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Effect of Hyperosmolar Therapy on Outcome following Spontaneous Intracerebral Hemorrhage: ERICH Study

Manan Shah, MD¹, Lee Birnbaum, MD, MS², Jennifer Rasmussen, MD³, Padmini Sekar, MS⁴, Charles J. Moomaw, PhD⁴, Jennifer Osborne, RN, BSN⁴, Anastasia Vashkevich, BA⁵, and Daniel Woo, MD, MS⁴

¹Department of Neurology, UT Health Houston

²Department of Neurology, UT Health San Antonio

³Department of Neurology, Baylor Scott and White, University of Cincinnati College of Medicine

⁴Department of Neurology and Rehabilitation Medicine, University of Cincinnati College of Medicine

⁵Department of Neurology, Massachusetts General Hospital/Harvard Medical School

Abstract

Purpose—We aimed to identify the effect of hyperosmolar therapy (mannitol and/or hypertonic saline) on outcomes after intracerebral hemorrhage (ICH) in the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study.

Methods—Comparison of ICH cases treated with hyperosmolar therapy versus untreated cases was performed using a propensity score based on age, initial Glasgow Coma Scale, location of ICH (lobar, deep, brainstem, cerebellar), log-transformed initial ICH volume, presence of intraventricular hemorrhage, and surgical interventions. ERICH subjects with a pre-ICH modified Rankin Scale (mRS) ≥ 3 were included. Treated cases were matched 1:1 to untreated cases by closest propensity score (difference ≤ 0.15), sex, and race/ethnicity (non-Hispanic white, non-Hispanic black, or Hispanic). The McNemar and Wilcoxon signed-rank tests were used to

Corresponding author: Lee Birnbaum, MD; 7703 Floyd Curl Dr., MC 7843, San Antonio, TX 78229-3900; Fax: 210-567-6066; Tel: 210-567-5625; Birnbaum@uthscsa.edu.

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compare 3-month mRS outcomes between groups. Good outcome was defined as 3-month mRS 3.

Results—As of 12/31/2013, the ERICH study enrolled 2279 cases, of which 304 hyperosmolar-treated cases were matched to 304 untreated cases. Treated cases had worse outcome at 3 months compared with untreated subjects (McNemar, $p=.0326$), and the mean 3-month mRS was lower in the untreated (Wilcoxon, $p=.0174$). Post-hoc analysis revealed more brain edema, herniation, and death at discharge for treated cases.

Conclusions—Hyperosmolar therapy was not associated with better 3-month mRS outcomes for ICH cases in the ERICH study. This finding likely resulted from greater hyperosmolar therapy use in patients with edema and herniation rather than those agents leading to worse outcomes. Further studies should be performed to determine if hyperosmolar agents are effective in preventing poor outcomes.

Keywords

hyperosmolar therapy; spontaneous intracerebral hemorrhage; outcome; mannitol; hypertonic saline

Introduction

Spontaneous, non-traumatic intracerebral hemorrhage (ICH) is a significant cause of morbidity and mortality throughout the world. Best clinical management of ICH remains unclear due to unproven therapies, such as craniotomy, craniectomy, and hyperosmolar agents. Prior ICH trials of clinical outcomes have shown mixed results.^{1,2,3} Therefore, current treatment strategies are not standardized, and they focus on variables associated with poor outcome, such as intracranial hypertension and cerebral edema.⁴

The use of hyperosmolar therapy in ICH is based on its action of intracranial pressure (ICP) reduction. Physiologic actions of hyperosmolar agents have been known since early 1900s.^{5,6} Mannitol and hypertonic saline (HTS) have shown the most promise in clinical application and potential efficacy. Both mannitol (5%–15%) and HTS (2%–23.4%) have been used in varying concentrations and methods. Hyperosmolar therapy is thought to reduce tissue volume by inducing fluid transfer down osmotic gradients of capillaries and cell membranes.⁷ A few studies have demonstrated efficacy of hyperosmolar therapy for lowering ICP in traumatic brain injury (TBI)^{8–13} but have failed to show improved clinical outcomes.¹⁴ Furthermore, data is sparse regarding its efficacy and ICP-lowering action in spontaneous ICH and post-ischemic edema. It may be possible that the use of such agents, while temporarily relieving increased ICP, does not ultimately affect outcome. Therefore, we sought to demonstrate if there was benefit compared to no-treatment after matching on factors associated with use of hyperosmolar therapy such as severity of ICH factors.

