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Hypertonic Saline as a Therapy for Pediatric Concussive Pain:

A Randomized Controlled Trial of Symptom Treatment in the Emergency Department

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Abstract

Objective: Three-percent hypertonic saline (HTS) is a hyperosmotic therapy used in pediatric traumatic brain injury to treat increased intracranial pressure and cerebral edema. It also promotes plasma volume expansion and cerebral perfusion pressure, immunomodulation, and anti-inflammatory response. We hypothesized that HTS will improve concussive symptoms of mild traumatic brain injury.

Methods: The study was a prospective, double-blind, randomized controlled trial. Children, 4 to 7 years of age with a Glasgow Coma Scale score greater than 13, were enrolled from a pediatric emergency department following closed-head injury upon meeting Acute Concussion Evaluation criteria with head pain. Patients were randomized to receive 10 mL/kg of HTS or normal saline (NS) over 1 hour. Self-reported pain values were obtained using the Wong-Baker FACES Pain Rating Scale initially, immediately following fluids, and at 2 to 3 days of discharge. The primary outcome measure was change in self-reported pain following fluid administration. Secondary outcome measures were a change in pain and postconcussive symptoms within 2 to 3 days of fluid administration. We used an intention-to-treat analysis.

Results: Forty-four patients, ranging from 7 to 16 years of age with comparable characteristics, were enrolled in the study; 23 patients (52%) received HTS, and 21 (48%) received NS. There was a significant difference ($P < 0.001$) identified in the self-reported improvement of pain following fluid administration between the HTS group (mean improvement = 3.5) and the NS group (mean improvement = 1.1). There was a significant difference ($P = 0.01$) identified in the self-reported

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improvement of pain at 2 to 3 days after treatment between the HTS group (mean improvement = 4.6) and the NS group (mean improvement = 3.0). We were unable to determine a difference in other postconcussive symptoms following discharge.

Conclusions: Three-percent HTS is more effective than NS in acutely reducing concussion pain in children.

Keywords

concussion; pediatric mild traumatic brain injury; hypertonic saline; pediatric head injury; mild traumatic brain injury; pediatric concussion; concussion therapy; concussion treatment; closed-head injury; mTBI; TBI; HTS

The Centers for Disease Control supported by Congress' Children's Health Act of 2000 have called pediatric traumatic brain injury (TBI) a national health problem.¹ Children younger than 15 years with trauma-induced brain injury account for 473,947 emergency department (ED) visits and 35,136 hospitalizations per year.² Seventy-five percent of pediatric TBI is considered mild, and most of these patients are discharged from the ED with active concussive symptoms.^{1,2}

Concussion is a type of mild TBI caused by complex pathophysiologic processes initiated by neurometabolic cascades resulting in hypometabolism and axonal injury.^{3,4} Pathologic hypoperfusion and brain injury demonstrated by cytotoxic axonal edema may be seen in the concussed brain.⁵⁻⁸ Impaired cerebral CO₂ vasoreactivity can persist for days after TBI.^{9,10} Pediatric and animal studies have shown cerebral blood flow metabolism uncoupling after injury.^{11,12}

Signs and symptoms of concussion traditionally fall into 4 domains: physical, cognitive, emotional, and sleep.¹³ Headache is the most commonly reported symptom of concussion.¹⁴⁻¹⁶ These symptoms can persist for weeks, evolve into postconcussive syndrome, and increase the risk of second impact syndrome. Concussion costs the United States approximately /17 billion per year with the only acute treatment being supportive care.¹

The acute management of pediatric concussion includes recognition, analgesics, antiemetics, rest, and prevention of reinjury. Concussion authorities recommend a stepwise return to school and play over multiple days beginning with both cognitive and physical rest and progressing to full activity if concussive symptoms do not recur.^{13,17,18}

