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ORIGINAL ARTICLE

Effects of Osmotic Therapy on Pupil Reactivity: Quantification Using Pupillometry in Critically Ill Neurologic Patients

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Abstract

Background: Osmotic therapy is a critical component of medical management for cerebral edema. While up to 90% of neurointensivists report using these treatments, few quantitative clinical measurements guide optimal timing, dose, or administration frequency. Its use is frequently triggered by a qualitative assessment of neurologic deterioration and/or pupil size, and anecdotally appears to improve pupil asymmetry suggestive of uncal herniation. However, subjective pupil assessment has poor reliability, making it difficult to detect or track subtle changes. We hypothesized that osmotic therapy reproducibly improves quantitative pupil metrics.

Methods: We included patients at two centers who had recorded quantitative pupil measurements within 2 h before and after either 20% mannitol or 23.4% hypertonic saline in the neurosciences intensive care unit. The primary outcome was the Neurologic Pupil Index (NPi), a composite metric ranging from 0 to 5 in which > 3 is considered normal. Secondary outcomes included pupil size, percent change, constriction and dilation velocity, and latency. Results were analyzed with Wilcoxon signed-rank tests, Chi-square and multi-level linear regression to control for other edema-reducing interventions.

Results: Out of 72 admissions (403 paired pupil observations), NPi significantly differed within 2 h of osmotic therapy when controlling for other commonly used interventions in our whole cohort ($\beta = 0.08$, $p = 0.0168$). The effect was most pronounced ($\beta = 0.57$) in patients with abnormal NPi prior to intervention ($p = 0.0235$).

Conclusions: Pupil reactivity significantly improves after osmotic therapy in a heterogenous critically ill population when controlling for various other interventions. Future work is necessary to determine dose-dependent effects and clinical utility.

Keywords: Cerebral edema, Mannitol, Hypertonic saline

Introduction

The medical management of increased intracranial pressure (ICP) and brain herniation is comprised of a number of interventions depending on the severity and nature of the injury including head positioning, hyperventilation, cerebrospinal fluid (CSF) diversion, blood pressure manipulation, hypothermia, pharmacologic coma, and osmotic therapy [1]. While many neurocritical care programs use combinations of the above-mentioned interventions, osmotic therapy is a mainstay of medical treatment for cerebral edema and herniation, used by over 95% of surveyed neurointesivists [2]. Small retrospective studies have shown that osmotic therapy, including 20% mannitol or 23.4% hypertonic saline boluses, can reverse transtentorial herniation and decrease intracranial pressure [3–5]. However, clinicians are limited in their ability to optimize dosing and timing due to their

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inability to easily measure the medications' intended effect.

In the cases of both focal and diffuse mass effect, asymmetric changes in pupil size and reactivity (anisocoria) may occur. Different theories regarding the cause of ipsilateral (or sometimes contralateral [6]) pupillary dilation include direct pressure on the third nerve [7] or horizontal displacement of the midbrain [8–10]. Clinically, the resolution of drastic and asymmetric changes in pupil size and reactivity may provide reassurance to physicians that osmotic medication administration successfully reduced mass effect leading to less lateral displacement of midline structures [9, 10]. However, subtler pupillary changes that could potentially alert clinicians earlier to the development of profound anatomic shifts may be missed as precise pupil measurements are not routinely tracked, and the inter-rater reliability of subjective pupil assessment has been shown to be poor [11, 12].

We considered whether the effects of osmotic therapy administration could be measured by repeated quantitative pupillary measurements. However, in order to answer this question, the relationship between osmotic medication administration and pupillary reactivity must be better understood. We tested the hypothesis that in patients with poor pupil reactivity or anisocoria, the administration of bolused osmotic therapy would significantly improve pupil metrics.

Methods

Population and Study Design

We conducted a prospective observational study of patients at two medical centers who received bolused osmotic medications including 20% mannitol or 23.4% hypertonic saline in the neurosciences intensive care unit (neuro-ICU) and had quantitative pupil measurements within 2 h of medication administration. Inclusion consisted of patients greater than 18 years of age who were admitted to the neuro-ICU who met the above criteria. Patients were excluded if periorbital swelling prevented pupillary examination, if they had bilateral unreactive pupils throughout their admission, or if they were comfort measures only upon admission (full criteria in Supplementary Methods). Pupillometry data were prospectively collected between December 2016 and February 2018. Trained nurses recorded pupil measurements as standard of care every 2 h in addition to at the time and at the end of infusion of osmotic medication administrations (Supplementary Methods). Measurements were taken at usual ambient light levels in typical ICU rooms. Additional clinical data were gathered retrospectively through chart review. Our local Institutional Review Board approved the study.

