Review Article

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Efficacy and Renal Safety of Protocol-based 11.7% Hypertonic Saline Infusion Compared with 20% Mannitol in Patients with Elevated Intracranial Pressure: A Study Protocol for a Randomized Clinical Trial

Sunggyul Lim, MD[1], Yongjin Yi, MD, MPH[2]

[1]*Division of Nephrology, Department of Internal Medicine, Dankook University Hospital, Republic of Korea;*
[2]*Department of Internal Medicine, College of Medicine, Dankook University, Republic of Korea*

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Corresponding Author: Yongjin Yi, MD, MPH
Department of Internal Medicine, College of Medicine, Dankook University, 119 Dandae-ro, Dongnam-gu, Cheonan-si, Chungcheongnam-do, Korea
Tel: +82-10-9090-5404; Fax: +82-41-559-7940
E-mail: yongjin.neph@gmail.com

Background: Elevated intracranial pressure (ICP) is a potentially life-threatening condition requiring prompt intervention. While both mannitol and hypertonic saline (HTS) are commonly used hyperosmotic agents for treating elevated ICP, there is insufficient evidence comparing their renal safety profiles and overall effectiveness. This study protocol outlines a pragmatic randomized trial to compare protocol-based 11.7% HTS with 20% mannitol in patients with elevated ICP, focusing particularly on renal outcomes and treatment efficacy.

Methods: This single-center, pragmatic randomized trial will enroll 116 intensive care unit patients with elevated ICP. Participants will be randomly assigned to receive either 11.7% HTS or 20% mannitol following a schedule-based randomization approach, with HTS administration during odd-numbered months and mannitol during even-numbered months. The study will regularly monitor serum electrolytes, osmolarity, and renal function, with brain CT evaluations conducted on days 3 and 7. Comprehensive clinical assessments, including neurological evaluations and laboratory tests, will be performed at specified intervals throughout the study period.

Measured Outcomes: Primary outcomes include the incidence of acute kidney injury within 7 days according to KDIGO guidelines, requirement for mechanical ventilation, development of pulmonary edema, and significant fluid retention. Secondary outcomes encompass ICU and hospital length of stay, 30- and 90-day mortality rates, and neurological outcomes assessed by Glasgow Coma Scale scores at days 7 and 30. The study hypothesizes that protocol-based HTS administration will demonstrate a lower incidence of acute kidney injury and related complications while maintaining comparable efficacy in managing elevated ICP.

Conclusion: This study aims to provide definitive evidence regarding the relative efficacy and safety profiles of HTS compared to mannitol in managing elevated ICP. The findings will help establish clearer clinical guidelines for selecting appropriate hyperosmotic agents, potentially improving patient care outcomes and reducing treatment-related complications. This research will address a significant gap in current clinical knowledge and practice by focusing on treatment efficacy and renal safety considerations in patients with elevated ICP.

Key Words: Intracranial pressure, Acute kidney injury, Hypernatremia, Study protocol, Pragmatic clinical trial

BACKGROUND

Elevated intracranial pressure (ICP) presents as an acute, potentially fatal condition, leading to cerebral edema and further clinical deterioration[1-3]. Normal ICP values generally range from 5 to 15 mm Hg. Intracranial hypertension is characterized by a sustained ICP exceeding 20 mmHg[4,5]. Elevated ICP can precipitate serious consequences such as cerebral hypoxia, coma, brain herniation, and in severe cases, potentially fatal outcomes[6,7]. Despite limited practical evidence for the selection and monitoring of therapies aimed at elevated ICP management, the administration of hyperosmotic solutions is a widely adopted therapeutic strategy for patients with elevated ICP[8,9]. Mannitol and hypertonic saline (HTS) are employed as hyperosmotic agents in the treatment of elevated ICP[10]. These agents facilitate osmotic fluid shifts, dehydrate endothelial cells, and improve perfusion in ischemic areas. Mannitol and HTS share underlying mechanisms in the reduction of increased ICP[11,12]. Recent attention has been drawn to the adverse effects associated with the administration of mannitol. Notable among these are hypotension and dehydration, primarily resulting from over-diuresis, along with the development of hypernatremia and acute kidney injury (AKI)[13,14]. The pathophysiological mechanisms potentially contributing to these outcomes include elevated plasma oncotic pressure, a reduction in the glomerular filtration rate due to tubular lumen constriction, and pronounced vacuolization in the renal tubules[15,16].

