ECRONICON OPEN ACCESS

EC NEUROLOGY
Research Article

Treatment of Malignant Cerebral Infarction with 3% Hypertonic Saline Infusion Is Not Associated with Good Outcome: A Case-Control Study

Fahad J Laghari[1], Elizabeth J O'Neill[2], Christopher D Streib[1] and Maxim D Hammer[1]*

[1]Stroke Institute, Department of Neurology, University of Pittsburgh Medical Center (UPMC), Pittsburgh, Pennsylvania, USA

[2]University of Pittsburgh School of Medicine, M240 Scaife Hall, Pittsburgh, Pennsylvania, USA

***Corresponding Author:** Maxim D Hammer, Stroke Institute, Department of Neurology, University of Pittsburgh Medical Center (UPMC), Pittsburgh, Pennsylvania, USA.

Received: July 28, 2017; **Published:** September 05, 2017

Abstract

Background and Purpose: Malignant cerebral infarction has high mortality. Continuous infusion of 3% hypertonic saline is commonly used to control cerebral edema, despite the lack of evidence regarding efficacy. The purpose of this study is to determine if the continuous infusion of 3% hypertonic saline impacted the outcome in malignant cerebral infarction at our institution.

Methods: Consecutive cases of malignant cerebral infarction (defined as NIHSS > 15, infarct volume > 80cc) between 2006 - 2012 at a single institution were identified. Subjects were either treated only with the continuous infusion of 3% hypertonic saline ("treatment") or no edema-modifying therapy ("controls"). Outcomes were dichotomized as "good" or "poor." Poor outcome was defined as the impending herniation requiring hemicraniectomy or in-hospital death. We applied chi-square and logistic regression analyses to determine the association between treatment and outcome.

Results: Two hundred and sixty total cases were reviewed: 54 treatment and 206 controls. In the treatment group, 30 (56%) patients had poor outcome compared to 76 (37%) in control subjects. There was a significant (p = 0.013) association between treatment with the continuous infusion of 3% hypertonic saline and poor outcome by chi-square analysis. When multivariable logistic regression was applied to control for the effects of independent predictors of poor outcome, the association between treatment with continuous infusion of 3% hypertonic saline and poor outcome was just short of significance (odds ratio 1.914, p = 0.0545). Individual patient response to continuous 3% hypertonic saline infusion did not affect the outcome.

Conclusions: Our findings suggest that the osmolar therapy with continuous infusion of hypertonic saline only is not effective in preventing herniation and death. Prospective analysis is warranted.

Keywords: *Stroke; Neurocritical Care; Hypertonic Saline; Cerebral Edema; Outcomes*

Introduction

Malignant cerebral infarction (MCI), defined as a large infarction of the middle cerebral artery territory accompanied by a space-occupying mass effect, occurs in approximately 10 percent of all ischemic strokes.1 Medically managed, the mortality rate of MCI may be as high as 80 percent [1,2]. Clinically, patients present with hemispheric syndromes secondary to acute ischemic stroke followed by neurological deterioration due to cerebral edema, which may progress to decreased level of consciousness, coma, and death [3]. Early hemicraniectomy has been shown to reduce mortality in malignant cerebral edema patients; however, medical management with osmotic

agents, such as mannitol and hypertonic saline (HTS), are commonly used prophylactically in an attempt to reduce cerebral edema and ultimately avoid decompressive hemicraniectomy. HTS is also commonly used in patients who do not clearly require urgent hemicraniectomy and those who are poor surgical candidates [1,4].

Hypertonic saline is an ideal osmotic agent. It is pharmacologically inert and relatively excluded from an intact blood-brain barrier with a reflection coefficient of 1.0 [4-7]. We focused our study on 3% hypertonic saline (3%HTS) because it is typically administered through continuous infusion with the aim of preventing herniation, whereas higher concentrations of HTS and mannitol are more commonly given in boluses and used as a "bridge" to definitive therapy, such as hemicraniectomy. This practice is common at our institution and elsewhere [1].

