Journal of Society Medicine
Research & Review Articles on Diseases
Journal of Society Medicine. 2023; 2(7)

Osmolarity Changes after Mannitol Administration in Cerebral Edema Patients

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ARTICLE INFO

Article history:
Received
21 June 2023

Revised
15 July 2023

Accepted
31 July 2023

Manuscript ID:
JSOCMED-210623-27-5

Checked for Plagiarism: Yes

Language Editor:
Rebecca

Editor-Chief:
Prof. Aznan Lelo, PhD

ABSTRACT

Introduction: Cerebral edema is commonly associated with cerebral pathology, and the clinical manifestation is greatly influenced by the underlying damaged tissue. Mannitol is the most widely used osmotic agent to reduce intracranial pressure. Giving osmotic therapy with 20% mannitol has the benefit of reducing ICP but can increase plasma osmolarity which can increase the risk of kidney disorders in patients with cerebral edema. This study aimed to assess osmolarity changes after mannitol administration in cerebral edema patients.

Method: This is a pre-experimental study with a one-group pretest-posttest design. The research subjects were taken from the patient population of H. Adam Malik General Hospital Medan and Network Hospitals. The determination of research subjects was carried out according to the non-random sampling method consecutively and obtained as many as 32 research samples conducted from December 2022-April 2023. To determine changes in plasma osmolarity, a paired t-test was performed.

Results: The mean osmolarity before mannitol administration was 303.74±11.59 mOsm/L and after mannitol administration was 307.01±14.83 mOsm/L, with an average change in osmolarity was 3.27±12.19 mOsm/L. There were no significant changes in mean plasma osmolarity after administration of mannitol (p=0.139). Based on the analysis of laboratory components, a significant increase in BUN values was found after the administration of mannitol (p=0.003).

Conclusion: In patients with cerebral edema, mannitol treatment is generally safe and does not result in clinically significant electrolyte abnormalities. But during and after mannitol therapy, electrolyte and renal function monitoring is required.

Keywords

Cerebral edema, Plasma osmolarity, Mannitol

How to cite: Tampubolon M*, Iqbal KM, Pujiastuti RAD. Osmolarity Changes after Mannitol Administration in Cerebral Edema Patients. *Journal of Society Medicine*. 2023; 2(7): 248-253. **DOI: https://doi.org/10.47353/jsocmed.v2i7.71**

INTRODUCTION

Brain edema and elevated intracranial pressure (ICP) are potentially devastating complications following various types of cerebral insults, and appropriate treatments improve cerebral perfusion and reduce damage by local compression of brain tissue.[1] Mannitol and hypertonic saline (HS) are the two hyperosmolar medications that have been most thoroughly investigated and used in clinical practice to treat brain edema and intracranial hypertension.[2]

Interruption of the blood-brain barrier, local inflammation, vascular abnormalities, or altered cellular metabolism can all lead to cerebral edema. The identification and treatment of cerebral edema is central to the management of critical intracranial pathologies. Indirect methods, such as using intracranial pressure (ICP) monitoring devices or surrogate markers detected in imaging examinations, such as tissue shifts or structural alterations, are typically used to measure cerebral edema. It is one of the more typical causes of increased ICP,

which has been linked to a worse prognosis for individuals with stroke, traumatic brain injury (TBI), and other intracranial pathologies.[3]

In order to remove water from brain tissue and move it back into the intravascular space, the primary mechanism by which hyperosmolar medicines manage brain edema relies on the increased osmotic gradient across the blood-brain barrier during drugs infusion. Clinical research revealed that an osmotic gradient between blood and brain of just above 10 mOsmol/kg was effective in reducing ICP. With either mannitol or HS, serum osmolarity can be utilized as a stand-in indicator of the impact of hyperosmolar drugs in clinical practice. Cryoscopic technique is frequently used in laboratories to assess serum osmolarity as the reference method. However, in clinical setting, it is not always possible to monitor serum osmolarity routinely at the bedside, whether in an intensive care unit (ICU) or a neurology ward. In this case, clinicians usually calculate the serum osmolarity using formulas derived from serum osmoles that can be determined through regular laboratory chemical analysis, such as serum sodium, potassium, urea, and glucose. Initial serum osmolarity targets are frequently set just slightly above the upper bound of the normal range. When serum osmolarity during mannitol infusion exceeds 320 mOsm/kg, acute renal failure may occur. Therefore, measuring serum osmolarity during the infusion of a hyperosmolar drug is crucial for assessing clinical effectiveness, adjusting dosage, and preventing side effects.[4]

