14] randomized 20 patients to receive a single dose of either 255 mOsm 7.45% HTS or 255 mOsm 20% man-

TABLE 4: Studies of continuous infusion*

Authors & Year	Study Design	No. of Pts	Neuro/Mortality Outcome
Harutjunyan et al., 2005	RCT	32	41% in HTS group died vs 60% in mannitol group
De Vivo et al., 2001	RCT	30	GOS Score 1 in 22 pts & Score 2 in 8 pts at discharge
Simma et al., 1998	RCT	32	longer ICU stay in LR group; no difference in survival or hospital stay
Rockswold et al., 2009	prospective, observational	25	14 pts w/ favorable GOS scores at 12 mos
Khanna et al., 2000	prospective, observational	10	median GOS Score 4 at 6 mos
Härtl et al., 1997	prospective, observational	6	4 of 6 w/ 6-mo GOS Score 5; 1 of 6 w/ GOS Score 4; & 1 pt died
Yildizdas et al., 2006	retro	67	lower mortality rate & duration of comatose state in HTS group compared w/ mannitol group
Larive et al., 2004	retro cohort analysis	28	21% died; median hospital stay 14 days
Peterson et al., 2000	retro	68	6-mo avg GOS Score 3.9 (4.4 in survivors)
Qureshi et al., 1999	retro, case control	36	no difference in mean GOS score at discharge; in-hospital mortality rate higher in HTS group
Qureshi et al., 1998[32]	retro	27	avg 1-mo GOS Score 3.6 in TBI, 2.8 in postop, 4.6 in intracranial hemorrhage, 4 in infarction groups

* avg = average.

nitol for ICP > 20 mm Hg. There was an equal reduction in ICP at all time points during the 120-minute study period. Five other RCTs demonstrated better ICP with HTS than with mannitol,[3,4,19,38,44] only 1 of which also administered HTS and mannitol in equimolar doses.[3] Last, 1 RCT compared 10 ml/kg of 3% HTS with NS infusions in pediatric patients and found better ICP reduction 2 hours after infusion.[12] Significant reduction in ICP from base-

TABLE 5: Studies of bolus therapy

Authors & Year	Study Design	No. of Pts	Neuro/Mortality Outcome
Ichai et al., 2009	RCT	34	better 1-yr GOS scores in HTS group
Francony et al., 2008	RCT	20	unspecified
Bentsen et al., 2006	RCT	22	unspecified
Battison et al., 2005	RCT, crossover	9	unspecified
Vialet et al., 2003	RCT	20	no difference in mortality rate or 90-day neuro outcome
Schwarz et al., 1998	RCT, crossover	9	3 pts w/ 2-wk GOS Score 5, other 6 pts w/ GOS Score 3
Fisher et al., 1992	RCT, crossover	18	unspecified
Oddo et al., 2009	prospective nonrandomized	28	4 pts died
Bourdeaux & Brown, 2010	prospective observational	7	unspecified
Al-Rawi et al., 2010	prospective observational	44	64% 1-yr unfavorable outcome rate based on mRS score
Rockswold et al., 2009	prospective observational	25	14 pts w/ favorable GOS scores at 12 mos
Tseng et al., 2007	prospective observational	35	40% w/ favorable outcome based on mRS score at discharge; 31% died
Lescot et al., 2006	prospective observational	14	unspecified
Huang et al., 2006	prospective observational	18	unspecified
Al-Rawi et al., 2005	prospective observational	14	unspecified
Bentsen et al., 2004	prospective observational	7	unspecified
Tseng et al., 2003	prospective observational	10	unspecified
Schwarz et al., 2002	prospective observational	8	at 2-wk FU, 4 pts had died, 4 had GOS Score 3
Munar et al., 2000	prospective observational	14	bad outcome at 6 mos in 43% of pts
Horn et al., 1999	prospective observational	10	6-mo GOS Score 4 in 2 pts, 2 in 1 pt, & 1 in 7 pts
Schatzmann et al., 1998	prospective observational	6	unspecified
Kerwin et al., 2009	retro	22	unspecified
Koenig et al., 2008	retro	68	46 pts died; mRS scores at discharge for other 22 were 1–3 in 5 pts, 4–5 in 17 pts
Bentsen et al., 2008	retro	20	65% poor outcome rate based on 3-mo GOS score
Ware et al., 2005	retro	13	6-mo EGOS Score 1 in 4 pts, 6 in 4 pts, & 5 in 1 pt; 4 pts lost to FU
Suarez et al., 1998	retro	8	7 pts died, 1 pt had mod disability at 3 mos

line was seen in all 13 prospective observational trials. The mean maximum ICP reduction ranged from 38% to 93% in studies that provided those numbers. Significant reduction in ICP was also seen in all retrospective trials. Serum Na concentration after HTS infusion varied considerably among the bolus studies. In half of the 26 studies, the average serum Na (in mmol/L) ranged in the 140s.[8,14,17–19,22,24,28,29,37,38,44,45] In a few studies, the average serum Na ranged in the 150s,[1,3,4] and in 1 study it ranged in the 160s.[34] No significant incidence of complications secondary to hypernatremia was seen in any study.

