Comparison of Equivolume, Equiosmolar Solutions of Mannitol and Hypertonic Saline with or without Furosemide on Brain Water Content in Normal Rats

Liang Chao Wang, M.D.,* Alexander Papangelou, M.D.,† Christopher Lin, B.A.,‡ Marek A. Mirski, M.D., Ph.D.,§ Allan Gottschalk, M.D., Ph.D.,# Thomas J. K. Toung, M.D.§

ABSTRACT

Background: Mannitol and hypertonic saline (HS) are used by clinicians to reduce brain water and intracranial pressure and have been evaluated in a variety of experimental and clinical protocols. Administering equivolume, equiosmolar solutions in healthy animals could help produce fundamental data on water translocation in uninjured tissue. Furthermore, the role of furosemide as an adjunct to osmotherapy remains unclear.

Methods: Two hundred twenty isoflurane-anesthetized rats were assigned randomly to receive equivolume normal saline, 4.2% HS (1,368 mOsm/L 25% mannitol (1,375 mOsm/L), normal saline plus furosemide (8 mg/kg), or 4.2% HS plus furosemide (8 mg/kg) over 45 min. Rats were killed at 1, 2, 3, and 5 h after completion of the primary infusion. Outcome measurements included body weight; urinary output; serum and urinary osmolarity and electrolytes; and brain, lung, skeletal muscle, and small bowel water content.

Results: In the mannitol group, the mean water content of brain tissue during the experiment was 78.0% (99.3% CI, 77.9–78.2%), compared to results from the normal saline (79.3% [99.3% CI, 79.1–79.5%]) and HS (78.8% [99.3% CI, 78.6–78.9%]) groups ($P < 0.001$), whereas HS plus furosemide yielded 78.0% (99.3% CI, 77.8–78.2%) ($P = 0.917$). After reaching a nadir at 1 h, brain water content increased at similar rates for mannitol (0.27%/h [99.3% CI, 0.14–0.40%/h]) and HS (0.27%/h [99.3% CI, 0.17–0.37%/h]) groups ($P = 0.968$).

Conclusions: When compared to equivolume, equiosmolar administration of HS, mannitol reduced brain water content to a greater extent over the entire course of the 5-h experiment. When furosemide was added to HS, the brain-dehydrating effect could not be distinguished from that of mannitol.

What We Already Know about This Topic

- Despite years of use, controversy remains regarding the optimal osmotherapy for brain swelling
- The efficacies of mannitol or hypertonic saline in reducing brain water were studied in anesthetized rats

What This Article Tells Us That Is New

- The efficacies of mannitol or hypertonic saline in reducing brain water were studied in heterogenous experimental models
- Reduction in brain water is proportional to increases in serum osmolarity, which is enhanced by the addition of furosemide to hypertonic saline

MANNITOL is currently the standard osmotic agent for treatment of brain edema with or without intracranial hypertension. During the past few decades, hypertonic saline (HS) has emerged as an effective osmotic agent for treatment of cerebral edema of diverse causes. Mannitol and HS have similar mechanisms of action in the brain, using an osmotic gradient–induced shift of extravascular to intravascular water across the blood–brain barrier. Theoretically, HS should be a

* Assistant Professor, Department of Surgery, College of Medicine, National Cheng Kung University, Tainan, Taiwan, Republic of China. † Assistant Professor, Department of Anesthesiology and Critical Care Medicine and Department of Neurology, ‡ Research Assistant, § Professor, # Associate Professor, Department of Anesthesiology and Critical Care Medicine, Department of Neurology, and Department of Neurosurgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

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Address correspondence to Dr. Papangelou: The Johns Hopkins Hospital, Department of Anesthesiology and Critical Care Medicine, 600 North Wolfe Street, Meyer 8-134A, Baltimore, Maryland 21287. apapang1@jhmi.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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more effective osmotic agent than mannitol because it has a higher osmotic reflection coefficient (1 *vs.* 0.9).[1] Moreover, HS use is not associated with a risk of acute rebound intracranial pressure (ICP) elevation as a consequence of sequestration, which may occur with mannitol across a disrupted blood–brain barrier.[2–6] In addition, in contrast to mannitol, HS is also a clinically proven volume expander.[7–9] Therefore, HS may be superior to mannitol for treatment of intracranial hypertension, particularly in traumatic head injury,[7–9] where hypotension is commonly encountered. In animal studies of traumatic head injury where equiosmolar doses were studied, HS was shown to be superior to mannitol in the control of elevated ICP.[10–12] However, because the HS tonicities varied in these studies, it is difficult to view them cohesively.

Only two studies have investigated the cerebral effects of mannitol and HS in equivolume, equiosmolar doses. In a model of acute cryogenic brain injury in rabbits, Scheller *et al.* reported that equiosmolar solutions of HS (3.2%) and mannitol (20%) reduced ICP and brain water content equally well when infused at equal volumes.[13] A recent clinical study using equivolume, equiosmolar solutions of 20% mannitol and 3% HS revealed no difference in brain relaxation as judged by the surgeon's subjective assessment.[14] However, in uninjured animals, no fundamental data exist on reduction of brain water by these agents while maintaining parity with respect to administered volume and solute load.

Furthermore, evidence exists supporting the use of combination therapy of osmotherapy with furosemide.[15–19] Furosemide has been combined with mannitol and studied in dogs with elevated ICP (inflated epidural balloon model),[16,19] normal rats,[18] and humans undergoing intracranial surgery.[17] Whether furosemide is added to mannitol or HS, the results from these studies suggest that combination therapy maintains an elevated serum osmolarity, prolongs duration of effect, and augments brain tissue dehydration and ICP reduction, compared with osmotherapy alone. In the only study assessing combination HS therapy, Mayzler *et al.* administered a 3% HS infusion followed by 2 mg/kg of furosemide to rats with closed head injury and found a favorable effect on brain water content at 120 min compared with HS alone.[15]

In the current study, we administered equivolume, equiosmolar HS and mannitol to determine the extent and duration of their ability to reduce water content of cerebrum, lung, skeletal muscle, and small bowel in uninjured rats. Moreover, because HS produces substantially less diuresis than does mannitol, we also investigated whether the magnitude of diuretic effect contributes to tissue water extraction by following HS with furosemide in a separate group of animals.

Materials and Methods

In the first set of experiments, 220 male Wistar rats (250–450 g) were used in an animal protocol approved by The Johns Hopkins Animal Care and Use Committee (Baltimore, MD). Rats were anesthetized with a 1.5% isoflurane–oxygen mixture by mask for placement of a femoral venous catheter and, after a short period of stability, anesthesia was reduced to 1.25% isoflurane for the remainder of the experimental period. Rectal body temperature was maintained between 37 and 38°C with a thermostatically regulated heating lamp. Rats were placed in the prone position. Urine was collected with a moderately inflated size 1 pediatric laryngeal mask airway shortened to 2–3 cm that accommodated securely to the rat's perineum and emptied into a urine receptacle. Baseline body weight, serum electrolytes, and serum osmolarity were measured. Serum osmolarity was determined with an automated freezing point depression microosmometer (Advanced Instruments, Norwood, MA). Rats were randomized into groups of five or six to study solution and study termination time point by computer-generated list. All experiments were performed sequentially and completed before experimentation on the next randomized group was initiated. Each rat received a bolus infusion of either normal saline (NS) (308 mOsM/L), 25% mannitol (1,375 mOsM/L), or 4.2% HS (1,368 mOsM/L), in a volume of 3.2 ml/100 g body weight. Rats in two of the groups received a secondary slow injection of furosemide (8 mg/kg body weight). The five groupings were as follows: NS, NS plus furosemide, mannitol, HS, and HS plus furosemide. Each intervention grouping (n = 44) was divided into subgroupings (n = 11) based on the point at which the animals were killed, specifically, 1, 2, 3, or 5 h after completion of the study solution infusion.