The purpose of our study was to evaluate the use of continuous infusion of 3%HTS in the setting of MCI at our institution. Specifically, we investigated whether 3%HTS prevents brain herniation in the setting of MCI. Additionally, we assessed whether the degree and intensity of therapy, as measured by the rate of infusion, the volume of 3%HTS administered, and increase in serum sodium concentration, correlated with outcomes.

Methods

We performed a retrospective case series at the University of Pittsburgh Medical Center Presbyterian Hospital, conducted via Cerner electronic medical record review of patients admitted between January 2006 and December 2012. We obtained IRB approval from the University of Pittsburgh Institutional Review Board. Subjects included in the analysis were 18 to 80 years of age with documented ischemic stroke, and National Institutes of Health Stroke Scale Score (NIHSS) greater than or equal to 15 (n = 2370). Subjects were further stratified into two groups: subjects who had infarct volumes between 80-140cc, on MRI/DWI imaging (n = 118), and subjects who had infarct volumes greater than 140cc on MRI/DWI imaging (n = 142) [3].

Basic demographics, vital signs, lab values, baseline serum sodium levels, peak on-treatment sodium levels, duration of 3%HTS treatment, and the total volume of 3%HTS treatment were included in our analysis. Subjects were excluded from the analysis if they had infarct volumes less than 80cc on MRI/DWI imaging or if they did not have an MRI (n = 1602). Other exclusion criteria included an incomplete medical record for the aforementioned treatment parameters or concomitant administration of other forms of osmotherapy, such as higher concentrations of HTS boluses or mannitol (n = 508). Subjects who were treated with 3%HTS were in the "treatment" group (n = 54), and subjects with no edema-modifying therapy were in the "control" group (n = 206).

Data Analysis

Our primary outcome measure was the clinical outcome. The poor clinical outcome was defined as patients who required hemicraniectomy or died during the admission. We applied Chi-square and logistical regression analyses using the SAS statistical program (v9.2) to assess the effect of continuous infusion of 3%HTS on clinical outcome. To assess whether 3%HTS might be more beneficial to patients with larger infarcts, we conducted a subgroup analysis of patients with infarct volumes greater than 140cc.

We initially performed a univariate analysis of patient demographics and stroke characteristics including infarct volume, average serum glucose, average serum potassium, average serum creatinine, baseline serum sodium, the presence of atrial fibrillation or flutter, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, gender, and age. We then used multivariable logistic regression to evaluate the treatment effect of 3%HTS while controlling for any variables that were significant predictors of outcome as determined by our univariate analysis. Finally, we used univariate logistic regression to specifically analyze the impact of treatment parameters and physiologic response to 3%HTS. These variables include the rate of 3%HTS infusion, duration of 3%HTS infusion, average serum sodium while on treatment, baseline serum sodium, peak serum sodium on treatment, the total change in serum sodium, time to peak serum sodium, and the total volume of 3%HTS given during treatment. For all analyses, statistical significance was defined as $p < 0.05$.

Results

A total of 260 cases were included in the analyses; 54 subjects were treated with 3%HTS, and 206 were untreated control subjects (Figure 1). There was a significant difference in age (treatment mean age = 65 years [IQR: 56 - 74] versus control mean age = 73 years [IQR: 60 - 82]) and infarct volume (treatment median infarct volume = 164.5cc [IQR: 137.2 - 212.2]) versus control mean infarct volume = 142.4cc [IQR: 108.9 - 185.0]). Additional demographics were not statistically different (Table 1).