There are significantly more data on the administration of HTS as a bolus than as a continuous infusion; however, the available data suggest that both routes can be effective at reducing ICP.

Traumatic Brain Injury

Sixteen of the 36 studies included only patients with TBI (Table 6).[8,12,15,18–21,24,28–30,33,34,40,44,45] Four were RCTs, 1 was a prospective nonrandomized trial, 7 were prospective observational, and 4 were retrospective studies. The total number of patients in each study ranged from 6 to 68. In 12 studies short infusions for acute spikes in ICP were administered, whereas in 4 studies long infusions of 1.5%–3% HTS were given over several days, titrated to either a target ICP level or serum Na level. Serum Na levels varied significantly among trials. In 8 trials the serum Na after HTS therapy was in the 140s (mmol/L), and in 3 trials the serum Na was > 160 mmol/L.

A clinical benefit due to ICP control from HTS infusion was seen in all but one study, a retrospective case-control study.[33] Two RCTs were pediatric studies, one of them with 32 and the other with 18 patients with TBI; these patients exhibited superior ICP control with HTS compared with LR and NS, respectively.[12,40] Mannitol was used additionally in both trials. The other two RCTs both used bolus HTS therapy for ICP > 25 mm Hg.[19,44] One trial demonstrated better average ICP reduction in 34 patients with TBI after administration of 3% HTS during the 4-hour study period postinfusion,[19] and the other demonstrated fewer ICP episodes per day in 20 patients with TBI in the group receiving 7.5% HTS than in those receiving mannitol.[44]

Hypertonic saline was compared with mannitol in 5 studies.[19,20,29,44,45] Oddo et al.[29] prospectively treated 12 patients with both mannitol and HTS for episodes of ICP > 20 mm Hg. Mannitol was given for the first episode in all patients. A 44% maximum ICP reduction after HTS was seen at 60 minutes after infusion, compared with a 28% maximum reduction at 30 minutes after mannitol therapy. The 2 retrospective studies[20,45] comparing HTS and mannitol both used 30-ml boluses of 23% HTS for ICP reduction in a total of 35 patients with TBI. Better ICP reduction after HTS was seen in both, but a longer duration of effect with HTS was only seen in the study by Ware et al.[45]

There was a significant reduction in ICP from baseline in all 7 prospective observational studies. The average reduction ranged from approximately 20%–60% in those that provided absolute numbers. The observational period for most was 6 hours or less. The time to peak effect ranged from 10 minutes to 5 hours postinfusion. One group administered a continuous infusion over 72 hours and used 6-hour ICP averages for data analysis.[21] The time to peak effect in that study was 48 hours. No rebound increase in ICP was seen in any of the studies.[8,15,18,21,24,28,34]

Eight of the TBI studies measured neurological outcome at follow-up.[15,19,21,28,30,34,44,45] Two were randomized trials comparing HTS with mannitol,[19,44] only 1 of which demonstrated a significant improvement in neurological outcome with HTS compared with mannitol. The 1-year GOS score was significantly higher in patients treated with a bolus of approximately 3% HTS/lactate.[19] The other study compared 90-day neurological outcome between those treated with a bolus of 7.5% HTS and those treated with mannitol, and found no difference between groups.[44] Six-month to 1-year follow-up to assess neurological outcomes in 4 observational studies demonstrated poor outcomes in 15%–45% of patients;[15,21,28,34] poor outcome was defined as a GOS Score < 4. The average baseline GCS scores were < 8 in all but one study, in which the baseline GCS score was < 13, and in which poor outcomes were seen in 43% of patients.[28] Last, Ware et al.[45] obtained a long-term EGOS score in 9 of the 14 patients with TBI: 4 patients died, 4 had an upper moderate disability, and 1 had a lower moderate disability. These authors used the EGOS, which is an 8-level scale in which the levels are defined as follows: 1, dead; 2, vegetative state; 3, lower severe disability; 4, upper severe disability; 5, lower moderate disability; 6, upper moderate disability; 7, lower good recovery; and 8, upper good recovery.