The pathogenesis of mannitol-related AKI is not fully understood. A high dose or concentration of mannitol may cause renal vasoconstriction, which is one of the suggested processes. Another isomeric tubular vacuolization, also known as tubular cell swelling, or so-called osmotic nephropathy, is another. Additionally, it has been demonstrated that patients who already have risk factors for developing drug-related osmotic nephropathy, such as advanced age, underlying renal disease, and concurrent use of nephrotoxic drugs, are more likely to do so.[5]

METHOD

This is a pre-experimental study with a one-group pretest-posttest design including 32 samples conducted at Haji Adam Malik General Hospital and Network Hospital from December 2022 to April 2023, which has been approved and passed the ethical review from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara with number 125/KEP/USU/2023, which was issued on January 27, 2023. The inclusion criteria were patients with traumatic brain injury (TBI), cerebral infarct, or intracerebral hemorrhage with cerebral edema, mean arterial pressure >80 mmHg, and plasma osmolarity <320 mOsm/kg. Patients who are hemodynamically unstable and have already received medications or treatments to lower their ICP are excluded. Mannitol 20% is given as an IV drip for 15-20 minutes with a dose of 0.5-1 gr/kg every 4-8 hours for 72 hours. Plasma osmolarity was checked again on the 5th day following mannitol infusion. Research data were analyzed statistically with the help of Windows SPSS (Statistical Product and Science Service) version 26.0. Analysis and presentation of data were carried out to see changes in plasma osmolarity before and after administration of 20% mannitol boluses using paired t-tests if the data were normally distributed. If not normal, the Wilcoxon test is used.

RESULT

Based on the characteristics of the 32 research subjects, the mean age of the study subjects was 52.44±15.16 years, with an age range of 18–30 years for 3 people (9.4%), >30–45 years for 6 people (18.8%), >45–60 years for 15 people (46.9%), and 8 people (25%) aged >60 years. The sex of the study subjects was mostly found in males, amounting to 21 people (65.6%) compared to women, amounting to 11 people (34.4%).

Of the 32 study subjects, the median Glasgow Coma Scale (GCS) score was 12 (5–15). A total of 13 research subjects (40.6%) had a GCS awareness level of 8–10. On a CT scan of the head without contrast, the most common radiologic features were spontaneous ICH (intracerebral hemorrhage) in 19 subjects (59.4%), followed by cerebral contusions in 4 subjects (12.5%), ischemic stroke in 3 subjects (9.4%), ischemic stroke with hemorrhagic transformation in 3 subjects (9.4%), and traumatic ICH in 3 subjects (9.4%). A total of 24

subjects (75%) had a history of comorbid diseases, while 8 subjects (31.3%) had no previous comorbid history. The comorbid diseases found in this study were hypertension in 21 subjects (65.6%), type 2 diabetes mellitus in 7 subjects (21.9%), heart disease in 5 subjects (15.6%), history of previous stroke in 2 subjects (6.3%), renal impairment in 2 subjects (6.3%), and hemophilia in 1 subject (3.1%).

Table 1. Characteristics of Research Subjects

Characteristics of Research Subjects	n=32
Age (years), mean±SD	52.44±15.16
Age group, n(%)	
18-30 years	3 (9.4%)
>30-45 years	6 (18.8%)
>45-60 years	15 (46.9%)
>60 years	8 (25.0%)
Gender, n (%)	
Male	21(65.6%)
Female	11 (34.4%)
Glasgow Coma Scale (GCS), median (min-max)	12 (5 – 15)
GCS 3-7	1 (3.1%)
GCS 8-10	13 (40.6%)
GCS 11-12	4 (12.5%)
GCS 13-14	5 (15.6%)
GCS 15	9 (28.1%)
Radiologic features , n=32	
Spontaneous Intracerebral hemorrhage	19 (59.4%)
Ischemic stroke	3 (9.4%)
Ischemic stroke with hemorrhagic transformation	3 (9.4%)
Traumatic Intracerebral hemorrhage	3 (9.4%)
Cerebral contusion	4 (12.5%)
History of comorbid, n=32	
With comorbid	24 (75.0%)
Without comorbid	8 (25.0%)
Type of comorbid	
Hypertention	21 (65.6%)
Type 2 diabetes mellitus	7 (21.9%)
Heart disease	5 (15.6%)
Previous stroke	2 (6.3%)
Renal impairment	2 (6.3%)
Hemophilia	1 (3.1%)

