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Hypertonic Saline Ameliorates Cerebral Edema Associated With Experimental Brain Tumor

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Summary: Cerebral edema commonly accompanies brain tumors and frequently leads to lethal intracranial compartmental shifts and elevated intracranial pressure. Therapeutic modalities for tumor–associated cerebral edema include diuretics, osmotherapy, and corticosteroids. Recently, hypertonic saline (HS) has received attention as an osmotic agent in the treatment of cerebral edema from diverse causes. The effects of continuous HS infusion in brain tumor–associated edema have not been previously reported. Therefore, we tested the hypothesis that HS given as a continuous intravenous infusion ameliorates tumor-associated edema in a rat model of brain tumor. 9L gliosarcoma, propagated as a solid flank tumor, was implanted intracranially over the left hemisphere in adult female Fischer 344 rats (180–220 g). On day 11 after implantation, rats were divided in a blinded, randomized fashion into groups that received no treatment or continuous infusion of 0.9% saline (NS) (0.3 mL/h) and in a subsequent series that included NS + intravenous furosemide 2.5 mg/kg every six hours, NS + intravenous mannitol 2.5 g/kg every six hours, or continuous infusion 7.5% HS (chloride:acetate 50:50) (0.3 mL/h). Hemispheric water content ipsilateral (IH) and contralateral to tumor implantation was determined at day 13 by wet-to-dry weight ratio after 48 hours of therapy. Ipsilateral hemispheric water content (mean ± SEM) was significantly increased in rats with intracranial tumor on day 11 (80.3 ± 0.5%) (n = 7) and day 13 (81.4 ± 0.3%) (n = 10), as compared to naive weight-matched rats without tumor implant (79.3 ± 0.1%) (n = 13) ($P < .05$). After 48 hours of treatment, IH water content was attenuated with continuous HS (n = 15) (79.3 ± 0.2%), mannitol (n = 14) (80.1 ± 0.2%), and furosemide (n = 15) (79.9 ± 0.2%) as compared to NS (n = 7) (80.8 ± 0.5%). Continuous HS infusion attenuated cerebral edema in the affected hemisphere as well as the contralateral noninjured hemisphere to a larger extent than was observed with furosemide or mannitol. These findings suggest a potential new treatment strategy for tumor–associated cerebral edema. **Key Words:** Furosemide—Hypertonic saline—Mannitol—Edema—Tumor—Osmotic

Cerebral edema is a frequent cause of morbidity and mortality from lethal intracranial compartmental shifts with or without elevated intracranial pressure (ICP) in patients with brain tumors (1–3). Therapeutic modalities used for the treatment of tumor–associated cerebral edema include systemic administration of diuretics, osmotherapy, and corticosteroids (2,3). Conventional therapies for cerebral edema are aimed at improving intracranial compliance by altering the three major compartments of the intracranial vault: blood, cerebrospinal fluid (CSF), and

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brain (3). This can be achieved by facilitating cerebral venous outflow, maintaining adequate cerebral perfusion and oxygenation, controlled hyperventilation, external CSF drainage for hydrocephalus and cerebral osmotic "dehydration" with osmotic agents and diuretics (3). Acute administration of osmotic agents has a potent antiedema action, primarily on undamaged brain regions with an intact blood–brain barrier, theoretically drawing water from the interstitial and extracellular space into the intravascular compartment, thereby at least transiently improving intracranial compliance (3–5). In addition, osmotic agents may exert beneficial nonosmotic cerebral effects, including enhancing cerebral blood flow by reducing blood viscosity (4–6), free radical scavenging (7), enhancing oxygen delivery, and affecting CSF dynamics (8). A variety of osmotic agents have been studied including mannitol, glycerol, urea, sorbitol, and more recently, hypertonic saline (HS) (3–5).