From the 16 articles reviewed, including 4 RCTs and multiple observational studies, the data support the use of HTS as an effective method of reducing ICP in patients with TBI. All 5 studies comparing HTS with mannitol demonstrated a more significant reduction in ICP after administration of HTS. Only 1 study (an RCT) of the 36 articles reviewed found a better long-term outcome in patients treated with HTS than with mannitol.[19]

Nontraumatic Neurological Injury

Eleven studies included exclusively patients with nontraumatic neurological injury (Table 7).[1,2,4–6,10,37,38,42,43,48] Neurological injuries varied from nontraumatic SAH, intracranial hemorrhage, and infarction to tumors and infections. Three studies were RCTs, 6 were prospective observational trials, and 2 were retrospective. The total number of patients in each study ranged from 7 to 67. Bolus therapy was used to treat acute spikes in ICP in 4 studies[4,5,37,38] and to increase CBF for poor-grade spontaneous SAH in 5 studies.[1,2,6,42,43] A continuous infusion of HTS was given for postoperative edema in one trial[10] and to maintain a target serum Na in another.[48]

One of the 3 RCTs compared bolus therapy of HTS/HES with NS for ICP control in patients with SAH, and found better reduction throughout the 210-minute study period with HTS/HES. Baseline ICP was required to be < 20 mm Hg to have a placebo-controlled study.[4] The other 2 RCTs compared HTS with mannitol. One was a crossover trial in which the study fluid was randomized for the first treatment but alternated for subsequent episodes. Better ICP control was found following HTS/HES thera-

TABLE 6: Studies of TBI

Authors & Year	Study Design	No. of Pts	Neuro/Mortality Outcome
Ichai et al., 2009	RCT	34	better 1-yr GOS scores in HTS group
Vialet et al., 2003	RCT	20	no difference in mortality rate or 90-day neuro outcome
Simma et al., 1998	RCT	32	longer ICU stay in LR group, no difference in survival or hospital stay
Fisher et al., 1992	RCT, crossover	18	unspecified
Oddo et al., 2009	prospective nonrandomized crossover	12	4 pts died
Bourdeaux & Brown, 2010	prospective observational	7	unspecified
Rockswold et al., 2009	prospective observational	25	14 pts w/ favorable GOS scores at 12 mos
Lescot et al., 2006	prospective observational	14	unspecified
Huang et al., 2006	prospective observational	18	unspecified
Munar et al., 2000	prospective observational	14	bad outcome at 6 mos in 43% of pts
Khanna et al., 2000	prospective observational	10	median GOS Score 4 at 6 mos
Härtl et al., 1997	prospective observational	6	4 of 6 w/ 6-mo GOS Score 5; 1 of 6 w/ GOS Score 4; & 1 pt died
Kerwin et al., 2009	retro	22	unspecified
Ware et al., 2005	retro	13	6-mo EGOS Score 1 in 4 pts, 6 in 4 pts, & 5 in 1 pt; 4 pts lost to FU
Peterson et al., 2000	retro	68	6-mo avg GOS Score 3.9 (4.4 in survivors)
Qureshi et al., 1999	retro, case control	36	no difference in mean GOS score at discharge; in-hospital mortality rate higher in HTS group

py than with mannitol in cerebral infarction. No rebound intracranial hypertension was seen during the 4-hour study period after administration of either study fluid.[38] In the other prospective randomized trial described above, the investigators studied intraoperative brain relaxation and postoperative ICP control and found no difference between HTS and mannitol.[10]

Significant reduction in ICP from baseline was seen in all 6 prospective observational studies.[1,2,5,37,42,43] Maximum reduction ranged from 38% to 93% at an average of 30–60 minutes postinfusion. Study time periods ranged from 1 to 6 hours postinfusion. No rebound ICP was seen in any of the trials during their respective study periods. The concentration of HTS used was 23.5% in 4 of the 6 studies, 10% in 1, and 7.2% HTS/6% HES in 1.

Seven of 11 studies included only patients with nontraumatic SAH.[1,2,4–6,42,43] A clinical benefit in ICP control was seen in all 7 trials. The mean maximum ICP reduction ranged from 35% to 93% at an average of 30–64 minutes postinfusion. No rebound ICP was seen in any trial during the study period. One retrospective trial investigated the effect of HTS on ICP pulsatility and found a significant reduction in mean ICP wave amplitudes following HTS/HES administration.[6] Clinical follow-up was obtained in only 1 study. One-year mRS scores demonstrated a 64% unfavorable outcome.[1] The mRS scores were obtained in another study at discharge. A positive correlation between the mRS score and the degree of CBF enhancement following HTS therapy was seen.[42] Two of 11 trials exclusively considered patients with cerebral infarction/intraparenchymal hemorrhage; one was a prospective randomized crossover trial that compared HTS/HES with mannitol as discussed above, and the other was an observational study that used a bolus of 10% HTS for ICP > 20 mm Hg or a pupillary abnormality.[37,38] Two-week follow-up GOS scores were obtained in both