We used the NeurOptics NPi™-200 (NeurOptics Inc., Irvine CA, USA) pupillometer, a portable handheld device that has been shown to more reliably record and identify changes in pupil characteristics than manual measurement alone [12, 13]. In addition to recording data including minimum pupil diameter and percent pupillary change, the device calculates a Neurological Pupil Index (NPi), a proprietary metric based on the comparison of characteristics of the measured pupillary response against a normative model of the pupil's reaction to light. The values range between 0 and 5. A measurement equal to or above 3 indicates that the intensity of the pupil response falls within the range of a NeurOptics "normal" population, and a measurement below 3 is consistent with "poor pupil reactivity." For the purposes of this study, we defined patients with poor pupil reactivity as those who had a recorded NPi of < 3.

Outcomes

The primary outcome was the NPi of the "pathologic" eye, defined as the eye with the lowest NPi in a single observation. If the NPi was equal between eyes, we used the NPi of the eye with the larger resting pupil size for analysis. We excluded any paired observations in which a "pre-osmotic therapy" pupillary measurement also occurred within 2 h after a medication administration, to eliminate misclassifying a post-intervention pupillary measurement incorrectly. Secondary outcomes included resting pupil size, constricted pupil size (minimum constricted size when exposed to the pupillometer's light) (mm), change in pupil size (%), constriction velocity (mm/s), dilation velocity (mm/s), and latency (mm/s).

Statistical Analyses

Preliminary analysis was conducted with Wilcoxon signed-rank and Chi-square tests. We subsequently constructed a multi-level linear regression model in which each patient served as his or her own control to account for both intra- and inter-patient variability. To satisfy normality assumptions for multi-level modeling, pupil metrics were transformed as appropriate (Supplementary Methods). When analyzing only observations with NPi < 3, all data remained untransformed as residuals followed a normal distribution.

We used a random slope model estimated with restricted maximum likelihood to control for each patient's baseline NPi and variability between each patient's individual responses to osmotic therapy. To control for the effect of other interventions employed to reduce intracranial pressure, we included the following other interventions in our model: (1) initiation or increase in anesthetic or analgesic agents; (2) interventions aimed to achieve optimal blood pressure and maintain cerebral perfusion pressure to 60–70 mm Hg; (3) CSF diversion; and (4) hyperventilation. All

interventions were considered fixed effects. Bonferroni corrections were applied to all pupil metrics except for our primary outcome of change in NPi, in which significance was defined as $p \leq 0.05$. Further explanation of our methods is included in the Supplementary Methods section.

We also performed an exploratory sensitivity analysis to determine the effect of interventions surrounding osmotic medication administration on pupil measurements at times extending beyond 2 h, as well as subgroup analyses on patients with hemicraniectomy, different osmotic medications, and poor pupil reactivity. All statistical analyses were performed with R Version 3.4.2 [14]. Further information on the statistical methods and specific R packages is included in the Supplementary Methods Section.

Results

We included 72 patient admissions with 403 paired pupil measurements within 2 h of either 23.4% hypertonic saline (30 mL) or 20% mannitol (dose range 0.11–1.52 gm/kg). Baseline characteristics are included in Table 1. The mean age was 57.4, and the most frequent diagnoses included intraparenchymal hemorrhage (36.1%), traumatic brain injury (15.3%), and anterior circulation stroke (13.9%). Twenty-four patients with 63 paired pupillary measurements had at least one eye with an abnormal NPi before osmotic medication administration. Anisocoria (resting pupil size difference of 1 mm or more) was present in 24 patients prior to ICP reducing interventions (44 measurements), 15 of whom also had at least one instance of an abnormal NPi in our paired pupil observations. Mortality was 34 (47.2%), and 23 patients (31.9%) received a hemicraniectomy. Thirty-three patients (45.8%) had an extraventricular drain or ICP monitor, 21 (29.2%) were started or received increased continuous antihypertensive medications and 12 (16.7%) were started on or received increased vasopressor agents in between pupil measurements. Analgesic or anesthetic agents were initiated or increased on 33 patients (45.8%) between pupil measurements and included propofol (31.9%), fentanyl (19.4%), midazolam (4.2%), and pentobarbital (1.4%).

