DOI: 10.7860/JCDR/2020/44376.13839

Original Article

Internal Medicine Section

Complications Associated with Osmotic Therapy in Acute Stroke Patients- A Prospective Longitudinal Observational Study

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ABSTRACT

Introduction: Mannitol is one of the most frequently used drugs to treat cerebral oedema resulting from ischemic and haemorrhagic strokes. Mannitol administration is associated with complications such as Acute Kidney Injury (AKI) and electrolyte imbalance.

Aim: To study effect of mannitol therapy on electrolyte levels and renal function in acute stroke patients.

Materials and Methods: The present prospective longitudinal observational study was carried out from January 2019 till September 2019 in Father Muller Medical College, Mangalore, India. After taking informed consent, patients with acute stroke who received mannitol were recruited into the study. Nature of the stroke, presence of comorbidities and dosage of mannitol given were recorded. Serum electrolytes, Serum urea and creatinine were recorded at admission and on fifth day. Serum urea was measured by enzymatic photometric method using urease and glutamate dehydrogenase and serum creatinine was measured by Jaffe's kinetic method. Comparison of data among different groups was performed using student t-test, ANOVA test, Mann-whitney test and Pearson test. The p-values <0.05 were taken as statistically significant.

Results: Total of 72 patients were included in the study. Mean age was 57.7±14.6 years and male: female ratio was 2.27:1. Of the total study subjects, 16 suffered from diabetes (22.22%), 40 from hypertension (55.55%). Ischemic stroke was seen in 41.66% patients and haemorrhagic stroke was seen in 58.33% of the patients. The dose of mannitol administered to all the patients was less than 1 gram/kg/day (low dose mannitol). Cumulative dose of mannitol was 180±177.3 grams. Serum sodium levels were significantly lower on fifth day compared to admission (p-value 0.030) whereas serum potassium and chloride levels were not significantly changed during therapy. There was statistically significant elevation in serum urea levels from admission to fifth day (p-value <0.001) whereas creatinine levels were not significantly altered. Total cumulative dose was compared to serum electrolyte levels and urea and creatinine at admission and fifth day and no significant changes were found. On analysing comorbidities, electrolyte fluctuations were more common in diabetics and Chronic Kidney Disease (CKD) patients whereas renal function parameters were abnormal in diabetics, CKD and hypertensive patients. None of the patients needed any corrective measures to treat the dyselectrolytemias or altered renal function.

Conclusion: Low dose mannitol therapy does not produce any significant electrolyte or renal function abnormality in patients with acute stroke. Careful monitoring may be required while treating patients with additional comorbidities.

Keywords: Cerebrovascular accident, Chronic kidney disease, Mannitol

INTRODUCTION

The World Health Organisation (WHO) defines stroke as 'rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin' [1]. Stroke is a leading cause of mortality and long-term disability globally [2,3]. The incidence of stroke in low and middle-income countries has more than doubled and the prevalence of stroke and stroke related deaths have increased in absolute numbers, particularly in the elderly [4,5].

Cerebral oedema is a well-described stroke complication and is associated with poor outcome [6-10]. Current guidelines (American Stroke Association) mention that osmotic therapy is reasonable in patients with clinical deterioration from cerebral oedema resulting from cerebral infarction [11]. Drugs such as mannitol, hypertonic saline, glycerol, corticosteroids, barbiturates and diuretics have been commonly used to treat cerebral-oedema [12,13]. Mannitol is administered intravenously as a 20% solution and dosage is adjusted according to the body weight and severity of brain oedema. Various studies have described low dose mannitol therapy as dosage of 1 g/kg/day and high dose mannitol therapy as greater than 1 g/kg/day [14].

However, only a few studies [15-20] have evaluated the effects of mannitol on the clinical parameters of these patients. Mannitol administration is also associated with frequent complications such as Acute Kidney Injury, electrolyte imbalance, volume overload, rebound oedema, thrombophlebitis [21-29] and has thus led to controversies regarding its use in acute stroke care.

Aim of the present study were to look into evaluation of short-term fluctuations in serum electrolytes and renal function in patients with acute stroke receiving mannitol therapy and to correlate the fluctuations if any with comorbidities, in order to help with appropriate monitoring during osmotic therapy.

