

Repeated Dosing of 23.4% Hypertonic Saline for Refractory Intracranial Hypertension. A Case Report

Abstract

Background: Hypertonic saline (HTS) at a concentration of 23.4% is an emerging therapy for intracranial hypertension. Compared to mannitol which can be given as a single bolus or as repeated bolus dosing, little data exists regarding safety or efficacy of repeated dosing of 23.4% HTS. We report the first case of 16 doses of 23.4% HTS over a 5 day period in a patient with refractory intracranial hypertension.

Case Report: A 43-year-old woman with Fisher 3 subarachnoid hemorrhage and hydrocephalus requiring an external ventricular drain developed global cerebral edema on computed tomography. Medically refractory intracranial hypertension ensued which required repeated dosing of 23.4% HTS. Reductions in intracranial pressure (ICP) occurred after each dose of 23.4% HTS. No central nervous system complications occurred. Anasarca was the only observed complication, which responded to furosemide diuresis.

Conclusion: Repeated dosing of 23.4% HTS was effective in reducing ICP in a case of medically refractory intracranial hypertension without major systemic complications. Prospective studies should address the safety and efficacy of repeat dose 23.4% HTS on serum sodium, intracranial pressure, and complications.

Keywords: Intracranial hypertension, hypertonic saline, subarachnoid hemorrhage

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Alden K Valentino, PharmD
Karen M Nau, PharmD
David A Miller, MD
Ricardo A Hanel, MD, PhD
WD Freeman, MD

Address correspondence to:
Alden K Valentino, PharmD, Department of Pharmacy,
Mayo Clinic Jacksonville, Mayo Clinic College of
Medicine
valentino.alden@mayo.edu

Intracranial hypertension and cerebral edema treatment improves cerebral perfusion and decreases damage to tissue in the brain.¹ Hypertonic saline (HTS) at a concentration of 23.4% is an emerging therapy for managing elevated intracranial pressure (ICP) and cerebral edema. HTS is an osmotic agent that leads to a reduction in ICP.¹ However, there is no data regarding the duration and number of repeated doses of HTS that can be safely administered.^{2,3} To our knowledge, we report on the first case which received 16 total doses of 23.4% (30mL) HTS over five days, 10 doses of which were administered within 48 hours for the management of refractory intracranial hypertension.

Case Report

A 43-year-old woman had a Fisher 3 grade aneurysmal (anterior communicating artery) subarachnoid hemorrhage on 3/25/08 and developed severe bilateral anterior cerebral artery (ACA), bilateral middle cerebral artery (MCA), and bilateral posterior cerebral artery (PCA) vasospasm. An external ventricular drain (EVD) was placed for communicating hydrocephalus and ICP monitoring. The patient underwent bilateral ACA-A1, MCA-M1, and PCA-P1 angioplasties over 2 consecutive days. Two days after angioplasty, the patient developed a dilated left pupil and ICP rose above 20 mmHg. Emergent cerebral computed tomography (CT) angiogram and perfusion revealed no vasospasm of the treated vessels, but showed global cerebral hyperemia and edema (Figures 1 and 2A). Hypothermia, sedation, neuromuscular blockade, thiopental, continuous EEG monitoring, and hyperosmolar therapy (target serum sodium: 150 – 155 mEq/L) were required for refractory intracranial hypertension. Mannitol was initially used but required escalating doses, so 23.4% HTS therapy was added on 4/10/08. After HTS, the ICP transiently normalized, but required repeat doses (Figure 3). From 4/10/08 to 4/15/08, the patient received a total of 16 doses of 23.4% HTS. Within 48 hours (4/13/08 to 4/15/08), the patient received 10 doses of 23.4% (30 mL) HTS (Table 1, Figure 3). Serum sodium peaked at 155 mEq/L; coexistent salt wasting was noted on urine sodium studies. Similar to published data, continuous arterial blood pressure and heart rate data showed no cardiovascular compromise after HTS administration.¹⁻³ The patient's ICP gradually improved, and the EVD was removed (Figure 4). Anasarca developed which responded to several days of furosemide diuresis. The patient required placement of a tracheostomy on 4/15/08 and a percutaneous gastrostomy tube 4/17/08. The patient improved neurologically and went to a rehabilitation hospital on 5/7/08. After 3 months of rehabilitation, she returned to normal activities of daily living.

