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Clinical Study

A case-cohort study with propensity score matching to evaluate the effects of mannitol on venous thromboembolism

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ABSTRACT

Mannitol has been shown to damage endothelial cells and activate coagulation pathways leading to intravascular thrombosis. Dehydration and hemagglutination have also been associated with mannitol use, although the risk of clinically evident venous thromboembolism (VTE) disease is not well-defined. The aim of this study was to compare the risk of VTE in critically ill neurological patients who received mannitol compared to only hypertonic saline. A case-cohort study design with propensity score matching was used to evaluate the risk of VTE among patients who received mannitol compared to those who received hypertonic saline alone. The odds of thrombosis were evaluated by the Cochran-Mantel-Haenszel method and conditional logistic regression was used to adjust for year of treatment. Ninety-one of 330 patients (27.6%; 95% confidence interval [CI] 23–33%) developed a VTE; however, the yearly proportion remained unchanged over the 8 year study period. Cumulative use of mannitol declined and use of hypertonic saline increased significantly. The odds of thrombosis for those exposed to mannitol compared to hypertonic saline alone was 1.11 (95% CI 0.65–1.73; $p = 0.75$). This remained insignificant after adjusting for year of injury. In conclusion, despite a significant change in the pattern of osmotic therapy used at our institution, the proportion of patients with VTE remained unchanged. We found no evidence that mannitol use was associated with VTE compared to hypertonic saline alone.

1. Introduction

Despite the lack of any appropriately powered, high quality evidence, osmotic agents are the cornerstone of treatment for elevated intracranial pressure following traumatic brain injury [1,2]. However hyperosmotic agents may cause cell stress that physically damages cells, induces apoptosis, and activates proinflammatory cytokine and coagulation pathways [3,4]. Specifically, mannitol in hyperosmolar concentrations has been shown to induce apoptosis in bovine endothelial cells in a dose-dependent manner as well as activate inflammatory and coagulation pathways leading to intravascular thrombosis [5–7]. Recently, hyperosmotic mannitol solution has been used as a liquid chemoembolization agent in tumors to damage endothelial cells leading to thrombosis and induced cell death [3].

Though venous thrombosis or phlebitis extending from the injection site is listed as a possible side-effect of mannitol, there is a paucity of data on whether clinical venous thromboembolism (VTE) in hospitalized patients can be attributable to mannitol. In addition to cellular stress mechanisms, some reports suggest that mannitol may be hazardous due to hemagglutination causing thromboembolism, although data supporting this are scarce [8,9]. Additionally, as an osmotic diuretic, mannitol may lead to dehydration predisposing to VTE. Though the majority of the literature fails to support the widely held belief that dehydration predisposes to VTE, dehydration was found to strongly predict VTE following stroke [10]. Interestingly, we previously demonstrated an increased risk of peripherally inserted central venous catheter (PICC)-related deep and large vein thrombosis in neurological intensive care unit patients who received mannitol, but not hypertonic saline [11].

Given the multiple potential mechanisms for VTE during intravenous mannitol administration, we chose to investigate the association between mannitol and VTE in a high-risk group of brain injured patients requiring osmotic therapy. Our hypothesis was that our previous finding of an association between mannitol use and thrombosis would generalize to all brain injured patients requiring osmotic therapy. We chose to compare patients who received mannitol to those who did not in a case-cohort study by

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using propensity score matching to reduce selection bias and control for confounding status to simulate a randomized trial.

2. Methods

The University of Michigan Institutional Review Board approved a waiver of informed consent for this observational study.

2.1. Patient population

2.1.1. Cohort

A search strategy was designed to identify consecutive patients who required more than one dose of osmotic therapy for intracranial hypertension, significant brain tissue shifts, or brain compression.

2.1.2. Search strategy

We included consecutive patients admitted to the University of Michigan Health System from 1 January 2005 through 31 December 2012 with aneurysmal subarachnoid hemorrhage, intracerebral hemorrhage, or moderate-to-severe traumatic brain injury who required osmotic therapy. Only the first admission during the study period was used in our analysis. A patient list was generated using an ongoing subarachnoid hemorrhage outcomes registry, the institution's trauma registry, and by searching discharge International Classification of Diseases revision 9 code 431 through all positions [12]. This patient list was cross-referenced with an electronic pharmacy database to select patients who had received intravenous osmotic therapy with either 3% sodium chloride or 20% mannitol, the only agents used in our institution for intracranial hypertension or significant brain tissue shifts during the study period. We excluded patients who were under 18 years of age, who received osmotic therapy only for correction of hypo-osmolar states, had hospital length of stay less than 3 days, who received no osmotic therapy, only one dose of osmotic therapy, or a 3% hypertonic saline infusion lasting less than 12 hours. Patients who did not require osmotic therapy, or received only one dose or a short infusion, were excluded for the following reasons: (1) this knowledge would not be very useful clinically, given the requirement for osmotic therapy in patients with intracranial hypertension or significant brain tissue shifts is not considered optional by most clinicians and is recommended by all major guidelines following trauma or stroke [2,13–15], and (2) patients who require recurrent dose of osmotic therapy have a different risk of thrombosis than those who do not and residual confounding would be hard to adjust for.