MATERIALS AND METHODS

Patients admitted to the Neurology Department of Father Muller Medical College Hospital, Mangalore from January 2019 to September 2019 were included in the study. This study was approved (Approval letter number: FMMCIEC/CCM/122/2019) by the Father Muller Medical College Institutional Ethics Committee. Written informed consent was obtained.

Inclusion criteria: Patients above 18 years of age and clinically diagnosed as Ischemic or Haemorrhagic stroke were included, if

patient or their attendants consented to take part in the study.

Exclusion criteria: Patients below the age of 18 years and/or those not willing to give consent, were excluded from the present study.

Data on demographics, risk factors, co-morbidities of the patients were noted and data on mannitol dosage in: 1) grams/kilograms/day; and 2) total cumulative dosage administered to the present study population was obtained. Dosage of mannitol received by patients of study population was adjusted based on weight and severity of cerebrovascular accident. The cumulative dose received by each patient was then calculated and used for further analysis. Dose of mannitol administered to all patients of the study population was 0.2 grams/mL, which was given as 100 mL infusion. Values of Serum electrolytes and Renal function test parameters on admission and on fifth day following mannitol therapy were obtained. Local complications such as thrombophlebitis, Intravenous block and limb swelling [30-33] if any, arising during mannitol therapy in the study population were also recorded.

Electrolytes were measured by Ion Selective Electrodes (ISE) which measured the activity of ions in water which is directly proportional to their concentration. Serum urea was measured by enzymatic photometric method using urease and glutamate dehydrogenase and serum creatinine was measured by Jaffe's kinetic method. The tests were done by Cobas 6000 automated analyser.

STATISTICAL ANALYSIS

Collected data was tabulated and entered using Microsoft Excel 365 into an excel proforma sheet and analysis was done using SPSS Software Version 21.0. Further evaluation of the data of comparing the means of more than 2 different groups was performed using student t-test, ANOVA test, Mann-whitney test and Pearson test. The p-values <0.05 were taken as statistically significant.

RESULTS

In the present study, 72 stroke patients were recruited with the mean age being 57.72±14.60 with minimum age of 26 and maximum age of 84 years. Among the study population, 50 were males and 22 were females with an M:F ratio of 2.27:1. In the study cohort, 16 suffered from diabetes (22.22%), 40 from hypertension (55.55%), 5 from CKD (6.94%), 3 from ischemic heart disease (4.16%) and one patient each (1.38%) from Pneumonia, Dyslipidemia, Peripheral Artery Occlusive Disease and previous episode of stroke respectively.

Thirty patients (41.66%) were diagnosed as ischemic stroke and 42 (58.33%) patients were diagnosed as haemorrhagic stroke. All 72 patients received Intravenous mannitol as anti-oedema therapy.

The mean cumulative dose of mannitol administered to study population was 180.00±177.39 grams with a minimum dose of 20 grams and maximum dose of 1020 grams. The cumulative dose of mannitol administered to all the patients was less than 1 gram/kg/day and was thus categorised as low dose mannitol [14].

Serum Electrolyte Changes with Mannitol Therapy

Serum sodium, potassium and chloride were measured at admission and on fifth day. On employing ANOVA test, there was a statistically significant reduction in serum sodium levels whereas potassium and chloride levels were not significantly altered [Table/Fig-1]. There was also no statistically significant co-relation of change in sodium, potassium or chloride levels with cumulative dose of mannitol.

Renal Function Changes with Mannitol Therapy

There was an increasing trend in serum urea levels from admission to fifth day, which was statistically significant when employing Friedman test while serum creatinine was not significantly altered [Table/Fig-2]. On using Pearson's coefficient analysis, there was no statistically significant co-relation of cumulative dose of mannitol with change in serum urea or creatinine levels [Table/Fig-3].

Parameter	Day of measurement	Mean	Standard deviation	p-value
Serum Cl {mEq/L (milliequivalents per litre)}	Admission	96.99	9.46	0.904
	Fifth day	97.17	6.17	
Serum K {mmol/L (millimole per litre)}	Admission	3.89	0.66	0.225
	Fifth day	4.02	0.49	
Serum Na {mEq/L (milliequivalents per litre)}	Admission	136.67	6.83	**0.030**
	Fifth day	135.53	6.36	

[Table/Fig-1]: Change in electrolyte levels of patients receiving mannitol therapy by applying ANOVA Test (p-values <0.05 were taken as statistically significant).