We have previously shown that continuous HS infusion is efficacious in some forms of neuroinjury by ameliorating elevated ICP and midline shift in patients with edema associated with resection of brain tumors postoperatively and in traumatic brain injury (6). However, there have been no direct comparisons between efficacy of continuous HS therapy and standard osmotic or diuretic agents, for example, mannitol and furosemide (2,5,8,9), respectively, in reducing tumor–associated cerebral edema. Accordingly, the present study was designed 1) to compare the effects of furosemide, mannitol, and HS on brain water content, and 2) to test the hypothesis that maintenance of a constant osmotic gradient with continuous HS infusion is more efficacious in ameliorating edema in a well-characterized model of intracranial tumor in the rat.

MATERIALS AND METHODS

The experimental protocol was approved by the Institutional Animal Care and Use Committee and conforms to the National Institutes of Health guidelines for the care and use of animals in research.

Tumor Implantation

All methods have been previously described (10–14). 9L gliosarcoma was propagated as a solid tumor in the flanks of adult female Fischer 344 rats (180–200 g). For intracranial implantation, tumor fragments were trimmed to pieces measuring approximately 2 × 2 × 1 mm. Rats were anesthetized with an intraperitoneal injection of 3 to 5 mL/kg of a stock solution containing ketamine hydrochloride (25 mg/mL), xylazine (2.5 mg/mL), and ethyl alcohol (14%) in normal saline. Skin was prepared in an aseptic fashion with 70% ethyl alcohol and providone-iodine solution. Using microsurgical technique, a midline incision was made over the skull, and the periosteum was displaced. A 3-mm burr hole was drilled over the left hemisphere with its center 5 to 6 mm behind the coronal suture and 3 to 4 mm lateral to the sagittal suture. The dura was opened sharply in a cruciate fashion, and the cortex was aspirated to expose the highly vascular sulcus between the thalamus and the superior colliculus. Bleeding was allowed to subside spontaneously, and the tumor fragment was implanted into the brain defect. The surgical wound was thoroughly irrigated, and the skin was closed with surgical clips.

Instrumentation

All techniques are as previously described (15). In brief, on day 11, tumor-implanted rats were anesthetized with halothane (1.0–2.0%) in oxygen-enriched air and were allowed to ventilate spontaneously. Using aseptic surgical technique, the right femoral artery was cannulated to monitor arterial blood pressure and arterial blood gases, and the femoral vein was cannulated for vascular access. After cannulation, both catheters were exteriorized in the posterior midthorax. Incision sites for intravascular catheters were injected locally with 0.25% bupivacaine. Rectal temperature was maintained with a heating lamp (38.0–39.0°C) throughout the surgical procedure. Rats were then allowed to emerge from anesthesia and were housed in separate cages maintained at room temperature and allowed free access to food and water.

Experimental Groups

Brain was harvested from age- and weight-matched naive (without tumor implants) Fisher 344 rats (n = 13) and tumor-implanted rats on day 11 (n = 7) and day 13 (n = 10) and analyzed for hemispheric water content. After surgical interventions on day 11, tumor-implanted rats were divided in a blinded, randomized fashion into experimental groups that received no treatment (n = 7) or continuous infusion of 0.9% saline (NS) (0.3 mL/h) (n = 7) and in a subsequent series that included NS + intravenous furosemide 2.5 mg/kg every six hours (n = 15), NS + intravenous mannitol 2.5 g/kg every six hours (n = 14) or continuous infusion 7.5% HS (chloride:acetate 50:50) (0.3 mL/h) (n = 15). Treatments were continued for 48 hours (day 13 of tumor implantation), and then tissue was harvested.

Assessment of Brain Edema and Plasma Osmolality

Arterial blood was sampled for determination of hematocrit, serum sodium, and for plasma osmolality (mOSm/L) as measured by freezing-point depression micro-osmometer (Advanced Instruments, Norwood, MA) at baseline and the end of 48 hours of treatment. After 48 hours of treatment, brain edema was estimated by comparing wet to dry tissue weight ratios (15,16). Briefly, rats were decapitated while under deep halothane anesthesia. The brain was quickly removed, blotted to remove residual adsorbent moisture, and dissected through the interhemispheric fissure into right and left hemispheres. Wet weight was determined with a resolution of 0.1 mg. Dry weight of whole ipsilateral and contralateral hemispheres was determined after heating the tissue for 3 days at 100°C in a drying oven. Tissue water content was then calculated as % H_2O = (1-dry wt/wet wt) × 100% (15,16).

