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Journal of NEUROSURGICAL ANESTHESIOLOGY

Comparison Between Hypertonic Saline and Mannitol in the Reduction of Elevated Intracranial Pressure in a Rodent Model of Acute Cerebral Injury

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Table of Contents:

≪ The Effect of Cerebrospinal Fluid Drainage on Cerebral Perfusion in Traumatic Brain Injured Adults.

≫ NPS 1506: A Novel NMDA Receptor Antagonist: Neuroprotective Effects in a Model of Closed Head Trauma in Rats.

Links

Abstract

Complete Reference

Summary:

Clinically both mannitol and hypertonic saline (HTS) have been used successfully to treat elevated intracranial pressure (ICP), although which therapy is superior is yet unclear. Most experimental data have been derived from animal models of

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≪ Table of Contents

About

ExternalResolverBasic

Outline

- Summary:
- MATERIALS AND METHODS
  - Cryogenic Lesion
  - Hypertonic Fluid Injection
  - Lesion Volume
  - Statistical Analysis
- RESULTS
- DISCUSSION
- REFERENCES

Graphics

- Table 1
- Fig. 1
- Fig. 2
- Fig. 3
- Fig. 4
- Fig. 5
- Fig. 6
- Fig. 7
- Table 2

this Journal ≫

brain injury using general anesthesia, which may not be applicable under other conditions. Our laboratory compared the efficacy of single, equi-osmolar bolus doses of HTS and mannitol in reducing elevated ICP in a lightly sedated, unrestrained rodent model of acute brain injury. Sprague-Dawley rats were mask anesthetized for craniectomy and placement of invasive monitors. Following emergence from anesthesia, continuous sedation was provided (0.25% halothane in oxygen). A focal, liquid nitrogen cold lesion was introduced to the right parietal cortex. Animals were continuously monitored and then treated with a single bolus of 0.9% saline (control group) or 11.0 mOsm/kg equivalents of either mannitol or HTS (experimental groups) at time of maximal ICP increase (60 minutes). Both mannitol and HTS reduced ICP, but HTS was more effective—53.9% reduction versus 35.0% ($P < .01$). The therapeutic action of HTS was also more durable, lasting up to 500 minutes whereas the mannitol treated animals were observed to return to, and overshoot the baseline elevated ICP by 10% to 25% by 120 minutes following dosing ($P < .01$). Despite these differences, brain water content was similar between groups. We conclude that HTS was more effective in reducing elevated ICP in this awake model of traumatic brain injury.

Since 1919 when the first report of the beneficial effects of hypertonic saline (HTS) on reducing intracranial pressure (ICP) was described by Weed and McKibben, the use of hyperosmolar agents has become commonplace as acute therapy for ICP management (1-6). Through the years, a variety of compounds have been utilized, including mannitol, urea, sorbitol, glycerol, and several concentrations of HTS solutions. Although several mechanisms of action have been suggested, the reduction of ICP appears primarily because of the egress of water from the intracranial compartment as a response to an increase in plasma osmolarity (6-11). Abundant data now clearly demonstrate that hyperosmolar mannitol and saline therapy can also increase both cerebral blood flow (CBF) and brain O_2 delivery (12-16). Recent clinical attention has been in the specialty area of trauma and the resuscitation of patients with hypovolemic shock. Data analysis suggest that trauma patients in shock have approximately a two-fold higher chance of survival when administered HTS/dextran solutions as resuscitation fluid rather

than isotonic fluid media (17).

Which hypertonic medium is superior, however, has not been clarified. Mannitol remains the historic standard, but its use risks several untoward complications, including hypotension (18,19), rebound intracranial hypertension (18,20), and renal failure (20,21). Therefore, there has been a clinical resurgence of interest in HTS solutions for the treatment of elevated ICP. However, few experimental comparisons between HTS and mannitol have been performed using models that closely mirror clinical pathophysiological conditions. Recent animal studies have employed mammalian models of traumatic brain injury where general anesthesia is employed (18,22-24). Large doses of intravenous or volatile anesthetic agents have a profound effect on CBF, cerebral metabolic rate ($CMRO_2$), and ICP which may influence experimental results. Our laboratory compared the efficacy of equi-osmolar bolus doses of HTS and mannitol in reducing elevated ICP, both magnitude and duration of effect, in a sedated, unrestrained rat model of acute brain injury. We also evaluated the effects of each treatment on hemodynamic parameters, serum electrolytes, and alterations in brain water content both in injured and normal brain regions.