TABLE 7: Studies of nontraumatic injury

Authors & Year	Study Design	No. of Pts	Neuro/Mortality Outcome
Bentsen et al., 2006	RCT	22	unspecified
De Vivo et al., 2001	RCT	30	GOS Score 1 in 22 pts & 2 in 8 pts at discharge; did not distinguish groups
Schwarz et al., 1998	RCT, crossover	9	3 pts w/ 2-wk GOS Score 5, other 6 pts w/ GOS Score 3
Al-Rawi et al., 2010	prospective observational	44	64% 1-yr unfavorable outcome rate based on mRS score
Tseng et al., 2007	prospective observational	35	40% w/ favorable outcome based on mRS score at discharge; 31% died
Al-Rawi et al., 2005	prospective observational	14	unspecified
Bentsen et al., 2004	prospective observational	7	unspecified
Tseng et al., 2003	prospective observational	10	unspecified
Schwarz et al., 2002	prospective observational	8	at 2-wk FU, 4 pts died, 4 had GOS Score 3
Bentsen et al., 2008	retro	20	65% poor outcome rate based on 3-mo GOS score
Yildizdas et al., 2006	retro	67	lower mortality rate & duration of comatose state in HTS group compared w/ mannitol group

studies, with a poor outcome rate of 60% and 100%, respectively.

Two of 3 RCTs and multiple observational studies support the use of HTS for reducing ICP in patients with nontraumatic neurological injury. A better outcome in patients treated with HTS compared with those treated with mannitol was only seen in 1 retrospective study.[48] Hypertonic saline was compared with mannitol in 2 other trials, but neither compared outcomes.

Mixed Traumatic and Nontraumatic Neurological Injury

Nine studies included patients with both traumatic and nontraumatic neurological injury.[3,14,16,17,22,23,32,36,41] These are summarized in Table 8. Three studies were RCTs, 2 were prospective observational studies, and 4 were retrospective. The total number of patients ranged from 6 to 68. Small volume infusions were given for acute ICP spikes in 6 trials.[3,14,16,17,36,41] Koenig et al.[22] administered small-volume boluses of HTS for impending transtentorial herniation. Longer infusions were given in 2 studies to maintain a target serum Na range.[23,32] All but one trial made no distinction among patients based on injury mechanism. The exception was Qureshi et al.,[32] who found a difference between postoperative and TBI patients and those with cerebral infarction and intracranial hemorrhage in a retrospective study, as discussed above.

Better ICP control with HTS was seen in 2 of the 4 experimental trials comparing HTS with mannitol.[3,14,16,23] Harutjunyan et al.[16] demonstrated a 7% greater maximum ICP reduction at 30 minutes postinfusion with HTS/HES therapy than with mannitol. Battison et al.[3] performed a crossover study comparing equimolar doses of mannitol and HTS/dextran. Each patient received 2 treatments with each study fluid for treatment of ICP spikes. The order was randomized and the time between treatments varied. There was a 28% greater median reduction in ICP at 1 hour posttherapy with HTS/dextran. Francony et al.[14] found no difference in ICP between groups receiving each study fluid as described above. Only 3 of 20 patients in that study had nontraumatic injuries. No ICP monitoring was performed in the mannitol group reported by Larive et al.;[23] however, ICP was maintained below the target of 20 mm Hg 98% of the time during the several day–long infusions of HTS.

Koenig et al.[22] retrospectively reviewed cases in which HTS was used to reverse impending transtentorial herniation. Patients with acute onset pupillary defects and decline in their GCS scores were treated with a bolus of 23.4% HTS. Clinical reversal was achieved in 75% of episodes. The ICP was significantly lower than baseline 1 and 24 hours after bolus administration. The mean serum Na at 1 hour posttherapy was 145 mmol/L. Patients with successful reversal had significantly higher serum Na levels. The 2 prospective observational studies demonstrated maximum ICP decreases of 43%–45% at 24 and 98 minutes postinfusion. These effects lasted between 101 and 163 minutes.[17,36] Follow-up was obtained in 1 of the prospective observational studies, demonstrating a 20% favorable outcome rate by 6 months based on the GOS score in patients with TBI and SAH, with the average baseline GCS Score < 8.[17]

In this group, 2 of 3 RCTs and multiple observational studies supported the use of HTS for reduction of ICP. One RCT demonstrated a better mortality rate in patients treated with HTS than in those treated with mannitol, but it failed to achieve statistical significance.[16]

Pediatric Studies

Five pediatric studies that used HTS were identified.[12,21,30,40,48] These are summarized in Table 9. Two studies were RCTs, 1 was a prospective observational trial, and 2 were retrospective. A clinical benefit in ICP control or patient outcome was seen in all. Two RCTs demonstrated better ICP control with HTS than control fluid (LR or NS) in trauma patients. Only 1 trial compared HTS and mannitol. There was no ICP monitoring in that study; however, the cohort receiving HTS demonstrated a lower mortality and duration of comatose state.[48] An inverse correlation between serum Na level and ICP was found in 2 studies.[21,40]

All 5 pediatric studies supported the use of HTS for reduction of ICP. Only 1 retrospective study demonstrated a better outcome in terms of the mortality rate in patients treated with HTS.[48]

Treatment Failure or Insufficiency With HTS Versus Mannitol or NS for Intracranial Hypertension—Meta-Analysis