The primary solution was infused over 45 min. Animals randomized to a furosemide group had furosemide administered as a slow injection during the first 5 min of the observation period after completion of the primary infusion. Animals remained anesthetized for 1, 2, 3, or 5 h without receiving additional fluids. Urinary output was reported as a cumulative total measured only at the experimental endpoint. At the conclusion of the experiment, animals were weighed and killed under deep anesthesia. Blood and urine samples were collected to measure osmolarity and electrolytes. Whole brain (typical sample size, 1–1.5 g wet weight), trachea and lungs (typical sample size, 1.1–1.8 g wet weight), quadriceps femoris muscle (typical sample size, 1.5–3 g wet weight), and the entire small bowel (mucous contents gently extracted with typical sample size, 3–4 g wet weight) were harvested for determination of tissue water content. All tissues were dried at 95°F for 2 days. Tissue water content was calculated as follows: % H_2O = (1 – dry weight/wet weight) × 100%.

In a second experiment, rats were anesthetized in the same fashion. After femoral venous and arterial access were obtained, they were assigned randomly to receive one of the same five infusions (n = 7 each group). As with the first set of experiments, they were kept under general anesthesia (1.25% isoflurane) for the 5-h experimental period. Their physiologic state was allowed to fluctuate freely and was recorded at 15-min intervals for the first 75 min, then 30 min later at 105 min, and then every 60 min thereafter.

Statistical Analysis

Data in graphical form are reported as mean, and, when present, error bars represent the SD. Baseline values for

physiologic parameters obtained before intervention are reported as mean (SD) and were compared with ANOVA. All physiologic parameters except for mean arterial blood pressure were analyzed by linear regression over time with robust error analysis. Quadratic or cubic terms were not considered, given that data were obtained at only four points in time. Regressions were performed with respect to intervention and time of observation, and an intercept and slope were obtained for each intervention. For parameters where baseline data were available before the intervention, deviations from the baseline values were determined, and these were analyzed and reported. Intercepts were chosen so that they provide the group mean over the entire course of the experiment. This would correspond to the value of the regression line 2.75 h (mean, 1, 2, 3, and 5 h) after the completion of the infusion. *P* values are given for group differences for both intercept and slope for planned comparisons against both the NS and the mannitol groups. Overall, there are seven (4 + 4 – 1) planned comparisons and therefore differences between groups for each parameter are considered significant only for $P \leq 0.007$. The criterion for significance was obtained using the Bonferroni correction for seven comparisons and $P = 0.05$ ($0.007 \approx 0.050/7$). Similarly, CIs given for the intercepts and slopes of the regression lines incorporate a Bonferroni correction to 99.3% ($100 \times [1 - 0.007]$).

In contrast to the tissue water measurements, which required animals to be killed at each observation time, observations of arterial blood pressure were obtained for the same animal over the duration of the experiment. Therefore, longitudinal analysis was performed using a general estimating equation approach with robust error estimation. Analysis is presented for the entire experiment, including study solution infusion, and did consider the initial blood pressure of each animal before the intervention and group interactions with time. The intercept was adjusted so that its value represents the mean over the entire experiment, which corresponds to the value of the regression line 2.25 h into the experiment. Comparisons were performed only with respect to the mannitol group. Therefore, for comparisons of blood pressure, *P* values were considered significant only for $P \leq 0.0125$, which was obtained using the Bonferroni correction for four comparisons ($0.0125 = 0.050/4$). Similarly, CIs are reported for 98.75% ($100 \times [1 - 0.0125]$). Although mean arterial pressure (MAP) was measured at a considerably larger number of time points than for the other types of data, only a linear fit was obtained. Here, the goal was not to model the time course of the MAP data but to obtain a representative measure of MAP during the course of the entire experiment, and this is contained in the intercept.

All reported *P* values are those from two-sided tests. Statistical analysis was facilitated by the use of Stata 12.0 (StataCorp, College Station, TX).

Results

All animals survived for the duration of the experiment and were included in the analysis. Data on weight, serum, and urine electrolytes are listed in table 1 and summarized by the intercepts and slopes of the corresponding regression lines. The intercept was selected so that its value provides the mean of the variable over the entire course of the experiment. Data

Table 1. Physiologic Parameters (Weight, Serum and Urine Electrolytes)

Parameter	Baseline	Intercept (2.75 h)†	Slope (units/h)†	*P* (Intercept, Ref: NS)‡	*P* (Slope, Ref: NS)‡	*P* (Intercept, Ref: MAN)‡	*P* (Slope, Ref: MAN)‡
Weight change (g for baseline, then % change from baseline)							
NS	373 (58)	2.3 (2.1–2.5)	0.1 (–0.1 to 0.2)	Ref	Ref	<0.001*	<0.001*
NS + FUR	321 (56)	–0.6 (–1.0 to –0.3)	–0.8 (–1.1 to –0.5)	<0.001*	<0.001*	<0.001*	0.808
MAN	384 (54)	–5.5 (–6.0 to –5.0)	–0.9 (–1.1 to –0.6)	<0.001*	<0.001*	Ref	Ref
HS	364 (40)	0.1 (–0.2 to 0.4)	–0.7 (–0.9 to –0.5)	<0.001*	<0.001*	<0.001*	0.298
HS + FUR	390 (48)	–4.0 (–4.4 to –3.6)	–1.0 (–1.3 to –0.7)	<0.001*	<0.001*	<0.001*	0.265
Serum Na^+ (mEq/l baseline then change from baseline)							
NS	140 (1)	0.3 (–0.5 to 1.1)	–0.1 (–0.7 to 0.5)	Ref	Ref	<0.001*	<0.001*
NS + FUR	140 (2)	–4.0 (–5.3 to –2.7)	–0.5 (–1.2 to 0.3)	<0.001*	0.344	0.465	<0.001*
MAN	140 (2)	–5.0 (–8.3 to –1.7)	2.5 (1.3–3.6)	<0.001*	<0.001*	Ref	Ref
HS	141 (1)	11.7 (10.1–13 to2)	–1.0 (–2.1 to 0.1)	<0.001*	0.060	<0.001*	<0.001*
HS + FUR	140 (1)	21.8 (20.3–23.2)	–1.0 (–1.9 to –0.2)	<0.001*	0.019	<0.001*	<0.001*
Serum Cl^- (mEq/l, baseline then change from baseline)							
NS	101 (3)	0.8 (–0.5 to 2.0)	–0.4 (–1.4 to 0.6)	Ref	Ref	<0.001*	<0.001*
NS + FUR	101 (3)	–5.1 (–6.8 to –3.5)	–2.5 (–3.9 to –1.2)	<0.001*	0.001*	0.951	<0.001*
MAN	102 (3)	–5.2 (–7.7 to –2.7)	5.0 (3.3–6.6)	<0.001*	<0.001*	Ref	Ref
HS	103 (3)	14.8 (12.6–17.0)	–1.0 (–2.4 to 0.4)	<0.001*	0.343	<0.001*	<0.001*
HS + FUR	104 (3)	16.7 (14.6–18.6)	–0.9 (–2.0 to 0.2)	<0.001*	0.384	<0.001*	<0.001*