MATERIALS AND METHODS

All animal experimentation was performed with Johns Hopkins Institutional Review Board approval for animal investigation. Sprague-Dawley rats (250-400 gm) were briefly anesthetized with 2% halothane/oxygen for placement of jugular central venous and femoral arterial catheters. Catheters were secured by suture at point of incision and behind the neck. Local infiltration of 1% lidocaine was used at all wound margins. Animals were then placed in a Kopf stereotactic frame where a scalp incision was performed to expose the cranium. A dental drill was used to enter the subdural space and P-50 tubing flushed with preservative free saline was inserted underneath the cranial defect and fixed with methylmethacrylate cement for recording of ICP. For animals undergoing cryogenic lesion (n = 121), a small funnel (7 mm dia. tip) was sealed within the craniectomy defect, with trace of epoxy resin around the outer edges of the funnel. Following surgery, additional topical lidocaine was applied and the animals were maintained under an 18 inch diameter glass dome supplied with minimal inhalational anesthesia (0.25% halothane in oxygen) to permit free roaming activity without the risk of injury or imperil invasive monitoring. A total of 0.5-1.0 cc of 0.9% saline was injected through the central venous catheter each hour to maintain patency (1.5-2.5 cc/

and water was additionally provided. Mean arterial (MAP) and central venous pressures (CVP) and ICP were monitored continuously and displayed using an analog strip chart recorder. Blood samples, one per animal in volumes of 100-200 µL, were collected for determination of arterial blood gas tensions and hematocrit (HCT), and serum osmolarity and sodium concentration. Replacement fluid other than the treatment volumes were not given. Few animals (< 7%) suffered significant morbidity during craniotomy and line insertion and were excluded from the study. A total of 196 animals were utilized in all experiments evaluating dose-response in normal brain, effects of hypertonic media on elevated ICP, and quantification of lesion volume following cryogenic brain injury (Table 1).

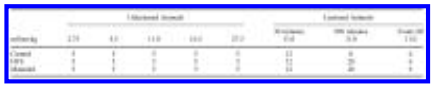

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TABLE 1. *Experimental groups in hypertonic protocol*

At the end of experimentation, animals were euthanized with an IP injection of pentobarbital 80 mg/kg, and their brains were rapidly removed within 60 seconds. Wet weights were determined to the nearest 0.1 gm for each hemisphere or subdivided cortical (including hippocampus) and subcortical (basal ganglia, thalamus, brainstem) regions. The brain tissue was then desiccated in a vacuum dryer for 4 days for determination of dry weights. Brain water content was calculated by the wet to dry weight difference: (wet wt. - dry wt.)/wet wt. × 100% = % water content (25).

Cryogenic Lesion

Following more than 1 hour recovery from surgery and general anesthesia, baseline hemodynamic and ICP measurements were performed. Liquid nitrogen was poured through the funnel. Following 90 seconds of cold exposure, the liquid nitrogen was suctioned off and the funnel removed. For 10 minutes, the animal was removed from the anesthesia chamber to permit safe recovery from the acute insult. Thereafter, the animal was placed back inside the chamber for the duration of the experiment. Before injury, animals were ambulatory without gross neurologic impairment. The cryogenic lesion induced

a result of the cerebral injury and were not included in the study. Animals continued to take water by mouth intermittently although none engaged in feeding throughout the time period. All catheter injections and blood withdrawals were performed from outside the chamber.