NPi in the pathologic eye differed significantly after ICP reducing interventions compared to pre-medication NPi when treating all observations as independent (Median 4.1 [IQR 3.4–4.6] v 4.2 [IQR 3.5–4.6], $p = 0.0031$). This was also true for patients with abnormal (Median 2.4 [IQR 1.75–2.65] v 3.0 [IQR 1.9–3.45], $p < 0.0004$) and normal NPi (Median 4.4 [IQR 3.8–4.7] v 4.5 [IQR 4.0–4.7], $p < 0.0322$) prior to medication administration. Constricted pupil size also significantly differed before and after osmotic medication administration in patients with NPi < 3. When we conducted a sensitivity analysis of pupil measurements extending the time point after ICP reducing interventions, we found that change in NPi remained significant up to 5 h after therapeutic administration in patients with sluggish pupils (Median 2.45 [IQR 1.6–2.63] v 3.0 [IQR 1.88–3.53], $p < 0.0274$) (Supplementary Table 1).

In a multi-level model controlling for commonly used interventions to reduce ICP and intra- and inter-patient variability, the difference in NPi remained significant for both the total cohort and patients NPi < 3 prior to intervention ($\beta = 0.08$, $p = 0.0168$ and $\beta = 0.57$, $p = 0.0235$, respectively) within 2 h (Table 2). In patients with NPi < 3, osmotic therapy was also associated with a decrease in constricted pupil size ($\beta = -0.46$, $p = 0.0045$). No other ICP reducing interventions affected pupil metrics. In patients with anisocoria, the median size difference between eyes before and after osmotic therapy (1.29 mm v. 0.7 mm) was also statistically significant when accounting for intra- and inter-patient variability ($p < 0.0001$) (Table 3).

In a stratified analysis of blood pressure interventions, we found that administration of vasopressors was also associated with a change in NPi in the opposite direction in both the total cohort ($\beta = -0.27$, $p = 0.0084$) and patients with normal NPis ($\beta = -1.2$, $p < 0.0001$), but not in observations with abnormal NPi (Supplementary Table 2).

We also performed several subgroup analyses to better understand the effects of specific interventions including observations that occurred after hemicraniectomy and observations surrounding the isolated administration of mannitol or hypertonic saline. In paired pupil observations that occurred after a hemicraniectomy, no intervention was significantly associated with a change in NPi. We also analyzed the effect of 20% mannitol and 23.4% hypertonic saline separately. Both mannitol (235 paired observations and 62 patients) and hypertonic saline (166 paired observations and 38 patients) were associated with a change in NPi by Wilcoxon testing ($p = 0.0329$ and $p = 0.0421$, respectively) (Supplementary Table 1). When accounting for other interventions and intra/inter-patient variability, both agents demonstrated a trend ($p = 0.0896$ and $p = 0.1076$) but was not significant in the entire cohort (Table 4). Sample size was too small to compare in sluggish cohorts accounting for other interventions.

In patients with ICP monitors, we conducted exploratory analysis of the relationship between the change in ICP and NPi (Table 5). ICP was significantly reduced after medical interventions in our cohort ($\beta = -5.78$, $p < 0.0001$). When accounting for intra- and inter-patient variability, there was no significant association between the percent change in NPi and percent change in ICP

Table 1 Baseline characteristics

	All patients *n* (%)	Abnormal NPi < 3	Normal NPi ≥ 3
Admissions[a]; paired observations	72, 403	24 (33.3), 63	48 (66.7), 177
Gender, female	32 (44.4)	10 (41.7)	22 (45.8)
Age [mean (sd)]	57.4 (16)	49.8 (15.7)	61.2 (14.9)
Mortality	34 (47.2)	10 (41.7)	24 (50)
Primary diagnosis			
Intraparenchymal hemorrhage	26 (36.1)	6 (25.0)	20 (41.7)
Traumatic brain injury	11 (15.3)	6 (25.0)	5 (10.4)
Anterior circulation stroke	10 (13.9)	2 (8.3)	8 (16.7)
Brain tumor	8 (11.1)	5 (20.8)	3 (6.3)
Posterior circulation stroke	7 (9.7)	2 (8.3)	5 (10.4)
Subarachnoid hemorrhage	5 (6.9)	2 (8.3)	3 (6.3)
Other[b]	5 (6.9)	1 (4.2)	4 (8.3)
Pathology location			
Isolated supratentorial	43 (59.7)	13 (54.2)	30 (62.5)
Multiple territories	22 (30.6)	10 (41.7)	12 (25)
Cerebellum	7 (9.7)	1 (4.2)	6 (12.5)
Intraventricular hemorrhage during admission	46 (63.9)	14 (58.3)	32 (66.7)
Osmotic therapy			
Mannitol (20%)	62 (86.1)	21 (87.5)	41 (85.4)
Hypertonic saline (23.4%)	40 (55.6)	18 (75)	22 (45.8)
Both mannitol and hypertonic saline	30 (41.7)	15 (62.5)	15 (31.3)
Extraventricular drain/ICP monitor	33 (45.8)	13 (54.2)	20 (41.7)
Hemicraniectomy	23 (31.9)	8 (33.3)	15 (31.3)
Medical ICP reducing interventions			
Δ CSF drainage	23 (31.9)	8 (33.3)	15 (31.3)
Increase or initiation of continuous sedation[c]	33 (45.8)	14 (58.3)	19 (39.6)
Propofol	23 (31.9)	10 (41.7)	13 (27.1)
Fentanyl	14 (19.4)	8 (33.3)	6 (12.5)
Midazolam	3 (4.2)	2 (8.3)	1 (2.1)
Pentobarbital	1 (1.4)	1 (4.2)	0 (0)
Increase or Initiation of Continuous Blood Pressure Agents	29 (40.3)	9 (37.5)	20 (41.7)
Antihypertensives	21 (29.2)	6 (25)	15 (31.3)
Nicardipine	20 (27.8)	6 (25)	14 (29.2)
Labetalol	1 (1.4)	0 (0)	1 (2.1)
Vasopressors[d]	12 (16.7)	6 (25)	6 (12.5)
Phenylephrine	10 (13.9)	4 (16.7)	6 (12.5)
Norepinephrine	6 (8.3)	6 (25)	0 (0)
Hyperventilation	11 (15.3)	6 (25)	5 (10.4)