To test this hypothesis, we examined the effect of hyperosmolar therapy on patient outcomes enrolled in the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) Study. Given that specific features likely predict which patients would be placed on hyperosmolar agents (such as large volume and mass effect or herniation), we identify these risk factors for hyperosmolar agents and then matched for the propensity of use to cases that did not receive

hyperosmolar agents. We utilized a propensity score model to ensure that the baseline characteristics of the treated and untreated groups were not significantly different.

Methods

Study Protocol

A detailed methodology of the ERICH Study has been published previously.¹⁵ In brief, the ERICH Study is a large, multicenter, ICH study that aims to identify genetic variation, differences in the distribution of risk factors and imaging characteristics, and outcomes in non-Hispanic white, non-Hispanic black, and Hispanic patients. Cases are identified using a prospective hot-pursuit method of subject enrollment to limit survival bias. The Institutional Review Boards of each enrolling site approved the study. Informed consent was obtained from all subjects or their legal representatives. For the purpose of the present investigation, we chose a case-case comparison analysis with propensity score matching.

Case Definition

All spontaneous ICH phenotypes in the ERICH database met the following eligibility criteria: age ≥ 18; residency for at least 6 months within a 75- or 100-mile radius of the recruiting center, depending on the population of the region; white, black, or Hispanic race/ethnicity by self-report; and ability of the patient or legal representative to provide informed consent.¹⁵ Research personnel reported the use of hyperosmolar agents on chart abstraction forms by reviewing hospital records. For the present analysis, “treated” cases received hyperosmolar agents including mannitol and/or HTS during hospitalization irrespective of concentration, frequency, or time to initiation.

Screened variables

Demographics, including age, sex, and ethnicity, were captured in a baseline interview with the patient or suitable proxy. Details of hospitalization for each ICH subject, including severity variables that could independently affect outcome, were obtained through chart abstraction and recorded on case report forms by research personnel. Among the data included were ICH Score variables, serial CT results, surgical interventions, and complications such as brain edema or herniation. Pre-admission functional status was assessed and recorded on the chart abstraction form as a modified Rankin Scale (mRS) score. We excluded subjects with pre-morbid mRS ≥ 4, multiple ICH locations, missing data regarding initial CT results, Glasgow Coma Scale (GCS), surgical procedures, or 3-month mRS. Because GCS data was collected only for cases that presented to an emergency department (ED), in-hospital cases, direct admits, and cases with unavailable ED data could not be included in the analysis.

ICH Score variables

The ICH Score incorporates age, GCS on ED presentation, ICH location (supratentorial vs. infratentorial), ICH volume, and presence of intraventricular hemorrhage (IVH). Although the original purpose of the ICH score was to predict 30-day mortality, the individual variables have been validated as independent predictors of long-term outcome in ICH populations.^{16,17} CT scans for all study subjects were reviewed by a central imaging center

in a standardized fashion. ICH location was categorized as deep, lobar, brainstem, or cerebellar. Deep ICH was defined as originating from the thalamus, basal ganglia, internal capsule, or deep periventricular white matter. Lobar ICH was defined as originating at the cortex or cortical-subcortical junction. ICH volume was measured with Analyze version 9.0 (Mayo Clinic) software, using previously described methods.¹⁸ Presence of IVH was reported separately by the central imaging center and was not included in ICH volume calculations.

Surgical interventions

Major neurosurgical procedures included craniotomy or craniectomy for clot evacuation, stereotactic clot aspiration, thrombolytic injection into ventricles, and other neurosurgeries deemed major by the clinical team. Other interventions, though not major neurosurgical procedures, included external ventricular drain (EVD) without thrombolytic injection and ventriculoperitoneal shunt placement.