From the Departments of Pharmacy (AKV, KMN), Neuroradiology (DAM), Neurosurgery (RAH) and Neurology (WDF), Mayo Clinic, Jacksonville, FL

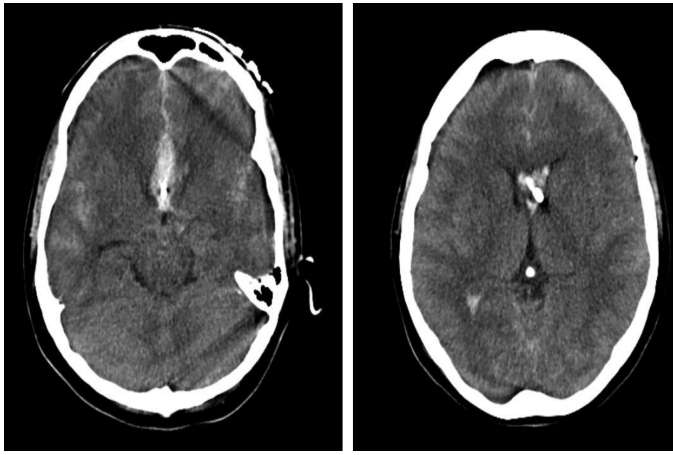


Figure 1. Non-contrast computed tomography of the head following aneurysm coil-embolization on 3/27/08. There is inter-hemispheric septal hemorrhage, subarachnoid, and intraventricular hemorrhage.

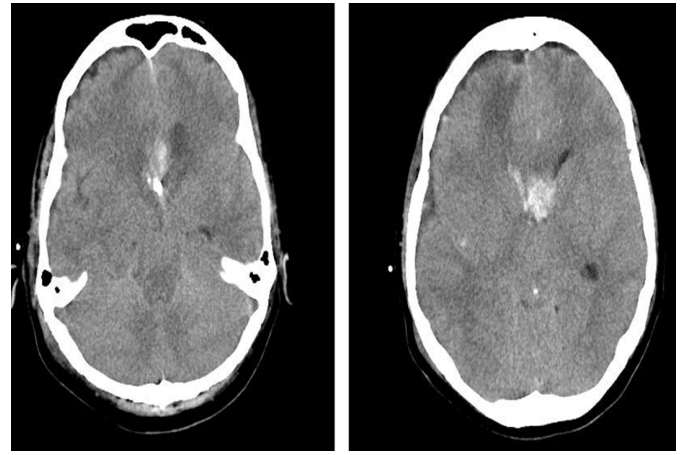


Figure 2A. Non-contrast computed tomography showing global cerebral edema on 4/4/08.

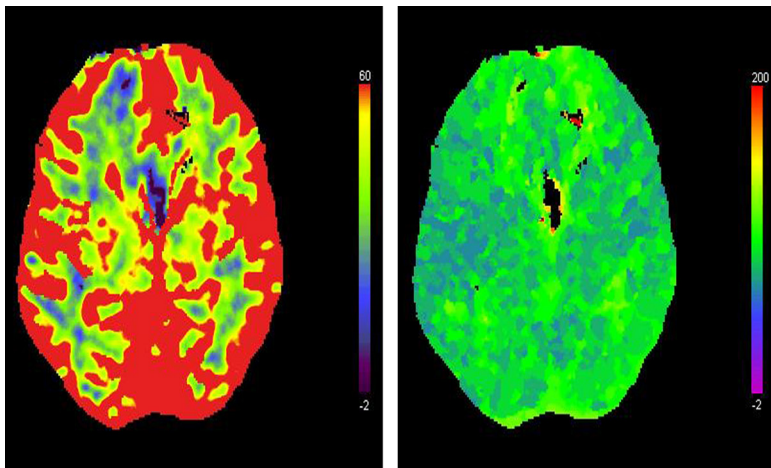


Figure 2B. Computed tomography perfusion images on 4/4/08. Cerebral blood volume (left) is increased diffusely consistent with hyperemia. Time to peak (right) is abnormally prolonged in both frontal regions and slightly prolonged (more so on the left) in the posterior temporal regions bilaterally.

Discussion

HTS is an emerging therapy for the treatment of elevated ICP and cerebral edema after brain injury¹⁻³, and has been administered in various concentrations (3%, 7.5%, 10%, and 23.4%) and dosing regimens.⁴ HTS at concentrations of 3% or higher must be given via central venous line, with concentrations of 3% to 7% usually given as a continuous intravenous infusion. Alternatively, 10% HTS has been given as an intravenous bolus of 75 mL over 15 minutes⁵ and 23.4% has been given as an intravenous bolus dose of 15-30 mL over 20 to 30 minutes.⁶ HTS acts as an osmotic agent by increasing the osmotic gradient between the blood and brain⁷ due to the low permeability of the BBB to sodium.⁴ HTS draws fluid from the interstitial compartment to the intravascular compartment^{1,4,7} resulting in a reduction of ICP, mass effect, and water content.¹ HTS can also enhance volume resuscitation, increase circulating blood volume,⁴ CBF, and MAP.^{1,4,7}