Hypertonic Fluid Injection

Single, intravenous injections of hypertonic solutions using an alternating randomization protocol between control, HTS, and mannitol were performed over 30 seconds at dose-response concentrations ranging from 2.75 mOsm/kg-27.5 mOsm/kg of 25% mannitol (5.5 mOsm/kg of mannitol = 1 gm/kg equivalent, 4 ml/kg injection) or HTS (23.4%) in groups of 5 animals each total (Table 1). No animal received more than a single bolus of fluid. Control animals were administered 2-20 ml/kg of isotonic saline (0.9% NaCl) depending on dose comparison. Maximal ICP reduction was observed at 11 mOsm/kg and this dose was used in the focal injury model for measurements of peak efficacy, duration of ICP control, and alterations in hemodynamics and serum chemistries. For evaluation of peak effect of hypertonic therapy in reducing elevated ICP, experiments were carried out for 30 minutes following fluid bolus administration. Duration of effect experiments were prospectively designed to monitor the effect of hypertonic treatment up to maximal period of 500 minutes.

Lesion Volume

To assess the extent of cryogenic injury, Evans Blue 1% (3 ml/kg) was intravenously injected in a separate group of control (n = 6), mannitol (11.0 mOsm/kg, n = 6), and HTS (11.0 mOsm/kg, n = 6) treated animals following cryogenic injury. The possible effects of Evans Blue injectate volume on brain water content in the larger experimental cohorts were thus avoided. Following 90 minutes post-injury as per the standard protocol, animals were sacrificed, brains perfused-fixed with intracardiac perfusion of phosphate buffered saline/paraformaldehyde (100 mM phosphate pH 7.4, 3.3% paraformaldehyde), and preserved in 10% formalin. Injury volumes were evaluated by sectioning the brain coronally at 2 mm increments and assessing for % cross-sectional area stained of each brain slice.

Statistical Analysis

All data were presented using mean values +/- SEM. Significance testing was by analysis of variance with Bonferroni

posthoc correction ($P < .05$ unless otherwise stated).

RESULTS

Compared to controls, unlesioned animals (n = 5), treatment with intravenous bolus infusion of either mannitol (n = 5) or HTS (n = 5) at a dose of 11.0-27.5 mOsm/kg (equivalent to 1-5 gm/kg of mannitol) was effective in reducing ICP by 30%-40% (Fig. 1). Maximal reduction in ICP occurred within 30 minutes following bolus and persisted for a minimum of 60 minutes. A dose of 11.0 mOsm/kg of either agent afforded the greatest effect with respect to ICP decrease per mOsm/kg dose, and no greater reduction of ICP was observed beyond that dose. Although hemodynamically the animals remained stable, CVP increased by 40%-60% in both groups following maximal dosing of mannitol and HTS.

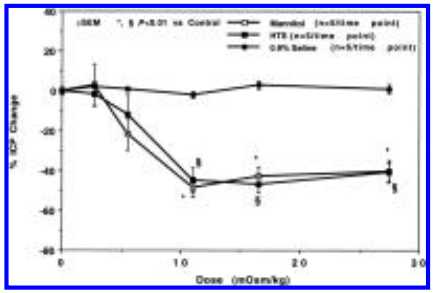

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FIG. 1. Dose response curves comparing the effects of a single, intravenous bolus infusion of mannitol or hypertonic saline (HTS) on the intracranial pressure (ICP) in nonanesthetized, unlesioned animals. Percent change in ICP is from baseline value (mm Hg) at T_0 and measured at 20-30 minutes following treatment at time of maximal decrease in ICP. Dose range in mOsm/kg are approximately equivalent to between 1-5 gm/kg of mannitol. Maximal ICP decrease is observed at 11.0 mOsm/kg, 2 gm/kg mannitol equivalent.