Outcomes

There were three categories of discharge disposition: (1) discharge to the home of the patient, relative, or friend, or to assisted living; (2) discharge to a medical facility, such as a rehab or skilled nursing facility, or to another acute-care hospital; and (3) inpatient death or discharge to hospice. Subjects who were made comfort care were included in the analysis. Trained research personnel interviewed subjects or proxies in person or via telephone at three months after ICH and assessed the subject's functional status with mRS scores. We defined bad outcome as a mRS of 4, which has been shown to be effective in shift analysis in large acute-stroke trials.¹⁹

Statistical analysis

Initial comparison of baseline characteristics between treated and untreated cases revealed significant differences in age, ICH location, log-transformed ICH volume, presence of IVH, presenting GCS, craniotomy for clot evacuation, stereotactic clot evacuation, EVD placement, and thrombolytic injection into ventricles. These variables were included in an initial stepwise analysis to create a propensity score model²⁰ to best emulate randomization in this observational study. After stepwise reduction, the effects of ICH location and presence of IVH were not significant but were forced into the final model because they are elements of the ICH Score. The effects of stereotactic clot evacuation and thrombolytic injection into ventricles were not significant and were excluded from the final model.

Based on the final model, treated cases were matched to untreated cases by closest propensity score (difference in scores ≤ 0.15), sex, and racial/ethnic group for comparisons in outcome analysis. By design, both groups were identical in terms of sex and race/ethnicity distribution. The significant variables in the initial baseline comparison were retested between the matched groups and verified to be non-significant after propensity matching.

Mean values for age, ICH volume, and IVH volume were compared between groups using Student's *t*-test. Wilcoxon rank-sum test was used for median GCS values. Pearson's chi-squared test was used for craniotomy, EVD placement, presence of IVH, and ICH location.

McNemar's test for matched pairs was used to compare the outcomes between treated and untreated cases. The Wilcoxon signed rank test was used to test for difference in 3-month mRS between the two groups. Pearson's chi-squared test was used in post hoc analysis to compare discharge dispositions, brain edema, and herniation between the two groups in unmatched analysis.

Results

Description of cohort

Between 9/22/2010 and 12/31/2013, the ERICH study enrolled 2279 cases, of which 410 were treated with hyperosmolar therapy. Following exclusion criteria, 330 treated cases remained, and 1446 untreated cases were available as potential untreated cases for propensity score modeling (Figure 1). The untreated cases were more likely to be excluded for loss to follow-up at 3 months ($p<.01$). The treated and untreated cases had significantly different baseline severity variables (Table 1).

Matching

Propensity scores were used to match the 330 treated cases 1:1 to 330 untreated cases. Twenty-six matched pairs were excluded because their propensity scores differed by more than 0.15, leaving 304 pairs for final analysis. Table 1 verifies that the variables used to calculate the propensity scores were not significantly different between the treated and untreated groups and indicating that the groups were well matched for variables associated with hyperosmolar therapy. Of the 304 treated cases, 238 (78.3%) received only mannitol, 17 (5.6%) received only hypertonic saline, and 49 (16.1%) received both treatments.

Outcome

Among the 304 matched pairs, 106 had different outcomes: in 64 pairs, the treated case had a bad outcome and the untreated case had a good outcome; whereas in 42 pairs, the opposite was noted (Table 2). A higher proportion of treated cases had poor 3-month mRS than the untreated cases (73.0% vs. 65.8%). Additionally, the mRS difference for each matched pair was calculated ($\text{mRS difference} = \text{untreated mRS} - \text{treated mRS}$). The mean value for mRS differences was -0.3322 ($p=0.0174$), indicating a worse outcome in the treated cases.

Post hoc analysis

All available data for discharge dispositions, brain edema, and herniation were compared in post hoc analysis between treated and untreated cases (Table 3). For discharge disposition, treated cases were less likely to be discharged home or to rehab/nursing facility and were more likely to have died. Additionally, treated cases had significantly more brain edema and herniation.