HTS therapy, a method used to reduce intracranial pressure, employs sodium—a physiological substance—in concentrations of 3% or higher[17-19]. This approach increases the osmotic pressure within the extracellular fluid (ECF), resulting in the withdrawal of water from brain cells. Unlike mannitol, HTS intravenous administration does not cause systemic dehydration[20]. It selectively enhances the osmotic pressure on the vascular side of the blood-brain barrier. In animal models, the gradient effect of HTS on osmotic pressure is observed to last approximately 1 to 4 hours. Additionally, hypertonic solutions have been found to improve oxygen delivery and cerebral perfusion[21,22].

Owing to these characteristics, recent clinical studies have been conducted to assess the efficacy and safety of HTS as an alternative treatment to mannitol in patients with elevated intracranial pressure[22-25]. The findings from these studies indicate that HTS offers comparable or superior results in comparison to mannitol[26,27]. This includes aspects such as mortality rates, effectiveness in reducing intracranial pressure, and overall safety in patients experiencing increased intracranial pressure[17,28].

However, there is a lack of comprehensive studies comparing the renal side effects, electrolyte balance, and body fluid homeostasis between HTS and mannitol therapy in the context of high osmotic pressure treatment. Consequently, most clinical guidelines currently recommend the use of both mannitol and HTS in patients with cerebral edema or elevated intracranial pressure. Yet, there is insufficient evidence to clearly define specific indications for each medication or to identify a more suitable patient group[29,30].

In this study, for this purpose, we plan to conduct a randomized controlled clinical trial and a randomized controlled clinical trial as a preliminary study. The purpose of the present study was to investigate the safety and efficacy of HTS compared with mannitol in patients with elevated intracranial pressure by randomized controlled clinical trial.

METHODS

Hypothesis

In patients with elevated intracranial pressure, the administration of protocol based HTS will reduce the incidence of acute kidney injury, edema, and metabolic acidosis. Additionally, HTS treatment will result in improvements in patient consciousness and mortality rates that are comparable to those achieved with mannitol administration. This hypothesis aims to address the gap regarding the differential impacts of these two treatments on complex clinical outcomes in patients with elevated intracranial pressure.

Objective of the Study

The primary objective of this study is to compare the efficacy and frequency of side effects between mannitol and protocol-based HTS administration in patients with elevated intracranial pressure. The study aims to provide clear,

Table 1. Inclusion and Exclusion Criteria
Abbreviations: ICU, intensive care unit; CNS, central nervous system; ARDS, acute respiratory distress syndrome.

Inclusion Criteria	Exclusion Criteria
1. Adults aged 18 to 80. 2. Diagnosed with conditions requiring intracranial pressure management in the ICU 3. Closed traumatic brain injury, intracranial hemorrhage, acute stroke, brain neoplasm, CNS infection, encephalitis, pseudotumor cerebri. 4. Agreement to participate in the study.	1. Receiving osmotic therapy prior to observation. 2. Acute kidney injury stage>3 (eGFR<15 ml/min or requiring RRT) 3. Heart failure (ejection fraction<40% on echocardiography). 4. Liver cirrhosis with ascites 5. PaO_2/FiO_2 ratio<200, indicating moderate to severe ARDS 6. Serum sodium<130 meq/L or >150 meq/L 7. Do not agree to participate in the study or cancel 8. Difficult to carry out the study by the principal investigator.

evidence-based insights into which of these treatments is more effective in managing the critical aspects of elevated intracranial pressure.