Weed and McKibben¹⁹ first described hypertonic saline (HTS) use in the management of increased intracranial pressure in 1919. Subsequent guidelines published in Pediatric Critical Care Medicine support HTS as a treatment for severe pediatric TBI with intracranial hypertension effectively at doses up to 10 mL/kg.²⁰ Three-percent HTS reduces increased intracranial pressure via osmolar gradient effects as compared with normal saline (NS) in pediatric patients following TBI.²¹ It facilitates normalization of the cellular resting membrane potential and functions as an effective plasma volume expander.^{22,23} Studies have shown HTS effects improved immunomodulation and decreases inflammatory effects of neutrophils.^{24,25}

GOALS AND OBJECTIVES

The purpose of this study was to investigate the use of 3% HTS in the acute management of concussion in children. We aimed to demonstrate an improvement of pain in children with concussion acutely, following the administration of 3% HTS in the pediatric ED, and at 2 to 3 days after injury. We hypothesized that 3% HTS would acutely treat pain in moderately to severely concussed pediatric patients as compared with NS upon self-assessment using the Wong-Baker FACES Pain Rating Scale²⁶ (Fig. 1). This study was designed to assess the effects of 3% HTS as compared with NS on concussive pain in compliance with the CONSORT 2010 checklist.²⁷

METHODS

The study was a prospective, double-blind, randomized controlled trial with 2 parallel groups: HTS and NS. No interim analyses were performed. The institutional review board approved the protocol, safety monitoring plan, and consent procedure. Informed consent was obtained from all enrolled patients and their parents. There was no expense or compensation to enrollees or study personnel. This study was registered at <http://ClinicalTrials.gov> (identifier NCT01612494).

SELECTION OF PARTICIPANTS

Pediatric patients 4 to 17 years of age with a chief complaint of closed-head injury were evaluated by the ED's pediatric emergency medicine physician. Those with a moderate to severe presentation of concussive symptoms, including pain, contributed to the physician's clinical suspicion for intracranial injury and generally were further evaluated with head computed tomography (CT). Only patients who had undergone head CT were eligible for this study because the potential therapeutic effect of reduced cerebral edema might temporarily mask further symptoms and timely diagnosis of intracranial injury. The subset of these patients with documented negative head CT results by an attending radiologist and who had intravenous access previously in place were eligible for enrollment. Concussive symptoms were defined according to the Acute Concussion Evaluation criteria including pain, nausea, vomiting, prior loss of consciousness, dizziness, speech difficulties, and amnesia.²⁸ Written consent from a guardian and assent from the patient were required. The single research investigator was on call to enroll 24 hours per day for the duration of the study with convenience sampling. Because of other research investigations at this institution analyzing similar patient populations, recruitment in this study was limited to the research investigator being on call 24 hours per day for 2 alternating weeks per month during the last 6 months of enrollment.

Patients were excluded for Glasgow Coma Scale score less than 14; radiographic evidence of any intracranial injury, history of posttraumatic seizure, developmental delay/disability, underlying cardiac or renal or neurologic pathology including chronic migraine, clinician suspicion or documented use of alcohol and/or illicit substances, associated injuries requiring the use of narcotics for analgesia, unstable multiple trauma, penetrating intracranial injury, intubation, absence of caretaker, or positive pregnancy test.

OUTCOME MEASURES

The primary outcome was the change in self-reported pain using the Wong-Baker FACES Pain Rating Scale following administration of fluids as compared with initial, pretreatment pain.²⁶ Secondary measures included change of pain, persistent nausea and/or number of emesis, or other concussive symptoms within 2 to 3 days of ED discharge upon follow-up phone call.

Study Design

The study took place in the pediatric ED at Rady Children's Hospital of the University of California, San Diego, from October 2010 to October 2011. Rady Children's Hospital has an ED census of 71,000 patients per year including a level I pediatric trauma center that sees more than 1000 trauma patients per year.

Treatment assignments were allocated via a computerized randomization plan generator using randomly permuted blocks. The allocation sequence was concealed from the enrolling researchers utilizing sequentially numbered, opaque, sealed envelopes, which were enclosed smaller sealed envelopes containing the designated treatment arm. Following blinded enrollment and documentation of the initial/pretreatment pain scale score, the sealed envelope was opened, and the patient was assigned to the specified treatment group by the enrolling investigator who did not have further contact with the patient.

