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Original Research Article

COMPARISON OF EFFICACY AND SAFETY OF PERIPHERAL IV-LINE MANNITOL VS HYPERTONIC SALINE FOR MANAGEMENT OF INTRACRANIAL PRESSURE

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Abstract: *Management of elevated intracranial pressure (ICP) in emergency settings often involves the administration of hyperosmolar agents such as mannitol and hypertonic saline (HTS). The choice between these agents and their safety profile, mainly when administered via peripheral intravenous (IV) lines, remains a clinical concern.* ***Objective:*** *To compare the safety and effectiveness of peripheral IV administration of mannitol and hypertonic saline in managing elevated intracranial pressure in the emergency department.* ***Methods:*** *A retrospective cohort study was conducted in the Emergency Department of Shifa International Hospital from June 2023 to June 2024. The study included 200 adult and pediatric patients who received hyperosmolar agents, specifically 110 patients administered with a 1 g/kg bolus dose of 20% or 25% mannitol and 90 patients with a 5 mL/kg bolus dose of 3% hypertonic saline. The administration was followed by repeated doses or continuous infusion at the attending physician's discretion. The primary endpoint was the incidence of extravasation. In contrast, secondary endpoints included hypokalemia, acute kidney injury (AKI) within two days of admittance, hypernatremia, hyperchloremia, ICP at admission and 24 hours post-administration, length of hospital and ICU stay, need for ventilator support, mortality rate, Glasgow Coma Scale (GCS) score at discharge, and severity of infusion-related adverse effects.* ***Results:*** *The mannitol group consisted of older patients (52.8 ± 21.3 years vs. 28.6 ± 23.1 years), who were also heavier (75.2 ± 21.8 kg vs. 57.5 ± 33 kilograms), had a higher prevalence of end-stage renal disease (ESRD) (7.3%), and were less likely to present with altered mental status (89.1% vs. 97.8%). There were no incidents of extravasation in either group ($p > 1$). No significant differences were observed between the groups concerning secondary outcomes. However, the mannitol group exhibited higher ICP after 24 hours (4.240 ± 7.9 vs. 2.111 ± 6), a lower GCS score at discharge (3 [3-14] vs. 13 [3-15]), a higher mortality rate (55.5% vs. 33.4%), and a longer duration of ventilator support (2 days vs. one day).* ***Conclusion:*** *Peripheral IV administration of hypertonic saline appears safer and more effective in reducing intracranial pressure than mannitol in emergency department settings. HTS demonstrated a more favorable safety profile with lower mortality and shorter ventilator support duration.*

Keywords: Acute Kidney Injury, Extravasation, Hypernatremia, Hyperosmolar Therapy, Intracranial Pressure, Mannitol, Retrospective Studies, Saline Solution, Hypertonic, Safety, Ventilator Support

Introduction

The administration of mannitol and hypertonic saline are first-line treatments to relieve the elevation of intracranial pressure in the emergency department. The efficacy and safety of these agents are reported to be similar and lead to the same clinical outcomes. (1). Mannitol is also effective in treating subarachnoid and intracerebral hemorrhage, liver failure, and malignant cerebral infarction. (2). A reduced mortality rate was reported in patients with traumatic brain injury, leading to elevated intracranial pressure. (3). However, adverse effects such as hypervolemia and renal failure have been observed after administration of mannitol. (4). Hypertonic saline has been reported to reduce pressure without risk of hypovolemia and nephrotoxicity. Some studies have also reported the superior effect of hypertonic solutions on mannitol, but this is not backed by clinical practice. (5, 6). With vast research on the effectiveness of mannitol and hypertonic saline, limited data is available on comparing both treatments' safety and adverse outcomes. Peripheral IV line administration of hypertonic saline has been reported to cause adverse effects, including thrombophlebitis, extravasation, and phlebitis in up to 10.7% of patients. (7). These complications are not observed in patients receiving mannitol. These conflicting opinions may confuse physicians and delay treatment. This study compared the safety of peripheral IV line administration of mannitol and hypertonic saline in managing intracranial pressure in the emergency department.