Study Participants and Measurements

Patients admitted to the intensive care unit (ICU) at the research medical institution who meet the selection criteria will be approached for participation in this study. The study will be proposed to eligible patients or their guardians, and their consent to participate in the clinical trial will be sought before the administration of any osmotic agents. Eligibility for the study is contingent upon participants meeting all the inclusion criteria, not being subject to any of the exclusion criteria, and providing written informed consent. (Table 1) The study is designed as a clinical trial with a total enrollment of 116 participants, divided equally into two groups of 58 each. This sample size is calculated to be the minimum required to confirm the statistical effects and side effects of the treatments under investigation.

Sample size estimates

In patients with brain hemorrhage, the predictive incidence of AKI is 10.5% when mannitol is administered according the previous study[13]. The frequency and severity of AKI increase with high dose of mannitol. Moreover, the presence of advanced age (≥70 years), along with pre-existing conditions such as hypertension and chronic kidney disease (CKD), further exacerbates the risk, leading to a substantial increase in the incidence of AKI. Additionally, hypernatremia occurs in approximately 16-40% of cases when mannitol is used[13]. The null hypothesis (H0) is that there is no difference in renal outcome, including electrolyte imbalance and renal dysfunction, 7 days after admission among patients with elevated intracranial pressure treated with mannitol or hypertonic saline. The alternative hypothesis (HA) is that there is a difference in renal outcome 7 days after admission among patients randomized to mannitol or hypertonic saline. A total sample size of 116 (58 per group) participants with increased intracranial pressure is required, assuming overall significance (alpha) = 0.05, power (1- beta) = 0.80. In this trial, the aim is to decrease renal-related side effects, such as AKI and hypernatremia, another electrolyte imbalance by 25%.

Randomization

In this clinical trial, the randomization process is designed as a pragmatic, schedule-based approach to ensure the integrity and scientific validity of the study (Fig. 1). The participants will be allocated based on the month of their admission. Patients admitted during odd-numbered months will receive HTS, while those admitted during even-numbered months will receive mannitol. This allocation is implemented immediately after obtaining informed consent and is coordinated by the research team. By using a monthly assignment strategy, the study maintains an impartial and transparent allocation process. Although blinding the clinical observers is impractical—given the distinct treatment protocols and monitoring indicators required for mannitol versus HTS—the pragmatic monthly allocation ensures that all participants receive prompt and appropriate treatment upon hospital admission, while preserving the scientific rigor and

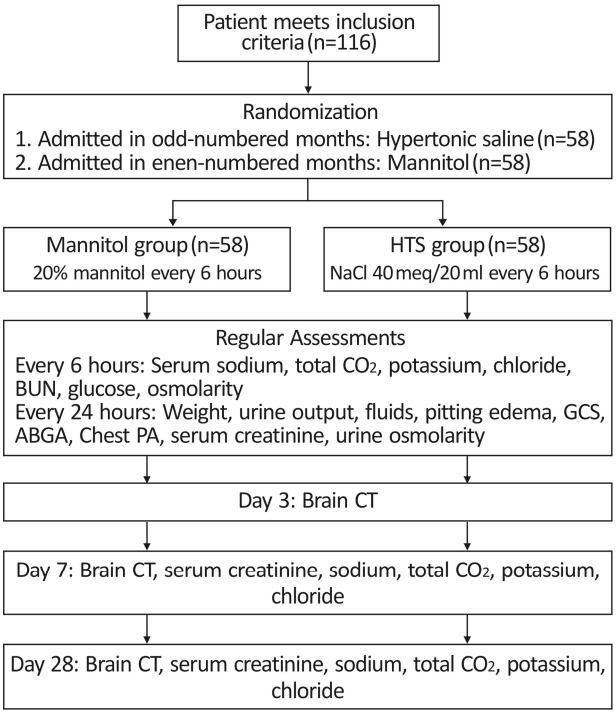

Fig. 1. Study protocol for HTS and mannitol group.
Abbreviations: HTS, hypertonic saline; GCS, Glasgow coma scale; ABGA, arterial blood gas analysis; CT, computed tomography.

fairness of the trial design.

