Effect of Hyperosmolar Therapy on Outcome Following Spontaneous Intracerebral Hemorrhage: Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) Study

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Purpose: We aimed to identify the effect of hyperosmolar therapy (mannitol and 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, and cerebellar), log-transformed initial ICH volume, presence of intraventricular hemorrhage, and surgical interventions. ERICH subjects with a pre-ICH modified Rankin Scale (mRS) score of 3 or lower were included. Treated cases were matched 1:1 to untreated cases by the closest propensity score (difference ≤.15), gender, and race and ethnicity (non-Hispanic white, non-Hispanic black, or Hispanic). The McNemar and the Wilcoxon signed-rank tests were used to compare 3-month mRS outcomes between the 2 groups. Good outcome was defined as a 3-month mRS score of 3 or lower. *Results:* As of December 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 cases (McNemar, $P = .0326$), and the mean 3-month mRS score was lower in the untreated group (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

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performed to determine if hyperosmolar agents are effective in preventing poor outcomes. **Key Words:** Hyperosmolar therapy—spontaneous intracerebral hemorrhage—outcome—mannitol—hypertonic saline.
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Introduction

Spontaneous, nontraumatic 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.[1-3] 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. Physiological actions of hyperosmolar agents have been known since the 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 the efficacy of hyperosmolar therapy in lowering ICP in traumatic brain injury[8-13] but have failed to show improved clinical outcomes.[14] Furthermore, data are sparse regarding its efficacy and ICP-lowering action in spontaneous ICH and postischemic edema. It may be possible that the use of such agents, although temporarily relieving increased ICP, does not ultimately affect outcome. Therefore, we sought to demonstrate if there was benefit compared with no treatment after matching factors associated with the use of hyperosmolar therapy, such as the severity of ICH.

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 identified these risk factors for hyperosmolar agents and then matched these factors 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 the 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 were 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 years or older; residency for at least 6 months within a 75- or 100-mi radius of the recruiting center, depending on the population of the region; white, black, or Hispanic race and ethnicity by self-report; and ability of the patient or the 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 HTS during hospitalization irrespective of concentration, frequency, or time to initiation.

Screened Variables

Demographics, including age, gender, 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 computed tomography (CT) results, surgical interventions, and complications such as brain edema or herniation. Preadmission functional status was assessed and recorded on the chart abstraction form as a modified Rankin Scale (mRS) score. We excluded subjects with a premorbid mRS score of 4 or higher, multiple ICH locations, missing

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