High-Osmolarity Saline in Neurocritical Care: Systematic Review and Meta-Analysis*

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Background and Purpose: Intracranial hypertension and cerebral edema are known contributors to secondary brain injury and to poor neurologic outcomes. Small volume solutions of exceedingly high osmolarity, such as 23.4% saline, have been used for the management of intracranial hypertension crises and as a measure to prevent or reverse acute brain tissue shifts. We conducted a systematic literature review on the use of 23.4% saline in neurocritically ill patients and a meta-analysis of the effect of 23.4% saline on intracranial pressure reduction.

Design: We searched computerized databases, reference lists, and personal files to identify all clinical studies in which 23.4% saline has been used for the treatment of neurocritical care patients. Studies that did not directly involve either effects on cerebral hemodynamics or the treatment of patients with clinical or radiographic evidence of intracranial hypertension and/or cerebral swelling were eliminated.

Measurements and Main Results: We identified 11 clinical studies meeting eligibility criteria. A meta-analysis was performed to evaluate the percent decrease in intracranial pressure and the 95% confidence intervals, from baseline to 60 minutes or nadir from the six studies from which this information could be extracted. A fixed effects meta-analysis estimated that the percent decrease in intracranial pressure from baseline to either 60 minutes or nadir after administration of 23.4% saline was 55.6% (se 5.90; 95% confidence interval, 43.99–67.12; $p < 0.0001$).

Conclusions: Highly concentrated hypertonic saline such as 23.4% provides a small volume solution with low cost and an over 50% reduction effect on raised intracranial pressure. Side effects reported are minor overall in view of the potentially catastrophic event that is being treated. High quality data are still needed to define the most appropriate osmotherapeutic agent, the optimal dose, the safest and most effective mode of administration and to further elucidate the mechanism of action of 23.4% saline and of osmotherapy in general. (*Crit Care Med* 2013; 41:1353–1360)

Key Words: cerebral blood flow; cerebral edema; hypertonic saline; intracranial pressure; mannitol; subarachnoid hemorrhage; traumatic brain injury

Intracranial hypertension and cerebral edema are cardinal manifestations of severe brain injury resulting from diverse insults including traumatic brain injury (TBI), ischemic stroke (IS), intracerebral hemorrhage (ICH), aneurysmal subarachnoid hemorrhage (aSAH), infections, and neoplasms; both are recognized contributors to secondary brain injury and to poor neurologic outcomes. As a final common pathway, uncontrolled cerebral edema and/or intracranial pressure (ICP) lead to tissue shifts, cerebral ischemia, and herniation, and eventual direct compromise of vital brain structures. Consequently, a major component of critical care in these patients centers on recognition and treatment of brain edema and high ICP. Osmotically active substances are a cornerstone in neurocritical care management protocols and are recommended in current guidelines for TBI, ICH, aSAH, and IS (1–5). Mannitol and hypertonic saline (HTS) are most commonly used and have gained widespread acceptance despite a lack of high quality clinical trials (6, 7). In the absence of definitive evidence, there is significant variance in both the choice and mode of use of these agents (8). HTS is used in many different concentrations, commonly as a 2% or 3% bolus or continuous infusion or in boluses of 5%, 7.5%, or 23.4% (9–12). Definitive evidence is lacking to support the superiority of either mannitol or HTS. Agent selection is often based on several factors: biologic and physiologic characteristics, actual or perceived adverse effects, intravascular volume status, rapid bedside availability, and location of intravenous access (8). A recent meta-analysis suggested that equiosmolar HTS (3%–7.5%) may be more effective than

mannitol for controlling acute increases in ICP (13). In our neurosciences ICU we have been using 23.4% saline boluses for the management of intracranial hypertension crises and as a measure to prevent or reverse acute brain tissue shifts. Accordingly, we conducted a systematic literature review on the use of 23.4% saline in neurocritically ill patients and for the studies that met inclusion criterion, a meta-analysis, with the primary aim of quantifying the effect of 23.4% saline on ICP reduction.