Parameter	Day of measurement	Mean	Standard deviation	p-value
Serum creatinine (mg/dL)	Admission	1.30	1.22	0.217
	Fifth day	1.36	1.38	
Serum urea (mg/dL)	Admission	34.61	24.23	**<0.001**
	Fifth day	39.42	30.98	

[Table/Fig-2]: Change in renal function parameters of patients receiving mannitol therapy by applying Friedman Test.

Values measured on admission and fifth day	Pearson correlation	p-value
Serum Cl changes {mEq/L (meq/ltr)} with cumulative dose	-0.017	0.885
Serum K changes {mmol/L (mmole/ltr)} with cumulative dose	0.012	0.919
Serum Na changes {mEq/L (meq/ltr)} with cumulative dose	-0.007	0.951
Serum Creatinine changes {mg/dL (mg/dL)} with cumulative dose	-0.119	0.318
Serum Urea changes {mg/dL (mg/dL)} with cumulative dose	-0.106	0.375

[Table/Fig-3]: Correlation between cumulative dose of mannitol with changes in electrolyte levels and renal function parameters.

Cumulative Dose of Mannitol and Electrolyte Changes and Renal Function Parameters in Patients with Comorbidities

Serum sodium changes were statistically significant in diabetic patients. Serum potassium changes were significant in patients with CKD and diabetics. There was no significant change in chloride levels with respect to comorbidities [Table/Fig-4].

Serum creatinine level changes were significant in patients with CKD and serum urea level changes were statistically significantly in patients with CKD, diabetes and hypertension [Table/Fig-5].

However, none of the patients had any clinical complications due to change in electrolytes or renal parameters. None of the patients needed any corrective measures to treat the dyselectrolytemias or altered renal function.

Local Complications with Mannitol Therapy

The complications observed, following the mannitol therapy in the study population were-Intravenous block (2.8%), Thrombophlebitis (1.4%) and limb swelling (5.6%).

Intravenous block and limb swelling were treated with Glycerin-Magnesium sulfate dressing, followed by changing of Cannula site. Thrombophlebitis was treated with analgesics and local application of Benzyl nicotinate and Heparin ointment.

DISCUSSION

The present study tried to correlate cumulative mannitol dose with short term fluctuations in serum electrolytes and renal parameters in patients suffering from acute stroke. All the patients received cumulative mannitol dose of equal to or less than 1 gm/kg/day.

Parameter	Co-morbidity		Mean	Standard deviation	p-value
Serum Cl {mEq/L (milliequivalents per litre)}	DM	No	96.7	5.42	0.235
		Yes	98.79	8.29	
	HTN	No	97.41	7.14	0.772
		Yes	96.98	5.35	
	IHD	No	97.33	6.15	0.292
		Yes	93.47	6.44	
	CKD	No	97.05	5.93	0.558
		Yes	98.74	9.62	
Serum K {mmol/L (millimole per litre)}	DM	No	3.95	0.40	**0.029**
		Yes	4.25	0.68	
	HTN	No	3.93	0.41	0.155
		Yes	4.09	0.53	
	IHD	No	4.03	0.48	0.589
		Yes	3.87	0.72	
	CKD	No	3.97	0.44	**<0.001**
		Yes	4.74	0.57	
Serum Na {mEq/L (milliequivalents per litre)}	DM	No	134.73	6.02	**0.046**
		Yes	138.31	6.93	
	HTN	No	135.34	5.99	0.828
		Yes	135.68	6.71	
	IHD	No	135.55	6.41	0.884
		Yes	135.00	6.08	
	CKD	No	135.49	6.41	0.865
		Yes	136.00	6.28	

[Table/Fig-4]: Correlation between cumulative dose of mannitol with changes in electrolyte levels in patients with comorbidities.
DM: Diabetes mellitus; HTN: Hypertension; IHD: Ischemic heart disease; CKD: Chronic kidney disease