Personnel involved in the care of patients during their ED stay were blinded with respect to treatment assignments.

Treatment

All patients received treatment administration according to standardized protocols after their pain score was identified on their first Wong-Baker FACES Pain Rating Scale (FPS1). This 6-faced, 10-point pain scale has been validated for pediatric pain with a change greater than 1 interval and for pediatric pain in the ED setting.^{26,29} Headache in mild TBI has been evaluated for using the Wong-Baker Faces Pain Rating Scale³⁰ (Fig. 1). Infusion of assigned study fluid was initiated by nursing using identically sized intravenous fluid bags. The enrolling research investigator entered computerized nursing orders for the administration of standard protocols of 10 mL/kg over 60 minutes (not to exceed 1000 mL) of study fluid.

Following fluid administration, and after completion of the patient's second FACES Pain Scale, the treating physician reevaluated the patient as part of standard ED care. All subsequent care was at the discretion of the treating physician.

Before discharge, all patients and their caretakers received head injury discharge instructions, which included recommendations not to return to activity until symptom-free with reevaluation by a physician.

Data Collection

The presence or absence of pain was assessed and identified as part of the standard of care and evaluation in the ED. Head CT imaging results were noted, although all were required to

be negative for intracranial injury upon attending pediatric radiologist interpretation according to inclusion criteria.

The FPS1, initial symptoms, Glasgow Coma Scale score, presence or absence of specific concussive symptoms, demographics, mechanism of injury, diagnoses, previous relevant medical history, emesis, and outcome were obtained prospectively at the initial time of enrollment in a formatted questionnaire by the enrolling investigator.

Following study fluid administration, the patients independently identified their pain score on a second Wong-Baker FACES Pain Scale (FPS2) at the bedside.

A third Wong-Baker FACES Pain Scale (FPS3) was provided to the family in a worksheet upon discharge to be recorded within 2 to 3 days of discharge and reported upon phone call follow-up by the research assistant along with a scripted questionnaire of postconcussive symptoms, which was verbally performed at that time.

Statistical Analysis

Statistical analysis was performed using the Mann-Whitney *U* test. Power calculations suggested obtaining target sample sizes of 54 participants in the experimental HTS group and 54 in the NS group. This sample size was calculated to be sufficient in identifying a statistically significant difference (at 80% power) between treatment and control for a difference in pain improvement of 1 interval between the 2 groups following fluid administration.

The comparison between groups used an intention-to-treat approach, with all randomized subjects included according to their randomization assignment. The primary outcome, the change in pain value on the Wong-Baker FACES Pain Scale between initial pain (FPS1) and pain immediately following fluid administration (FPS2), was compared using the Mann-Whitney *U* test. In addition, 95% confidence intervals (CIs) for this difference in change in pain score were computed from the 2-sample *t* test. To account for differences in initial pain between groups, analysis of covariance was used including FPS1 and the change in pain (FPS2 – FPS1) as covariates. For each outcome, a change variable was computed, with values +2 for each face interval of improvement, 0 for no change, and –2 for each face-interval worsening, and a group comparison was performed using the Mann-Whitney *U* test. All tests were 2-sided, and $P < 0.05$ was considered significant. Data on presenting concussive symptoms of nausea, vomiting, number of emesis, slurred speech, dizziness, amnesia, and loss of consciousness were evaluated in comparison to symptoms reported on the follow-up phone call.

RESULTS

The study recruitment was carried out between October 2010 and October 2011. Because of the limitations of our convenience sample and training constrictions of the primary fellow investigator, enrollment ceased in October 2011 with a total of 44 patients enrolled (Fig. 2). There were no adverse events reported during the trial. Neither fluid type was discontinued early for any reason. All enrolled patients were randomized and included in the analysis. No

patients were lost to follow-up. Researchers were blinded to data analysis until enrollment was completed.