METHODS
Study Identification
We conducted a systematic review of the published literature to identify all clinical studies in which 23.4% saline has been used for the treatment of neurocritical care patients. (We considered 23.4% and 23.5% equivalent for the purpose of this analysis.) Using text words or MeSH headings containing "23.4% hypertonic saline," "23.5% hypertonic saline," "intracranial pressure," "intracranial hypertension," "cerebral edema," "cerebral herniation," "traumatic brain injury," "subarachnoid hemorrhage," "stroke," "intracerebral hemorrhage," "neurosurgery," and "neurocritical care," we performed computerized searches for relevant articles on MEDLINE (1948–present), EMBASE (1980–present), and evidence-based medicine databases (Cochrane DSR, ACP Journal Club, DARE, and the Cochrane Controlled Trials Register from 1990 to present); in addition we examined the use of 23.4% saline in 41 papers identified in a recent meta-analysis on HTS treatment for raised ICP (14). We also searched personal files and reference lists. There were no language restrictions. Studies that were either not related to neurocritical care problems or that did not directly involve either 23.4% saline effects on cerebral hemodynamics or the treatment of patients with clinical or radiographic evidence of intracranial hypertension and/or cerebral swelling were eliminated. The search was performed independently by two investigators (C.L., R.N.) and was completed on November 10, 2011.

Data Extraction
We extracted the following data from each study: its design, objective, number of patients, method of delivery, timing of measurements, main results of the study, and follow-up results. The outcomes assessed included ICP, cerebral blood flow (CBF), brain tissue oxygen (PbtO$_2$), brain water content, radiographic improvement, Glasgow Outcome Score, and adverse outcomes directly attributable to 23.4% saline.

Data Synthesis
The estimated effects of 23.4% saline in each study were extracted in terms of percent decrease in mean ICP from baseline to 1 hour or to minimum ICP and the standard error of this estimate. For the three studies by Koenig et al, Ware et al, and Kerwin et al (12, 23, 25) in which mean ICP values only at baseline and follow–up were published, the mean percent difference was calculated as,

$$\%change = \frac{ICP_{end} - ICP_{BL}}{ICP_{BL}} \times 100 \, ,$$

where *end* denotes the 60 minutes or nadir and *BL* denotes baseline. Similarly for these studies, the standard errors (SE) for the mean difference were obtained by Taylor series expansion (e.g., the delta method [15]). Accordingly, the SE for percent change was calculated as,

$$SE = \left| \frac{ICP_{end}}{ICP_{BL}} \right| \sqrt{ \frac{SE^2_{end}}{ICP^2_{end}} + \frac{SE^2_{BL}}{ICP^2_{BL}} } \times 100 \, .$$

Although this calculation does not directly account for the correlation between ICP measures within individuals, this correlation cannot be determined from studies that do not report patient level data, so it is ignored in the meta-analysis. A combined estimate of percent decrease in ICP was obtained via a meta-analysis conducted using the R 2.13.0 programming language package metafor (16). A Q test for heterogeneity of effect sizes was conducted and a linear mixed effects model weighted by the inverse of the study-specific variance was fit in order to get a combined estimate (17). The Q test for heterogeneity [$Q(df = 5) = 8.57$, $p = 0.13$] indicated that there was no significant heterogeneity among study-specific estimates; thus, the fixed effects meta-analysis is reported. However, both fixed and random effects meta-analysis gave similar results.

RESULTS
Systematic Review
Thirty-seven papers were identified using our search strategy. Twenty-two were excluded as unrelated, six were excluded as experimental animal studies, one case report was excluded for using 18% HTS, and one paper was excluded for being a review. Seven studies were included. In addition, four relevant studies were identified among the 41 papers included in the meta-analysis by Mortazavi et al (14). In total, 11 studies were included (12, 18–27) of which only one was a prospective randomized controlled trial (RCT), and these studies are summarized in **Table 1**. Search strategy, flow diagram of studies, and reasons for exclusion are shown in **Figure 1**. These studies reported specifically on the use of 23.4% saline in the neurocritical care of patients of diverse pathologies including TBI, aSAH, ICH, IS, and patients with brain tumors.