Table 2. Changes in Laboratory Results

Variable	Before mannitol (n=32)	After mannitol (n=32)	p value
Lab chemical analysis, mean±SD			
Sodium	140.63±5.17	141.03±5.47	0.630[a]
Potassium	3.99±0.73	3.91±0.66	0.518[a]
BUN	14.99 (5.9 – 47.35)	17.9 (6.8 – 105.4)	0.003[b]
Glucose	129.5 (76 – 583)	127.5 (83 – 399)	0.829[b]

Noted: [a] paired t-test; [b] Wilcoxon test

In calculating plasma osmolarity, the results of blood chemistry tests for sodium, potassium, blood urea nitrogen (BUN), and glucose are needed. In this study, plasma osmolarity was obtained from the following formula: 2(Na+K) + (Glucose/18) + (BUN/2.8). Based on the paired t-test, there was no difference in the average levels of sodium, potassium, and blood glucose levels before and after mannitol administration ($p > 0.05$), but there was a significant changes in the mean BUN values before and after mannitol administration (p

= 0.003), where the median BUN value before administration of mannitol was 14.99 (5.9–47.35) mg/dL and after administration of mannitol was 17.9 (6.8–105.4) mg/dL, with data not normally distributed.

In 32 study subjects, changes in plasma osmolarity after administration of mannitol with an increase in plasma osmolarity occurred in 21 of 32 subjects (65.6%), with the remaining 11 subjects experiencing a decrease in plasma osmolarity after administration of mannitol. Among the 21 subjects who experienced an increase in plasma osmolarity after administration of mannitol, 7 subjects (33.3%) experienced an increase in osmolarity to >320 mOsm/L.

Table 3. Osmolarity Changes in Research Subjects

Variable	n (%)
Osmolarity changes (n=32)	
Increased osmolarity	21 (65.6%)
Decreased osmolarity	11 (34.4%)
Increased osmolarity (n=21)	
<320 mOsm/L	14 (66.7%)
>320 mOsm/L	7 (33.3%)

The mean plasma osmolarity value before mannitol administration was 303.74±11.59 mOsm/L, while the mean plasma osmolarity value on day 5 after mannitol administration was 307.01±14.83 mOsm/L. The mean change in plasma osmolarity after administration of mannitol was 3.27±12.19 mOsm/L. Based on the paired t-test, there was a difference in mean plasma osmolarity before and after administration of mannitol, but it was not significant with a value of p=0.139 (95% CI -1.1–7.7).

Table 4. Plasma Osmolarity in Research Subjects

	Mean±SD	Mean changes±SD	CI95%	p value
Osmolarity before mannitol (n=32)	303.74±11.59	3.27±12.19	-1.1 – 7.7	0.139
Osmolarity after mannitol (n=32)	307.01±14.83			

Note: *paired t-test

DISCUSSION

Brain edema is a well-described stroke complication and is associated with poor outcome. The midline structures may be compressed as a result of cerebral edema, which limits cerebral circulation and may also lead to transtentorial herniation. Decompressive hemicraniectomy decreases mortality in patients with malignant middle-cerebral artery infarction, although it is not commonly used, leaves the majority of patients with moderate to severe disabilities, and it has not been tested in cases with less severe brain edema. In order to reverse brain edema and preserve cerebral circulation, numerous non-surgical procedures are often used. However, there are very limited data on the safety and efficacy of these modalities. Hyperventilation and the elevated head position both had relatively modest advantages.[6,7]