Following acute focal cerebral injury, ICP in control animals (n = 12) significantly increased from 5.8 ± 0.2 (SEM) mm Hg to a peak of 27.2 ± 0.5 mm Hg at 60 minutes post-injury (Fig. 2). Thereafter, the ICP remained elevated at peak levels for a minimum of 120 minutes. Both mannitol (n = 12) and HTS (n = 12) in doses of 11.0 mOsm/kg induced an acute reduction in ICP when administered at the peak of ICP elevation. Hypertonic saline was, however, more effective than mannitol, promoting a mean decrease of ICP by 43.0% (30.6 ± 1.7 mm Hg to 16.2 ± 0.8 mm Hg) compared to a 30.8% decrease with mannitol (29.5 ± 1.7 mm Hg to 20.4 ± 1.4 mm Hg, $P < .01$ HTS compared to mannitol).

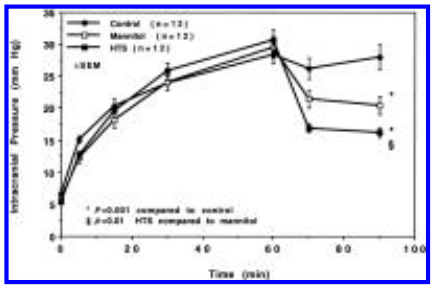

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FIG. 2. Comparison of maximal effect of mannitol and hypertonic saline (HTS), each given as a single intravenous bolus (11.0 mOsm/kg) in reducing elevated intracranial pressure (ICP) following focal cerebral injury. Hyperosmolar agents were administered at 60 minutes post-injury, at time of peak ICP elevation. Maximal ICP decrease was observed within 20-30 minutes following bolus dose of either agent. ICP decreased by a mean of 53.9% with HTS, 35.0% with mannitol.

The action of HTS on reducing ICP was not only greater in potency compared to mannitol, but was more sustained.

When administered in cerebral injured animals at the point of maximal ICP elevation (60 minutes), mannitol (n = 28) exhibited maximal ICP reduction action at 10-20 minutes, and by 60 minutes the ICP began to reverse upward. A return to the post-injury ICP plateau was uniformly demonstrated in the mannitol treated animals by 120 minutes (Fig. 3). Thereafter, ICP continued to rise to 110%-125% of peak values before declining 1-2 hours later and remained near the maximal ICP plateau for the experimental duration of 8 hours. In animals treated similarly with HTS (n = 28), ICP remained more than 30% below peak levels for 3 hours ($P < .01$ compared to mannitol for time points between 100 minutes-250 minutes), then continued 10%-15% below maximum for the duration ($P < .05$ compared to mannitol). Never did the ICP return to, or overshoot the preinfusion peak.

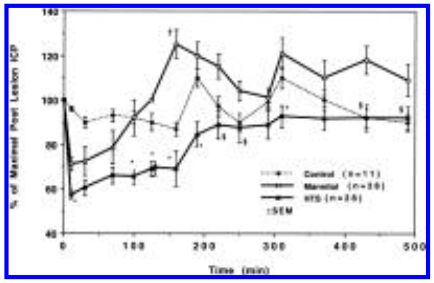

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FIG. 3. Comparison of the magnitude and duration of therapeutic intracranial pressure (ICP) reduction between control (saline), mannitol, and hypertonic saline (HTS) administered 60 minutes following acute focal cerebral injury. The efficacy of HTS was greater both in regards to maximal ICP decrease and enduring effect. A rebound ICP elevation was noted for mannitol (110%-125% of peak ICP values) approx. 2-4 hours following administration. As in Figure 1, ICP in HTS and mannitol groups were significantly lower than control at time points between 10-90 minutes. * $P < .01$ HTS vs mannitol and control group; §$P < .05$ HTS vs mannitol; †$P < .05$ mannitol vs control. By ANOVA, data set for HTS was significantly different compared to mannitol and control ($P < .01$).