Methodology

A retrospective cohort study was conducted in the Emergency Department of Shifa International Hospital from June 2023 to June 2024. A total of 200 adult and pediatric patients receiving hyperosmolar agents, including mannitol and HTS, were included in the study. Pregnant women, patients who received both agents via the same IV, and patients who administered mannitol for hemodialysis were excluded. All patients provided their informed consent

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to participate in the study, which was approved by the hospital's ethical committee.

One hundred ten patients were administered 1g/kg bolus dose of 20 or 25% mannitol through peripheral IV, while 90 patients were administered 5mL/kg bolus dose of 3% hypertonic saline. The doses were repeated, or continuous infusion was administered at the physicians' discretion. The primary endpoint was the incidence of extravasation. The secondary endpoint was the incidence of hypokalemia, AKI within two days of admittance, hypernatremia, hyperchloremia, intracranial pressure at admission, and 24 hours after drug administration, length of hospital and ICU stay, need of ventilator, mortality rate, GCS score at discharge and severity of infusion-related adverse effects.

Patient data, including complete medical history, age, gender, BMI, medication history, lab results, physical assessment, neurological tests, drug administration in the emergency department, ICU and hospital stay, ventilator duration, and indication for mannitol or hypertonic saline, was recorded. All data was analyzed using SPSS version 24. Mean ± SD was used to present continuous parameters for normally distributed data, and interquartile range was used for non-normal data. Percentage was used to present categorical data. T-tests were used to compare continuous data when parametric tests were satisfied, or the Mann-Whitney U test was used otherwise. Categorical variables between both groups were compared using c2 tests, or Fisher's test was used otherwise. A p-value of 0.05 was taken as significant.

Results

A total of 200 patients were included, of which 54 (27%) were pediatric patients. 110 (55%) patients were administered mannitol and 90 (45%) were administered hypertonic saline. The Mannitol group was older (52.8 ± 21.3 vs. 28.6 ± 23.1), heavier (75.2 ± 21.8 vs. 57.5 ± 33), had more ESRD patients (7.3%), and less likely to have altered mental status (89.1% vs. 97.8%). The baseline features of patients of both groups are shown in Table I. 90% of patients in the saline group and 99.1% in the mannitol group received bolus doses. 83.6% of patients in the mannitol group were administered 25% agent (Table II). No patients in the study had an incidence of extravasation (p >1). The groups did not differ concerning secondary outcomes, as shown in Table III. Table IV shows the efficacy outcomes of both treatments. Mannitol group had higher intracranial pressure after 24 hours (4.240 ± 7.9 vs. 2.111 ± 6), lower GCS at discharge (3 (3-14) vs. 13 (3-15)), high mortality (55.5 vs. 33.4%) and more duration of ventilator support (2 days vs one day).

Table 1: Patients' baseline characteristics

Parameters	Hypertonic saline group (n=90)	Mannitol group (N=110)	P
Mean age	28.6 ± 23.1	52.8 ± 21.3	<0.001
Female gender	36 (40%)	42 (38.2%)	0.470
Mean weight	57.5 ± 33	75.2 ± 21.8	<0.001
Mean BMI	24.3 ± 11.4	27.6 ± 8.1	0.061
Median GCS score	6 (3-15)	5 (3-15)	0.601
Altered mental status	88 (97.8%)	98 (89.1%)	0.030
Hypotensive at admission	11 (12.2%)	11 (10%)	0.682
Diabetics	14 (15.6%)	18 (16.4%)	0.830
Peripheral vascular disease	4 (4.5%)	8 (7.3%)	0.524
IV drug use	3 (3.4%)	9 (8.2%)	0.188
End-stage renal disease	-	8 (7.3%)	0.217
Obesity	12 (13.4%)	22 (20%)	0.179
Anticoagulant use at home	4 (4.5%)	11 (10%)	0.1
Antiplatelet use at home	9 (10%)	20 (18.2%)	0.1
Need of ventilator	64 (71.2%)	92 (83.7%)	0.061
Indication			
Acute ischemic stroke	3 (3.4%)	4 (3.7%)	1
Traumatic brain injury	51 (56.7%)	43 (39.1%)	0.018
Intracerebral hemorrhage	18 (20%)	50 (45.5%)	0.001
Other	18 (20%)	17 (15.5%)	0.254