CSF cerebrospinal fluid, *ICP* intracranial pressure, *NPi* Neurologic Pupil Index, *sd* standard deviation

[a] One patient in the full cohort was admitted under two separate admissions with two separate diagnoses. Percents are calculated from 72 admissions

[b] Other diagnoses included (1) venous sinus thrombosis, (2) infection, (3) primary intraventricular hemorrhage, (4) status epilepticus, and (5) subdural hemorrhage

[c] Six patients had two or more classes of sedative

[d] Four patients received multiple vasopressor agents

($\beta = 0.02$, $p = 0.660$) after osmotic medication administration in the whole cohort. However, in patients with elevated ICP > 25 prior to intervention, there was a significant association between the change in NPi and change in ICP ($\beta = -0.20$, $p = 0.0461$).

Discussion

We found that osmotic medication administration was significantly associated with improved pupil reactivity within 2 h of delivery. This result remained significant after controlling for other interventions aimed at

Table 2 Multi-level model assessing pupil metrics before and after osmotic therapy controlling for patient, eye and adjusting for ICP reducing interventions

	NPi		Resting pupil size		Constricted pupil size		% Size change		Constriction velocity		Max constriction velocity		Dilation velocity		Latency	
	Beta	*p* value	Beta	*p* value	Beta	*p* value	Beta	*p* value	Beta	*p* value	Beta	*p* value	Beta	*p* value	Beta	*p* value
(A) All patients; 72 admissions, 403 paired observations																
Intercept	4.0155		3.5749		2.5333		21.2765		1.4338		2.3094		0.5948		0.2553	
Osmotic therapy	0.0786	0.0168*	−0.1167	0.0717	−0.0958	0.0091	0.2046	0.7431	−0.0180	0.6929	−0.0343	0.6418	0.0226	0.2867	0.0018	0.5666
Sedation intervention	0.0077	0.8878	−0.1368	0.1867	−0.0622	0.2950	−1.2619	0.2167	−0.1093	0.1452	−0.1398	0.2481	−0.0402	0.2362	0.0004	0.9421
BP intervention	−0.0090	0.8756	−0.2191	0.0451	−0.1041	0.0927	−1.2399	0.2494	−0.1439	0.0691	−0.2709	0.0340	−0.0756	0.0342	−0.0040	0.4601
CSF diversion	0.0081	0.2567	−0.0072	0.5970	−0.0052	0.5106	0.0429	0.7473	0.0024	0.8060	0.0016	0.9209	0.0008	0.8673	−0.0008	0.2134
Hyperventilation	0.0436	0.7057	−0.1892	0.3953	−0.1256	0.3144	−1.2495	0.5656	−0.1493	0.3489	−0.1596	0.5351	−0.0247	0.7322	−0.0065	0.5554
(B) Patients with NPi < 3; 24 admissions, 63 paired observations																
Intercept	2.1737		4.6632		4.0378		13.0599		1.1114		1.7475		0.4770		0.2828	
Osmotic therapy	0.5706	0.0235*	−0.3965	0.0311	−0.4618	0.0045*	2.2911	0.1742	0.0176	0.8831	0.0608	0.7580	−0.0090	0.8654	−0.0123	0.3904
Sedation intervention	−0.1989	0.4697	−0.6601	0.0513	−0.2680	0.3398	−4.5544	0.0744	−0.3208	0.1695	−0.5212	0.1390	−0.1637	0.1176	−0.0355	0.0569
BP intervention	−0.0053	0.9852	−0.1638	0.6376	−0.0879	0.7613	−2.8962	0.2657	−0.3998	0.0947	−0.6223	0.0845	−0.1973	0.0673	0.0099	0.5870
CSF diversion	0.0003	0.9934	−0.0013	0.9656	−0.0136	0.6184	−0.1751	0.4923	−0.0073	0.7368	−0.0258	0.4479	−0.0086	0.3845	−0.0025	0.0874
Hyperventilation	−0.2531	0.6281	0.4257	0.4421	0.2242	0.6274	2.6613	0.5390	0.1983	0.5931	0.4005	0.4881	0.0883	0.5967	−0.0527	0.0411
(C) Patients with NPi ≥ 3; 48 admissions, 177 paired observations																
Intercept	4.2063		2.9465		2.2726		22.8816		1.4614		2.3668		0.6015		0.2450	