(*continued*)

Table 1. (*Continued*)

Parameter	Baseline	Intercept (2.75 h)†	Slope (units/h)†	*P* (Intercept, Ref: NS)‡	*P* (Slope, Ref: NS)‡	*P* (Intercept, Ref: MAN)‡	*P* (Slope, Ref: MAN)‡
Serum K^+ (mEq/l, baseline then change from baseline)							
NS	4.1 (0.3)	0.3 (0.0–0.5)	0.0 (–0.2 to 0.2)	Ref	Ref	0.005*	0.848
NS + FUR	3.7 (0.4)	0.4 (0.2–0.6)	0.1 (–0.1 to 0.2)	0.150	0.399	0.047	0.572
MAN	4.2 (0.3)	0.7 (0.4–1.1)	0.0 (–0.2 to 0.3)	0.005*	0.848	Ref	Ref
HS	4.1 (0.4)	0.5 (0.2–0.8)	–0.1 (–0.4 to 0.1)	0.085	0.247	0.173	0.189
HS + FUR	3.7 (0.3)	0.9 (0.7–1.1)	–0.1 (–0.2 to 0.1)	<0.001*	0.459	0.286	0.350
Urine osmolarity (mOsM/L)							
NS	n/a	886 (826–945)	40 (–4 to 85)	Ref	Ref	<0.001*	0.109
NS + FUR	n/a	419 (392–447)	3 (–18 to 25)	<0.001*	0.042	<0.001*	0.269
MAN	n/a	513 (498–528)	13 (1–25)	<0.001*	0.109	Ref	Ref
HS	n/a	744 (720–768)	6 (–8 to 20)	<0.001*	0.047	<0.001*	0.299
HS + FUR	n/a	468 (453–483)	8 (1–16)	<0.001*	0.055	<0.001*	0.361
Urine Na^+ (mEq/l)							
NS	n/a	122 (111–134)	12 (2–22)	Ref	Ref	<0.001*	0.002*
NS + FUR	n/a	116 (110–122)	–3 (–8 to 1)	0.198	<0.001*	<0.001*	0.051
MAN	n/a	29 (27–32)	0 (–2 to 2)	<0.001*	0.002*	Ref	Ref
HS	n/a	251 (230–273)	–6 (–19 to 6)	<0.001*	0.001*	<0.001*	0.132
HS + FUR	n/a	187 (179–196)	2 (–2 to 6)	<0.001*	0.009	<0.001*	0.425
Urine Cl^- (mEq/l)							
NS	n/a	166 (153–178)	13 (5–22)	Ref	Ref	<0.001*	<0.001*
NS + FUR	n/a	161 (153–170)	–6 (–13 to 0)	0.440	<0.001*	<0.001*	0.047
MAN	n/a	14 (12–16)	–1 (–2 to 0)	<0.001*	<0.001*	Ref	Ref
HS	n/a	207 (192–222)	–8 (–17 to 0)	<0.001*	<0.001*	<0.001*	0.026
HS + FUR	n/a	194 (190–198)	1 (–2 to 3)	<0.001*	<0.001*	<0.001*	0.057
Urine K^+ (mEq/l)							
NS	n/a	73 (68–78)	–2 (–6 to 1)	Ref	Ref	<0.001*	0.585
NS + FUR	n/a	52 (44–59)	1 (–4 to 7)	<0.001*	0.157	<0.001*	0.047
MAN	n/a	21 (18–25)	–3 (–5 to 1)	<0.001*	0.585	Ref	Ref
HS	n/a	65 (56–75)	7 (0–13)	0.041	0.001*	<0.001*	<0.001*
HS + FUR	n/a	31 (29–33)	1 (0 to 2)	<0.001*	0.020	<0.001*	<0.001*

For each parameter where it is available, baseline data are provided as mean (SD) for each intervention. The results of the interventions are summarized for the 5-h experiments by the intercepts and slopes of the corresponding regression lines, where the intercept indicates mean of the parameter over all observations for the given intervention and corresponds to the value of the regression line 2.75 h after completion of the infusion. Regression weights are given along with their CI, which were corrected to account for the comparison of multiple groups as described in the text. The results from each intervention were compared to both normal saline and mannitol, with the significance of these differences indicated in the table for both the intercept and slope of the corresponding regression lines. Results are considered significant only for $P \leq 0.007$ (≈0.05/7), which reflects the seven possible comparisons depicted. Baseline values are available only for weight and serum electrolytes. For weight, baseline values are expressed in absolute terms, whereas the remainder of the weight data are given as percentage change with respect to the starting weight. Serum electrolytes are expressed as their change from their starting value. All other parameters are presented as absolute, not relative, values.

* Differences are considered significant and denoted if $P \leq 0.007$ to account for multiple comparisons as described in the text. † Intercepts and slopes of the regression lines are given with 99.3% CI, which correspond to $P = 0.007$ (≈0.05/7) using a Bonferroni correction for multiple comparisons. ‡ *P* values represent differences in intercepts and slopes of the regression lines compared with either of the reference solutions (NS or MAN). Baseline values are averaged for each intervention group for animals from all four observation times. Initial animal weights did vary over intervention ($P < 0.001$) and observation time ($P < 0.001$). Small but significant group differences ($P = 0.008$) in initial serum Na^+ concentrations were also observed. Small differences in initial K^+ concentration are present for both group and time ($P < 0.001$). Finally, for serum Cl^- concentrations, differences were observed in initial values between groups ($P < 0.001$) and for the different observation times ($P = 0.022$). For these reasons, changes in weight were reported as a percentage change in initial weight, and serum electrolytes are reported as changes from baseline values.

HS = hypertonic saline; HS + FUR = hypertonic saline plus furosemide; MAN = mannitol; NS= normal saline; NS + FUR = normal saline plus furosemide; n/a = not available; Ref = reference.

on serum osmolarity and urine output are given in figure 1, data on tissue water content are given in figure 2, and data on MAP are given in figure 3. Whenever baseline values of a parameter were available, changes from that value are what are presented and analyzed. Raw data on serum osmolarity and brain water are displayed in table 2.