Eight studies reported treatment failure or insufficiency according to the following criteria: 1) failure to re-

TABLE 8: Studies of mixed traumatic and nontraumatic injury

Authors & Year	Study Design	No. of Pts	Neuro/Mortality Outcome
Francony et al., 2008	RCT	20	unspecified
Harutjunyan et al., 2005	RCT	32	41% in HTS group died vs 60% in mannitol group
Battison et al., 2005	RCT, crossover	9	unspecified
Horn et al., 1999	prospective observational	10	6-mo GOS Score 4 in 2 pts, 2 in 1 pt, & 1 in 7 pts
Schatzmann et al., 1998	prospective observational	6	unspecified
Koenig et al., 2008	retro	68	46 pts died; mRS scores at discharge for other 22 were 1–3 in 5 pts, 4–5 in 17 pts
Larive et al., 2004	retro, cohort analysis	28	21% died; median hospital stay 14 days
Suarez et al., 1998	retro	8	7 pts died; 1 pt had mod disability at 3 mos
Qureshi et al., 1998[32]	retro	27	avg 1-mo GOS Score 3.6 in TBI, 2.8 in postop, 4.6 in intracranial hemorrhage, 4 in infarction groups

TABLE 9: Studies in pediatric patients*

Authors & Year	Study Design	Study Description	No. of Pts	Concentration of HTS	Bolus vs Cont Inf	Fluid Administration	Results
Simma et al., 1998	prospective RCT	HTS vs LR in pts w/ GCS score <8; ICP spikes >15 mm Hg treated w/ standard therapies including mannitol	32	268 mmol/L Na (1.5%)	cont inf	given over 72 hrs to maintain serum Na at 145–150 mmol/L	1: no difference in mean ICP btwn groups; 2: more ICP spikes requiring intervention in LR group; 3: inverse correlation btwn serum Na & ICP
Fisher et al., 1992	prospective RCT, crossover	HTS vs NS for intracranial hypertension refractory to standard therapies including mannitol	18†	3%	10 ml/kg (6.5–8.5 ml/kg in 3 pts)	given when ICP >15 or CPP <50 mm Hg; 2nd episode treated w/ opposite study fluid (avg of 22 hrs after trauma)	1: avg ICP < baseline after HTS but not after NS during 2 hrs postinfusion; 2: ICP increased in 6 HTS trials
Khanna et al., 2000	prospective observational	HTS for intracranial hypertension refractory to standard therapies including mannitol	10	3%	cont inf	mean enrollment time 3.2 days after admission; infusion titrated to maintain ICP at <20 mm Hg	1: decrease in ICP spike frequency up to 72 hrs; 2: inverse correlation btwn serum Na & ICP
Yildizdas et al., 2006	retro	HTS vs mannitol for treatment of cerebral edema determined clinically & radiographically; no ICP monitoring	67	3%	1 ml/kg & cont inf	given for clinical &/or radiographic evidence of cerebral edema; infusion given to maintain serum Na in 155–165 mmol/L range; treatments stopped at GCS score >8	lower mortality rate & duration of comatose state in HTS group compared w/ mannitol group
Peterson et al., 2000	retro	HTS therapy for intracranial hypertension & diffuse injury or mass lesion on CT	68	3%	cont inf	infusion titrated to maintain ICP <20 mm Hg over 7 days	ICP <20 mm Hg 92% of time during 7-day period

* Cont Inf = continuous infusion.
† Each patient received 1 bolus of each study fluid.

duce ICP below 16–18 mm Hg following each infusion;[3] 2) reduction in ICP of < 20% of baseline value 60 minutes after therapy;[14] 3) sustained ICP elevation despite treatment requiring thiopental administration;[16] 4) inability to reduce ICP to < 35 mm Hg or to increase CPP to > 70 mm Hg with 2 consecutive infusions;[44] 5) reduction in ICP of < 10% of baseline value 60 minutes after infusions or persistence of pupillary dilation;[38] 6) elevation in ICP within 2 hours after the start of infusion, necessitating another intervention;[12] 7) failure to reduce ICP by > 5 mm Hg or to reduce it to at least 20 mm Hg within 15 minutes of infusion;[19] and 8) inability to reduce ICP to < 20 mm Hg and to increase CPP to > 60 mm Hg within 210 minutes of infusion.[4] Nineteen of 117 patients or episodes treated with HTS and 39 of 113 episodes treated with mannitol or NS had treatment failure. The difference was significant (OR 0.36, CI 0.19–0.68; p = 0.002). Figure 1 shows a Forrest plot comparing the rates of treatment failure or insufficiency with HTS versus mannitol or NS for intracranial hypertension.