Parameter	Co-morbidity		Mean	Standard deviation	p-value
Serum creatinine {mg/dL (milligram per dL)}	DM	No	1.25	1.26	0.220
		Yes	1.74	1.74	
	HTN	No	1.02	0.91	0.061
		Yes	1.63	1.63	
	IHD	No	1.32	1.34	0.257
		Yes	2.25	2.35	
	CKD	No	1.09	0.92	**<0.001**
		Yes	4.99	1.55	
Serum urea {mg/dL (milligram per dL)}	DM	No	34.41	21.15	**0.009**
		Yes	56.94	49.83	
	HTN	No	30.25	18.38	**0.024**
		Yes	46.75	36.81	
	IHD	No	38.65	30.42	0.319
		Yes	57.00	46.03	
	CKD	No	33.34	19.78	**<0.001**
		Yes	120.80	41.06	

[Table/Fig-5]: Correlation between cumulative dose of mannitol with changes in renal function parameters in patients with comorbidities. The p-values <0.05 were taken as statistically significant.
DM: Diabetes mellitus; HTN: Hypertension; IHD: Ischemic heart disease; CKD: Chronic kidney disease

The present study found that serum sodium levels were statistically significantly lower from admission to fifth day on mannitol therapy, however clinically there was no significant hyponatremic episodes needing correction. The reduction in sodium may occur due to mannitol being an osmotic diuretic, which increases urinary excretion of sodium. Reduction in sodium levels on mannitol therapy has also been observed in multiple other studies [16,17,29]. There was no significant change seen in other serum electrolyte levels on mannitol therapy and there was also no significant correlation between cumulative dose of mannitol and electrolyte changes. Hence, low dose mannitol therapy does not produce clinically significant electrolyte changes during acute stroke treatment.

The present study found a significant correlation between fluctuation of serum sodium levels with cumulative mannitol dose in patients with Diabetes. Serum sodium levels in patients with diabetes receiving mannitol therapy tended to be slightly higher than that of other patients. Hypernatremia is described as a complication associated with diabetes [34]. However, a literature search did not reveal any study correlating mannitol therapy in diabetics to hypernatremia.

The present study also showed an increase in serum potassium levels with cumulative mannitol dose in patients with diabetes and CKD. A study done by Nicolis GL et al., also shows significant correlation of change in potassium levels in diabetes patients causing glucose-induced hyperkalemia [35]. Hyperkalemia in CKD patients is likely due to insufficient clearance of mannitol from circulation leading to increased tubular reabsorption of potassium [14]. The present study shows that although electrolyte fluctuations tend to occur during mannitol therapy especially in diabetics and CKD patients, low dose mannitol therapy appears to be relatively safe.

Although serum urea and creatinine levels were higher in CKD patients and diabetics along with serum urea levels being higher in diabetic patients after receiving mannitol, it did not translate to clinically significant renal dysfunction. Mannitol is found to have both renal damaging [17] and renal protective [18] properties in literature. With regards to renal functions, the present study showed low dose mannitol therapy did not affect renal parameters in the short term.

The present study also shows that complications arising due to Intravenous mannitol therapy are relatively uncommon with limb swelling, Intravenous block and thrombophlebitis being encountered during the present study.

Limitation(s)

Due to the time bound nature, this study was conducted only on a small sample size of the population. Treatment with mannitol therapy was not standardised and hence uniformity in administration of dosage was not maintained. Other co-morbidities such as infections, systemic illnesses, nephrotoxic drugs and administration of other drugs were not taken into consideration. The interval of measurement of electrolytes was not strictly standardised.

CONCLUSION(S)

The present study findings showed that low dose mannitol therapy of less than 1 gm/kg/day is relatively safe and does not produce clinically significant electrolyte disturbance or renal dysfunction in acute stroke patients. However, monitoring of serum sodium, potassium and renal function may be useful in patients with comorbidities such as diabetes and CKD.

Further studies with a larger study population with standardised administration of dosage of mannitol and interval of measurement of electrolytes, urea and creatinine would be needed to further elucidate the relationship.

Declaration: Part of this study was presented as an E-poster titled "Complications of mannitol therapy in patients with acute stroke-A prospective observational study" in European Academy of Neurology Virtual Congress held on 23-27th May 2020.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 19, 2020
- Manual Googling: May 12, 2020
- iThenticate Software: Jun 22, 2020 (10%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 18, 2020**
Date of Peer Review: **Apr 10, 2020**
Date of Acceptance: **May 13, 2020**
Date of Publishing: **Jul 01, 2020**