Study Algorithm for HTS and Mannitol Groups

In this study, a total of 116 eligible patients, meeting inclusion criteria and without any exclusion criteria, were enrolled. These patients were randomly assigned to receive either hypertonic saline or mannitol treatment based on a pragmatic schedule-based randomization approach, with treatment alternating between odd (HTS) and even (mannitol) months. The mannitol group received 20% mannitol 100cc every 6 hours, while the hypertonic saline group received NaCl 120 mEq, 60 cc every 6 hours.

Serum sodium, osmolarity, blood urea nitrogen (BUN), and glucose levels were measured every 6 hours, while assessments of body weight, urine output, presence of pitting edema, serum creatinine, and urine osmolarity were performed every 24 hours. During the 3rd, 7th, and 28th days of the study period, participants undergo brain CT for neurological evaluation and serum levels of creatinine, sodium, potassium, chloride, and total CO_2 were assessed. biochemical analyses are performed to assess serum levels of creatinine, sodium, potassium, chloride, and total CO_2, providing valuable insights into renal function and electrolyte balance. On the 3rd day, a brain CT evaluation was performed, and on the 7th day, 28th day, assessments included serum creatinine, serum sodium, potassium chloride, and total CO_2. Furthermore, on the 28th day, evaluations were conducted for mortality, the duration of ICU admission, and other clinical parameters.

If serum sodium exceeds 155 meq/L, HTS administration is discontinued and serum sodium is reassessed after 6 hours. If the serum sodium remains elevated, it leads to replacement with 5% dextrose fluid or 0.45% saline. The Mannitol Group receives 20% mannitol every 6 hours, with serum osmolarity evaluated prior to each dose to ensure proper management. Fluid replacement is adjusted based on clinical judgment, using 5% dextrose fluid or 0.45% saline as needed. This algorithm ensures that both groups receive appropriate interventions to correct and stabilize serum sodium and osmolarity levels, thereby minimizing the risk of complications associated with hypernatremia and hyperosmolarity.

Observations and Assessments

In this clinical trial, patients undergo extensive clinical and laboratory evaluations to assess treatment effects and overall health. Initial assessments at enrollment include clinical measurements (weight, height, age, medical history), neurological evaluation (Modified Glasgow Coma Scale score), and various laboratory tests (serum sodium, BUN, creatinine, glucose, osmolarity, ABGA, CO_2, potassium, chloride, BNP), along with urinalysis and imaging/cardiac assessments (Chest PA, Brain CT, Electrocardiogram, Echocardiography within 72 hours). Regular assessments are conducted every 6 hours (serum levels and osmolarity) and every 24 hours (weight, urine output, administered fluids, pitting edema, Glasgow Coma Scale (GCS) score, ABGA, Chest PA, serum creatinine, urine osmolarity). Specific timepoint assessments include Brain CT scans on Day 3 and Day 7. Additional assessments and data collection cover cardiomegaly suspicion (echocardiography) and comprehensive history and follow-up (medication history, surgical history, infectious history, hospitalization and ICU period, time of death, sur-

Table 2. Observations and Assessments Schedule during study protocol
Abbreviations: GCS, Glasgow coma scale; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; CT, computed tomography; ECG, electrocardiogram; ABGA, arterial blood gas analysis.

Assessment Type	Frequency	Parameters
Initial Assessments	At Enrollment	Weight, height, age, medical history, GCS, serum levels (sodium, BUN, creatinine, glucose, osmolarity, CO_2, potassium, chloride, BNP), urinalysis, Chest PA, Brain CT, ECG, Echocardiography
Regular Assessments	Every 6 Hours	Serum sodium, CO_2, potassium, chloride, BUN, glucose, osmolarity
	Every 24 Hours	Weight, urine output, fluids, pitting edema, GCS, ABGA, Chest PA, serum creatinine, urine osmolarity
Timepoint Assessments	Day 3, 7, 28	Brain CT
Additional Assessments	Indicated	Echocardiography, comprehensive medical history, hospitalization details

vival after 30 days) (Table 2).