A total of 44 patients were enrolled with 23 patients (52%) randomly assigned to the HTS group and 21 (48%) to the NS group. Ages of enrolled patients ranged from 7 to 16 years of age with a mean age of 12 years and median age of 13 years (Fig. 2). Characteristics of patients randomly assigned to HTS or NS group were comparable (Table 1 and Fig. 3).

Wong-Baker FACES Pain Scale values were analyzed at 3 time points: initially before treatment (FPS1), immediately following treatment (FPS2), and within 2 to 3 days after treatment (FPS3). The HTS group had a higher reported mean pain level at time point FPS1 of 5.7 (SD, 2.03) versus NS group of 4.29 (SD, 1.82); $P = 0.022$. The groups had similar mean pain values at time FPS2 ($P = 0.17$) and FPS3 ($P = 0.73$) (see Table 2 and Figure 4 for additional details).

The primary outcome was the change in pain between time points FPS1 and FPS2. The HTS group had a mean improvement of pain of 3.52, and the NS group had a mean improvement of pain of 1.14. The difference in the mean change of pain from FPS1 to FPS2 between the 2 groups was significant, $P < 0.001$ and 95% CI -0.3 to -1.4 (Table 2 and Fig. 5). We used a multiple-regression model to adjust for higher initial pain reports in the HTS group and other potential confounders and still found a significant difference ($P < 0.001$) between the HTS and NS groups; the HTS group achieved a greater reduction in pain (difference between groups -1.86 ; 95% CI, $0.92-2.79$). When controlling for initial pain and for other potential confounders (sex, age, mechanism of injury, and wearing a helmet), using backward model selection with a 0.15 threshold for retention in the model, only initial pain was a significant variable ($P = 0.003$).

The main secondary outcome of interest was the change in pain scores between time points FPS1 and FPS3. There was a significant difference (-1.61 ; 95% CI, -2.9 to -0.3 ; $P = 0.014$) in the change of pain initially to within 2 to 3 days after treatment between the groups. The HTS group had a mean improvement of pain of 4.61, and the NS group had a mean improvement of pain of 3 (Table 2 and Fig. 6). However, when controlling for initial pain, this difference was no longer significant (-0.46 ; 95% CI, -1.4 to 0.5 ; $P = 0.32$).

Five patients from the HTS group and 2 patients from the NS group received analgesia in the form of acetaminophen or ibuprofen 1 hour or more before the study protocol initiation. The peak therapeutic effect of these medications occurred before the initiation of the treatment protocol conforming to the primary outcome of a change in reported pain, not initial pain level. Regardless, upon reevaluation of the data set excluding these patients, the greater mean change in pain in the HTS group was still significant with a $P < 0.001$. A single patient in the NS group received ketorolac tromethamine (Toradol) after study fluids and after their FPS2 in the ED because of persisting headache.

Successful contact via phone due to unanswered phone calls, missed phone calls, and lack of returned calls varied within the week of the patients' discharge, with the mean day of follow-up being 5 days. While the FPS3 was a worksheet given to the family to complete on days 2 to 3 after discharge, the post-concussive symptoms scripted questionnaire was conducted

verbally on follow-up phone call and thus had variability in time of completion. χ^2 analysis, independent *t* test, and Mann-Whitney *U* test analysis of these secondary outcomes demonstrated no statistically significant difference between postconcussive symptoms of the HTS and NS group within 1 week following treatment.

DISCUSSION

This interventional trial of HTS as a therapy for concussive pain in children establishes several important findings. Both HTS administration and NS administration were shown to be associated with improved concussive pain on the self-assessed Wong-Baker Faces Pain Scale value immediately following fluid administration and within 2 to 3 days of administration. Most notably, this study demonstrated that among the 2 groups of similar sex and age, 3% HTS fluid administration was associated with a greater improvement of self-assessed pain values immediately following administration as compared with NS. In adjusted analysis, the study did not show a difference in improvement of pain between both groups at 2 to 3 days. It is unclear if the improvement in concussive pain at 2 to 3 days in both HTS and NS groups represents the natural course of disease or if both HTS and NS have an effect on recovery.