Osmotic therapy	−0.0040	0.9474	−0.0381	0.6034	−0.0491	0.2827	0.7170	0.4288	0.0189	0.7586	0.0072	0.9459	0.0374	0.1827	0.0100	0.0455
Sedation intervention	−0.0194	0.8292	−0.2635	0.0360	−0.1324	0.0925	−2.5989	0.1191	−0.2149	0.0594	−0.3457	0.0731	−0.0982	0.0460	0.0081	0.3141
BP intervention	−0.1375	0.0893	−0.1520	0.1848	−0.0919	0.1964	−1.1241	0.4498	−0.1098	0.2805	−0.1446	0.4012	0.0001	0.9981	0.0051	0.4787
CSF diversion	0.0107	0.2778	0.0027	0.8479	0.0019	0.8247	0.0496	0.7766	0.0030	0.7991	0.0072	0.7219	0.0016	0.7583	−0.0006	0.5206
Hyperventilation	0.0884	0.6837	−0.4850	0.0788	−0.2647	0.1353	−3.8464	0.3182	−0.3869	0.1387	−0.4370	0.3247	−0.1308	0.2462	0.0029	0.8802

BP blood pressure, *CSF* cerebrospinal fluid, *ICP* intracranial pressure, *NPi* Neurologic Pupil Index

*p values of all secondary outcomes were adjusted with Bonferroni's correction to be significant if $p < 0.0071$

Table 3 Multi-level model assessing difference in resting pupil size (mm) in (A) all patients and (B) patients with anisocoria before osmotic therapy

	Median size difference		Beta	*p* value
Admissions, paired observations 72, 394[a]				
(A) All patients				
Before osmotic therapy	0.3	Intercept	0.3256	
After osmotic therapy	0.3	Osmotic therapy	− 0.006	0.795
Admissions, paired observations 24, 44				
(B) Patients with anisocoria before osmotic therapy				
Before osmotic therapy	1.29	Intercept	1.4314	
After osmotic therapy	0.70	Osmotic therapy	− 0.7471	< 0.0001*

[a] Paired observations are 394 instead of 403 because 9 observations had missing values for either the left or the right eye

reducing ICP including CSF diversion, blood pressure management strategies, initiation or increase in anesthetic and analgesic agents, and hyperventilation.

These findings add to the literature by examining the measurable effect of medical therapy, and specifically osmotic medication administration on the quantitative marker of pupil reactivity. Our results are consistent with research showing that in 12 episodes of herniation secondary to supratentorial mass lesions, NPi was improved after various medical interventions including bolused osmotic medications [15]. Another group found that in patients who received high dose mannitol (1.4 g/kg), pupil "widening" improved 5–10 min after the end of the mannitol infusion compared to lower dose mannitol infusions [16], though the validity of the findings was later questioned [17]. We found no similar study on bolused hypertonic saline.

While the medical interventions and CSF diversion are frequently initiated interventions in cases in which clinicians are concerned for life-threatening swelling, their durations of action are often transient and imprecisely understood. Mannitol, an alcohol derivative of the sugar mannose given as a 20% solution, and hypertonic saline often used in concentrations ranging from 3 to 23.4% are thought to mitigate swelling through the establishment of an osmolar gradient and diuresis. Mannitol may have additional edema-reducing properties such as decreasing blood viscosity [18] and acting as a free radical scavenger [19]. The peak effect of the reduction in brain water is thought to occur 15–35 min after completion of a mannitol infusion [20], with a halftime of elimination of 0.5–2.5 h, and prolonged in patients with impaired renal function [18, 21, 22].