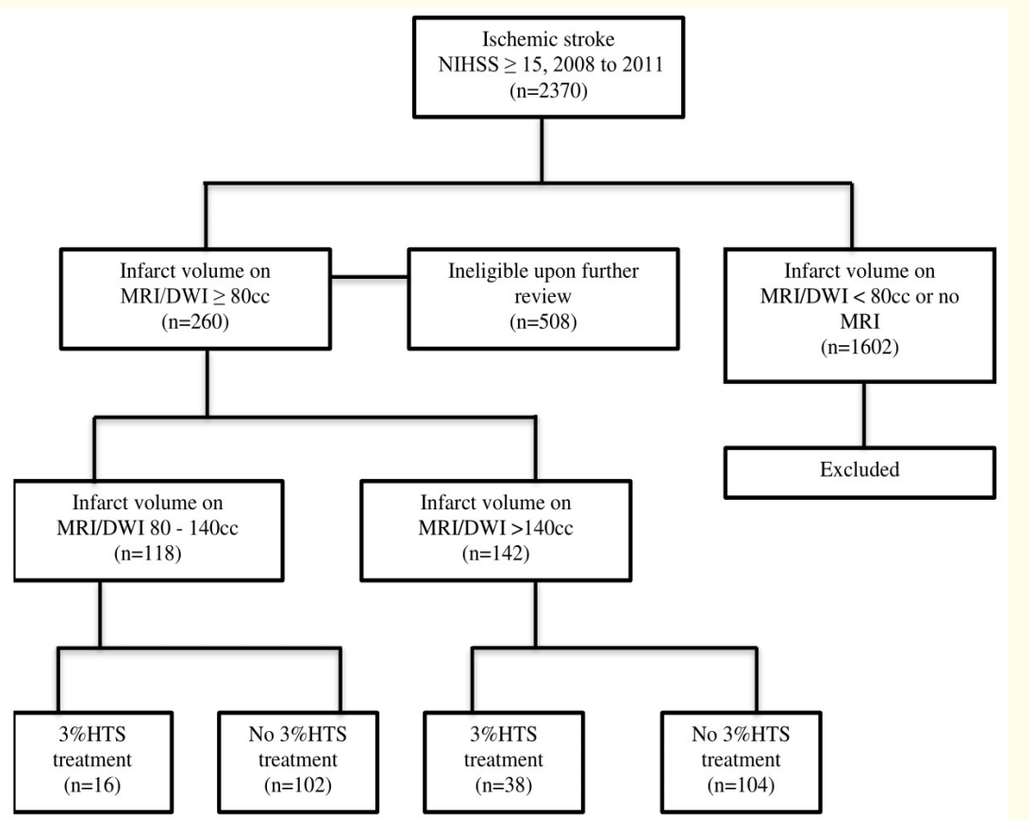

Figure 1: *Flow diagram of the study selection process.*

	Control	3% HTS treatment
Number of Patients	206	54
Age*	73 [60 - 82]	65 [56 - 74]
Infarct volume*	142.4 [108.9 - 185.0]	164.5 [137.2 - 212.2]
Serum glucose*	133.9 [116.6 - 152.1]	132.6 [117.3 - 165.3]
Serum potassium*	4.0 [3.8 - 4.3]	3.9 [3.7 - 4.0]
Serum creatinine*	0.9 [0.7 - 1.2]	0.8 [0.7 - 1.1]
Baseline serum sodium*	138 [136 - 140.3]	138 [136 - 141]
Atrial fibrillation or flutter**	0.29	0.19
Hypertension**	0.68	0.63
Diabetes mellitus**	0.24	0.30
Dyslipidemia**	0.42	0.50
Coronary artery disease**	0.32	0.17

Table 1: *Baseline characteristics of control subjects and subjects treated with 3% hypertonic saline (3%HTS) treatment.*

**indicates median [interquartile range], **indicates percent*

The rate of poor outcome in patients treated with 3%HTS was 56% (30 of 54) compared to 37% (76 of 206) of control patients, with a significant (p = 0.01299) association between 3%HTS treatment and poor outcome (Table 2). In our unadjusted subgroup analysis of large volume infarcts (> 140cc), there was no significant difference (p = 0.5111) in outcomes between treatment and control groups (Table 2).