The potential negative effects of the hyperosmolar drug are considered while deciding whether to administer it. Strong diuretics like mannitol can increase the risk of kidney damage in hypovolemic patients. Mannitol causes an osmotic diuresis, but the first quick rise in intravascular volume can paradoxically lead to abrupt hypervolemia, which in vulnerable people might lead to heart failure or pulmonary edema. The brain tries to make up for the osmotic gradient in individuals with chronically raised ICP who need extended mannitol therapy by producing "idiogenic osmoles." These osmoles are thought to be oncotically active despite their lack of understanding, which emphasizes the significance of gradually weaning both drugs with prudence. If abruptly stopped, the gradient for water transport is reversed, allowing an intracranial volume and pressure increase as a rebound. The aggregation of osmotically active molecules brought on by blood brain barrier rupture can also result in localized edema or rebound rises in ICP.[8]

In this study, there was a difference between BUN levels before and after mannitol administration (p=0.003). The increase in BUN levels in this study was in line with research by Sari et al. that is, from 11.27±2.75 mg/dl before administration of mannitol to 17.08 ± 8.59 mg/dl after mannitol administration.[9] Urea is the largest nitrogen product from food and endogenous protein which is filtered by the glomerulus and partially reabsorbed by the tubules. Mannitol is an osmotic diuretic of the polysaccharide class which works to carry fluid from the interstitial to the intravascular which increases blood flow to the kidneys resulting in excessive diuresis, resulting in hemoconcentration which increases plasma osmolarity. This excessive diuresis affects electrolytes and fluid changes, which are one of the factors that can increase BUN.[5] The incidence of acute kidney failure due to mannitol is known to be 6.5% with independent risk factors including history of diabetes (OR 3.62; p=0.005), decreased eGFR before mannitol administration (OR 0.98; p=0.03), higher NIHSS score (OR 1.06; p=0.048) and history of previous use of diuretics (OR 8.50; p=<0.001).10 Other studies have found a higher incidence of kidney injury i.e. 28% in patients receiving mannitol with risk factors including age >65 years (OR 2.55; p=0.01), Systolic Blood Pressure >160mmHg (OR 2.065; p=0.05), Diastolic blood pressure >90mmHg (OR 2.03; p= 0.05) and increased hypertension on mannitol administration (OR 2.76; p=0.01).[11]

In this study, the mean osmolarity level before mannitol administration was 303.74±11.59 mOsm/L while the mean osmolarity level on day 5 after mannitol administration was 307.01±14.83 mOsm/L. Based on the paired t-test, it was found that the osmolarity level after administration of mannitol was higher than before but not statistically significant (p=0.139). Positive osmolarity changes occurred in 21 people (65.6%) while negative osmolarity changes occurred in 11 people (34.4%). Among the 21 subjects who experienced an increase in plasma osmolarity after administration of mannitol, 7 subjects (33.3%) experienced an increase in osmolarity to >320 mOsm/L. In this study, the osmolarity was found to increase because from the analysis of the plasma osmolarity component, there was an increase in BUN after administration of mannitol (p=0.003). However, the increase was not significant because according to theory, the difference in osmolarity was reported to increase statistically significantly at 15-30 minutes after mannitol administration due to inversion of plasma sodium concentration, but this gradually decreased at 60-360 minutes.[9] Other studies reported that the peak decrease in ICP after administration of mannitol occurs the first 30-45 minutes and is known to last up to 6 hours later.[11] This is in line with a research by Wardoyo et al. in 2020 who found an increase in plasma osmolarity 3 days after administration of mannitol but not statistically significant (p> 0.05).[12] Another study by Li in 2015 found that plasma osmolarity increased within 15-30 minutes after administration of mannitol (p<0.05) then falls below baseline within 240-360 minutes after mannitol administration.[2]

In this study other factors such as urine volume, blood pressure, creatinine levels and eGFR have not been investigated to establish the possibility of acute kidney injury due to mannitol administration. Mannitol administration was also given in the same dose range for all subjects so that it could not further compare changes in osmolarity based on different doses of mannitol and duration of mannitol administration.

CONCLUSION

In patients with cerebral edema, mannitol treatment is generally safe and does not result in clinically significant electrolyte abnormalities. But during and after mannitol therapy, electrolyte and renal function monitoring is required.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and Haji Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

FUNDING
This research has received no external funding.

COMPETING INTERESTS
The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS
All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS
None

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