Physiological perturbations resulting from the injury and hyperosmolar treatment were recorded continuously (MAP, CVP, ICP) or analyzed at the time of peak effect (10-20 minutes following bolus, HCT, and serum osmolarity and sodium concentration). Following injury, control animals received 4 ml/kg of isotonic saline, and this fluid bolus was well tolerated and resulted in only small, nonsignificant alterations in CVP, MAP, or HCT (Fig. 4). Animals observed for 500 minutes did not demonstrate significant disturbances in MAP, although CVP trended downward through the course of experimentation. Arterial blood gas measurements consistently demonstrated pO_2 values >100 mm Hg and pCO_2 for control (34.8 ± 1.7), mannitol (36.3 ± 1.5), and HTS (32.9 ± 2.2) groups at the time of peak drug efficacy-20 minutes post-bolus infusion, 80 minutes post-injury—were similar. Both mannitol and HTS (11.0 mOsm/kg) resulted in a significant reduction in the HCT while the CVP trended higher in the HTS group ($P = .07$). Both hyperosmolar therapies precipitated a rise in serum osmolarity compared to controls, mannitol by 2.6 ± 0.7% ($P < .01$) and HTS by 3.8 ± 0.9% ($P < .01$) (Fig. 5). Serum sodium declined by 5.4 ± 1.8% with the use of mannitol ($P < .01$ compared to control), while HTS infusion resulted in an increase of 9.9 ± 1.5% ($P < .001$).

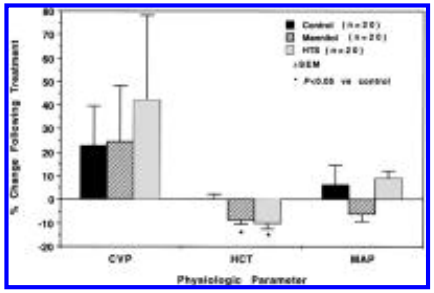

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FIG. 4. Alteration of physiological parameters induced by control saline, mannitol, and hypertonic saline (HTS). Measurements were taken at time of peak efficacy of the hyperosmolar agents—20 minutes post-administration and 80 minutes post-induction of focal cerebral injury. The hematocrit (HCT) was significantly reduced by both hypertonic agents and a trend towards a greater central venous pressure (CVP, mm Hg) was recorded in all three groups (non-significant, NS) following bolus injection of drug and diluent (4 ml/kg).

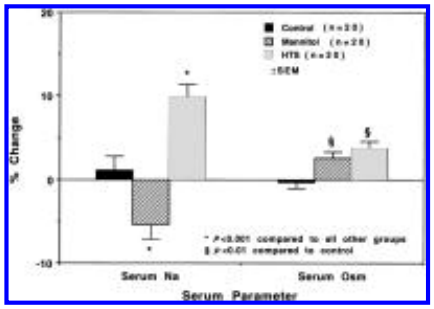

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FIG. 5. Effects of treatment on serum chemistry following bolus infusion of 4 ml/kg 0.9% saline (control) or equiosmolar mannitol or hypertonic saline (HTS, 11.0 mOsm/kg). Measurements were taken at time of peak efficacy of the hyperosmolar agents—20 minutes post-administration and 80 minutes post-induction of focal cerebral injury. Serum sodium (Na) was elevated (HTS) or decreased (mannitol) depending on hyperosmolar agent used. Serum osmolarity (Osm) was elevated compared to control following mannitol or HTS.

Evaluation of the cryogenic lesion volumes induced by the liquid nitrogen technique demonstrated relative uniformity of volume and location of cerebral injury as measured by Evans Blue staining (Fig. 6). Approximately 30%-35% of the right hemisphere sustained injury with this cryogenic technique and the left hemisphere remained injury free. No significant differences were observed between groups with respect to anterior-posterior location or volume of the lesion.

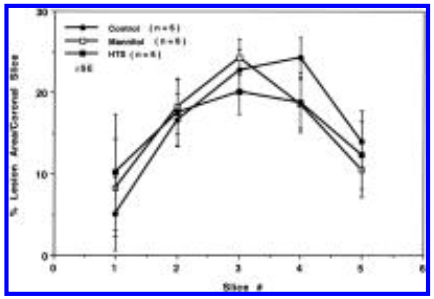

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FIG. 6. Comparison of cryogenic lesion size and relative location in right hemisphere between control, mannitol, and hypertonic saline (HTS) treated animal groups. Perfused-fixed brains treated with Evans Blue prior to sacrifice were cut coronally in 2 mm slices and % area stained of entire slice was calculated. Slice #3 represents coronal section through center of lesioned cortex. Slices #1, 2 and 4, 5 represent sections progressively anterior and posterior respectively to central slice. No difference was observed both for anterior-posterior location or total volume of lesion.