Histopathology

On days 11 and 13 after implantation, additional cohorts (n = 3 each) were deeply anesthetized, and the brains were perfused-fixed with 10% neutral buffered formalin. Tissue was paraffin-embedded, sectioned (10 μm), and stained for standard hematoxylin and eosin histology.

Statistical Analysis

All values are expressed as mean ± SEM. Physiologic parameters among groups were subjected to repeated-measures analysis of variance. Differences in cerebral edema among treatment groups were determined by two-way analysis of variance with post hoc Newman-Keuls test. The criterion for statistical significance was $P < .05$.

FIG. 1. Representative photomicrograph of brain from a tumor-implanted rat on day 13 demonstrating tumor in the right parietal region.

RESULTS

Untreated tumor-implanted rats demonstrated significant infiltrative tumor growth between day 11 and day 13, causing a significant midline shift (Fig. 1 and 2). In rats randomized to various treatment groups, mean arterial blood pressure, arterial carbon dioxide ($PaCO_2$) and oxygen (PaO_2), and pH were within normal physiologic ranges in all groups immediately after placement of intravascular catheters (data not shown). Baseline serum osmolality, Na^+, and hematocrit were similar in all treatment groups (Table 1). At 48 hours, serum Na^+ was significantly higher in rats treated with HS (157 ± 2 mEq/L) and furosemide (150 ± 1) ($P < .05$) as compared with rats treated with NS (144 ± 1) and mannitol (141 ± 2). Serum osmolality was similar in rats treated with HS (311 ± 3 mOsm/L) and mannitol (308 ± 4) but significantly elevated as compared to the NS-treated group (265 ± 1) ($P < .05$). Serum osmolality in the furosemide-treated rats at 48 hours (271 ± 3) was also significantly elevated as compared to baseline (264 ± 2 mEq/L). No rats died in any of the treatment groups before completion of the experimental protocol. Ipsilateral hemispheric water content on day 11 (80.3 ± 0.5%, n = 7) and day 13 (81.4 ± 0.3%, n = 10) was significantly increased in rats with intracranial tumor, as compared to naive rats with no tumor implants (79.3 ± 0.1%, n = 13) ($P < .05$) (Fig. 3). Ipsilateral hemispheric water content was attenuated to a larger extent with continuous HS (79.3 ± 0.2%, n = 15), as compared to 0.9% saline (80.8 ± 0.5%, n = 7), mannitol (80.1 ± 0.2%, n = 14), or furosemide treatment (79.9 ± 0.2%, n = 15). Furthermore, contralateral hemispheric water content was lower in HS-treated animals as compared to untreated brain or the alternative treatments.