We consider the known mechanisms of osmotic gradient effects and plasma volume expansion, vasoregulatory mechanisms, and immunomodulation as possible explanations for this study's outcomes. This study was implemented for both sexes with similar ages, addressing falls and direct blow mechanisms, using a pediatric ED validated pain scale, and using weight-based fluid administration supported in the literature. This suggests that our findings can be implemented in the treatment of pediatric concussive pain.

LIMITATIONS OF THE STUDY

The primary limitation of this pilot study was the small sample size. A single enrolling research investigator was on call to enroll patients 24 hours per day for the first 6 months and then 24 hours per day for 2 alternating weeks per month for the last 6 months of study enrollment because of similar enrolling studies at this institution. Emergency department staff had to notify the enrolling investigator of potentially eligible patients. Both of these requirements limited the study by convenience sampling and lent to the inability of researchers to attain a powered sample size. Study enrollment ceased before attaining the projected sample size because the primary fellow investigator graduated and left the institution. Increased sample sizes would permit more power to identify small differences between the treatments, should they exist.

Although CT imaging was not a component of the study procedures, patients were eligible for enrollment only if they had previous head CT imaging in the ED. This not only limited the sampling size, but it also stratified for patients with moderate to severe concussive symptoms. We did not evaluate the effects of HTS in patients with mild symptoms of concussion.

Although groups were randomly allocated with adequate concealment of allocation, there was a limiting difference between comparison groups in initial self-reported pain. Initial

pretreatment pain was significantly greater (+1.45) in the HTS group ($P = 0.017$) as compared with the NS group. Therefore, the HTS group had more opportunity of pain relief than the NS group. Adjusted analyses addressed this limitation and gave further strength to the evidence of HTS's superiority to NS for acute pain treatment (FPS2 –FPS1). However, adjusted analysis was unable to show a significant difference in pain reduction at 2 to 3 days (FPS3 –FPS1). Larger sample sizes would reduce the likelihood of comparison group differences and allow for more accurate interpretation of pain change between groups on days 2 to 3.

An important limitation was the variation in time to follow-up phone call. Although all families were initially called at 2 to 3 days after ED discharge, some were not reached until 7 days later. Although families had been given a worksheet at discharge to complete their Wong-Baker FACES Pain Scale on days 2 to 3, the postconcussive symptoms scripted questionnaire was verbally performed during the follow-up phone call, which had significant variability in the time completed during the following week. This imparted a recall bias regarding their postconcussive symptoms at 2 to 3 days. For these reasons, a comparison of results of the postconcussive symptom scale was considered invalid.

In the advent of validated neurocognitive testing and advanced imaging techniques such as diffusion tensor imaging, we can demonstrate measurable pathophysiologic changes in pediatric concussion. This study was limited to an outcome of self-reported symptoms. Future studies will address neurocognitive testing outcomes and advanced imaging techniques following HTS administration.

Finally, this study compared HTS and NS administration to children with concussion. Normal saline administration has beneficial properties of plasma volume expansion, and this study demonstrated that patients who received NS had an acute improvement of pain immediately following administration. This study was limited in that there was not a comparison group who did not receive treatment whatsoever.

CONCLUSIONS

Pediatric head injury is common, and concussion is a frequent diagnosis in the ED. Concussive symptoms can be severe, resulting in school and sports absence, repeated clinical evaluations, postconcussive syndrome, and significant monetary costs. Pediatric concussive pain in otherwise healthy children may be treated acutely by the administration of 3% HTS. Treatment can result in improvement in patient comfort. Future studies with measured pathophysiologic outcomes are necessary to further support this treatment.

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REFERENCES

1. Centers for Disease Control and Prevention (CDC), National Center for Injury Prevention and Control. Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem Atlanta, GA: Centers for Disease Control and Prevention; 2003.