Determining the time to effect of hypertonic saline is even less well verified. Various studies have evaluated the timing of hypertonic saline on intracranial pressure and found time to effect varied from immediate to 30 min [2, 23], with duration of action lasting 4–6.3 h [24, 25]. Because both bolused hypertonic saline and mannitol's mechanisms of action are primarily through the creation of an osmotic gradient, once a static level of osmolarity has been achieved, further doses are required to sustain the water gradient outward from the brain [26]. There has also been historical debate about whether rebound swelling and increased ICP occurs after its initial effect [18, 27, 28]. Traditionally, these medications are dosed every 4–6 h, guided by an upper limit in osmotic gap or a sodium concentration ceiling. However, this gap is frequently used to determine a threshold at which to hold medications for unclear risks of adverse effects [18] rather than dosing for efficacy.

Our results raise the question as to whether quantitative improvement in pupil reactivity could serve as a non-invasive marker of clinically relevant edema reduction after osmotic therapy. Displacement of midbrain and/or medullary structures and involvement of the third cranial nerve have been associated with worsened pupil reactivity and anisocoria development [6, 8, 9], and previous work suggests an association between elevations in global ICP and NPi [29], which is also reflected in our results (Table 5). The duration of pupil reactivity improvement after medical interventions we found in our study (approximately 5 h) is consistent with the timing of sustained lowering in intracranial pressure found in previous studies [25, 30]. We also found that osmotic therapy causes quantitative pupil changes that are independent of commonly used medical interventions used to reduce ICP. This suggests that serial pupil measurements may be of clinical utility in measuring the effect of medical therapies in reducing pressure and/or displacement of midbrain and medullary structures in the ICU setting.

Several other findings generated by our results warrant discussion. While osmotic therapy significantly improved NPi both in our total cohort and in the subgroup of

Table 4 Subgroup multi-level model assessing pupil metrics before and after osmotic therapy controlling for patient, eye and adjusting for ICP reducing interventions