Aneurysmal Subarachnoid Hemorrhage
Suarez et al discussed eight patients (five with aSAH) who failed conventional measures to control ICP and thus were deemed to have refractory intracranial hypertension (18). These measures included furosemide, mannitol, hyperventilation, and barbiturates. Twenty instances of refractory intracranial hypertension were treated with 23.4% saline; ICP was more than halved after administration and the effect was sustained for 6 hrs. No changes in levels of serum Na, mean arterial pressure, central venous pressure, or urine output were noted. Seven patients

TABLE 1. Clinical Studies of 23.4% Hypertonic Saline in Neurocritical Care Patients

Author, Year	Objective	Design	Number of Patients	Pathology	Description	ICP Effect	Other and Adverse Effects	Clinical Outcome
Suarez, 1998	23.4% on RIH (30 mL over 20 min)	Retrospective chart review	8	SAH (5), TBI (1), tumor (1), ICH (1)	20 episodes of RIH: failure of conventional measures to decrease ICP by > 50% of max abnormal reading	Median reduced from 41.5 to 17 at 1 hr, 14 at 3 hr. Sustained effect 6 hr	No changes in Na, MAP, CVP, or UOP. No complications	Withdrawal in 7 patients, 2 SAH patients had postmortem, no evidence of CPM
Tseng, 2003	23.5% on CBF (2 mL/kg)	Prospective, nonrandom	10	SAH (poor grade)	Monitoring with TCD, ICP, and in 6 patients Xe-CT	74.7% fall at 1 hr, 139 min $T_{1/2}$	Increased CPP, MAP, FV, Xe-CT, CBF, and decreased CVR. Fall of CBF in a single ROI. Na and Osm rose, Hgb/Hct decreased	Not reported
Ware, 2005	23.4% on ICP-resistant to mannitol (30 mL)	Retrospective chart review	13	TBI	Mannitol (0.25–1.9 g/kg) as first line. When ICP > 20 mm Hg > 60 min, 23.4% 30 mL given	Reductions not significantly different, mannitol vs. 23.4%. Latter more durable, 96 vs. 56 min	23.4%: Na 140 to 145 mmol/L, no adverse effects. Substantial ICP reduction in 6/7 patients with pre-treatment Na > 150 mmol/L	Discharge GOS: 3 moderate. disability, 4 severe, 2 vegetative, 4 died
Al-Rawi, 2005	23.5% on CBF and metabolism (2 mL/kg)	Prospective, nonrandom	14	SAH (poor grade)	Continuous monitoring MAP, ICP, CPP, FV, PbtO$_2$, and MD data	Baseline of 20.8 to 5.9 at 30 and 60 min	Increased MAP, CPP, FV, and PbtO$_2$. CBF increased in 7 and decreased in 2 patients. Trend of improvement in MD data	Not reported
Tseng, 2007	23.5% on CBF auto-regulation, clinical outcome (2 mL/kg)	Prospective, nonrandom	35	SAH (poor grade)	Continuous monitoring MAP, ICP, CPP, FV. Xe-CT in 17 patients	Max decrease by 93.1% at 60 min. Sustained > 180 min	Increased MAP, CPP, FV. Impairment of autoregulation contralateral to aneurysm	Favorable 14, unfavorable 21, died 11. Dose-dependent effect of CBF on outcome
Koenig, 2008	23.4% on TTH (30 mL over 20 min)	Retrospective cohort	68	ICH (29), SAH (16), IS (8), tumor (8), SDH (5), EDH (1), meningitis (1)	76 TTH episodes, 23.4% on top of standard medical and surgical management	From 23 ± 16 to 14 ± 10 mm Hg at 1 hr and 11 ± 12 mm Hg at 24 hr among 22 patients	TTH reversal was predicted by a ≥5 mmol/L rise in Na or an absolute Na of ≥145 mmol/L 1 hr after 23.4% saline. Transient hypotension in 13 events (17%); no evidence of CPM on post-TTH MRI (18 patients)	22 patients (32%) survived to discharge, severe disability in 17, mild to moderate in 5

(Continued)

TABLE 1. (*Continued*). Clinical Studies of 23.4% Hypertonic Saline in Neurocritical Care Patients