	Control ≥ 80cc (n = 206)	Control > 140cc (n = 104)	3%HTS ≥ 80cc (n = 54)	3%HTS > 140cc (n = 38)	Total ≥ 80cc (n = 260)	Total > 140cc (n = 142)
Survived Without Hemicraniectomy (n, %)	(130, 63%)	(53, 50.9%)	(24, 44%)	(17, 44.7%)	(154, 59%)	(70, 49%)
Underwent Hemicraniectomy (n, %)	(20, 9.7%)	(14, 13%)	(11, 20%)	(8, 21%)	(31, 11.9%)	(22, 15.5%)
In-Hospital Death (n, %)	(56, 27%)	(37, 35.6%)	(19, 35%)	(13, 34%)	(75, 28.8%)	(50, 35%)
Total Poor Outcome (n, %)	(76, 36.9%)	(51, 49%)	(30, 55.6%)	(21, 55%)	(106, 40.7%)	(72, 50.7%)

Table 2: *3% hypertonic saline (3%HTS) treatment versus outcome in all subjects with infarct volumes ≥ 80cc and with stroke volumes > 140cc.*

**denotes significance*

3%HTS associated with poor outcome by chi-squared test for infarct volumes ≥ 80cc (p = 0.01299)*

3%HTS had no effect on outcome by chi-squared test for infarct volumes > 140cc (p = 0.5111)

Using univariate regression analyses, we determined that infarct volume (OR: 1.010, p < 0.0001) and average serum glucose (OR: 1.009, p = 0.0149) were significant predictors of poor outcome. Additionally, average serum potassium was inversely associated with poor outcome (OR: 0.511, p = 0.0304). No other variables were associated with poor outcome (Table 3). We used multiple logistic regression to control for differences in infarct volume, serum glucose, and serum potassium between the two treatment groups. Although the association was no longer statistically significant, an inclination toward poor outcome remained (OR: 1.914, p = 0.0545) for patients treated with 3%HTS.

Factor	p-value	Odds Ratio, [95% CI]
Infarct volume	<0.0001*	1.010, [1.006 - 1.015]
Average serum glucose	0.015*	1.009, [1.002 - 1.017]
Average serum potassium	0.03*	0.511, [0.279 - 0.939]
Atrial fibrillation/flutter	0.07	1.656, [0.952 - 2.883]
Hypertension	0.24	0.731, [0.432 - 1.237]
Diabetes mellitus	0.26	1.381, [0.785 - 2.430]
Dyslipidemia	0.48	0.834, [0.504 - 1.379]
Coronary artery disease	0.51	0.831, [0.477 - 1.450]
Gender	0.52	1.176, [0.715 - 1.936]
Average serum creatinine	0.64	0.918, [0.638 - 1.320]
Age	0.85	0.998, [0.982 - 1.015]
Baseline serum sodium	0.99	1.000, [0.936 - 1.069]

Table 3: *Factors and their impact on outcome using univariate logistic regression.*

**denotes significance*

Furthermore, in the treatment group, baseline serum sodium, change in serum sodium, peak serum sodium, average serum sodium and total volume of 3%HTS treatment were not statistically correlated with outcome, whereas rate of 3%HTS infusion (OR: 1.091, p = 0.0046), duration of 3%HTS infusion (OR: 0.989, p = 0.0476) and time to peak serum sodium (OR: 0.977, p = 0.0179) were statistically correlated with poor outcome (Table 4).

Factor	p-value	Odds Ratio, [95% CI]
Rate of 3% HTS infusion	0.005*	1.091, [1.027 - 1.159]
Duration of 3% HTS infusion	0.048*	0.989, [0.979 -1.000]
Time to peak serum sodium	0.018*	0.977, [0.959 - 0.996]
Total volume of 3% HTS given	0.06	1.000, [0.999 - 1.000]
Baseline serum sodium	0.77	0.981, [0.860 - 1.118]
Change in serum sodium	0.24	0.961, [0.899 -1.027]
Peak serum sodium on treatment	0.18	0.955, [0.893 - 1.021]
Average serum sodium on treatment	0.37	0.954, [0.861 - 1.057]

Table 4: *Factors and their poor impact on outcome in the 3% hypertonic saline (3%HTS) treated subjects using univariate logistic regression.*