2. Faul M, Xu L, Wald MM, et al. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
3. Barkhoudarian G, Hovda D, Giza C. The molecular pathophysiology of concussive brain injury. *Clin Sports Med* 2011;30:33. [PubMed: 21074080]
4. Harmon KG, Drezner JA, Gammons M, et al. American Medical Society for Sports Medicine position statement: concussion in sport. Endorsed by the National Trainers' Athletic Association and the American College of Sports Medicine. *Br J Sports Med* 2013;47: 15–26. [PubMed: 23243113]
5. Aoki Y Diffusion tensor imaging studies of mild traumatic brain injury: a meta-analysis. *J Neurol Neurosurg Psychiatry* 2012;83:870–876. [PubMed: 22797288]
6. Chu Z, Wilde EA, Hunter JV, et al. Voxel-based analysis of diffusion tensor imaging in mild traumatic brain injury in adolescents [published online ahead of print December 3, 2009]. *AJNR Am J Neuroradiol* 2010;31:340–346. [PubMed: 19959772]
7. Vespa P, Bergsneider M, Hattori N, et al. Metabolic crisis without brain ischemia is common after traumatic brain injury: a combined microdialysis and positron emission tomography study. *J Cereb Blood Flow Metab* 2005;25:763–774. [PubMed: 15716852]
8. Vavilala MS, Lee LA, Boddu K, et al. Cerebral autoregulation in pediatric traumatic brain injury. *Pediatr Crit Care Med* 2004;5: 257–263. [PubMed: 15115564]
9. Lee JH, Kelly DF, Oertel M, et al. Carbon dioxide reactivity, pressure autoregulation, and metabolic suppression reactivity after head injury: a transcranial Doppler study. *J Neurosurg* 2001;95:222–232. [PubMed: 11780891]
10. Carmona Suazo JA, Maas AI, van den Brink WA, et al. CO₂ reactivity and brain oxygen pressure monitoring in severe head injury. *Crit Care Med* 2000;28:3268–3274. [PubMed: 11008991]
11. Maugans TA, Farley C, Altaye M, et al. Pediatric sports-related concussion produces cerebral blood flow alterations. *Pediatrics* 2012;129:28–37. [PubMed: 22129537]
12. Richards HK, Simac S, Piechnik S, et al. Uncoupling of cerebral blood flow and metabolism after cerebral contusion in the rat. *J Cereb Blood Flow Metab* 2001;21:779–781. [PubMed: 11435789]
13. Centers for Disease Control. Heads Up; Facts for Physicians About Mild Traumatic Brain Injury Available at: http://www.cdc.gov/concussion/headsup/pdf/Facts_for_Physicians_booklet-a.pdf. Accessed January 8, 2013.
14. Babcock L, Byczkowski T, Wade SL, et al. Predicting postconcussion syndrome after mild traumatic brain injury in children and adolescents who present to the emergency department. *JAMA Pediatr* 2013;167:156–161. [PubMed: 23247384]
15. Meehan WP, III, d'Hemecourt P, Comstock RD. High school concussions in the 2008–2009 academic year: mechanism, symptoms, and management. *Am J Sports Med* 2010;38:2405–2409. [PubMed: 20716683]
16. Makdissi M, Darby D, Maruff P, et al. Natural history of concussion in sport: markers of severity and implications for management. *Am J Sports Med* 2010;38:464–471. [PubMed: 20194953]
17. Practice parameter: the management of concussion in sports (summary statement). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1997;48:581–585. [PubMed: 9065530]
18. Aubry M, Cantu R, Dvorak J, et al. Summary and agreement statement of the first International Conference on Concussion in Sport, Vienna 2001. *Phys Sportsmed* 2002;30:57–63. [PubMed: 20086514]
19. Weed L, McKibben P. Experimental alteration of brain bulk. *Am J Physiol* 1919;48:531–555.
20. Kochanek PM, Bell MJ, Carney N, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents-second edition. *Pediatr Crit Care Med* 2012;13:252.
21. Fisher B, Thomas D, Peterson B. Hypertonic saline lowers raised intracranial pressure in children after head trauma. *J Neurosurg Anesthesiol* 1992;4:4–10. [PubMed: 15815431]
22. Nakayama S, Kramer GC, Carlsen RC, et al. Infusion of very hypertonic saline to bleed rats: membrane potentials and fluid shifts. *J Surg Res* 1985;38:180–186. [PubMed: 3968876]