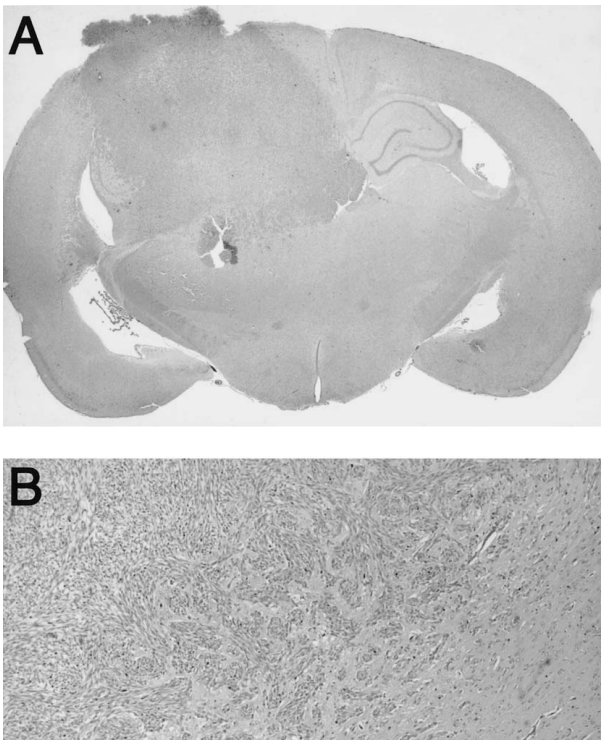

FIG. 2. **A.** Representative photomicrograph of hematoxylin and eosin (H&E) stain of coronal section of brain from a tumor-implanted rat on day 13 demonstrating midline and compartmental shift. **B.** Representative photomicrograph (×20) of H&E stain of a section demonstrating the tumor infiltrating into normal surrounding brain tissue.

DISCUSSION

This study demonstrates two important findings. First, ipsilateral hemispheric brain water content accumulates over time after tumor implantation in this well-characterized experimental model of brain tumor. Second, this increase in water content is responsive to a conventional osmotic agent, mannitol, as well as the diuretic furosemide. For the treatment doses used here, maintenance of a constant osmotic gradient with continuous HS therapy was more efficacious in ameliorating cerebral edema in the injured hemisphere than these conventional therapies were.

Cerebral edema invariably accompanies brain tumor in patients, and its cause is thought to be largely vasogenic (3,5,17). The location and degree of edema are variable and dependent on size, regional location, and tumor histology. Surgical tumor resection remains the definitive management in most cases. Nevertheless, emergent medical therapies comprising steroids, osmotic agents, and/or diuretics are important adjuncts in "brain resuscitation" from lethal intracranial compartmental shifts (3,5,18,19). Although some brain tumors are steroid responsive and undergo reduction in size, the initial favorable response in tumor–associated cerebral edema to steroid treatment is often short-lived (20). Mannitol has long been designated as the osmotic agent of choice (5,21). Hypertonic saline solutions have recently received renewed attention as hyperosmolar agents and are used increasingly in a variety of brain injury paradigms (3,6,21–26). A variety of experimental evidence and clinical case series reports suggest that HS may be superior to mannitol in some settings (3,22). Sodium chloride (reflection coefficient = 1.0) (3,22) is completely excluded from brain as long as the blood–brain barrier is intact. Like mannitol (27), HS also exerts nonosmotic cerebral effects including improved cerebral perfusion and oxygen delivery (28) and decreases CSF formation (29). Furthermore, HS may maintain a desirably "euvolemic hyperosmolar" state in a variety of brain injury paradigms (3). In our retrospective clinical series (6), continuous 3% HS therapy attenuated ICP and improved midline shifts in patients with traumatic brain injury and in postoperative neurosurgical patients with intracranial lesions. In contrast, patients with intracerebral hemorrhage and cerebral infarction did not benefit from HS therapy. The value of HS therapy remains unproven in clinical stroke.

In the present study, wet-to-dry weight comparisons were used as a simple and reproducible assessment of hemispheric brain water, without subdissection to identify regional water content differences or differential treatment effects in tumoral or peritumoral regions. We confirmed infiltrative tumor growth in the window of 48 hours (between days 11 and 13) in our experimental model with histopathologic studies. As expected, there were increases in brain water content in rats with brain tumor implants compared to naive controls, and this increase was time dependent. We tested the various treatments between days 11 and 13 because it was likely that maximal effects would be observed, given that mortality in this animal model approaches 100% by day 16 after tumor implantation. The doses of mannitol and furosemide employed here were chosen based on previous reports of efficacy (30,31). Furosemide, a potent loop diuretic, has been less rigorously and extensively studied than mannitol for treatment of vasogenic cerebral edema. The potent antiedema actions of both mannitol and furosemide are complex and thought to be secondary to a combination of osmotic dehydration (32), reduction of choroidal CSF formation (33) and decreased cerebral blood volume secondary to reflex vasoconstriction (a response to decreased blood viscosity)

TABLE 1. *Summary of selected physiologic variables at baseline and after 48 hours of treatment in tumor-implanted rats*