2.2. Osmotic therapy

Mannitol consisted of 20% mannitol given as recurrent intravenous bolus to obtain trough serum osmolality of 310–320 mOsmo/L. Hypertonic saline consisted of only 3% sodium chloride administered intravenously to obtain serum sodium values between 150–160 mEq/L. Our institutional protocol for hypertonic saline is administration as a continuous infusion with or without an initial bolus dose. Hypertonic saline was always administered via a central venous catheter, whereas mannitol was administered via central or peripheral venous catheters. Osmotic therapy was not administered as prophylactic therapy.

2.3. Data collection

2.3.1. Explanatory variable

Mannitol dose was documented as cumulative dose in grams.

2.3.2. Potential confounders

Age and length of stay were coded as continuous variables. Sex was coded as male or female. Primary diagnosis was coded as subarachnoid hemorrhage, intracerebral hemorrhage, or traumatic brain injury. Glasgow Coma Scale score was coded as 3–8, 9–12, or 13–15. All other variables (deep venous thrombosis [DVT] prophylaxis, surgery lasting >1 hour prior to diagnosis of thrombosis, or hypertonic saline use) were coded as categorical yes/no variables. DVT prophylaxis was coded as "yes" if chemical prophylaxis was instituted prior to the diagnosis of thrombosis.

2.3.3. Response variable

Thrombosis (synonymous for VTE) was coded as a dichotomous variable and included the composite of any large or DVT of the upper or lower extremities or pulmonary embolus. In the lower extremity, small perforating veins were not included as thrombosis. In the upper extremity, DVT was defined as thrombosis of the brachial, axillary, or subclavian vein and the basilic and cephalic veins above the elbow were considered large veins. Thrombosis distal to the elbow was excluded from the endpoint as well as any superficial thrombophlebitis. In sensitivity analysis, thrombosis of the upper extremity was coded as any large vein thrombosis or DVT of the upper extremity and lower extremity thrombosis was excluded.

Thrombosis was only diagnosed in symptomatic patients, as routine surveillance was not performed during the study period. Diagnosis was made by reviewing venous duplex ultrasonography reports interpreted by board-certified radiologists as part of clinical care. All venous duplex ultrasonography was performed with a portable Siemens Sonoline Antares (Siemens Medical Solutions, Inc., Malvern, PA, USA) or Toshiba Xario XG (Toshiba America Medical Systems, Inc., Tustin, CA, USA). Non-compressibility as well as Doppler mode were used during evaluation. CT venography of the pelvis and lower extremities were also used to document lower extremity thrombosis. Pulmonary embolus was defined, similarly, by reviewed radiology reports of helical CT angiography scans of the pulmonary vessels or a high-probability ventilation perfusion scan of the chest. All CT scans were performed on a 64-MDCT scanner (Light Speed VCT, GE Healthcare, Little Chalfont, Buckinghamshire, UK) and the protocol used 1.25 mm collimation reconstructed at 0.625 mm intervals and 125 ml of intravenous contrast material (Isovue-300, Bracco Diagnostics, Monroe Twp., NJ, USA).

DVT prevention was performed with sequential compression devices on the lower extremities unless contraindicated due to injury. Chemical prophylaxis is typically started 24 hours after traumatic brain injury or intracerebral hemorrhage and within or at 24 hours after securing a ruptured aneurysm.

2.4. Statistical analysis

Continuous variables were screened for normality using histograms and QQ plots. Cumulative mannitol dose was expressed as median and interquartile range and the Wilcoxon rank sum test was used to compare median dose in these patients with compared to those without thrombosis. Age and length of stay met the normality assumption and were expressed as mean ± standard deviation with Student's *t*-test used for descriptive bivariate analysis. Categorical variables were expressed as proportions and compared with the chi-squared test.

Trends of mannitol use and hypertonic saline use were explored over time by plotting average cumulative mannitol dose and proportion of patients receiving hypertonic saline by year. Similarly, the proportion of thrombosis was plotted over time. To test the significance of these trends, year was entered as an ordinal variable predicting cumulative mannitol dose in a linear regression model

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