Overall, in the NS group, serum osmolarity (fig. 1A) did not vary from baseline over time (slope, 0.6 mOsmL/h [99.3% CI, −1.2 to 2.3 mOsmL/h]). Compared to NS-treated rats, change in serum osmolarity was different in all groups ($P < 0.001$), with higher values observed in HS, HS plus furosemide, and mannitol groups. Serum osmolarity in the HS group declined at a rate of −5.7 mOsmL/h (99.3% CI, −7.4 to −4.1 mOsm/h) but remained relatively constant in the NS, mannitol, and HS plus furosemide groups for the course of the experiment. Serum osmolarity was greatly elevated immediately at 1 h and remained so through 5 h in the HS plus furosemide and mannitol groups (fig. 1A). Compared to the relatively flat time course of both mannitol (0.5 mOsm/h [99.3% CI, −1.2 to 2.3 mOsm/h]) and NS, only the HS group differed ($P < 0.001$).

Compared to NS, rats treated with HS or HS plus furosemide experienced higher serum sodium concentrations, whereas sodium concentration decreased after mannitol or NS plus furosemide administration ($P < 0.001$) (table 1). In addition, serum potassium concentration increased in mannitol and HS plus furosemide–treated rats ($P \leq 0.005$), although no differences were seen with the other groups compared to NS (table 1). Because nonbuffered HS was administered, rats were hyperchloremic in both HS groups, whereas chloride concentration diminished in the mannitol and the NS plus furosemide groups ($P < 0.001$) (table 1).

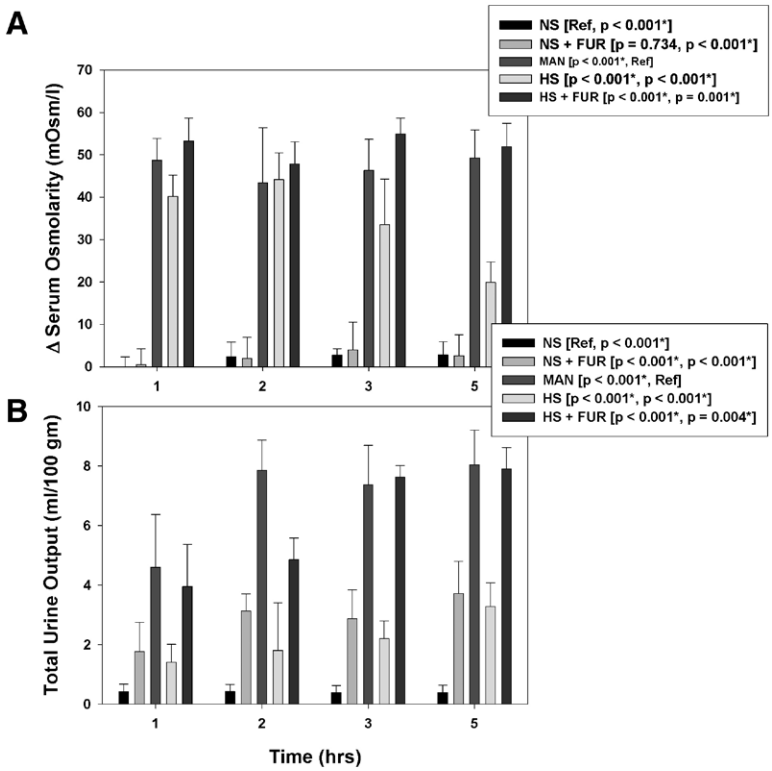

Fig. 1. Change in serum osmolarity (*A*) with respect to initial value, and total urine output (*B*) over the course of the experiment for each intervention. Serum osmolarity was determined before the intervention and 1, 2, 3, and 5 h after completion of the 45-min infusion of normal saline (NS) with or without furosemide (FUR), 25% mannitol (MAN), or 4.2% hypertonic saline (HS) with or without furosemide. Differences with respect to initial serum osmolarity were then determined and are displayed. The data used to compute these differences are listed in table 2. Urine outputs represent the total from the beginning of the experiment until the indicated time and are normalized to each animal's initial weight in units of 100 g. The significance values in the *insets* (comparison with NS [Ref] noted on the *left* and mannitol [Ref] on the *right*) arise from comparisons of the intercepts where the regression line passes through 2.75 h. Thus, these represent comparisons of the overall mean for each group over the course of the experiment. In addition, for serum osmolarity, the slope of the regression line for HS differed from both NS and mannitol ($P < 0.001$). The slopes for the other interventions did not differ from either NS or mannitol ($P \geq 0.511$). For urine output, the slopes of all interventions differed from NS ($P < 0.001$), whereas there were no differences when compared to mannitol (excluding NS, $P > 0.075$). All values in the figure are expressed as mean (SD). An *asterisk* indicates statistical significance using a value of $P \leq 0.007$ to account for multiple comparisons as described earlier under Materials and Methods. See text for additional detail.