Several small studies have concluded that HTS may be beneficial in the management of intracranial hypertension.^{3,6,8} Ware et al⁶ looked at adult patients with traumatic brain injury to determine the safety and efficacy of 23.4% HTS in patients that had become tolerant to mannitol. They found that 23.4% HTS can be safely administered and produces a significant decrease in ICP. Additionally, they determined that the significant beneficial effects of 23.4% saline may be attributed to its rapid infusion and increases in serum sodium. Despite the benefits of HTS, no definitive recommended dose, frequency, or concentration of HTS solutions are established for the treatment of intracranial hypertension.^{4,7} Our patient received 10 bolus doses of 23.4% HTS within a 48 hour period. ICP showed an 84% reduction after the first dose and an 86% reduction after the last dose of HTS (mean 61%, median 64%) (Table 1). This suggests that repeated bolus dosing was beneficial and effective and that tolerance did not develop in our patient. It remains unknown the exact mechanism of benefit of repeated doses of 23.4% HTS. We speculate that repeated dosing of 23.4% HTS may create a stronger osmotic gradient between edematous brain and intravascular volume. This is supported by the Ware et al⁶ study, in which HTS contributed to better control of ICP possibly due to increases in serum sodium or hyperosmolar state. Our case and the Ware study demonstrate that serum sodium does not always correlate with ICP reduction yet serum sodium levels above 150 mmol/L seem to be associated

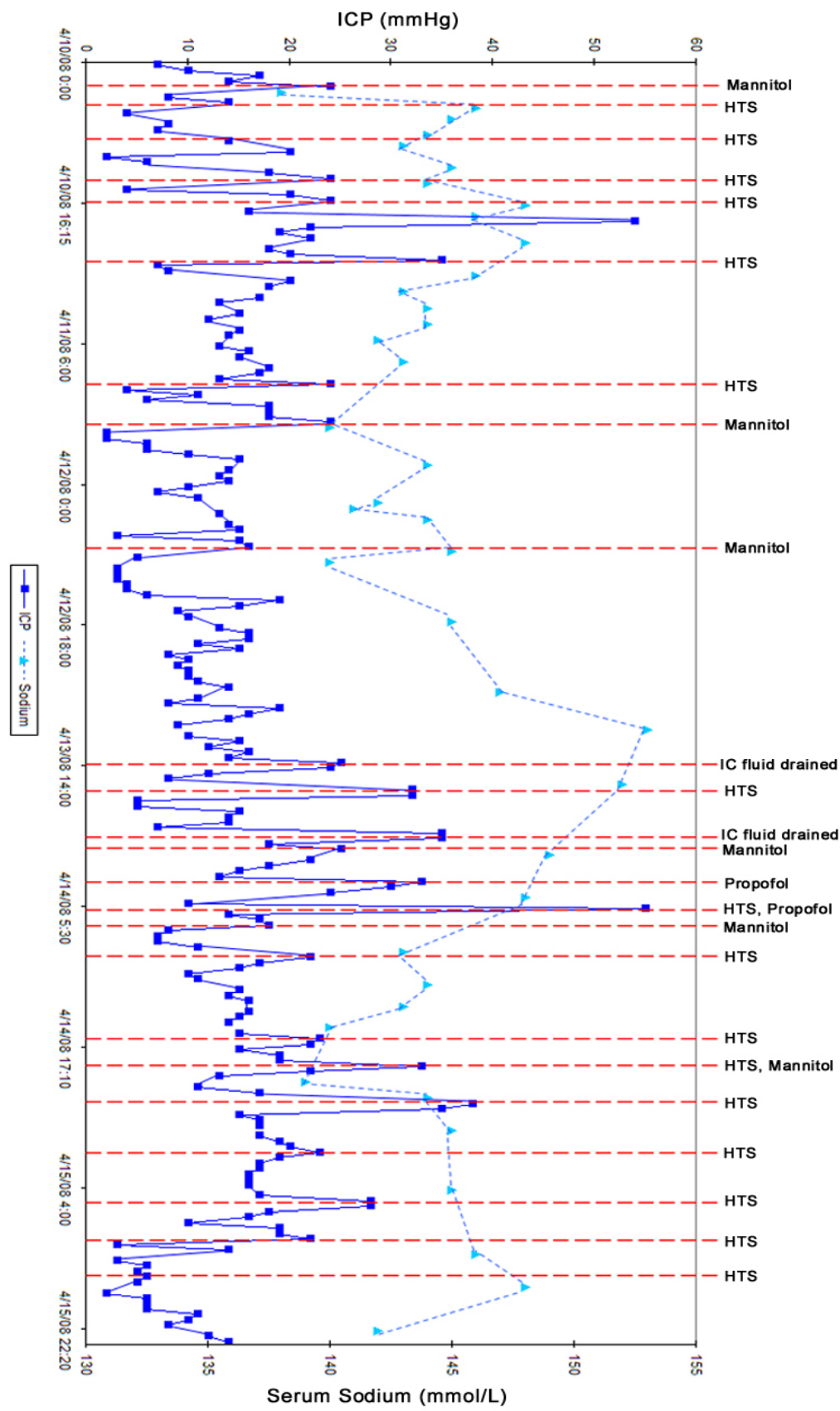


Figure 3. Relationship of HTS Administration with ICP and Serum Sodium over time.
 ICP - Intracranial pressure on first vertical axis (dark blue); HTS - Hypertonic saline. Horizontal axis denotes time in days. Serum sodium on second vertical axis (light blue).
 IC - Intracranial