Table 2: Dosage details of mannitol and hypertonic saline

	Hypertonic saline group	Mannitol group
Bolus administration	81 (90%)	109 (99.1%)
Continuous infusion	9 (10%)	1 (0.9%)
Mean dosage		
mL	281.5 ± 182.4	-
mL/kg	7 ± 8.86	-
g	-	74.3 ± 41.9
g/kg	-	0.1 ± 0.52
Mannitol concentration		
20%	-	18 (16.4%)
25%	-	92 (83.6%)

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Table 3: Safety of Treatments

Outcomes	Hypertonic saline group	Mannitol group	P
Extravasation	-	-	>1
Electrolyte imbalance	44 (48.9%)	59 (53.7%)	0.520
Hypokalemia	23 (25.6%)	29 (26.4%)	0.868
Hyperchloremia	35 (39%)	43 (39.1%)	0.921
Hypernatremia	9 (10%)	16 (14.6%)	0.273
Acute kidney injury	9 (10%)	7 (6.4%)	0.476

Table 4: Efficacy of Treatments

	Hypertonic saline group	Mannitol group	P
Intracranial pressure after treatment	2.111 ± 6	4.240 ± 7.9	0.051
GCS at discharge	13 (3-15)	3 (3-14)	0.005
Mortality rate	30 (33.4%)	61 (55.5%)	0.004
Expansion of hematoma after treatment	8 (8.9%)	11 (10%)	0.448
Duration of ventilator support	1 (0-55)	2 (0-55)	0.019
Length of ICU stay	3 (0-55)	3 (0-55)	0.663
Length of hospital stay	4 (2-11)	5 (1-14)	0.878

Discussion

This study compared the safety and efficacy of mannitol and hypertonic saline administered via peripheral IV to manage intracranial pressure in emergency patients. The results showed that both treatments did not differ concerning primary outcome, i.e., extravasation incidence, but hypertonic saline was more effective and safer in secondary patient outcomes.

No incidence of extravasation indicated the efficacy of both treatments. Several other studies have also reported the efficacy of HTS and mannitol in traumatic brain injury patients.(8, 9) HTS was more effective in reducing intracranial pressure to 2.111 mm Hg than 4.240 mm Hg in the mannitol group. A meta-analysis of five studies also showed that the ICP reduction was significantly lower in patients administered hypertonic sodium solution.(10) Singla et al. defined ICP reduction as less than 18 mm Hg within 1 hour. They reported that the HTS group had an ICP reduction of 13.0 (11.5–17.3) while the mannitol group showed an ICP reduction of 7.5 (5.8–11.8), with a weighted mean difference of 5 (1.22,8.78) indicating the effectiveness of HTS treatment.(11) This is also true in the pediatric population.(12, 13) Chen et al. contradict our study results. They showed no difference in the efficacy of both treatments for ICP reduction, but HTS had a lasting effect.(14)

Concerning secondary endpoints, the mortality rate was 33.4% in the HTS group, significantly lower than 55.5% in the mannitol group. However, Huang et al. reported a relative mortality risk of 0.78 (0.53-11.6), which indicated no significant association between the administration of HTS and a reduction in mortality.(15) Both groups did not differ in length of ICU and hospital stay. Mangat et al. agree with these outcomes.(16)

The complication rate in our study was 15%, which is lower than reported by a recent meta-analysis, i.e., 21-79%.(17) The inclusion of patients with intracranial hemorrhage in that group can explain a high adverse effects rate and poor prognosis in the mannitol group.

Our study has some limitations. We included pediatric and adult patients who differ significantly in indicators and baseline features for treatment agents. Secondly, the retrospective design could not evaluate confounding factors for secondary outcomes and their associations.

Conclusion

When administered through a peripheral IV line in the emergency department, hypertonic saline was safer and more effective in reducing intracranial pressure.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate
Approved by the department concerned. (IRB/SIHISB-0248/23)

Consent for publication
Approved

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Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

HAFSA ASHRAF (Postgraduate Trainee)
Study Design, Review of Literature.
Conception of Study, Development of Research Methodology Design, Study Design, manuscript Review, and final approval of manuscript.
FATIMA ASHRAF (House Officer)
Conception of Study, Final approval of manuscript.
SARA MALIK (Associate Consultant)
Coordination of collaborative efforts.
Manuscript revisions, critical input.

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