Author, Year	Objective	Design	Number of Patients	Pathology	Description	ICP Effect	Other and Adverse Effects	Clinical Outcome
Rockswold, 2009	23.4% on ICP, CPP, PbtO₂ (30 mL over 15 min)	Prospective, nonrandom	25	TBI	ICP > 20 mm Hg for >20 min. 23.4% after failure of hyperventilation, CSF drainage, and sedation	Mean pre-treatment ICP of 25.9 m Hg decreased by a mean of 8.3. ICP > 31 mm Hg decreased by 14.2 mm Hg	Improvement in PbtO₂ of 3.1 mm Hg. Pretreatment CPP < 70 mm Hg increased by a mean of 6 mm Hg. No complications	6 mo mortality of 28%, favorable outcome in 48% of patients
Kerwin, 2009	23.4% vs. mannitol	Retrospective chart review	22	TBI	22 patients received 210 doses of either mannitol or 23.4%. 23.4% patients had significantly higher pre-treatment ICP	Greater reduction for 23.4% (9.3±7.37 mm Hg vs. 6.4±6.57 mm Hg). No difference in duration	No adverse events. Mean change in Na 1.9 mM and in Osm (2.8 mOsm/kg). Max increase of Na was 11 mM, whereas max Osm increase was 27 mOsm/kg	Not reported
Al-Rawi, 2010	23.5% on CBF and PbtO₂ (2 mL/kg)	Prospective, nonrandom	44	SAH (poor grade)	Continuous monitoring MAP, ICP, CPP, FV, PbtO₂. Xe-CT in 16 patients. CBF in ROI surrounding PbtO₂ sensor calculated	Baseline ICP of 17.5±9.1 mm Hg decreased to 5.4±4.2 mm Hg at 30 min. ICP remained reduced > 300 min	Increased MAP, CPP, FV, PbtO₂, brain tissue pH, and CBF. Sustained increase in PbtO₂ was associated with favorable outcome. No adverse effects	Unfavorable GOS in 64% with mortality of 33%
Diringer, 2011	23.4% vs. mannitol on CBF, CBV, OEF, CMRO₂	Prospective, randomized	9	IS	Patients with clinical deterioration and >2 mm MLS.¹⁵O-PET performed before and 1 hr afterRandomly assigned equi-osmolar Mannitol (1.0 g/kg) or 23.4% saline (0.686 mL/kg)	ICP not measured	CBF trend to rise in the contralateral hemisphere after mannitol but not 23.4%. CBV, OEF, and CMRO₂ did not change for either agent. Found no support for osmolar agents reducing CBV	Not reported
Paredes-Andrade, 2011	23.4% (30 mL over 15 min) on ICP in the presence of a range of serum and CSF Osm	Retrospective chart review	18	TBI	42 doses of 23.4% for RIH, 37 analyzed. CSF, serum Osm, Na, hourly ICP, BUN, and creatinine measured	Mean reduction of 8.8 mm Hg. Decreased ICP irrespective of Osm	No adverse effects	Favorable GOS in 53% with mortality of 35% at 6 mos