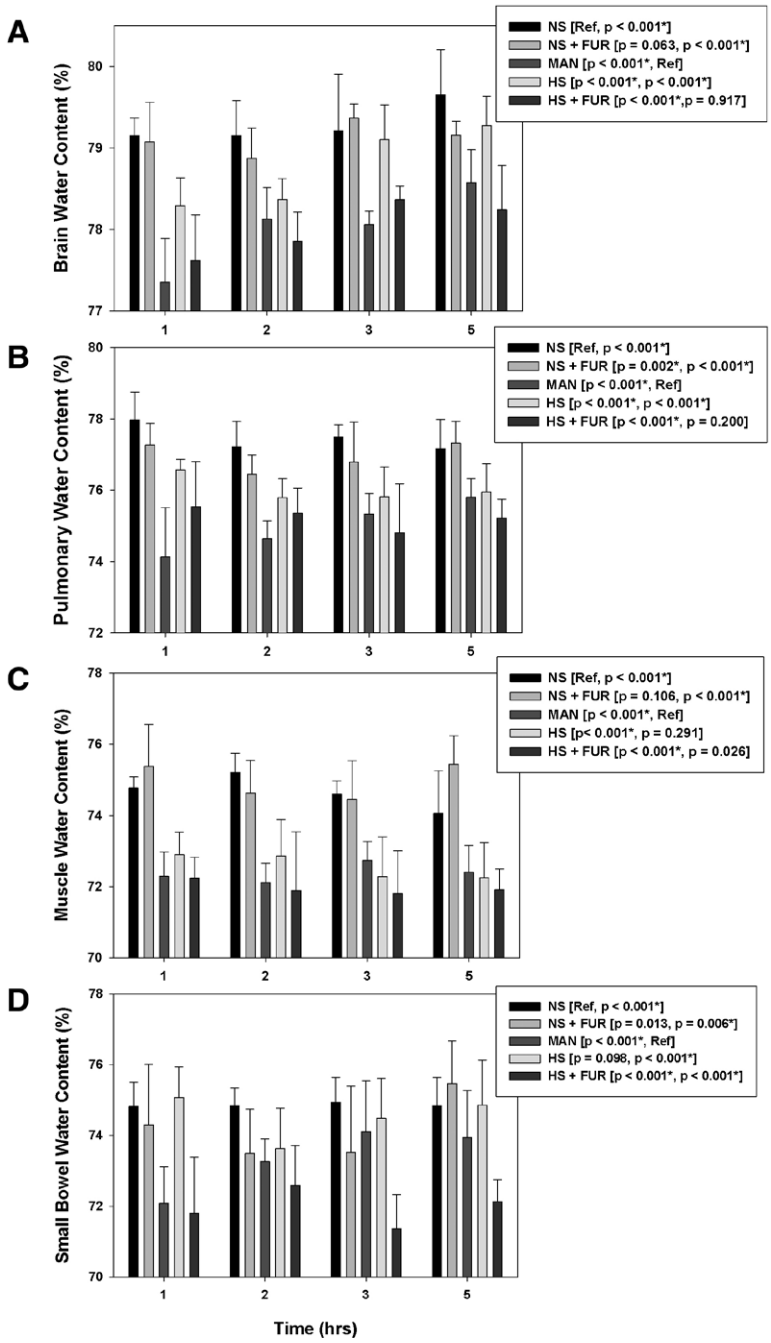

Fig. 2. Tissue water content over time with respect to intervention for brain (*A*), lung (*B*), muscle (*C*), and small bowel (*D*). Significance levels indicated in the *inset* to each panel are for the differences between intercepts of the regression over time when compared to either normal saline (NS) (Ref, *left of inset*) or mannitol (MAN) (Ref, *right of inset*). For brain, the slope of the regression line is less for NS plus furosemide (FUR) compared to mannitol ($P < 0.001$). For lung, the slopes for all of the regression lines differ with respect to mannitol ($P \leq 0.003$). For muscle, the slopes are similar ($P \geq 0.019$). For small bowel, the slope of the regression line for NS differs with respect to mannitol ($P = 0.004$). As described in the text, the location of the intercept was adjusted so that its value corresponds to the mean of the variable over the course of the experiment, which occurs when the regression line passes through 2.75 h. For brain, the intercepts and slopes are given for each intervention: NS, 79.3 (99.3% CI, 79.1–79.5) and 0.13 (99.3% CI, 0.00–0.26); NS plus furosemide, 79.3 (99.3% CI, 79.0–79.3) and 0.05 (99.3% CI, −0.05 to 0.14); mannitol, 78.0 (99.3% CI, 77.9–78.2) and 0.27 (99.3% CI, 0.14–0.40); HS, 78.8 (99.3% CI, 78.6–78.9) and 0.27 (99.3% CI, 0.17–0.37); and HS plus furosemide, 78.0 (99.3% CI, 77.8–78.2) and 0.16 (99.3% CI, 0.01–0.31). CI and significance levels were adjusted to account for multiple comparisons. See text for additional detail.

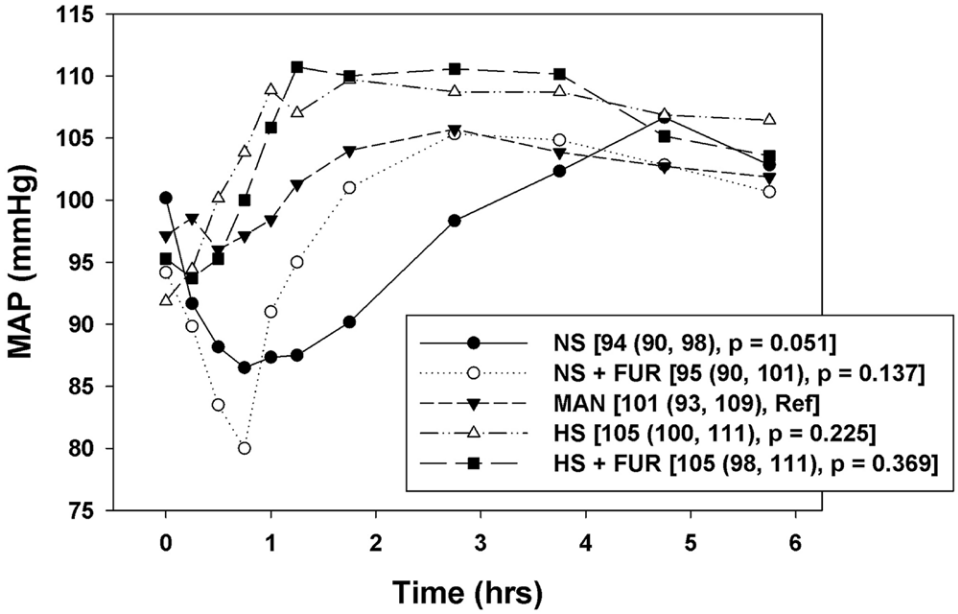

Fig. 3. Mean arterial pressure (MAP) over time with respect to intervention. Rats (n = 7 each group) were anesthetized with a 1.5% isoflurane–oxygen mixture. MAP was determined from the beginning (time = 0) of the 45-min infusion at predesignated intervals as described earlier under Materials and Methods. Groups include normal saline (NS) with or without furosemide (FUR), 25% mannitol (MAN), and 4.2% hypertonic saline (HS) with or without furosemide. MAP was allowed to fluctuate freely over the entire experiment. The mean value of MAP (99.3% CI, adjusted for multiple comparisons) over the course of the experiment is indicated in the *inset* of the figure. These means correspond to the value of the corresponding regression lines 2.25 h from the start of the experiment. The *P* value indicates the significance of differences when these are compared to the mannitol (Ref) group. The slope of the NS group was steeper than the mannitol group ($P < 0.001$), but the slopes of the other groups did not differ from mannitol (*P* 0.030). Although the initial values of MAP (time = 0) did differ between groups ($P < 0.001$), these differences did not appear to contribute to the observed values of MAP over the course of the experiment ($P = 0.289$).

Mean urinary output and the change in output over time differed in all groups compared with NS ($P < 0.001$) (fig. 1B). The mean urine output for mannitol (7.0 ml/100 g body weight [99.3% CI, 6.3–7.6 ml/100 g body weight]) was greater compared with all groups ($P \leq 0.004$). Although the change in urine output with time following HS plus furosemide administration was the greatest in absolute terms (slope, 1.0 ml $100\,g^{-1}\,h^{-1}$ [99.3% CI, 0.7–1.3 ml $100\,g^{-1}\,h^{-1}$]), there was no difference in the time course of any group (except NS) when compared with mannitol ($P \geq 0.075$). Most of the urine production in the mannitol-treated groups had occurred within 2 h, whereas urine output appeared to increase more uniformly over 5 h with HS plus furosemide (fig. 1B). In assessing urine composition, urinary excretion of sodium was reduced with mannitol and increased with HS and HS plus furosemide compared with NS alone ($P < 0.001$) (table 1).

Mannitol, HS, and HS plus furosemide all reduced brain water content relative to NS ($P < 0.001$), whereas NS plus furosemide was no different than NS (fig. 2A). The mean brain water content of mannitol-treated rats was 78.0% (99.3% CI, 77.9–78.2%), which was lower than the brain water content of NS- (79.3% [99.3% CI, 79.1–79.5%]) and HS-treated rats (78.8% [99.3% CI, 78.6–78.9%]). Because brain water increased at similar rates ($P = 0.968$) in mannitol (0.27%/h [99.3% CI, 0.14–0.40%/h]) and HS (0.27%/h [99.3% CI, 0.17–0.37%/h]) groups, mannitol's overall larger effect could be attributed to its robust early brain dehydration. Administration of HS plus furosemide (78.0% [99.3% CI, 77.8–78.2%]) resulted in similar brain water reduction as mannitol ($P = 0.917$) with a similar time course (0.16%/h [0.0– 0.31%/h; $P = 0.147$).