Discussion

Any injury or mass-occupying lesions in the brain can cause edema and increased ICP. Treatment of increased ICP is one of the most important and most common problems in a neurointensive care facility. The treatment arsenal expands over a variety of medical and surgical interventions. Mannitol has been seen as one of the first choices in the immediate-treatment of increased ICP.[9,39] Even for cases that have required emergent surgery, mannitol has been a good temporizing choice. However, mannitol has several adverse effects, including hypotension secondary to osmotic diuresis, as well as renal function compromise.[25] Also, it may exacerbate cerebral edema if administered late after cerebral injury due to disrupted BBB.[27]

During the last decade, HTS has received increasing attention as a good substitute for mannitol due to its excellent tonic properties, and the lack of hypovolemic hypotension that mannitol causes. Various studies have reported various results when using different concentrations and different modes of administration of HTS. Because mannitol has been the standard treatment of choice, it is obvious that any Level 1 evidence should compare HTS to mannitol. Therefore, the literature was searched for all the studies in which HTS was used for treatment of ICP, no matter its cause, and special attention was given to RCTs comparing HTS to mannitol. We also documented the reported role of HTS in intracranial hypertension secondary to trauma, nontraumatic causes such as SAH, and mass lesions. We also asked if a certain concentration of HTS is most optimal. Hypertonic saline has also been administered as a continuous drip or as a bolus. Although some studies have had ICP goals, others have had serum Na goals for HTS administration. In summary, there is a significant lack of standardized treatment protocols with respect to optimal concentration, administration route, and length of treatment as well as possible rebound for the use of HTS in the treatment of raised ICP.

In our review, we found that a majority of the studies showed a more favorable short-term ICP outcome for HTS, no matter what the concentration or administration mode (bolus or continuous drip). Also, there has been no report of a serious adverse effect of HTS, which is not surprising because it is given in closely monitored intensive care environments, and hence too quick a rise of Na will be corrected almost immediately. Also, HTS appears to have a favorable outcome in all types of intracranial hypertension, no matter the origin. However, there is no consensus on the most optimal concentration, because all concentrations appear to have favorable effects on ICP. It is logical to assume that, in the end, it is the serum Na that effectively causes the final osmotic effect on the brain. Therefore, any future studies, no matter what the mode of infusion, whether continuous drip or bolus, should monitor serum Na. Studies looking into the rebound risk of HTS alone and in comparison with mannitol are also lacking. Those few studies mentioning the rebound phenomenon have inadequately monitored for it.

Conclusions

Multiple studies, including RCTs, show superior ef-

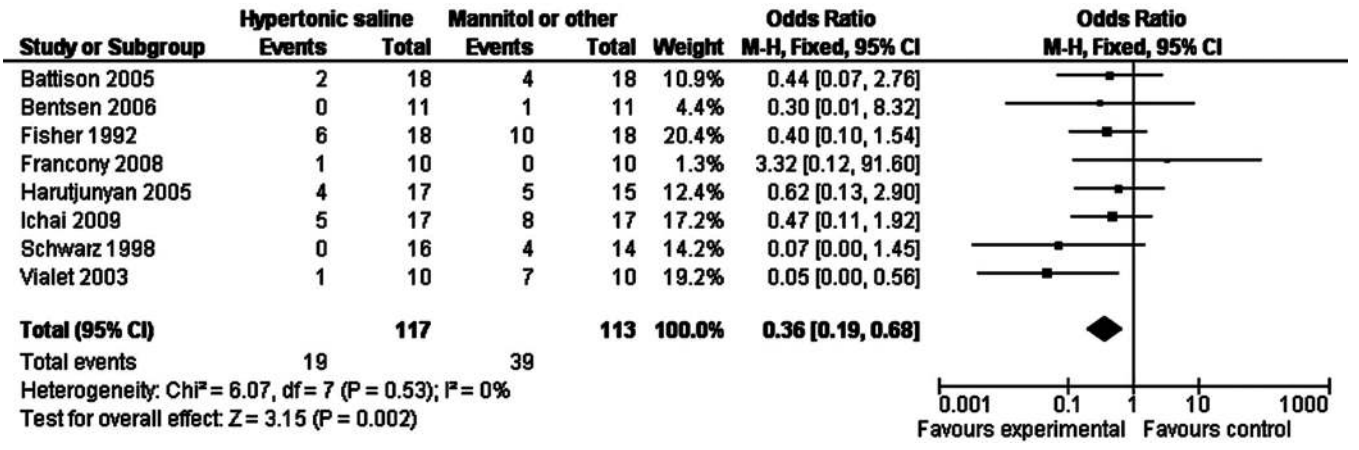

Fig. 1. Forrest plot comparing the rates of treatment failure or insufficiency with HTS versus mannitol or NS for intracranial hypertension. M-H = Mantel-Haenszel.

fectiveness of HTS compared with mannitol in decreasing ICP. However, there is not a clear benefit compared with mannitol in regard to neurological outcome, even though there is a minor positive trend for HTS. Furthermore, HTS does not cause the hypotension seen when mannitol is used.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Tubbs, Mortazavi, Deep, Fisher. Acquisition of data: Mortazavi, Romeo. Analysis and interpretation of data: Tubbs, Mortazavi, Shoja. Drafting the article: Tubbs, Mortazavi, Romeo. Critically revising the article: Tubbs, Mortazavi, Deep, Griessenauer. Statistical analysis: Tubbs, Shoja. Administrative/technical/material support: Tubbs. Study supervision: Fisher.