ICP = intracranial pressure; RIH = refractory intracranial hypertension; SAH: subarachnoid hemorrhage; TBI = traumatic brain injury; ICH = intracerebral hemorrhage; Na: serum sodium concentration; MAP = mean arterial pressure; CVP = central venous pressure; UOP = urine output; CPM = central pontine myelinolysis; CBF = cerebral blood flow; TCD = transcranial Doppler; Xe-CT = xenon computed tomography; $T_{1/2}$: half time; CPP = cerebral perfusion pressure; FV = flow velocity(TCD); CVR = cerebrovascular resistance; ROI = region of interest; Osm = serum osmolarity; Hgb = hemoglobin level; Hct = hematocrit level; GOS = Glasgow Outcome Scale; PbtO₂ = partial brain tissue oxygen tension; MD = microdialysis; TTH = transtentorial herniation; IS = ischemic stroke; SDH = subdural hematoma; EDH = epidural hematoma; MRI = magnetic resonance imaging; CSF = cerebrospinal fluid; CBV = cerebral blood volume; OEF = oxygen extraction fraction; CMRO₂ = cerebral metabolic rate for oxygen; MLS = midline shift; PET = positron emission tomography; BUN = blood urea nitrogen.
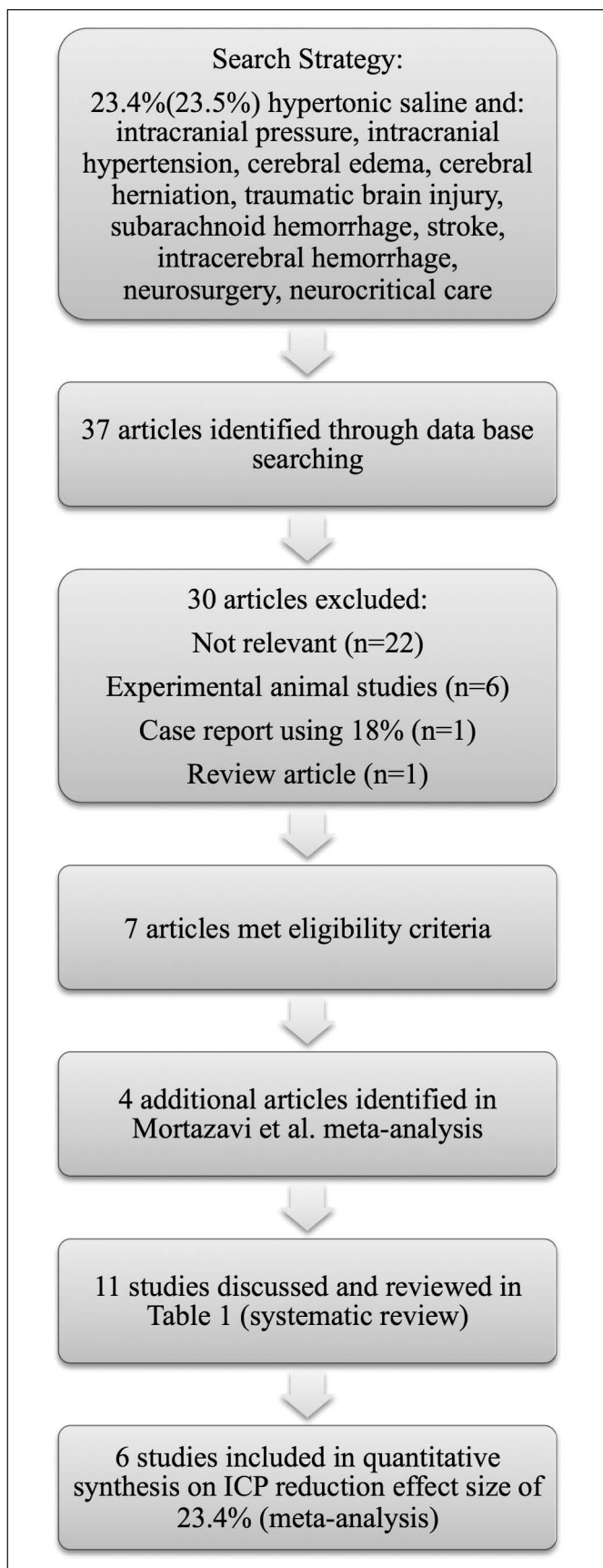
Search Strategy:

23.4%(23.5%) hypertonic saline and: intracranial pressure, intracranial hypertension, cerebral edema, cerebral herniation, traumatic brain injury, subarachnoid hemorrhage, stroke, intracerebral hemorrhage, neurosurgery, neurocritical care

37 articles identified through data base searching

30 articles excluded:

Not relevant (n=22)

Experimental animal studies (n=6)

Case report using 18% (n=1)

Review article (n=1)

7 articles met eligibility criteria

4 additional articles identified in Mortazavi et al. meta-analysis

11 studies discussed and reviewed in Table 1 (systematic review)

6 studies included in quantitative synthesis on ICP reduction effect size of 23.4% (meta-analysis)

Figure 1. Search strategy and flow chart of studies. ICP = intracranial pressure.

had care withdrawn reflecting the severity of neurologic injury in this cohort. Two patients had postmortem examinations that did not reveal evidence of cerebral pontine myelinolysis.