Finally, the alteration in water content induced by the cryogenic lesion and subsequent treatments was analyzed. The diencephalon had a nominally lower water content than did the hemispheric cortex in all three groups. In control animals treated with 0.9% saline (4 ml/kg), lesioned cortex had increased water content as compared to the contralateral hemisphere or when compared to cortex from naive, unlesioned, untreated animals (82.3 ± 0.5% compared to 80.1 ± 0.1% and 79.3 ± 0.1%

water respectively, $P < .05$ lesioned cortex versus either control). Treatment of injured brain with either mannitol or HTS (11.0 mOsm/kg) had no significant effect on decreasing cortical water, either from lesioned or unlesioned cerebral hemispheres (Fig. 7).

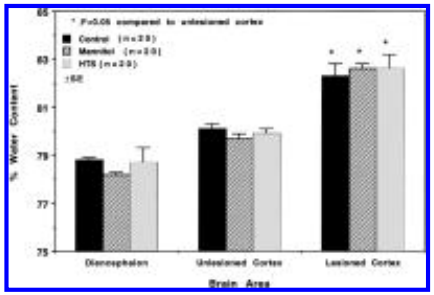

FIG. 7. Brain water content (%) of lesioned and unlesioned cerebral cortex as well as subcortical diencephalon from control (0.9% saline), mannitol, and hypertonic saline (HTS) treated animals. Cryogenic lesion was restricted to the right hemisphere (lesioned cortex, see text). Animals were sacrificed at time of peak efficacy of the hyperosmolar agents—20 minutes post-administration and 80 minutes post-induction of focal cerebral injury. Although lesioned cortex uniformly demonstrated a higher water content compared to unlesioned brain, no differences were noted between groups.

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DISCUSSION

The principal physiological mechanism underlying the efficacy of HTS, mannitol, and other osmotically active agents in decreasing ICP is believed to be an osmotic gradient-induced shift of extra-to intravascular water across the blood brain barrier (BBB) (10,11,23,26-29). Consistent with this concept, our data demonstrated that ICP was significantly reduced in unlesioned animals treated with HTS or mannitol. An important corollary is that an intact BBB is necessary for hypertonic therapy to be efficacious. Regions of cerebral injury with disrupted BBB are thus unamenable to osmotic gradient water shifts (23,29) and such data suggest that hypertonic therapy for ICP reduction is unlikely to be of benefit in conditions of global cerebral injury. TABLE

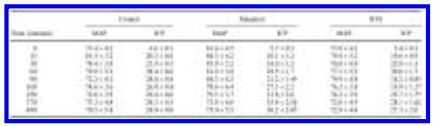

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TABLE 2. *Mean arterial blood pressure (MAP) and intracranial pressure (ICP) data*

Alternative mechanisms of decreasing ICP by hypertonic agents have been proposed. Evidence suggests that both HTS and mannitol decrease the formation of CSF, which may contribute to a reduction in ICP (30-32). Bolus administration of mannitol or HTS also leads to a decrease in plasma viscosity and an increase in cardiac output and CVP. As a consequence of reduced viscosity and improvement in oxygen delivery, a decrease in ICP is achieved through a reduction of CBF and blood volume (33). However, recent data from a canine cerebral injury model was unable to demonstrate significant differences in CBF between control, mannitol or HTS groups, despite significant control of ICP by the hypertonic agents (22).