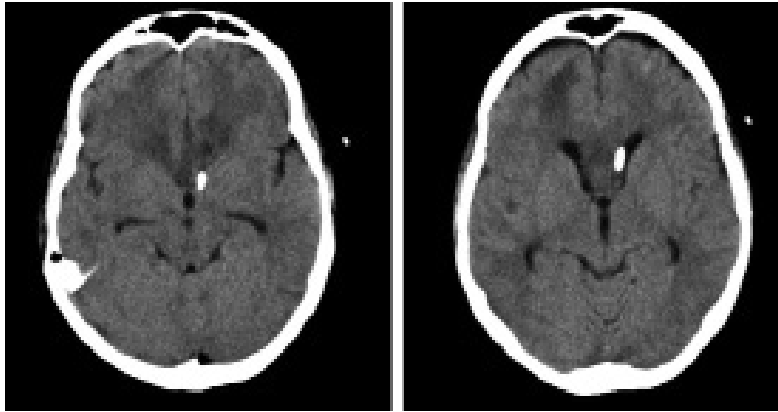


Figure 4. Non-contrast computed tomography of the head on 4/17/08. Almost two weeks after onset of global edema. Left ventricular drain, with resolution of global edema compared to prior exams.

Table 1. Timeline of repeated 23.4% hypertonic saline doses, effects on intracranial pressure (peak and duration) and serum sodium.

Date	Hypertonic Saline Dose	ICP (mmHg) peak/nadir (% reduction)	Time to peak effect (min)	Duration of effect (min)	Serum sodium (mEq/L) before/after
4/13/08	1	32/5 (84%)	10	180	152/149
4/14/08	2	55/14 (75%)	30	90	148/143
	3	22/10 (55%)	21	322	143/144
	4	23/15 (35%)	10	63	140/149
	5	33/11 (67%)	52	60	140/149
	6	38/15 (61%)	32	135	144/145
4/15/08	7	23/17 (26%)	20	195	145/145
	8	28/10 (64%)	98	135	145/146
	9	22/3 (86%)	30	270	145/146
	10*	6/2 (67%)	120	360	146/148
	Mean	31/11 (61%)	34	161	145/146
	Median	28/11 (64%)	30	135	145/146
	SD	10.8/4.7	27.3	90.5	3.7/2.3

Abbreviations used: ICP, intracranial pressure; SD, standard deviation

* Dose given as prophylaxis for tracheostomy placement, excluded from statistical analysis.

with reduction in ICP. This suggests that several mechanisms likely exist and the exact mechanism of repeated 23.4% HTS administration is theoretical in the absence of more data. For example, serum sodium may not always reflect total body sodium and water concentrations or osmolality.

Additionally, fluid shifts and sodium equilibration between the interstitial and tissue compartments and the intravascular space needs to be considered. Over time as in our case, cerebral edema lessened while total body sodium (and water) became markedly excessive manifesting in anasarca. We feel this is an important distinction for repeated dose HTS, since mannitol eventually leads to intravascular volume depletion with repeated dosing while simultaneously creating an intravascular hyperosmolar state.

Potential adverse effects of HTS administration can include decreased level of consciousness, seizures, central pontine myelinolysis, subdural and intraparenchymal hemorrhage, rebound cerebral edema, hyponatremia, hyperosmolality, heart failure, renal failure, hypokalemia, coagulopathy, phlebitis, and hyperchloremic acidosis.^{1,6} Our patient received a total of 16 doses of 23.4% HTS over a 5 day period, with 10 doses being given within a 48 hour period. She did not develop any serious adverse effects associated with HTS administration. She did develop salt wasting as seen on urine sodium studies and anasarca. Her anasarca responded to several days of furosemide diuresis.

Conclusion

We report the first patient who received 10 doses of 23.4% HTS within a 48 hour period, without hemodynamic or CNS sodium complications. HTS therapy appears to be effective in transiently reducing ICP. Repeated HTS was associated with excess total body sodium which responded to furosemide diuresis. Fu-

ture studies are needed regarding repeated HTS dosing, safety, and potential use as an emerging therapy for refractory intracranial hypertension.

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