In the lung, all interventions reduced tissue water content greater than NS ($P \leq 0.002$) (fig. 2B), although the group changes over time were all similar, with the exception of mannitol (0.42%/h [99.3% CI, 0.17–0.67%/h]; $P < 0.001$). Absolute lung water reduction after mannitol administration (75.0% [99.3% CI, 74.6–75.3%]) was similar to HS plus furosemide (75.2% [99.3% CI, 74.8–75.6%]; $P = 0.200$). In the skeletal muscle, HS, HS plus furosemide, and mannitol reduced water content when compared to NS ($P < 0.001$) (fig. 2C), but the time course of all groups was similar ($P \geq 0.019$). In contrast to brain, the effect of HS in skeletal muscle and lung was more persistent (fig. 2, A–C). In the small bowel, water content was unchanged in rats that received HS or NS plus furosemide ($P \geq 0.013$) but decreased in animals receiving infusions of mannitol or HS plus furosemide ($P < 0.001$) (fig. 2D). HS plus furosemide (72.0% [99.3% CI, 71.5–72.5%]) appeared to be the most effective intervention at the small bowel, compared with mannitol (73.3% [99.3% CI, 72.8–73.8%]; $P < 0.001$).

Although the initial MAP did differ between groups ($P < 0.001$), these differences did not contribute to the observed

Table 2. Raw Data for Serum Osmolarity and Brain Water Content

Parameter	1 h	2 h	3 h	5 h
Before intervention:serum osmolarity (mOsM/L)				
NS	300 (2)	299 (2)	300 (1)	299 (1)
NS + FUR	294 (2)	293 (2)	296 (3)	296 (2)
MAN	300 (2)	297 (1)	301 (1)	301 (2)
HS	301 (1)	301 (1)	303 (3)	300 (2)
HS + FUR	301 (2)	300 (2)	301 (1)	302 (0)
Following intervention:serum osmolarity (mOsM/L)				
NS	300 (3)	301 (1)	303 (2)	302 (3)
NS + FUR	295 (3)	295 (4)	300 (5)	299 (4)
MAN	349 (4)	341 (13)	348 (8)	350 (7)
HS	342 (5)	345 (6)	337 (9)	320 (5)
HS + FUR	354 (5)	348 (6)	356 (4)	354 (5)
Change in serum osmolarity (mOsM/L)				
NS	0.1 (2.3)	2.4 (3.4)	2.7 (1.6)	2.8 (3.1)
NS + FUR	0.5 (3.7)	2.0 (4.9)	4.0 (6.5)	2.6 (4.9)
MAN	48.7 (5.1)	43.4 (13.0)	46.4 (7.3)	49.3 (6.6)
HS	40.2 (5.0)	44.2 (6.3)	33.5 (10.7)	19.9 (4.8)
HS + FUR	53.3 (5.3)	47.8 (5.3)	54.9 (3.7)	51.9 (5.6)
Following intervention:brain water content (%)				
NS	79.2 (0.2)	79.2 (0.4)	79.2 (0.7)	79.7 (0.6)
NS + FUR	79.1 (0.5)	78.9 (0.4)	79.4 (0.2)	79.2 (0.2)
MAN	77.4 (0.5)	78.1 (0.4)	78.1 (0.2)	78.6 (0.4)
HS	78.3 (0.3)	78.4 (0.3)	79.1 (0.4)	79.3 (0.4)
HS + FUR	77.6 (0.6)	77.9 (0.4)	78.4 (0.2)	78.2 (0.5)

Data used to compute the change in serum osmolarity are displayed in fig. 1A. Because animals were killed to obtain data for each time point, there exist baseline measurements and postintervention values for each time point. Differences in serum osmolarity were then computed for each animal from these data. For convenience, the differences used to generate figure 1A and the data on brain water content from figure 2A are also shown. For each parameter, data are provided as mean (SD) for each intervention and observation time. Differences in initial serum osmolarity could be appreciated for each group and observation time ($P < 0.001$), which encouraged the use of differences in serum osmolarity for comparing groups over time.

HS = hypertonic saline; HS + FUR = hypertonic saline plus furosemide; MAN = mannitol; NS = normal saline; NS + FUR = normal saline plus furosemide.

MAP (fig. 3) over the course of the experiment ($P = 0.289$). Trends in the NS and NS plus furosemide groups toward a lower MAP did not achieve significance ($P \geq 0.051$).

Discussion

This study evaluated the tissue-dehydrating effect of HS and mannitol in normal rats using equivolume, equiosmolar administration to achieve the greatest possible parity. Both agents effectively decreased brain water content, but mannitol had a larger effect. Compared to HS, the larger effect of mannitol was established early on, when elevation of serum osmolarity and urinary output was greatest. Tissue-dehydrating effects similar to those of mannitol were obtained when furosemide accompanied HS administration, and were driven by comparable levels of serum osmolarity and urinary output. The early large decrease in brain water is the basis for the longer term benefit for both mannitol and HS plus furosemide, as the reaccumulation of brain water occurs at the same rate for mannitol, HS, and HS plus furosemide.

In tissues other than brain, the findings were somewhat different. The dehydrating effect of mannitol was greater than that of HS in the lung, but there was no difference observed between the two agents in skeletal muscle. In the small bowel, the results contrasted with the findings in the brain greatly, with the effects of HS and NS being indistinguishable. The response in small bowel has been explained by differences in permeability of the vascular smooth muscle cells, basal vasomotor activity, compliance of the extravascular compartment, and, importantly, the metabolic response of the parenchyma cells.[20]

The principal mechanism of action of mannitol and HS on the brain results from the development of osmotic forces driving water across an intact blood–brain barrier.[21] With HS, the rise in brain water from its nadir can be explained by a concordant reduction in serum osmolarity. After 1 h, the mannitol and HS plus furosemide groups experienced a rise in brain water despite serum osmolarities that remained constant. This observation might partially be explained by mannitol's reflection coefficient of 0.9, but this explanation cannot be applied to HS plus furosemide. Importantly, because HS and mannitol are equiosmolar, the observed difference in cerebral effects cannot be explained by a difference in osmotic potency but may be attributable to another property of the respective agents.

The disparate mechanisms of diuresis may help explain some of the above observations. The postulated mechanism for HS-induced diuresis is through the release of atrial natriuretic peptide at the cardiac atrium or centrally at the hypothalamus.[22,23] Atrial natriuretic peptide reduces release of renin at the juxtaglomerular apparatus and therefore angiotensin II.[24] Sodium control in the proximal tubule, which handles 60–80% of sodium reabsorption, is influenced by the sympathetic nervous system and angiotensin II.[25] In contrast, the primary diuretic action of mannitol arises from filtration at the glomerulus, where it remains unabsorbed in the tubule and exerts an osmotic effect, inhibiting water reabsorption.[26] In our experiment, administration of 4.2% HS induced a substantial natriuresis that resulted in excretion of sodium at much greater levels than NS-treated animals. However, mannitol-treated rats produced nearly three times more urine than did HS-treated rats over the 5-h experimental period. The addition of furosemide, a loop diuretic that inhibits chloride and sodium absorption in the distal tubules, increased urinary output of HS-treated rats to a level nearing that obtained with mannitol while maintaining a substantial natriuresis.