Tseng et al were next to report on 10 patients with poor-grade aSAH (19). Apart from monitoring of ICP, patients were also monitored by transcranial Doppler and six of them had CBF measurements via Xe-enhanced computed tomography. ICP was found to decrease by close to 75%; in addition, augmentation of cerebral perfusion pressure, transcranial Doppler flow velocity, and CBF were recorded. Further insight into the mechanism of action was gained by the finding of enhanced CBF in the face of decreased cerebrovascular resistance, pointing to potential rheologic and cerebral vasodilatory properties of 23.5% saline. Concern was raised by a possible "steal phenomenon" in a single instance of a penumbral area that showed reduced perfusion after the administration of 23.5% saline. It is not clear whether this was an isolated event, but as the authors mentioned, it deserves further study. Subsequent reports on patients with aSAH, from the same group of investigators, has further elucidated mechanisms of action and also the potential utility of 23.5% saline in this group of patients. Al-Rawi et al demonstrated that increase in CBF is accompanied by improvement in tissue oxygenation and metabolism when poor-grade aSAH patients are treated with 23.5% saline and monitored with brain tissue oxygen and microdialysis probes (20). This increment in $PbtO_2$ has been more recently shown to correlate with improved neurologic outcome (21). Tseng et al further explored the effect of 23.5% saline on pressure-reactivity and CBF regulation in patients with aSAH (22). Consistent with previous reports, increases of cerebral perfusion pressure, mean arterial pressure, flow velocity, and Xe-computed tomography CBF were observed. Interestingly, a temporary disturbance of flow autoregulation and pressure reactivity was noted during 23.5% saline administration. The explanation offered by the group, and in conjunction with the earlier finding of decreased cerebrovascular resistance, indicates a transient vasoplegic effect. Importantly, in this study neurologic outcomes are reported showing a dose-dependent effect of CBF augmentation on favorable outcome.

Traumatic Brain Injury

Ware et al studied the effects of HTS in TBI patients with intracranial hypertension resistant to the administration of mannitol; 23.4% saline was only given after 60 minutes had elapsed from a mannitol dose with persistent ICP >20 mm Hg. They found HTS to have a more durable effect to ICP reduction (96 vs. 56 min) and to be also effective in patients with preadministration serum Na of >150 mEq/L. This latter finding suggesting ICP reduction mechanisms unrelated to an increase in serum Na and serum osmolarity (23). Rockswold et al examined the effects of 23.4% saline on ICP and $PbtO_2$ in 25 patients refractory to sedation, cerebrospinal fluid (CSF) drainage, and hyperventilation (24). Reduction in ICP was accompanied by an increase in tissue oxygenation. In the same year, Kerwin et al reported on a similarly sized cohort comparing 23.4% saline to mannitol in the management of

posttraumatic intracranial hypertension (25). Preadministration ICP and postadministration reduction were significantly higher for patients receiving HTS. There were no differences in duration of effect or adverse outcomes. No correlation to neurologic outcomes was made. Most recently, Paredes-Andrade et al examined the effect of 23.4% saline on ICP in the presence of a range of serum and CSF osmolarities (26). HTS was administered in the setting of refractory intracranial hypertension and was found to reduce ICP irrespective of the serum or CSF osmolarity, pointing again towards the involvement of nonosmotic mechanisms of action and also making high serum Na or osmolarity less of an absolute contraindication to the administration of HTS.

Ischemic Stroke

Diringer et al compared the effects of 20% mannitol and 23.4% saline on CBF, cerebral blood volume (CBV), oxygen extraction fraction, and cerebral metabolic rate for oxygen in nine deteriorating IS patients with midline shift (27). This was a prospective randomized study of equiosmolar doses of mannitol (1 g/kg) or 23.4% saline (0.686 mL/kg). The authors found a mean arterial pressure-dependent effect of these hyperosmolar agents on CBF, where only with an elevated blood pressure a significant rise of CBF was noticed in the contralateral (unaffected) hemisphere. In addition, no effect on CBV was observed after administration of either agent, arguing against the hypothesis of compensatory cerebral vasoconstriction as the mechanism of ICP reduction.

Brain Resuscitation

Koenig et al studied a retrospective cohort of neurocritically ill patients treated in a single center with 23.4% saline specifically as a means of transtentorial herniation reversal (12). Fifty-seven out of 76 episodes were successfully reversed, defined as a reduction in pupillary diameter with return of light responsiveness and associated with a ≥2-point increase in Glasgow Coma Scale within 1 hour of administration. Twenty-two patients (32%) survived to discharge (five with mild to moderate disability). Transient, mostly inconsequential, hypotension was the major side effect of HTS administration. No evidence of cerebral pontine myelinolysis was found in the 18 patients who underwent magnetic resonance imaging examination posttreatment. An editorial accompanying this study suggested inclusion of 23.4% saline in a potentially algorithmic approach to acute brain resuscitation or "brain code" (28).