**denotes significance*

Discussion

We are the first to report the effect of continuous infusion of 3%HTS infusion on clinical outcomes in a pure ischemic stroke patient cohort. 3%HTS is commonly used to attenuate cerebral edema resulting from ischemic stroke, yet there is sparse clinical data regarding its efficacy in humans. Studies on animal models have demonstrated that hypertonic saline reduces brain volume, lowers intracranial pressure, and results in increased intravascular volume, but these findings are inconsistent [8,9]. In general, human studies have shown that bolus infusions of high concentrations of hypertonic saline have been effective in reducing intracranial pressure in patients with traumatic brain injury [10]. The therapy has also been shown to be associated with a reversal of transtentorial herniation in patients with raised intracranial pressure resulting from various pathologies [11]. A big portion of the literature focuses on comparing the efficacy of bolus infusions of higher concentrations of hypertonic saline with mannitol therapy. Kamel., *et al.* performed a meta-analysis of randomized controlled trials that compare hypertonic saline with mannitol and concluded that bolus infusions of hypertonic saline are superior to mannitol therapy in treating raised intracranial pressure [12]. Continuous infusion of hypertonic saline and its effects on cerebral edema resulting from various pathologies have also been studied in the past. In a rat model of brain tumor, continuous infusion of 7.5% HTS reduced cerebral edema in the affected as well as the non-affected cerebral hemisphere [13]. While Wagner., *et al.* in their paper published in 2011 on patients with supratentorial bleeding, showed that continuous infusion of 3% HTS reduced intracranial pressure crisis and volume of peri-hemorrhagic edema [14]. Hauer., *et al.* reported similar findings with continuous infusion of 3% HTS in a group of patients with cerebral ischemia, intracerebral hemorrhage, and aneurysmal subarachnoid hemorrhage [15]. However, there remain concerns regarding continuous hypertonic saline infusion. One of the concerns is that it may cause rebound intracranial pressure. Because infarction of brain tissue would disrupt blood-brain barrier (BBB), it is possible that HTS, when given over prolonged period, may cross the BBB and bring with it more fluid into the brain tissue resulting in worsening edema and intracranial pressure [16]. These concerns, among others, were recently highlighted by Kahle and his colleagues [17]. Moreover, hypertonic saline may be useful for cerebral edema resulting from traumatic brain injury but not from non-traumatic insults like an infarction. Different neurological pathologies may have different pathophysiologic reasons for intracranial edema. Qureshi., *et al.* have shed light on this phenomenon, as their study showed that

unlike in patients with TBI, 3% HTS was not effective in non-TBI patients. In fact, the treatment was stopped in some patients because of the development of complications of pulmonary edema and diabetes insipidus [18]. Other adverse effects of concern include electrolyte abnormalities, fluid overload and resulting heart and kidney failure, acute renal failure, and bleeding complications [19].

Our findings do not demonstrate improved clinical outcomes in patients treated with 3%HTS. In fact, after controlling for infarct volume and other independent predictors of outcome, there was a tendency toward a poor outcome in the group of patients treated with 3%HTS.

The treatment and control groups were balanced with respect to medical comorbidities and measured laboratory values. The treatment group had a higher median infarct volume and lower median age. As expected, infarct volume was the prime determinant of menacing herniation (p-value < 0.0001). We controlled for infarct volume in our adjusted analysis. While age did not statistically predict poor outcome in this cohort, which may be because our primary outcome measured acute herniation requiring hemicraniectomy or death in the inpatient setting. Previous malignant cerebral infarction studies demonstrating an association between poor outcome and increasing age reported outcomes at much later time points [20-22]. For our primary analysis, we controlled for all significant predictors of poor outcome in our patient cohort, including infarct volume, hyperglycemia, and hypokalemia. In the adjusted analysis, 3%HTS was not correlated with good outcome.

Additionally, we investigated whether variations in treatment parameters and physiologic response influenced the outcome in the 3%HTS group. We analyzed the individual effects of baseline serum sodium levels, rate and magnitude of serum sodium level increase, and the total volume and duration of therapy with 3%HTS. None of these variables were associated with good outcome, whereas duration and the total volume of 3%HTS were associated with poor outcome. We found that baseline sodium, change in sodium, peak sodium on treatment, average sodium on treatment, and the total volume of 3%HTS given had no effect on the outcome. Although it is widely believed that hyponatremia should be corrected and that raising serum sodium levels attenuate cerebral edema, our findings do not support this theory [1].