23. Moss GS, Gould SA. Plasma expanders. An update. *Am J Surg* 1988;155:425–434. [PubMed: 3278640]
24. Isayama K, Murao Y, Saito F, et al. Effects of hypertonic saline on CD4+CD25+Foxp3+ regulatory T cells after hemorrhagic shock in relation to iNOS and cytokines. *J Surg Res* 2012;172:137–145. [PubMed: 20888597]
25. Khan R, Kirschenbaum LA, Larow C, et al. The effect of resuscitation fluids on neutrophil-endothelial cell interactions in septic shock. *Shock* 2011;36:440–444. [PubMed: 21921833]
26. Garra G, Singer AJ, Taira BR, et al. Validation of the Wong-Baker FACES pain rating scale in pediatric emergency department patients. *Acad Emerg Med* 2010;17:50–54. [PubMed: 20003121]
27. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Ann Int Med* 2010;152:726–732. [PubMed: 20335313]
28. Gioia GA, Collins M, Isquith PK. Improving identification and diagnosis of mild traumatic brain injury with evidence: psychometric support for the acute concussion evaluation. *J Head Trauma Rehabil* 2008;23:230–242. [PubMed: 18650767]
29. Bosenberg A, Thomas J, Lopez T, et al. Validation of a six-graded faces scale for evaluation of postoperative pain in children. *Paediatr Anaesth* 2003;13:708–713. [PubMed: 14535910]
30. Blume HK, Vavilala MS, Jaffe KM, et al. Headache after pediatric traumatic brain injury: a cohort study. *Pediatrics* 2012;129:e31–e39. [PubMed: 22144708]

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FIGURE 1.
Wong-Baker FACES Pain Rating Scale.

FIGURE 2.
Flow diagram of the study.

FIGURE 3.
Representation of treatment groups by sex and age.

FIGURE 4.

Mean pain severity before treatment (FPS1), immediately following fluid administration (FPS2), and 2 to 3 days after treatment (FPS3), for the NS and HTS treatment arms.

FIGURE 5.
Change in pain severity from FPS1 to FPS2 for the 2 groups.

FIGURE 6.
Change in pain severity from FPS1 to FPS3 for the 2 groups.

TABLE 1.

Characteristics of Patients in HTS and NS Groups

	3% HTS (n = 23)	NS (n = 21)
Mean age, y	12.1 (2.5)	11.9 (3)
Sex (male)	17 (74%)	11 (52%)
Mechanism of injury		
Direct blow	10 (43%)	10 (48%)
Fall	13 (57%)	11 (52%)
Mean initial systolic blood pressure, mm Hg	119 (4)	117 (4)
Patients with previously administered analgesic	5 (22%)	2 (10%)
Data are mean (SD) or counts, n (%).		

TABLE 2.

Pain Scale Reports in HTS and NS Treatment Groups

	3% HTS Therapy (n = 23), mean (SD)	NS Therapy (n = 21), mean (SD)	Mann-Whitney U Test (P)	Independent t Test (95% CI)
Pretreatment pain (FPS1)	5.74 (2)	4.29 (1.1)	0.02	—
Pain within 1 h posttreatment (FPS2)	2.22 (1.6)	3.14 (2.2)	0.11	—
Change in pain; FPS2 – FPS1	3.52 (1.6)	1.14 (1.5)	>0.001	(–0.3, to –1.4)
Pain within 2–3 d after ED discharge; (FPS3)	1.13 (1.5)	1.29 (1.5)	0.73	—
Change in pain; FPS3 – FPS1	4.61 (2.3)	3 (1.7)	0.01	(–2.9 to –0.3)