Outcome Evaluation

The primary outcome of our study defined as composite clinical events of acute kidney injury (stage 1 to 3) and hypernatremia (serum sodium > 150 mEq/L). These include the incidence of acute kidney injury within the 7 days of observation according to the 2012 KDIGO guidelines. The secondary outcomes include the duration of ICU admission, which reflects the severity of the patient's condition and the effectiveness of the treatment. The total hospitalization period is also recorded. Mortality is a critical measure, with specific time to death, and death occurrences within 30 and 90 days of treatment. Additionally, the GCS scores are assessed on the 7^{th} and 30^{th} days to evaluate neurological outcomes. Additionally, the need for mechanical ventilator application is monitored as an indicator of severe patient condition progression. In addition, pulmonary edema and fluid accumulation in pleural or pericardial spaces reflect potential complications in fluid management. The outcome of edematous event defined as composite event of the presence of Grade 3 or higher pretibial pitting edema, more than 10% of weight gain compared to the baseline, or significant pulmonary edema or pleural effusion on chest images.

Safety issues

Adverse reactions are closely monitored, with their details, severity, and causal relationship evaluated and reported to the principal investigator. This includes assessing the likelihood of the reaction being related to the study, ranging from certain to unrelated. Serious adverse reactions warrant immediate reporting to the principal investigator, who then notifies the participant protection center in compliance with their standards. This protocol ensures an ethical approach to handling adverse reactions, maintaining standards of participant safety and research integrity in clinical trials.

Data Analysis and Statistical Methods

The Kolmogorov-Smirnov Z Test is first used to check the normality of numeric variables. Primary categorical outcomes are analyzed using the Chi-square Test, with Fisher's Exact Test as an alternative for non-normal distributions. Secondary outcomes are examined using the Student's T-test and Chi-square Test, with non-normal distributions handled by the Mann-Whitney U Test and Fisher's Exact Test. For time-to-event data like mortality, neurologic recovery time, and ICU duration, we use the Kaplan-Meier Plot and Cox-Proportional Hazard Model.

Adverse Effects, Precautions, and Measures

In our clinical trial, significant adverse reactions are defined following Naranjo's criteria, encompassing severe outcomes like death, life-threatening situations, extended hospitalization, or serious disability. If any severe drug-related

adverse reactions occur, the trial will be immediately stopped and reported to the Institutional Review Board (IRB). The principal investigator is responsible for regular data and safety monitoring, adhering to strict guidelines and conducting monthly reviews. Unanticipated safety issues identified through various tests are reported to the IRB within 72 hours. All adverse reactions during the study are documented and communicated to the principal investigator. These reactions are evaluated at specific time points, particularly 7 days after randomization. Serious adverse reactions are thoroughly assessed to determine if they meet the criteria for reporting to the IRB and other relevant authorities, ensuring safety management throughout the study.

DISCUSSION

Elevated ICP presents as an acute, potentially fatal condition that can lead to cerebral edema and adverse outcomes. Hyperosmotic solutions like mannitol and HTS are commonly used to reduce ICP by facilitating fluid shifts and improving perfusion. While each treatment shares mechanisms in reducing ICP, recent attention has focused on mannitol's adverse effects, such as hypotension and dehydration. Although both mannitol and HTS have been shown to effectively reduce intracranial pressure in randomized controlled trials, there is a lack of studies comparing their safety profiles, including major side effects such as hypernatremia and acute renal injury, during treatment[1)]. As a result, current guidelines recommend the use of both mannitol and HTS for patients with elevated ICP, but specific indications for each medication remain unclear. In this study, led by nephrologists, a sufficient number of patients with elevated ICP will be enrolled using a pragmatic randomization approach to compare the outcomes of mannitol and HTS. It is anticipated that this will provide important evidence supporting the safe of elevated ICP using HTS, potentially reducing the occurrence of AKI, complications, and mortality rates.

Declaration of conflicting interests

The authors declared no potential conflicts of interest for the research, authorship, and publication of this article.

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