There are several possible explanations for the trend in poor outcome seen in malignant cerebral infarction patients receiving 3%HTS. Hypernatremia may worsen obtundation in patients with malignant cerebral infarction [22]. Additionally, there exists evidence that ischemic injury to brain disrupts BBB leading to increased permeability to sodium, which results in an influx of water [23]. Osmotic shifts can lead to whole body fluid imbalance and rebound cerebral edema, prolonging hospitalization [17,25,26]. Reported systemic side effects include acute heart failure and pulmonary edema associated with volume expansion, as well as acute kidney injury and acute renal failure [18,26-28].

There are several possible explanations for the trend in poor outcome seen in malignant cerebral infarction patients receiving 3%HTS. Hypernatremia may worsen obtundation in patients with malignant cerebral infarction [22]. Additionally, there exists evidence that ischemic injury to brain disrupts BBB leading to increased permeability to sodium, which results in an influx of water [23]. Osmotic shifts can lead to whole body fluid imbalance and rebound cerebral edema, prolonging hospitalization [17,25,26]. Reported systemic side effects include acute heart failure and pulmonary edema associated with volume expansion, as well as acute kidney injury and acute renal failure [18,26-28].

Limitations of our study include the retrospective design. We selected consecutive cases based on presenting NIHSS and thus may have failed to include patients with large infarcts and lower NIHSS, as can occur either with right hemispheric lesions or with strokes that worsen after the presentation. Additionally, we excluded cases treated adjunctively with mannitol or high-dose (e.g. 24%) hypertonic saline, for the purpose of isolating the treatment effect of 3%HTS. In doing so, we may have excluded a population that benefited from 3%HTS. At our institution, the decision to treat patients with 3%HTS is made on a case-by-case basis by treating physicians. The 3%HTS group was younger and had larger infarcts. We attempted to minimize the effects of selection bias by controlling for all significant predictors

of poor outcome, including baseline infarct volume, hyperglycemia, and hypokalemia, through multivariable logistic regression. Finally, our primary outcome could be contaminated by causes of in-hospital death unrelated to cerebral edema in this critically ill population.

There are several strengths of our analysis. Our study is limited to a pure treatment cohort of ischemic stroke patients receiving 3%HTS. Previous studies have included patients with heterogeneous neurologic pathology and various osmotic agents [15,18,22]. Other strengths include the relatively high number of patients, and the novel assessment of 3%HTS related treatment variables, including rate of 3%HTS infusion, baseline serum sodium, and absolute change in serum sodium levels in response to treatment.

Conclusion

Our study does not provide any evidence that 3%HTS treatment decreases the threat of brain herniation or death in patients with malignant cerebral infarction, including those patients with infarct volume > 140cc. Given the known adverse effects of hypertonic saline, the role of 3%HTS in malignant cerebral infarction remains unclear, and further studies are required. Additionally, we found that baseline hyperglycemia and hypokalemia correlated with poor outcome. Whether aggressive correction of underlying hyperglycemia and hypokalemia improve outcome in malignant cerebral infarction should also be a focus of future investigation.

Conflict of Interest

Dr. Laghari, Dr. O'Neill, Dr. Streib, and Dr. Hammer have nothing to disclose. There were no sources of funding for this project.

Bibliography

1. Simard JM., *et al*. "Managing malignant cerebral infarction". *Current Treatment Options in Neurology* 13.2 (2011): 217-229.

2. Singh V and Edwards NJ. "Advances in the critical care management of ischemic stroke". *Stroke Research and Treatment* (2013): 510481.

3. Krieger DW., *et al*. "Early clinical and radiological predictors of fatal brain swelling in ischemic stroke". *Stroke* 30.2 (1999): 287-292.

4. Lopez GA., *et al*. "Care of the stroke patient: routine management to lifesaving treatment options". *Neurotherapeutics* 8.3 (2011): 414-424.

5. Paczynski RP. "Osmotherapy: basic concepts and controversies". *Critical Care Clinics* 13.1 (1997): 105-129.

6. Jeon SB., *et al*. "Critical care for patients with massive ischemic stroke". *Journal of Stroke* 16.3 (2014): 146-160.