References

1. Al-Rawi PG, Tseng MY, Richards HK, Nortje J, Timofeev I, Matta BF, et al: Hypertonic saline in patients with poor-grade subarachnoid hemorrhage improves cerebral blood flow, brain tissue oxygen, and pH. **Stroke 41:**122–128, 2010
2. Al-Rawi PG, Zygun D, Tseng MY, Hutchinson PJ, Matta BF, Kirkpatrick PJ: Cerebral blood flow augmentation in patients with severe subarachnoid haemorrhage. **Acta Neurochir Suppl (Wien) 95:**123–127, 2005
3. 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. **Crit Care Med 33:**196–202, 257–258, 2005
4. 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 34:**2912–2917, 2006
5. 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 48:**1089–1095, 2004
6. Bentsen G, Stubhaug A, Eide PK: Differential effects of osmotherapy on static and pulsatile intracranial pressure. **Crit Care Med 36:**2414–2419, 2008
7. Berger S, Schwarz M, Huth R: Hypertonic saline solution and decompressive craniectomy for treatment of intracranial hypertension in pediatric severe traumatic brain injury. **J Trauma 53:**558–563, 2002
8. Bourdeaux C, Brown J: Sodium bicarbonate lowers intracranial pressure after traumatic brain injury. **Neurocrit Care 13:** 24–28, 2010
9. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS: Guidelines for the management of severe traumatic brain injury, ed 3. **J Neurotrauma 24 (Suppl 1):**S1–S106, 2007
10. De Vivo P, Del Gaudio A, Ciritella P, Puopolo M, Chiarotti F, Mastronardi E: Hypertonic saline solution: a safe alternative to mannitol 18% in neurosurgery. **Minerva Anestesiol 67:**603–611, 2001
11. Einhaus SL, Croce MA, Watridge CB, Lowery R, Fabian TC: The use of hypertonic saline for the treatment of increased intracranial pressure. **J Tenn Med Assoc 89:**81–82, 1996
12. Fisher B, Thomas D, Peterson B: Hypertonic saline lowers raised intracranial pressure in children after head trauma. **J Neurosurg Anesthesiol 4:**4–10, 1992
13. Forsyth LL, Liu-DeRyke X, Parker D Jr, Rhoney DH: Role of hypertonic saline for the management of intracranial hypertension after stroke and traumatic brain injury. **Pharmacotherapy 28:**469–484, 2008
14. Francony G, Fauvage B, Falcon D, Canet C, Dilou H, Lavagne P, et al: Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. **Crit Care Med 36:**795–800, 2008
15. Härtl R, Ghajar J, Hochleuthner H, Mauritz W: Hypertonic/hyperoncotic saline reliably reduces ICP in severely head-injured patients with intracranial hypertension. **Acta Neurochir Suppl (Wien) 70:**126–129, 1997
16. 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 [ISRCTN62699180]. **Crit Care 9:**R530–R540, 2005
17. Horn P, Münch E, Vajkoczy P, Herrmann P, Quintel M, Schilling L, et al: Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. **Neurol Res 21:**758–764, 1999
18. 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 65:**539–546, 2006
19. Ichai C, Armando G, Orban JC, Berthier F, Rami L, Samat-Long C, et al: Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. **Intensive Care Med 35:**471–479, 2009
20. Kerwin AJ, Schinco MA, Tepas JJ III, Renfro WH, Vitarbo EA, Muehlberger M: The use of 23.4% hypertonic saline for the management of elevated intracranial pressure in patients with severe traumatic brain injury: a pilot study. **J Trauma 67:**277–282, 2009
21. Khanna S, Davis D, Peterson B, Fisher B, Tung H, O'Quigley J, et al: Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. **Crit Care Med 28:**1144–1151, 2000
22. Koenig MA, Bryan M, Lewin JL III, Mirski MA, Geocadin RG, Stevens RD: Reversal of transtentorial herniation with hypertonic saline. **Neurology 70:**1023–1029, 2008
23. Larive LL, Rhoney DH, Parker D Jr, Coplin WM, Carhuapoma JR: Introducing hypertonic saline for cerebral edema: an academic center experience. **Neurocrit Care 1:**435–440, 2004
24. Lescot T, Degos V, Zouaoui A, Préteux 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 34:**3029–3033, 2006
25. Marik PE, Varon J, Trask T: Management of head trauma. **Chest 122:**699–711, 2002
26. Marmarou A: A review of progress in understanding the pathophysiology and treatment of brain edema. **Neurosurg Focus 22(5):**E1, 2007
27. McManus ML, Soriano SG: Rebound swelling of astroglial cells exposed to hypertonic mannitol. **Anesthesiology 88:** 1586–1591, 1998
28. Munar F, Ferrer AM, de Nadal M, Poca MA, Pedraza S, Sahuquillo J, et al: Cerebral hemodynamic effects of 7.2% hypertonic saline in patients with head injury and raised intracranial pressure. **J Neurotrauma 17:**41–51, 2000
29. Oddo M, Levine JM, Frangos S, Carrera E, Maloney-Wilensky E, Pascual JL, et al: Effect of mannitol and hypertonic saline on cerebral oxygenation in patients with severe traumatic brain injury and refractory intracranial hypertension. **J Neurol Neurosurg Psychiatry 80:**916–920, 2009
30. Peterson B, Khanna S, Fisher B, Marshall L: Prolonged hyper-