Discussion

ICH has a relatively high incidence (15–35 per 100,000 persons)^{21–23} and is associated with poor outcomes (30%–40% 30-day mortality rate).^{21,23–26} Management of ICH poses a significant challenge due to the lack of proven therapies. With the exception of the recently

published CLEAR III study²⁷, neither medical nor surgical interventions have been shown to significantly improve outcomes, including survival and quality of life.²³ Smaller studies of ICH have looked at hyperosmolar therapy and demonstrated no outcome improvement.^{28–30} A large-scale systematic effort to validate use of hyperosmolar therapy in primary ICH has not been previously performed.

The evaluation of hyperosmolar therapy in clinical practice is complicated by its frequent use in more severely ill patients. To minimize this bias, we used propensity score modeling to best match markers of illness severity, including the ICH Score and surgical interventions. Our results suggest that the use of hyperosmolar therapy does not improve clinical outcomes compared to expected based on severity characteristics. Our neutral results, however, are likely a result of limitations in our propensity score model, specifically the lack of intracranial pressure values and degree of cerebral edema. Furthermore, treated patients in our study design may trend towards worse outcome due to reverse causality; that patients who are imminently herniating or demonstrating substantial edema/mass effect are more likely to be treated with hyperosmolar therapy. Indeed, treated patients in our study had significantly more herniation and cerebral edema compared to untreated.

An additional limitation of the results is the paucity of details related to the hyperosmolar therapy regimens. We did not have specifics for strength of solution, duration of therapy, time to treatment initiation, or treatment setting (ICU vs. non-ICU). These factors are heterogeneous and likely influence clinical outcomes. For example, timing of therapy may influence its efficacy, as the predominant type of edema varies during different phases of ICH evolution. Significant regional and institutional differences exist in the clinical administration of hyperosmolar therapy and are influenced by physician experience with agent and dosing. Finally, although the data collected for hyperosmolar therapy included use of mannitol, HTS or both, we did not have sufficient power to evaluate these agents separately.

In addition to the previously mentioned study limitations, the pathophysiology of ICH may be less tolerant of hyperosmolar side effects and contribute to our negative results. Cerebral edema in ICH is predominantly vasogenic,²⁹ which is associated with disruption of the blood brain barrier. Hyperosmolar substances may be less effective in this type of edema because blood brain barrier disruption allows the passage of hyperosmolar agents into brain tissue which neutralizes the osmotic gradient and has been associated with rebound intracranial hypertension. Additionally, there are counter-acting, poorly understood brain adaptive mechanisms in place. After the initial effect of hyperosmolar therapy, brain cells tend to normalize by processes that increase cellular content of osmotic molecules. This process counteracts the desirable hypertonic osmotic effect, leads to normalization of cell volume, and may result in subsequent recurrence or worsening of tissue swelling.^{31,32}

Besides the molecular explanations, patients receiving hyperosmolar therapy may have worse outcomes due to unintended clinical consequences and side effects. Utilization of hyperosmolar therapy requires more intensive monitoring which may prolong their ICU stay, increase susceptibility to other medical complications, and delay rehabilitation evaluation and treatment. Potential side effects of hyperosmolar therapy include hemolysis,

hypotension, pulmonary edema, and renal insufficiency with electrolyte disturbances. Mannitol has been shown to have a strong osmotic diuretic effect, which may result in hyponatremia followed by hypernatremia.³³ Repeated infusions of hypertonic saline may increase sodium and chloride concentrations to critical values that result in hyperchloremic acidosis. Close monitoring of sodium is also important in these patients as severe hypernatremia, serum sodium > 160, is found to be an independent factor of mortality in literature.³⁴

Strengths of this study lie in its national, multi-center database with a large, tri-ethnic population. The size and breadth of this database provide sufficient power to use propensity score modeling with 1:1 matching to mimic the characteristics of a randomized controlled trial. Our study is unique in its design to adjust for numerous variables associated with severity and outcomes of ICH. Although some predictive variables were not available to include in the propensity score model, our conclusion is important for advancement to a clinical trial. We demonstrate that despite our best matching for the propensity of hyperosmolar agent utilization, this treatment did not render better outcomes than expected by available severity criteria. Nevertheless, some matched pairs did have better outcomes and many matched pairs had no benefit, but no worsening of outcomes. Thus, this report may help guide criteria/expectations for use of hyperosmolar therapy towards cases where benefit may exist or away from those where preliminary evidence suggests potential futility.