7. Ziai WC., *et al*. "Hypertonic saline: first-line therapy for cerebral edema?" *Journal of the Neurological Sciences* 261.1-2 (2007): 157-166.

8. Qureshi AI and Suarez JI. "Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension". *Critical Care Medicine* 28.9 (2000): 3301-3313.

9. Sousa LM., *et al*. "Evaluation of the Maintained Effect of 3% Hypertonic Saline Solution in an Animal Model of Intracranial Hypertension". *Medical Science Monitor Basic Research* 22 (2016): 123-127.

10. Ware ML., *et al*. "Effects of 23.4% sodium chloride solution in reducing intracranial pressure in patients with traumatic brain injury: a preliminary study". *Neurosurgery* 57.4 (2005): 727-736.

11. Koenig MA., *et al*. "Reversal of transtentorial herniation with hypertonic saline". *Neurology* 70.13 (2008): 1023-1029.

12. Kamel H., *et al*. "Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials". *Critical Care Medicine* 39.3 (2011): 554-559.

13. Toung TJ., *et al*. "Hypertonic saline ameliorates cerebral edema associated with experimental brain tumor". *Journal of Neurosurgical Anesthesiology* 14.3 (2002): 187-193.

14. Wagner I., *et al*. "Effects of continuous hypertonic saline infusion on perihemorrhagic edema evolution". *Stroke* 42.6 (2011): 1540-1545.

15. Hauer EM., *et al*. "Early continuous hypertonic saline infusion in patients with severe cerebrovascular disease". *Critical Care Medicine* 39.7 (2011): 1766-1772.

16. Qureshi AI., *et al*. "Malignant cerebral edema in patients with hypertensive intracerebral hemorrhage associated with hypertonic saline infusion: a rebound phenomenon?" *Journal of Neurosurgical Anesthesiology* 10.3 (1998): 188-192.

17. Kahle KT., *et al*. "Continuous hyperosmolar therapy for traumatic brain injury-associated cerebral edema: as good as it gets, or an iatrogenic secondary insult?" *Journal of Clinical Neuroscience* 20.1 (2013): 30-31.

18. Qureshi AI., *et al*. "Use of hypertonic saline/acetate infusion in treatment of cerebral edema in patients with head trauma: experience at a single center". *Journal of Trauma* 47.4 (1999): 659-665.

19. Forsyth LL., *et al*. "Role of hypertonic saline for the management of intracranial hypertension after stroke and traumatic brain injury". *Pharmacotherapy* 28.4 (2008): 469-484.

20. Juttler E., *et al*. "Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke". *New England Journal of Medicine* 370 (2014): 1091-1100.

21. Malm J., *et al*. "The Swedish malignant middle cerebral artery infarction study: long-term results from a prospective study of hemicraniectomy combined with standardized neurointensive care". *Acta Neurologica Scandinavica* 113.1 (2006): 25-30.

22. Froelich M., *et al*. "Continuous hypertonic saline therapy and the occurrence of complications in neurocritically ill patients". *Critical Care Medicine* 37.4 (2009): 1433-1441.

23. Gotoh O., *et al*. "Ischemic brain edema following occlusion of the middle cerebral artery in the rat. I: The time courses of the brain water, sodium and potassium contents and blood-brain barrier permeability to 125I-albumin". *Stroke* 16.1 (1985): 101-109.

24. White H., *et al*. "The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury". *Anesthesia and Analgesia* 102.6 (2006): 1836-1846.

25. Nau R. "Osmotherapy for elevated intracranial pressure: a critical reappraisal". *Clinical Pharmacokinetics* 38.1 (2000): 23-40.

26. Suarez JI. "Hypertonic saline for cerebral edema and elevated intracranial pressure". *Cleveland Clinic Journal of Medicine* 71.1 (2004): S9-S13.

27. Aiyagari V., *et al*. "Hypernatremia in the neurologic intensive care unit: how high is too high?" *Journal of Critical Care* 21.2 (2006): 163-172.

28. Huang PP., *et al*. "Hypertonic sodium resuscitation is associated with renal failure and death". *Annals of Surgery* 221.5 (1995): 543-554.

Volume 7 Issue 6 September 2017