Meta-Analysis

A meta-analysis was performed to evaluate the effect of 23.4% saline on ICP. **Figure 2** displays the percent decrease in ICP and the 95% confidence intervals, from baseline to 60 minutes or nadir from the six studies from which this information could be extracted (12, 19–23). A fixed effects meta-analysis estimated that the percent decrease in ICP from baseline to either 60 minutes or nadir after administration of 23.4% saline was 55.6% (se 5.90; $p < 0.0001$; 95% CI, 43.99, 67.12) as shown in Figure 2.
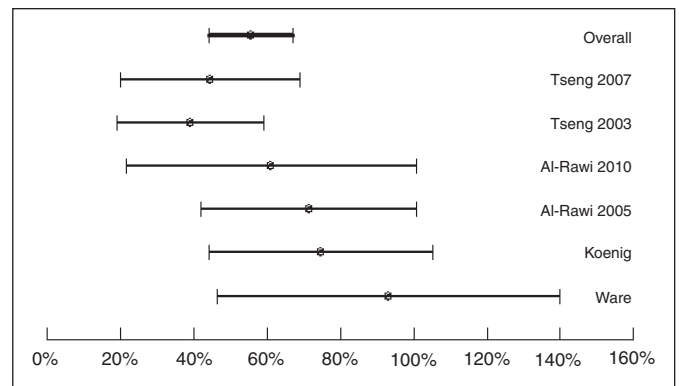

Figure 2. Meta-analysis of intracranial pressure reduction effect. Percent decrease in intracranial pressure and 95% confidence intervals, from baseline to 60 min/or nadir for each study, and the combined overall effect.

DISCUSSION

Highly concentrated hypertonic solutions (30% sodium chloride or saturated sodium bicarbonate in distilled water) were first described to decrease cerebrospinal fluid pressure and brain bulk following TBI in cats, in 1919 by Weed and McKibben (29). The exact mechanism of ICP reduction remains ill defined but potentially involves several characteristics: osmotic, rheologic, and metabolic. The osmotic effect relies on the principle that sodium exhibits low permeability across the blood-brain barrier as noted by its high reflection coefficient (σ = 1.0 on a scale of 0–1.0). High osmolar concentrations create a driving force to mobilize water from the interstitial and intracellular compartments of the brain into the intravascular compartment, therefore reducing brain water content, mass effect, and ICP. The model assumes an intact blood-brain barrier, expressing low hydraulic conductivity (30). The osmotic dehydration effect may predominately occur in normal brain tissue rather than injured locations, although this remains controversial (31–33). The rheologic effect of HTS relies on increasing red blood cell deformity resulting in reduced blood viscosity (34, 35); it is proposed that a reduction in viscosity promotes compensatory vasoconstriction in order to maintain CBF and thus reduces CBV and ICP (33, 36). This model assumes intact vascular reactivity and has been challenged (27). Although less understood, numerous other proposed mechanisms contributing to the therapeutic effect of HTS exist, including dehydration of cerebrovascular endothelial cells with ensuing increase in vessel diameter, immunomodulatory, and neuroendocrine effects. HTS may also assist in preserving the blood-brain barrier by restoring normal resting membrane potential (37–40). Pharmacokinetic data with HTS are lacking; however, studies with mannitol suggest that the effects on ICP begin within minutes, peak between 15 and 120 minutes, and last for up to 4 to 6 hours (41). It is the authors' experience that HTS solutions display a very similar rate of onset. A formal pharmacoeconomic analysis of mannitol and HTS solutions does not currently exist. The average acquisition cost is approximately $12/100 g of mannitol vs. $1.2/30 mL of 23.4% saline. An equiosmolar dose is 0.686 mL/kg 23.4% saline vs. 1 g/kg 20% mannitol.

Mounting evidence, including two meta-analyses, suggest that HTS may be more effective than mannitol in reducing ICP (13, 14, 42–45). Mortazavi et al identified 36 articles and in a meta-analysis of eight prospective RCTs showed a higher rate of treatment failure or insufficiency with mannitol or normal saline versus HTS (14). Kamel et al analyzed five trials comprising 112 patients with 184 episodes of elevated ICP, finding the relative risk of ICP control and the difference in mean ICP reduction, both favoring HTS over mannitol (13). We did not intend to compare the two agents but to quantify the effect of 23.4% saline on intracranial hypertension. Our meta-analysis shows 50% reduction of an elevated ICP after administration of 23.4% saline. Two of the studies we included, by Ware et al (23) and Kerwin et al (25), demonstrated effectiveness of 23.4% saline on ICP refractory to mannitol. Proper comparison of the two agents can only be done in a properly designed RCT, and it should be acknowledged that only one of the studies included in this systematic review (27) was a prospective RCT. It should also be kept in mind that clinical characteristics such as volume status and renal, cardiac, and hemodynamic functions become critically relevant when choosing among hyperosmolar treatments.