Summary

Hyperosmolar therapy was not associated with improved clinical outcome in our ERICH case-case comparison study. Although propensity score modeling was used for a quasi-randomized analysis, post-hoc analysis revealed an imbalance with treated cases having more cerebral edema. Further study of hyperosmolar therapy for ICH is needed and should consider matching on quantitative measurements of cerebral edema and intracranial pressure.

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References

1. Mendelow A, Gregson B, Fernandes H, Murray G, Teasdale G, Hope D, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet*. 2005 Jan 29.;387–97. F. [PubMed: 15680453]
2. Anderson C, Huang Y, Wang J, Arima H, Neal B, Peng B, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol*. 2008 May.;391–399. [PubMed: 18396107]

3. Mendelow A, Gregson B, Rowan A, Murray G, Gholkar A, Mitchell P. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet*. 2013 Aug.;397–409. [PubMed: 23726393]
4. Nader Pouratian N, Kassell N, Dumont A. Update on Management of Intracerebral Hemorrhage. *Neurosurg Focus*. 2003; 15
5. Sutheland W, MaCay D. Observations on influence exerted by hypertonic saline solution and calcium chloride solutions on action of specific hemolysins, with suggestions as to the therapy of blackwater fever. *Biochem J*. 1911; 5:1–22.
6. Weed M, McKibben L. Experimental alteration of brain bulk. *Am J Physiol*. 1919; XLVIII:531–560.
7. Grände P-O, Romner B. Osmotherapy in Brain Edema. *J Neurosurg Anesthesiol*. 2012; 24:407–412. [PubMed: 22955195]
8. Berger S, Schurer L, Hartl R, Messmer K, Baethmann A. Reduction of post-traumatic intracranial hypertension by hypertonic/hyperoncotic saline/dextran and hypertonic mannitol. *Neurosurgery*. 1995; 37:98–107. [PubMed: 8587698]
9. McGraw C, Howard G. Effect of mannitol on increased intracranial pressure. *Neurosurgery*. 1983; 13(3):269–271. [PubMed: 6413884]
10. Allen C, Ward J. An evidence-based approach to management of increased intracranial pressure. *Crit Care Clin*. 1998; 14:485–495. [PubMed: 9700443]
11. Bullock R. Mannitol and other diuretics in severe neurotrauma. *New Horiz*. 1995; 3:448–452. [PubMed: 7496753]
12. Roberts I, Schierhout G, Wakai A. Mannitol for acute traumatic brain injury (Cochrane Review). *Cochrane Database Syst Rev*. 2003; 2:CD001049.
13. Smith H, Kelly D, McWhorter J, Armstrong D, Johnson R, Transou C. Comparison of mannitol regimens in patients with severe head injury undergoing intracranial monitoring. *J Neurosurg*. 1986; 65:820–824. [PubMed: 3095507]
14. Guidelines for the Management of Severe Traumatic Brain Injury. *J Neurotrauma* (3rd). 2007; 24(Suppl 1)
15. Woo D, Rosand J, Kidwell C, Mccauley JL, Osborne J, Brown MW, et al. The ethnic/racial variations of intracerebral hemorrhage (ERICH) study protocol. *Stroke*. 2013; 44
16. Hemphill JC III. The ICH Score: A Simple, Reliable Grading Scale for Intracerebral Hemorrhage. *Stroke*. 2001; 32:891–897. [PubMed: 11283388]
17. Hemphill JC III. Prospective validation of the ICH Score for 12-month functional outcome. *Neurology*. 2009; 73:1088–1094. [PubMed: 19726752]
18. Goldstein JN, Fazen LE, Snider R, Schwab K, Greenberg SM, Smith EE, et al. Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage. *Neurology*. 2007; 68:889–894. [PubMed: 17372123]
19. Savitz SI LR. Shift analysis versus dichotomization of the modified Rankin scale outcome scores in the NINDS and ECASS-II trials. *Stroke*. 2007; 38:3205–3212. n. d. [PubMed: 17975102]
20. D'Agostino RB. Tutorial in Biostatistics: Propensity Score Methods for Bias Reduction in the Comparison of a Treatment to a Non-Randomized Control Group. *Stat Med* [Internet]. 1998; 17:2265–2281. Available from: <http://www.stat.ubc.ca/~john/papers/DAGostinoSIM1998.pdf>.
21. Broderick J, Brott T, Tomsick T. The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. *N Engl J Med*. 1992; 326:733–736. [PubMed: 1738378]
22. Broderick J, Brott T, Tomsick T. Intracerebral hemorrhage more than twice as common as subarachnoid hemorrhage. *J Neurosurg*. 1993; 78:188–191. [PubMed: 8421201]
23. Anderson C, Chakera T, Stewart-Wynne E. Spectrum of primary intracerebral haemorrhage in Perth, Western Australia, 1989–1990: incidence and outcome. *J Neurol Neurosurg Psychiatry*. 1994; 57:936–940. [PubMed: 8057117]
24. Broderick J, Brott T, Zuccarello M. Management of intracerebral hemorrhage. In: Batjer, HH., editor. *Cerebrovascular Disease*. Philadelphia: Lippincott-Raven; 1997. p. 611–627.
25. Cheung R, LY Z. Use of original, modified, or new intracerebral hemorrhage score to predict mortality and morbidity after intracerebral hemorrhage. *Stroke*. 2003; 34:1717–1722. [PubMed: 12805488]