	NPi		Resting pupil size		Constricted pupil size		% size change		Constriction velocity		Max constriction velocity		Dilation velocity		Latency	
	Beta	*p* value	Beta	*p* value	Beta	*p* value	Beta	*p* value	Beta	*p* value	Beta	*p* value	Beta	*p* value	Beta	*p* value
(A) Pupil measurements after hemicraniectomy; 20 admissions[a], 117 paired observations																
Intercept	4.0436		3.4687		2.6935		22.1847		1.5467		2.5045		0.6284		0.2478	
Osmotic therapy	0.0365	0.5099	−0.0802	0.5505	−0.0783	0.3267	0.2964	0.7967	0.0276	0.7506	−0.0077	0.9594	0.0370	0.3777	0.0057	0.3820
Sedation intervention	0.0685	0.4399	−0.1837	0.3233	−0.1704	0.1507	1.5831	0.3921	0.0254	0.8569	0.1481	0.5310	−0.0026	0.9689	0.0083	0.3601
BP intervention	−0.0613	0.5260	−0.1761	0.3760	−0.0535	0.6830	−3.0163	0.1191	−0.2918	0.0483	−0.4911	0.0478	−0.0729	0.2924	−0.0079	0.4130
CSF diversion	−0.0161	0.2207	0.0055	0.8499	0.0161	0.3893	−0.3157	0.2367	−0.0180	0.3733	−0.0315	0.3568	−0.0018	0.8485	−0.0016	0.2208
Hyperventilation	0.0983	0.5933	0.1001	0.8133	0.0672	0.8044	0.1769	0.9631	−0.2098	0.4713	−0.0531	0.9136	0.1859	0.1769	−0.0080	0.6817
(B) Pupil measurements in patients without hemicraniectomy; 55 admissions[b], 286 paired observations																
Intercept	3.9919		3.5138		2.4939		20.7274		1.3816		2.2168		0.5810		0.2580	
Osmotic therapy	0.0945	0.0158*	−0.1292	0.0692	−0.1022	0.0111	0.1106	0.8817	−0.0420	0.4312	−0.0541	0.5238	0.0156	0.5236	0.0006	0.8806
Sedation intervention	−0.0571	0.3879	−0.1287	0.2690	0.0004	0.9948	−2.8056	0.0212	−0.1803	0.0421	−0.2879	0.0401	−0.0685	0.0789	−0.0010	0.8706
BP intervention	0.0393	0.5645	−0.2158	0.0782	−0.1382	0.0475	−0.2186	0.8645	−0.0730	0.4358	−0.1552	0.2945	−0.0708	0.0847	−0.0040	0.5317
CSF diversion	0.0066	0.4295	−0.0042	0.7753	−0.0050	0.5687	0.0514	0.7394	0.0028	0.8029	0.0008	0.9662	−0.0016	0.7553	−0.0003	0.7487
Hyperventilation	−0.0160	0.9099	−0.2317	0.3591	−0.1858	0.1828	−2.1223	0.4167	−0.1370	0.4713	−0.2306	0.4434	−0.1214	0.1475	−0.0044	0.7412
(C) Pupil measurements after 20% mannitol; 62 admissions, 235 paired observations																
Intercept	4.0653		3.5512		2.4868		22.0784		1.5021		2.3965		0.6080		0.2550	
Osmotic therapy	0.0643	0.0896	−0.0958	0.2293	−0.0711	0.0958	0.1604	0.8390	−0.0099	0.8643	−0.0346	0.7171	0.0267	0.3138	0.0043	0.2635
Sedation intervention	−0.0158	0.8177	−0.2318	0.1032	−0.1046	0.1662	−2.6924	0.0624	−0.2713	0.0115	−0.3608	0.0395	−0.1111	0.0212	0.0042	0.5448
BP intervention	−0.0038	0.9526	−0.2926	0.0285	−0.1350	0.0550	−1.8725	0.1635	−0.2021	0.0423	−0.3257	0.0456	−0.0432	0.3303	−0.0006	0.9294
CSF diversion	0.0101	0.1890	−0.0234	0.1475	−0.0134	0.1310	−0.0027	0.9867	0.0011	0.9262	−0.0086	0.6598	−0.0008	0.8822	−0.0002	0.7731
Hyperventilation	0.1324	0.2529	−0.1715	0.4931	−0.1646	0.2096	0.5829	0.8159	0.0092	0.9601	0.0358	0.9060	0.0590	0.4744	0.0002	0.9891
(D) Pupil measurements after 23.4% hypertonic saline; 38 admissions[c], 166 paired observations																
Intercept	3.9303		3.6928		2.6666		20.8737		1.4333		2.2801		0.5963		0.2579	
Osmotic therapy	0.0948	0.1076	−0.1315	0.1928	−0.1191	0.0698	0.3289	0.7178	−0.0274	0.6805	−0.0257	0.8077	0.0130	0.6756	0.0007	0.8968
Sedation intervention	0.0518	0.5865	0.1001	0.5262	0.0136	0.8987	0.9631	0.5071	0.1331	0.2049	0.1989	0.2350	0.0915	0.0606	−0.0001	0.9913
BP intervention	−0.0879	0.4496	−0.0684	0.7116	−0.0555	0.6532	−1.5431	0.3682	−0.1832	0.1359	−0.3447	0.0791	−0.1704	0.0031*	−0.0067	0.4587
CSF diversion	0.0045	0.7648	0.0413	0.0914	0.0241	0.1512	0.2496	0.2663	0.0180	0.2596	0.0373	0.1457	0.0066	0.4171	−0.0023	0.0589
Hyperventilation	−0.0422	0.8841	−0.5623	0.2314	−0.1940	0.5161	−5.0268	0.2386	−0.5913	0.0548	−0.7983	0.1048	−0.3017	0.0360	−0.0288	0.2158

BP blood pressure, *CSF* cerebrospinal fluid, *ICP* intracranial pressure, *NPi* Neurologic Pupil Index

*p values of all secondary outcomes were adjusted with Bonferroni's Correction to be significant if $p < 0.0071$

[a] Out of the 23 patients in our cohort who received hemicraniectomy, 20 had paired pupil measurements that occurred after the hemicraniectomy and are included in this analysis

[b] Three patients who eventually had hemicraniectomies also had paired pupil observations prior to hemicraniectomy. Total number of patient admission was 72

[c] Two patient admissions were excluded from this analysis to avoid confounding because they were treated with both hypertonic saline and mannitol in between pupil measurements. Total number of patients receiving hypertonic saline was 40

Table 5 Correlation between percent change in ICP and NPi after ICP reducing interventions

			Spearman's rho			*p* value
(A) Spearman's rank correlation						
% Change in ICP and % change in NPi			− 0.0374			0.5822
Admissions, paired observations	**ICP**		**Δ NPi–Δ ICP**		**Δ NPi–Δ ICP, ICP > 25**	
	33, 219		**33, 219**		**11, 66**	
	Beta	***p* value**	**Beta**	***p* value**	**Beta**	***p* value**
(B) Multi-level model ICP after osmotic therapy with Δ NPi as the dependent variable						
Intercept	11.7541		5.2281		− 31.3048	
Osmotic therapy	− 5.7754	< 0.0001*	0.0236	0.660	− 0.2003	0.0461*