Importantly, the aim of this meta-analysis was to quantify the effect of 23.4% saline on raised ICP in patients with diverse intracranial pathologies; nevertheless, we recognize that the mere reduction of ICP is a practical goal but maybe a moot point if not accompanied by improved patient functional outcomes. Furthermore, successful control of intracranial hypertension does not guarantee an improved neurologic outcome, as demonstrated in patients with diffuse TBI randomized to decompressive craniectomy versus maximal medical management in the DECRA trial (46). Notwithstanding this crucial limitation, we believe that data on the effective management of intracranial hypertension are valuable to practicing clinicians in the daily management of patients with compromised intracranial compliance and in risk of cerebral herniation. It should also be appreciated that functional outcome is dependent on a series of clinical factors, and no single intervention to reduce ICP should be necessarily expected, by it self, to dramatically alter patient outcome.

Another limitation of our meta-analysis relates to the nonuniform dosing of 23.4% saline used in the six studies included. Koenig et al (12) and Ware et al (23) used 30 used 30-mL boluses of 23.4% saline where the studies by Tseng et al (19, 22) and Al-Rawi et al (20, 21) used 2 mL/kg doses of 23.5% saline. We decided to analyze them together to not further reduce the overall number of patients studied and because the effect size on ICP reduction was similar across studies, as can be seen in **Figure 2**.

The theoretical side effects and complications related to the administration of HTS include volume overload, severe hypernatremia (Na >160 mEq/L), kidney injury, the osmotic demyelination syndrome, rebound cerebral edema and ICP elevation, exacerbation of brain tissue shifts, systemic hemolysis and local infusion toxicity. In the studies comprising this systematic review, we found remarkably few adverse effects, which are reported in **Table 1**. The most common complication from administration of 23.4% saline is transient hypotension, overall benign and related to the rate of infusion. Koenig et al reported a 17% incidence; in all cases, hypotension resolved within minutes, either spontaneously or after administration of a vasopressor agent or fluid challenge. The same authors performed magnetic resonance imaging of the brain in 18 of 68 patients after 23.4% saline administration and found no evidence of cerebral pontine myelinolysis. Finally, Koenig et al also reported unexplained anemia and hyperbilirubinemia, suggestive of a hemolytic process, in 2 of 76 (2.6%) events requiring transfusion of packed red blood cells (12). Volume overload is less of a problem with the administration of 23.4% saline since the usual dose is 30 mL. Also, rebound phenomena would potentially be more expected where continuous hypertonic solutions are used for prolonged periods. Nevertheless, attention should always be paid in careful "weaning" of hypernatremic states in these patients. Overall, our experience matches the well-tolerated safety and efficacy profile of 23.4% saline as reflected in the above studies and, as other authors recently noted, we believe that the aforementioned theoretical risks maybe less common in practice than perceived (47).

CONCLUSION

HTS and mannitol are the mainstays of treating neurologic and neurosurgical emergencies related to brain edema and high ICP. Superiority of one agent over the other has not been conclusively shown; clinical scenario, mechanism of action, and patient characteristics need to be taken into account. Highly concentrated HTS such as 23.4% saline provides a small volume solution with exceedingly high osmolarity capable of resulting in an over 50% reduction effect on raised ICP. Side effects reported in the reviewed literature are minor overall in view of the potentially catastrophic events being treated. There is no adequate data to compare the effect of 23.4% saline to that of equiosmolar doses of mannitol. Nevertheless, a few of the studies reported examined 23.4% saline as a "rescue" after failed mannitol administration. Further, high quality, randomized trials are needed to define the more appropriate agent, the optimal dose, the safest and most effective mode of administration, to further elucidate the mechanism of action of 23.4% and of osmotherapy in general, and to examine the effects on functional outcomes.

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