26. Dennis M. Outcome after brain haemorrhage. *Cerebrovasc Dis*. 2003; 16(Suppl):9–13. [PubMed: 12698013]
27. Hanley DF, Lane K, McBee N, Ziai W, Tuhim S, Lees KR, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet*. 2017; 389:603–611. [PubMed: 28081952]
28. Misra U, Kalita J, Ranjan P. Mannitol in intracerebral hemorrhage: a randomized controlled study. *J Neurol Sci*. 2005; 234:41–45. [PubMed: 15936036]
29. Yang GY, Betz AL, Chenevert TL, Brunberg JA, Hoff JT. Experimental intracerebral hemorrhage: relationship between brain edema, blood flow, and blood-brain barrier permeability in rats. *J Neurosurg*. 1994; 81:93–102. [PubMed: 8207532]
30. Qureshi AI, Wilson DA, Traystman RJ. Treatment of elevated intracranial pressure in experimental intracerebral hemorrhage: Comparison between mannitol and hypertonic saline. *Neurosurgery*. 1999; 44:1055–1064. [PubMed: 10232539]
31. Gullans S, Verbalis J. Control of brain volume during hyperosmolar and hypoosmolar conditions. *Annu Rev Med*. 1993; 44:289–301. [PubMed: 8476251]
32. McManus M, Churchwell K, Strange K. Regulation of cell volume in health and disease. *N Engl J Med*. 1995; 333:1260–1266. [PubMed: 7566004]
33. Paczynski R. Osmotherapy: basic concepts and controversies. *Crit Care Clin*. 1997; 13:105–129. [PubMed: 9012578]
34. Aiyagari V, Diringier M. Hyponatremia and mortality in the neurology/neurosurgery intensive care unit. *Neurology*. 2001; 56(A):469.

Figure 1.

Patient selection and matching.

*Exclusion events are mutually exclusive. Once excluded, cases were not evaluated for subsequent exclusion categories.