The current data was derived by using an unanesthetized rodent model of closed head injury to demonstrate that HTS was more effective than mannitol in reducing elevated ICP. Despite equi-osmolar bolus doses, HTS treatment resulted both in a greater absolute ICP decrease as well as yielding a more durable effect than mannitol without a predisposition toward a rebound ICP elevation. That HTS was acutely more effective in controlling ICP may be a result of several factors. In the current study, mannitol and HTS had the same magnitude of ICP lowering effect when administered to control, unlesioned animals. However, when traumatized animals were evaluated, HTS had a greater effect. This observation suggests that the response to the hypertonic challenge by injured brain varies between agents. In normal brain tissue, mannitol has been shown to have a greater permeability across the BBB than sodium ion (Na^+), having a reflection coefficient of 0.9 as compared to 1.0 (34). In addition, the difference is magnified when alterations of BBB integrity occur as has been measured using radiolabeled drug. ^{14}C-mannitol concentrates in uninjured brain, but the gradient toward intracerebral accumulation was increased seven-fold when disruption of the BBB was present (20). Coupled with the rapid renal excretory mechanism of mannitol clearance from plasma, such cerebral sequestration will counter the action of the initial osmotic gradient, thereby limiting the efficacy of mannitol. Such sequestration and rapid elimination may lead to a more limited rise in serum osmolarity, as was observed between HTS and mannitol, although statistical significance was not reached. These data may help explain the relative brief duration of action, reduced potency compared to HTS, and also the potential for rebound intracranial

hypertension observed with mannitol. As the mannitol concentration in plasma falls, sequestration of the sugar moiety within cerebral tissue permits reversal of the osmotic gradient leading to free water transiting into the brain and a rebound ICP effect. This response would be expected to be more prominent following large or repeated dosing of mannitol, as has been reported (20).

The limited duration of effect of decreasing ICP by HTS is likely a consequence of both its pharmacokinetics in plasma and on the intrinsic mechanisms of cellular volume control that exist in brain tissue. While mannitol is rapidly metabolized and excreted, the redistribution of Na^+ within the extravascular/extracellular compartment limits the duration of the favorable plasma osmotic gradient. In addition, egress of fluid across the BBB reduces the extravascular brain compartment which draws water from the intracellular environment. Brain cells possess intrinsic volume-activated electrolyte transporters which counter acute perturbations of cell volume as occur during hypertonic fluid challenge or dehydration (35,36). These transporters temporarily increase solute within cells to force accumulation of water and maintain volume.

Despite the acute corrective actions that occur to limit the efficacy of hypertonic fluids in reducing ICP, a prolonged duration of action of HTS compared to mannitol was firmly demonstrated in the time course experiments. This is the first report measuring ICP in unanesthetized animals to greater than 1 to 2 hours following injury, and the data clearly illustrate the durable efficacy of HTS and lack of rebound action. The greater reflective coefficient coupled with the lack of metabolism of the osmotic moiety likely represent principal mechanisms for this effect.

Our data represent the first direct comparison of mannitol and HTS using the cold lesion model in awake and freely roaming animals. Cold lesion-induced cerebral injury model has been used previously (18,20,23,24,26,29). Following the cold insult, regional disruption of the BBB occurs leading to vasogenic edema surrounding focal brain necrosis extending from the cortical grey to the subcortical corona radiata (37). Such lesions have similar characteristics of pathology induced by blunt trauma, yet are more localized and highly reproducible (29,38). Because our model avoids the effects of general anesthesia, it may more closely resemble clinical therapeutic conditions. The data are consistent with a recent comparative canine study by Qureshi *et al*. where HTS was more effective than mannitol both in the acute and subacute post-administration time period (22). Other studies using anesthetized rabbits or sheep also demonstrated efficacy of both HTS and mannitol in reducing

ICP, although the duration of action of HTS was limited to the first 60 to 90 minutes post-injection (18,23,24).

Hypertonic saline has also been shown to be effective in controlling ICP in models of brain injury caused by space occupying lesions rather than direct injury to cerebral elements. These models attempt to mimic pathology as created by intracranial, subdural, or epidural hemorrhage. Data from Gunnar *et al*., and recently Prough *et al*. used inflated epidural or subdural, balloons in dogs to simulate an intracranial mass lesion in conjunction with a period of shock. In both studies, resuscitation with 3% or 7.2% HTS was able to maintain normal or reduced ICP values whereas a marked elevation was observed following administration of isotonic saline (15,39). Recently, Qureshi *et al*. observed that HTS was acutely as effective and more durable than equiosmolar mannitol in a canine model of intracerebral hemorrhage (22).