The combination of HS plus furosemide increased urinary output, elevated serum osmolarity in a sustained fashion, and reduced brain water to levels similar to those of mannitol. It could have been expected that adding furosemide to HS would only augment the diuretic effect, as NS plus furosemide had no effect on serum osmolarity or brain water content. HS administration likely created osmotic forces sufficient to draw water into the vasculature from peripheral tissues, but its weaker diuretic potency was insufficient to force elimination of much of this water, resulting in decreased serum osmolarity with time. The addition of furosemide seemed to remedy the shortfall in diuretic potency. Although it is impossible to definitively conclude whether the greater effect of mannitol on brain water is attributable to its diuretic action or to an intrinsic drug effect, it is striking that the decrease in brain water of HS plus furosemide at 1 h mirrored that of mannitol and far exceeded the initial change observed with HS alone. This profound early effect implies that diuretic potency has a central role in tissue dehydration.

Hydrostatic pressure is another potential cause of altered tissue water content. The literature suggests that a mean intracarotid luminal pressure of 180 mmHg (or an acute rise of approximately 60 mmHg) is required to produce dysfunction of the blood–brain barrier and brain edema in normal animals.[27–29] In our experiment, the absolute pressures and even small short-lived trends between experimental groups lie far below this range, making it unlikely that differences in blood pressure contributed to our observed group differences in tissue water content.

Most comparisons between HS and mannitol were performed in experimental models of acute brain injury, with limited data obtained in uninjured animals. Investigative approaches have included maintaining parity of infusate total osmotic load, volume, or both. The first approach uses equiosmolar doses but unequal volumes of the agents of interest. Berger *et al.* administered single, equiosmolar loads of 7.2% HS–10% dextran or 20% mannitol to rabbits with cryogenic brain injury.[10] Mannitol lowered the ICP for a longer duration than HS–dextran after the first administration (189 *vs.* 98 min), but no differences in duration were noted after the second administration. Interestingly, water content increased in the traumatized hemisphere and decreased in the uninjured hemisphere after HS administration, whereas no differences were found in water content in either hemisphere after mannitol administration. Qureshi *et al.*[30] compared the therapeutic efficacy of equiosmolar doses (5.5 mOsM/kg) of 25% mannitol, 3% HS, and 23.4% HS in a canine model of intracerebral hemorrhage. They found that 3% and 23.4% HS were as effective as mannitol in reducing intracranial hypertension. However, 3% HS had a longer duration of action (2 h). Mirski *et al.*[12] compared the efficacy of single, equiosmolar doses of 23.4% HS and 25% mannitol for reducing elevated ICP in a rat model of acute closed head injury. HS reduced ICP greater than mannitol, and the effect lasted substantially longer (500 *vs.* 120 min). In our recent study, equiosmolar doses of HS, at a concentration of 7.5% or higher, administered to uninjured rats produced a larger diuresis, greater reduction in brain water content, and a longer lasting effect than lower concentrations of HS.[31] The effectiveness of HS appears to increase with increasing tonicity, which was also linked to diuretic potency.

The second experimental approach uses equal volumes of solutions with different osmotic loads. Freshman *et al.*[11] administered a single bolus of 7.5% HS or 20% mannitol in equal volumes to sheep with acute head injury. Despite the fact that animals treated with HS had significantly higher serum sodium and osmolarity levels, the reduction in ICP and brain water content and the duration of action of the two agents were similar.

Finally, in the only other equivolume, equiosmolar comparison, Scheller *et al.*[13] demonstrated that 3.2% HS and 20% mannitol decreased ICP for 60–90 min and reduced water content in the contralateral noninjured cerebral hemisphere after 2 h with equal efficacy. Although our study also demonstrated the dehydrating potency of HS, it was not as great as the effect of mannitol throughout the entire 5-h observation period.

Clinical studies of the ICP-lowering effect of HS and mannitol have been carried out primarily in patients with acute intracranial injury. In most studies, either equiosmolar or equivolume doses of 7.5% HS or 20% mannitol were administered.[32–35] To date, no clinical study has used equivolume, equiosmolar treatments to evaluate ICP-lowering effect or any objective endpoint. However, Rozet *et al.* used equivolume, equiosmolar dosages for intracranial surgery with an endpoint defined by a surgeon's subjective assessment of brain relaxation.[14] Importantly, several clinical studies have shown that high-tonicity HS can successfully decrease elevated ICP

refractory to standard mannitol therapy. These studies again suggest that the cerebral effects of HS may be clinically superior when a concentration of 7.5% or greater is used.[36–38] At present, combination therapies are not typically used to treat cerebral edema and have not been subjected to clinical investigation in this setting. However, treatment with high-tonicity HS (such as 23.4%) followed by furosemide has the potential to be the therapy of choice for rapidly decompensating or refractory neurologic patients with cerebral edema.

Our study may be limited in its generalizability in that it was executed in an uninjured rat model, and these therapies are not used in subjects with normal brains. However, when administered in the setting of brain injury, the therapeutic effects of HS and mannitol ensue from action on healthy brain. As such, it was essential to characterize these agents in normal brain under conditions of greatest possible parity. A minor limitation arose from systemic errors introduced by small calibration errors in the micro-osmometer and instruments for measuring electrolyte concentrations, which resulted in group differences in the baseline determination of these variables. However, these differences, as well as those in baseline weight, were all accounted for statistically. Finally, the use of five interventions with 10 possible pairings raises concerns about multiple comparisons in the statistical analysis. Comparisons were restricted to just the NS and mannitol groups, leading to seven possible comparisons, and the criterion for significance was adjusted accordingly. Even if all 10 comparisons were permitted, the resulting criterion for significance using a Bonferroni correction would be 0.005, and virtually all reported differences would still be considered significant.

In summary, we have shown that under equivolume, equiosmolar conditions, 25% mannitol induces a longer lasting increase in serum osmolarity, resulting in a greater reduction in tissue water content than 4.2% HS. Although HS may be a potent osmotic agent, its diuretic effect is much weaker, especially at low concentrations. The addition of furosemide to HS not only enhanced the diuretic effect but also produced a sustained elevation in plasma osmolarity, which resulted in a reduction of brain water content that could not be distinguished from that of mannitol.