Table 1

Characteristics of treated and untreated cases before and after propensity score (PS) modeling.[†]

	Before PS Modeling		p [*]	After PS Modeling		p [*]
	Treated N= 330	Untreated N= 1445		Treated N= 304	Untreated N= 304	
Ethnicity – N (%)						
Black	118 (35.8)	515 (35.6)	0.0032	111 (36.5)	111 (36.5)	Matched
Hispanic	134 (40.6)	468 (32.4)		115 (37.8)	115 (37.8)	
White	78 (23.6)	462 (32.0)		78 (25.7)	78 (25.7)	
Gender – N (%)						
Female	137 (41.5)	590 (40.8)	0.8195	111 (36.5)	111 (36.5)	Matched
Male	193 (58.5)	855 (59.2)		193 (63.5)	193 (63.5)	
Age – yr, mean (SD)	57.7 (14.9)	62.6 (14.4)	<0.0001	58.2 (15.2)	58.2 (13.8)	0.9532
Craniotomy – N (%)	83 (25.2)	71 (4.9)	<0.0001	72 (23.7)	57 (18.8)	0.1368
External Ventricular Drain Placed	151 (45.8)	210 (14.5)	<0.0001	135 (44.4)	129 (42.4)	0.6235
GCS – (3–15), median (IQR)	10 (6, 14)	15 (12, 15)	<0.0001	11 (6, 14)	11 (6, 14)	0.9211
Presence of IVH – N (%)	195 (59.1)	591 (40.9)	<0.0001	180 (59.2)	174 (57.2)	0.6217
ICH Location – N (%)						
Lobar	106 (32.1)	470 (32.5)	0.2256	99 (32.6)	105 (34.5)	0.9152
Deep	173 (52.4)	783 (54.2)		160 (52.6)	158 (52.0)	
Brainstem	16 (4.9)	86 (6.0)		16 (5.3)	13 (4.3)	
Cerebellum	35 (10.6)	106 (7.3)		29 (9.5)	28 (9.2)	
ICH Volume – ml, Geometric Mean (CI)	23.8 (20.8, 27.3)	7.6 (7.1, 8.3)	<0.0001	23.6 (20.4, 27.3)	22.2 (19.7, 24.9)	0.5133
IVH Volume – ml,	1.4 (1.1, 1.9)	0.5 (0.4, 0.5)	<0.0001	1.4 (1.0, 1.9)	1.4 (1.0, 1.8)	0.8693

[†] Abbreviations: CI – confidence interval; GCS – Glasgow coma scale; ICH – intracerebral hemorrhage; IQR – interquartile range; IVH – intraventricular hemorrhage; ml – milliliter; SD – standard deviation

^{*} P-values for age, ICH and IVH volumes were derived using a t-test; for craniotomy, intraventricular drain placement, presence of IVH, and ICH location were derived using chi-square test; and for GCS were derived using Wilcoxon rank-sum test.

Table 2

Contingency table showing good vs. bad outcomes in matched treated vs. untreated cases. *

		Untreated		
	Outcome (mRS)	Good (3)	Bad (4)	Total
Treated	Good (3)	40 (13.16)	42 (13.82)	82 (26.97)
	Bad (4)	64 (21.05)	158 (51.97)	222 (73.03)
	Total	104 (34.21)	200 (65.79)	N = 304 (100)

* All numbers are shown as N (%)

Table 3

Discharge dispositions in treated and untreated groups. *

	Untreated N (%)	Treated N (%)	p-value
Edema	34 (11.2)	70 (23.0)	0.0001
Herniation/Brain Death	10 (3.3)	29 (9.5)	0.0017
Discharge disposition[#]:			0.0128
Home/Relative/Assisted Living	48(15.8)	32 (10.6)	
Rehab/SNF/Acute setting	179 (59.1)	165 (54.5)	
Hospice/Dead	76 (25.1)	106 (35.0)	

* Pearson's chi-squared test was used to compare groups in unmatched analysis.

[#]Two cases with unknown discharge disposition were excluded.