Percent change in ICP was calculated from the max ICP that occurred within 2 h prior to the pre-osmotic therapy pupil measurement and the minimum ICP that occurred within 2 h after the pre-osmotic therapy pupil measurement

No significant correlation was appreciated when treating all observations as independent (5A). When accounting for inter- and intra-patient variability in a multi-level model, no significant relationship between change in ICP or change in NPi was found in the whole cohort. However, a significant relationship was demonstrated in a subgroup of patients with an ICP > 25 mmHg (5B)

ICP intracranial pressure, *NPi* Neurologic Pupil Index

patients with an NPi < 3 prior to osmotic therapy administration, this finding was no longer significant in the subgroup of patients with a "normal" NPi prior to medication, which may suggest that therapy affects only pathological pupil reactivity. We also found that the effect of osmotic therapy on NPi was no longer significant in patients who had undergone hemicraniectomy, which is likely due to the substantial changes in global pressure and directional mass effect that occurs after removal of the skull and dura [31]. In variations of our model, we found that the initiation or increase in vasopressor medications had a significant effect on NPi but resulted in a negative association, suggesting that these agents counteracted the overall improvement in pupil reactivity. This is consistent with previous studies that observed quantitative and qualitative changes in pupil size and reactivity after the administration of medications including vasopressors and analgesic agents [32, 33].

Incidentally, our study demonstrated that not all patients who receive osmotic therapy necessarily demonstrate quantitative evidence of poor pupil reactivity. Abnormal NPi prior to medication administration was present in only in 24 out of 72 patient admissions. We hypothesize that this finding reflects the fact that osmotic therapy is used not only for edema that impinges upon midbrain and brainstem structures, the anatomic locations most closely associated with decreased pupil reactivity [8, 9, 34], but also for cortical swelling. We also found that mortality in patients with NPi < 3 was similar to the entire group, though this may be due to intrinsic bias of exclusion criteria. (Patients with bilateral unreactive pupils or who were comfort measures only on admission were excluded).

Our study has limitations. This was an observational study of pupillary observations and osmotic medication administration. Diagnoses and injury location were heterogeneous, and we were similarly not powered to detect differences in these subgroups. Sample size was small among patients with poor pupil reactivity or with a single osmotic therapy, and we were not powered to detect a dose-dependent effect of osmotic therapy. While we attempted to control for other accompanying interventions for elevated ICP including sedation, CSF drainage, blood pressure management, and hyperventilation, these measures were collected retrospectively and we cannot rule out the possibility that other elements of elevated ICP management including head of bed elevation and minimization of tracheal suctioning did not also contribute to changes in pupil reactivity, as these measures are standard in our institutions. We were also unable to measure dose-dependent effects that some of our confounders may have including continuous sedative and blood pressure medication escalation. Other factors that can affect pupillary responsiveness, including pain, emotional valence, and ambient light levels were not recorded. Nevertheless, despite these limitations, this study succeeded in demonstrating a significant relationship between acute osmotic therapy aimed at reducing edema and pupillary reactivity with high power to detect a change in NPi [35] (Supplementary Methods) in a heterogenous, multicentered cohort in the ICU setting.

Conclusion

In this study, we demonstrated a significant quantifiable improvement in pupillary reactivity after the administration of osmotic therapy in a heterogenous critically ill

population after controlling for the effect of other interventions commonly used to reduce edema. This relationship, while preliminary, warrants further investigation to determine whether more rigorous tracking of pupillary metrics can be useful for monitoring the effect of osmolar therapy for reducing edema on an individual basis. Future studies to determine dose-dependency and radiographic correlation may further demonstrate the utility of using serial quantitative pupil measurements to follow changes in cerebral edema and possibly help to guide medical management.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-018-0620-y) contains supplementary material, which is available to authorized users.

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Author Contribution
CO was responsible for study design, analysis, interpretation of results, and the writing of the manuscript. MH assisted in statistical analysis of results and entering demographic and clinical data for patients. MB provided pharmacological expertise regarding osmotic therapy and manuscript review. AK was responsible for collecting pupillometry smart guards, entering demographic and clinical data, manuscript review and administrative duties regarding IRB submission process. SZ assisted in study design and collection, manuscript review. SS oversaw study design and provided expertise regarding analysis and interpretation of results.

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Conflict of interest
Dr. Ong reports grants from American Brain Foundation, during the conduct of the study. All other authors have nothing to disclose.

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