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References

1. Fenstermacher JD: Volume regulation of the central nervous system, Edema. Edited by Staub NC, Taylor AE. New York, Raven Press, 1984, pp 383–404
2. García-Sola R, Pulido P, Capilla P: The immediate and long-term effects of mannitol and glycerol: A comparative experimental study. Acta Neurochir (Wien) 1991; 109:114–21
3. Kotwica Z, Persson L: Effect of mannitol on intracranial pressure in focal cerebral ischemia: An experimental study in a rat. Mater Med Pol 1991; 23:280–4
4. McManus ML, Soriano SG: Rebound swelling of astroglial cells exposed to hypertonic mannitol. Anesthesiology 1998; 88:1586–91
5. Palma L, Bruni G, Fiaschi AI, Mariottini A: Passage of mannitol into the brain around gliomas: A potential cause of rebound phenomenon. A study on 21 patients. J Neurosurg Sci 2006; 50:63–6
6. Sankar T, Assina R, Karis JP, Theodore N, Preul MC: Neurosurgical implications of mannitol accumulation within a meningioma and its peritumoral region demonstrated by magnetic resonance spectroscopy: Case report. J Neurosurg 2008; 108:1010–3
7. Holcroft JW, Vassar MJ, Perry CA, Gannaway WL, Kramer GC: Perspectives on clinical trials for hypertonic saline/dextran solutions for the treatment of traumatic shock. Braz J Med Biol Res 1989; 22:291–3
8. Holcroft JW, Vassar MJ, Perry CA, Gannaway WL, Kramer GC: Use of a 7.5% NaCl/6% Dextran 70 solution in the resuscitation of injured patients in the emergency room. Prog Clin Biol Res 1989; 299:331–8
9. Nakayama S, Sibley L, Gunther RA, Holcroft JW, Kramer GC: Small-volume resuscitation with hypertonic saline (2,400 mOsm/liter) during hemorrhagic shock. Circ Shock 1984; 13:149–59
10. Berger S, Schürer L, Härtl R, Deisböck T, Dautermann C, Murr R, Messmer K, Baethmann A: 7.2% NaCl/10% dextran 60 versus 20% mannitol for treatment of intracranial hypertension. Acta Neurochir Suppl (Wien) 1994; 60:494–8
11. Freshman SP, Battistella FD, Matteucci M, Wisner DH: Hypertonic saline (7.5%) versus mannitol: A comparison for treatment of acute head injuries. J Trauma 1993; 35:344–8
12. Mirski AM, Denchev ID, Schnitzer SM, Hanley FD: Comparison between hypertonic saline and mannitol in the reduction of elevated intracranial pressure in a rodent model of acute cerebral injury. J Neurosurg Anesthesiol 2000; 12:334–44
13. Scheller MS, Zornow MH, Seok Y: A comparison of the cerebral and hemodynamic effects of mannitol and hypertonic saline in a rabbit model of acute cryogenic brain injury. J Neurosurg Anesthesiol 1991; 3:291–6
14. Rozet I, Tontisirin N, Muangman S, Vavilala MS, Souter MJ, Lee LA, Kincaid MS, Britz GW, Lam AM: Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. Anesthesiology 2007; 107:697–704
15. Mayzler O, Leon A, Eilig I, Fuxman Y, Benifla M, Freixo PC, Gurevich B, Agassi R, Artru AA, Shapria Y: The effect of hypertonic (3%) saline with and without furosemide on plasma osmolality, sodium concentration, and brain water content after closed head trauma in rats. J Neurosurg Anesthesiol 2006; 18:24–31
16. Pollay M, Fullenwider C, Roberts PA, Stevens FA: Effect of mannitol and furosemide on blood-brain osmotic gradient and intracranial pressure. J Neurosurg 1983; 59:945–50
17. Schettini A, Stahurski B, Young HF: Osmotic and osmotic-loop diuresis in brain surgery: Effects on plasma and CSF electrolytes and ion excretion. J Neurosurg 1982; 56:679–84
18. Thenuwara K, Todd MM, Brian JE Jr: Effect of mannitol and furosemide on plasma osmolality and brain water. Anesthesiology 2002; 96:416–21
19. Wilkinson HA, Rosenfeld SR: Furosemide and mannitol in the treatment of acute experimental intracranial hypertension. Neurosurgery 1983; 12:405–10

20. Gazitùa S, Scott JB, Swindall B, Haddy FJ: Resistance responses to local changes in plasma osmolality in three vascular beds. Am J Physiol 1971; 220:384–91
21. Paczynski RP: Osmotherapy: Basic concepts and controversies. Crit Care Clin 1997; 13:105–29
22. Israel A, Barbella Y: Diuretic and natriuretic action of rat atrial natriuretic peptide (6-33) administered intracerebroventricularly in rats. Brain Res Bull 1986; 17:141–4
23. Lang RE, Thölken H, Ganten D, Luft FC, Ruskoaho H, Unger T: Atrial natriuretic factor: A circulating hormone stimulated by volume loading. Nature 1985; 314:264–6
24. McCann SM, Gutkowska J, Franci CR, Favaretto AL, Antunes-Rodrigues J: Hypothalamic control of water and salt intake and excretion. Braz J Med Biol Res 1994; 27:865–84
25. Bie P, Mølstrøm S, Wamberg S: Normotensive sodium loading in conscious dogs: Regulation of renin secretion during beta-receptor blockade. Am J Physiol Regul Integr Comp Physiol 2009; 296:R428–35
26. Gilman AG, Goodman LS, Gilman A: Goodman and Gilman's the Pharmacological Basis of Therapeutics, 6th edition. New York, Macmillan, 1980, pp 885–915
27. Hardebo JE: A time study in rat on the opening and reclosure of the blood-brain barrier after hypertensive of hypertonic insult. Exp Neurol 1980; 70:155–66
28. Kontos HA, Wei EP, Dietrich WD, Navari RM, Povlishock JT, Ghatak NR, Ellis EF, Patterson JL Jr: Mechanism of cerebral arteriolar abnormalities after acute hypertension. Am J Physiol 1981; 240:H511–27
29. Rapoport SI: Opening of the blood-brain barrier by acute hypertension. Exp Neurol 1976; 52:467–79
30. Qureshi AI, Wilson DA, Traystman RJ: Treatment of elevated intracranial pressure in experimental intracerebral hemorrhage: Comparison between mannitol and hypertonic saline. Neurosurgery 1999; 44:1055–63; discussion 1063–4
31. Toung TJ, Nyquist P, Mirski MA: Effect of hypertonic saline concentration on cerebral and visceral organ water in an uninjured rodent model. Crit Care Med 2008; 36:256–61
32. 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 2005; 33:196–202; discussion 257–8
33. Francony G, Fauvage B, Falcon D, Canet C, Dilou H, Lavagne P, Jacquot C, Payen JF: Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. Crit Care Med 2008; 36:795–800
34. Schwarz S, Schwab S, Bertram M, Aschoff A, Hacke W: Effects of hypertonic saline hydroxyethyl starch solution and mannitol in patients with increased intracranial pressure after stroke. Stroke 1998; 29:1550–5
35. Vialet R, Albanèse J, Thomachot L, Antonini F, Bourgouin A, Alliez B, Martin C: Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. Crit Care Med 2003; 31:1683–7
36. Suarez JI, Qureshi AI, Bhardwaj A, Williams MA, Schnitzer MS, Mirski M, Hanley DF, Ulatowski JA: Treatment of refractory intracranial hypertension with 23.4% saline. Crit Care Med 1998; 26:1118–22
37. Horn P, Münch E, Vajkoczy P, Herrmann P, Quintel M, Schilling L, Schmiedek P, Schürer L: Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. Neurol Res 1999; 21:758–64
38. Schwarz S, Georgiadis D, Aschoff A, Schwab S: Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. Stroke 2002; 33:136–40