The regional brain water content measured in our investigation is comparable to other rodent, feline, rabbit, and canine studies with percent water content in normal brain varying between 78% to 80%(11,18,20,23,24,40). As in previous studies, lesioned cortex became edematous and had an increased water content as compared to uninjured tissue. However, there was no significant difference between our treatment groups. The inability to record significant reductions in water content following hypertonic therapy is likely caused by the limitations of the methods used. Historically both the gravitrimetric (20,28,41-43) and wet-to-dry methods (11,25,31) have been employed with success, although each has inherent limitations. In rodent animal models, the alteration in brain water content—a fraction of a percent between active treatment groups—translates to very small differences in wet tissue weight. The imprecision of measurement of wet weight compared to dry weight no doubt increased the variance observed within treatment groups, and likely led to the inability to observe any significant differences. Whether the gravitrimetric method would have proved a more precise technique is unclear. In studies where both methods were utilized, discrepancies between their results have been observed, without preference to either technique (20,23). Kaufman *et al*., evaluating the effects of repeated mannitol dosing on ICP, were unable to detect a change in brain water content following a single bolus of hypertonic agent despite a significant reduction in ICP. Following multiple doses of mannitol, an increase in injured brain water content was then noted (20).

The present data support the growing clinical literature that HTS may be superior to mannitol in controlling ICP, and perhaps with fewer untoward effects. In addition to the rebound phenomenon, the diuretic effect of mannitol may result in

hypovolemia and hypotension that lead to potential compromise in cerebral perfusion pressure (19). Acute renal failure and hyperkalemia are also possible complications as reported in several studies (21,44-46). So far, clinical use of HTS appears effective and without serious adverse outcomes. A recent clinical trial compared 0.9% saline to 3% HTS in a double-blind crossover study in pediatric head trauma patients. Hypertonic saline effectively reduced ICP without any observed toxicity whereas standard isotonic saline therapy failed to reduce ICP in these trauma patients (47). Review of recent randomized double-blinded clinical trials evaluating the efficacy of HTS in trauma failed to identify any toxicity associated with its use (48-55). In neurosurgical patients with severe cerebral edema postoperatively or following head trauma, HTS has been observed to be effective as a component of comprehensive therapy to reduce brain swelling and elevated ICP (56). There are also additional reports of successful treatment of intracranial hypertension with HTS in patients who have failed to respond to large doses of mannitol (57).

Several limitations of this study must be acknowledged. Although the experiments were conducted in awake, unrestrained animals, a subanesthetic concentration of halothane was used to permit continuous invasive monitoring. The use of volatile anesthetics has been readily demonstrated to increase CBF and ICP (58). At low concentrations however, the effects are conflicting. A mild decrease in CBF may occur as a result of diminished cerebral metabolic rate that is masked at higher concentrations of volatile anesthetics by their primary vasodilatory action (59). The effects of trace halothane, however, should cause minimal perturbation of intracranial dynamics and manifest equally among the experimental animal groups. The small difference in concentration between mannitol (25%) and HTS (23.4%) necessitated small adjustments in volume of solutions administered to equalize the total mOsmoles of solute. This correction resulted in a maximal difference of 0.1 ml in volume between a mannitol versus HTS dose and thus unlikely to bias the hemodynamic or ICP results. Although pCO_2 was measured and found not to differ between groups, continuous monitoring was not performed and differences over time between treatment groups affecting ICP could have occurred influencing the results.

In summary, our observations support the efficacy of HTS in cerebral swelling as a consequence of head trauma. Most importantly, these results demonstrate both the acute benefit of HTS in reducing ICP as well as its durable effect as evaluated in an awake model of brain injury. Our data, together with those of previous investigators, strongly support the need for formal clinical comparisons between these two osmotic therapies before we acknowledge either treatment as optimal

hypertonic therapy.

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