		0.9% Saline (n = 7)	Mannitol (n = 14)	Furosemide (n = 15)	HS (n = 15)
Hematocrit (%)	Baseline	40 ± 1	39 ± 1	39 ± 1	40 ± 1
	48 h	37 ± 1*	34 ± 1*†	37 ± 1*	38 ± 1*
Osmolality (mOsm/L)	Baseline	264 ± 2	265 ± 1	263 ± 1	267 ± 1
	48 h	265 ± 1	309 ± 4*‡	271 ± 3*	311 ± 3*‡
Serum Na+ (mEq/L)	Baseline	141 ± 1	138 ± 1	139 ± 2	138 ± 1
	48 h	144 ± 1	141 ± 2	151 ± 1*†	157 ± 2*†

Values are mean ± SEM.
*$P < .05$ compared to Baseline; †p < 0.05 compared to 0.9% saline and mannitol;
†$P < .05$ compared to 0.9% saline, furosemide, and HS.
‡$P < .05$ compared to 0.9% saline and furosemide.
HS = hypertonic saline; Na+ = serum sodium.

(32,34). Both furosemide and mannitol were comparable in attenuation of brain water increase in our experimental paradigm. However, HS demonstrated the largest percent decrease in brain water content both in regions of intact blood–brain barrier integrity (contralateral hemisphere) and in the lesioned hemisphere. Although the present study was not designed to delineate mechanisms for these findings, several must be considered. The osmolar load of 7.5% HS (2310 mOsm/L) is slightly higher than 20% mannitol (1098 mOsm/L), potentially making it the more effective agent for brain "dehydration." This characteristic may explain the present observation that HS decreased brain water in the contralateral hemisphere to less than that of naive brain. Hypertonic saline solutions also modulate the inflammatory response of the brain to injury (35) by attenuating polymorphonuclear neutrophil cytotoxicity (36) and augmenting immune responses (37).

We have used HS safely as a continuous infusion rather than intravenous bolus in brain-injured patients with the premise that a constant osmotic gradient between brain and cerebral vasculature is better achieved and maintained with continuous infusion (6,42). Although there is considerable uncertainty about the absolute increase in plasma osmolality that is required to significantly decrease brain volume and therefore ICP, some investigators have suggested that increases of ≈ 30 mOsm/L are essential (38,39). Others have shown that serum osmolality of 300 to 320 mOsm/L (corresponding to serum Na^+ of 145–155 mEq/L) is optimal in patients with poor intracranial compliance (40). In many instances, the latter level is the currently accepted goal for clinical osmotherapy in brain-injured patients (3,40). We have recently shown that induced hypernatremia to these desired goals does not cause neuronal, glial, or myelin pathology in experimental