natremia controls elevated intracranial pressure in head-injured pediatric patients. **Crit Care Med 28:**1136–1143, 2000
31. Qureshi AI, Suarez JI, Bhardwaj A: Malignant cerebral edema in patients with hypertensive intracerebral hemorrhage associated with hypertonic saline infusion: a rebound phenomenon? **J Neurosurg Anesthesiol 10:**188–192, 1998
32. Qureshi AI, Suarez JI, Bhardwaj A, Mirski M, Schnitzer MS, Hanley DF, et al: 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 26:**440–446, 1998
33. 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 47:**659–665, 1999
34. Rockswold GL, Solid CA, Paredes-Andrade E, Rockswold SB, Jancik JT, Quickel RR: Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure, and brain tissue oxygen. **Neurosurgery 65:**1035–1042, 2009
35. Saltarini M, Massarutti D, Baldassarre M, Nardi G, De Colle C, Fabris G: Determination of cerebral water content by magnetic resonance imaging after small volume infusion of 18% hypertonic saline solution in a patient with refractory intracranial hypertension. **Eur J Emerg Med 9:**262–265, 2002
36. Schatzmann C, Heissler HE, König K, Klinge-Xhemajli P, Rickels E, Mühling M, et al: Treatment of elevated intracranial pressure by infusions of 10% saline in severely head injured patients. **Acta Neurochir Suppl 71:**31–33, 1998
37. Schwarz S, Georgiadis D, Aschoff A, Schwab S: Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. **Stroke 33:**136–140, 2002
38. 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 29:**1550–1555, 1998
39. Shenkin HA, Goluboff B, Haft H: The use of mannitol for the reduction of intracranial pressure in intracranial surgery. **J Neurosurg 19:**897–901, 1962
40. Simma B, Burger R, Falk M, Sacher P, Fanconi S: A prospective, randomized, and controlled study of fluid management in children with severe head injury: lactated Ringer's solution versus hypertonic saline. **Crit Care Med 26:**1265–1270, 1998
41. Suarez JI, Qureshi AI, Bhardwaj A, Williams MA, Schnitzer MS, Mirski M, et al: Treatment of refractory intracranial hypertension with 23.4% saline. **Crit Care Med 26:**1118–1122, 1998
42. Tseng MY, Al-Rawi PG, Czosnyka M, Hutchinson PJ, Richards H, Pickard JD, et al: Enhancement of cerebral blood flow using systemic hypertonic saline therapy improves outcome in patients with poor-grade spontaneous subarachnoid hemorrhage. **J Neurosurg 107:**274–282, 2007
43. 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 34:**1389–1396, 2003
44. Vialet R, Albanèse J, Thomachot L, Antonini F, Bourgouin A, Alliez B, et al: 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 31:**1683–1687, 2003
45. Ware ML, Nemani VM, Meeker M, Lee C, Morabito DJ, Manley GT: Effects of 23.4% sodium chloride solution in reducing intracranial pressure in patients with traumatic brain injury: a preliminary study. **Neurosurgery 57:**727–736, 2005
46. White H, Cook D, Venkatesh B: The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury. **Anesth Analg 102:**1836–1846, 2006
47. Worthley LI, Cooper DJ, Jones N: Treatment of resistant intracranial hypertension with hypertonic saline. Report of two cases. **J Neurosurg 68:**478–481, 1988
48. Yildizdas D, Altunbasak S, Celik U, Herguner O: Hypertonic saline treatment in children with cerebral edema. **Indian Pediatr 43:**771–779, 2006

Manuscript submitted December 23, 2010.
Accepted July 26, 2011.
Please include this information when citing this paper: published online September 23, 2011; DOI: 10.3171/2011.7.JNS102142.

Address correspondence to: R. Shane Tubbs, Ph.D., Pediatric Neurosurgery, Children's Hospital, 1600 7th Avenue South, ACC 400, Birmingham, Alabama 35233. email: shane.tubbs@chsys.org.