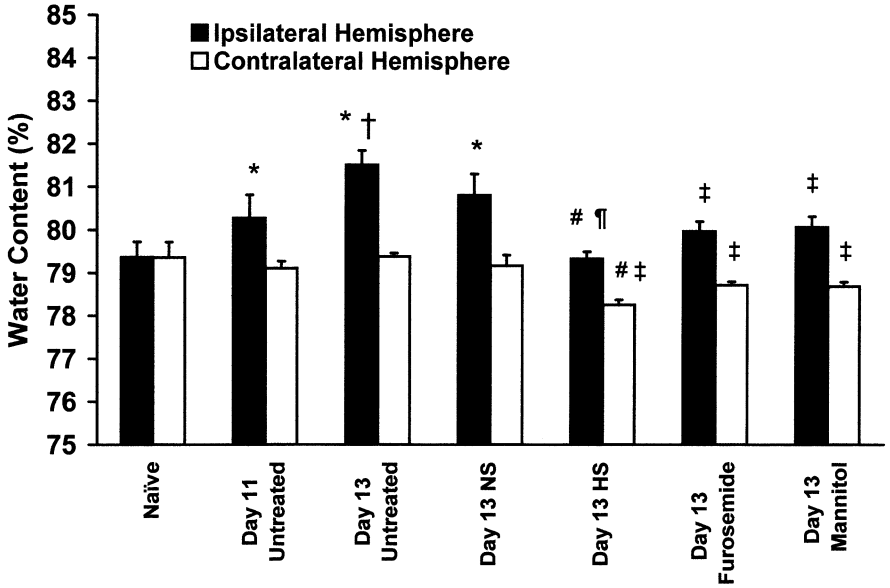

FIG. 3. Brain water content in the ipsilateral and contralateral hemispheres from naive controls and tumor-implanted rats and after treatment with 0.9% saline (NS), 7.5% hypertonic saline (HS), furosemide, and mannitol. *$P < .05$ versus naive; †$P < .05$ versus day 11; #$P < .05$ versus furosemide and mannitol of corresponding hemisphere; ‡$P < .05$ versus corresponding hemispheres in naive and on day 11 and day 13 of tumor-implanted rats; ¶$P < .05$ versus corresponding hemisphere in naive, untreated, and NS-treated tumor-implanted rats on day 11 and day 13.

stroke (15). In the present study, we compared 20% mannitol given as a bolus to continuous infusion of 7.5% HS because the targeted serum osmolality was achieved in both treatment groups.

Our study has some clear limitations. First, the data cannot address the potential for "rebound" cerebral edema. Although never definitively characterized, osmotherapy may be limited by secondary entry and accumulation of nonmetabolized osmotic agent in damaged tissue with disrupted barrier integrity and/or secondary to increases in idiogenic tissue osmoles (5). Second, we did not measure ICP or behavioral outcomes. Therefore, it is not certain whether the large reduction of ipsilateral hemispheric brain water observed here is translated into functional consequences for tumor-infiltrated brain. Mannitol and furosemide are known to cause systemic dehydration. To prevent intravascular volume depletion, a continuous intravenous infusion of normal saline was maintained in all animals for the duration of the experiment. While we attempted to create a "euvolemic hyperosmolar" state in each treatment group, we did not assess fluid status variables such as urinary output or central venous pressure in rat. While correlations have been described between postischemic brain water and body weight (41), body weight is greatly influenced in brain tumor–bearing rats that sustain diminished oral intake and a markedly catabolic state. Third, we only measured arterial blood pressure, blood gases, and rectal temperature after placement of intravascular catheters and did not monitor these parameters during the 48-hour treatment period in any of the treatment groups in our study. However, we have previously shown that continuous infusion of HS or NS does not affect these physiologic parameters (15). It is conceivable that there were alterations in blood pressure (possibly transient) in rats treated with bolus mannitol and furosemide. Serum osmolality, Na^+, and hematocrit were measured after placement of intravascular catheters, before randomization to any treatment groups (baseline) and at the end of 48 hours (day 13) in our study. More frequent measurements are not feasible in a small rodent model with limited tolerance of repeated blood loss for samples. Serum osmolality may fluctuate with bolus or pulse therapy with mannitol and furosemide, and this remains an important issue in clinical practice as well. Hematocrit was significantly elevated with HS and furosemide, as compared with mannitol treatment. Although the effects of mannitol on blood viscosity and red blood cell rheology have been well studied (43), similar studies have not yet been carried out with HS and furosemide.

In conclusion, our data demonstrate that significant cerebral edema occurs in tissue ipsilateral to brain tumor and progresses with a time course that simulates human disease. Although it is difficult to make comparisons between treatment regimens that are not iso-osmolar, our data indicate that maintenance of a constant osmotic gradient with continuous HS therapy appears to provide effective hyperosmolar "dehydration" of both lesioned and nonlesioned brain regions in our experimental model of brain tumor compared to that obtained with bolus mannitol and furosemide. Further study is required to determine the antiedema mechanisms and differential effect of HS in tumoral and peritumoral brain regions. Nevertheless, our study may have therapeutic implications, in that it provides further experimental evidence that HS may be another modality in the armamentarium of medical therapy for tumor-associated cerebral edema.

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