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ORIGINAL ARTICLE

Effect of intravenous administration of 20% Mannitol on optic nerve sheath diameter in patients with raised intracranial pressure

Shiva Poudel[1], M.D., Ankit Rimal[2], M.D., Ninadini Shrestha[1], M.D., Arjun Gurung[3], M.D., Anil Shrestha[1], M.D.

[1] Department of Anaesthesiology, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal;
[2] Department of Critical Care Medicine, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal;
[3] Department of Cardiothoracic and Vascular Anaesthesiology, Manmohan Cardiothoracic Vascular and Transplant Center, Maharajgunj, Kathmandu, Nepal

Corresponding author:
Dr. Shiva Poudel
M.D. Anaesthesiology
Tribhuvan University Teaching Hospital,
Maharajgunj, Kathmandu, Nepal
Email: rockaice@gmail.com

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ABSTRACT

Background and aims : Mannitol is commonly used to reduce elevated intracranial pressure (ICP) in patients with traumatic brain injury, intracranial hemorrhage and acute cerebrovascular accident. Optic nerve sheath diameter (ONSD) has high sensitivity and specificity in diagnosing raised ICP. This study aims to evaluate effect of Mannitol on ONSD in patients with raised ICP.

Methods : This was a prospective cohort observational study of adult patients receiving osmotherapy for increased ICP admitted to the ICU. Baseline ONSD (T1) was recorded bilaterally followed by administration of Mannitol. ONSD was remeasured bilaterally at 30 (T2), 60 (T3) and 120 (T4) minutes after completion of administration of mannitol. Peak inspiratory pressures and PEEP were recorded for patients on mechanical ventilation.

Results : Of the 40 patients included in the study, the mean age of patients was 54.03 ±19.15 years. Among them 26 were mechanically ventilated. Compared to the baseline values of 6.1 ± 0.74 mm, the mean ONSDs at T2, T3 and T4 were significantly lower after administration of 20% Mannitol with all p values < 0.001. A statistically significant correlation between change in ONSD (ΔONSD) at each time point and the dose of Mannitol administered was observed.

Conclusion : ONSD can be used for monitoring effectiveness of osmotherapy on a point-of-care basis in patients with elevated ICP.

Keywords: *mannitol, osmotherapy, ONSD, raised ICP*

INTRODUCTION

Osmotherapy with mannitol to reduce the intracranial pressure (ICP) in patients with elevated ICP is a common practice. The effect of mannitol on ICP can be monitored by various invasive and non-invasive methods with variable sensitivity and specificity. Optic nerve sheath diameter (ONSD) has been shown to have high sensitivity and specificity in diagnosing raised ICP based on its correlation with invasively measured ICP. However, its clinical applicability to monitor changes brought about by osmotherapy remain to be studied. Our study aims to explore the utility of this noble modality to evaluate ICP changes during osmotherapy.

Raised intracranial pressure is a common complication in patients with traumatic brain injury (TBI), intracranial hemorrhage, intracranial tumors and ischemic stroke.[1] Prompt diagnosis and treatment of elevated intracranial pressure is one of the primary cornerstones in the management of these conditions. The incidence of elevated ICP is more than 50% and ranging as high as 80% in patients with TBI.[2,3] The fundamental goal of management in TBI is based on managing the ICP and maintaining an adequate CPP in the background of an impaired cerebral autoregulation in order to prevent secondary insults to the injured brain. Similarly, incidence of raised intracranial pressure in patients with intracranial hemorrhage ranges from 36% to 80%.[4] Malignant cerebral edema leading to raised intracranial pressure is a major cause of adverse outcome in patients with acute ischemic stroke with an incidence of 10-20%.[3]

The current standard of care for diagnosing raised ICP involves intracranial placement of a variety of invasive monitoring devices. These techniques have the distinct benefit of providing continuous, real-time monitoring, with some allowing therapeutic interventions as well. They, however, are generally limited to patients in a neurocritical care or intensive care units.[3,4] Disadvantages of invasive ICP monitoring include the risk of hemorrhage, infection, catheter misplacement and the requirement of trained individuals to place the device, monitor, interpret findings and provide targeted therapy.

Various non-invasive techniques have been explored to avoid inherent disadvantages of invasive procedure and improve early detection of an elevated ICP, with variable results. The opportunity to diagnose a raised ICP earlier using an appropriate non-invasive technique makes the applicability of such a method more valuable. However, despite several promising advances, no single non-invasive method of assessing ICP has been accurate enough as a quantitative measure of ICP to replace invasive monitoring.[5,6]

Recent advances in application of ultrasonography, image quality and point-of-care techniques have stimulated the use of this modality as a diagnostic and monitoring utility.[6,7] The benefit of having a portable, cost-effective, quick modality in a resource-limited environment makes the prospect of its utility more attractive. Among the sonographic techniques utilized for measurement of ICP, ONSD and Trans-cranial Doppler (TCD) have been shown to have high positive and negative predictive values.[8]

The optic nerve has a length of about 40 – 50 mm, and an average diameter of about 4 mm.[5] This nerve is a white matter tract of the central nervous system that originates from within the diencephalon. The optic nerve is surrounded by CSF within the subarachnoid space and enveloped by the nerve sheath, which is a continuation of the intracranial dura mater. The subarachnoid space surrounding the optic nerve is a heterogeneous, cul de sac, which holds about 0.1 ml of CSF.

The sheath surrounding the optic nerve is made up of three layers, which are in continuity with the leptomeninges of the brain. The two layers of the dura are attached within the optic canal, but split at the orbital end of the canal, with the outer layer forming the orbital periosteum and the inner layer forming the dural optic nerve sheath.

An increase in ICP results in an increase in CSF within the space surrounding the optic nerve leading to expansion of the nerve sheath. The region of the nerve sheath located 3 mm posterior to the lamina cribrosa of the retina is considered the most distensible and recommended as the most consistent region to acquire the ONSD measurement.[9] Changes in the ONSD can be visualized using images from ultrasound, MRI and CT scans. Several studies have demonstrated a strong association between distension of the ONSD and an increase in ICP.[10,11]

Mannitol is a naturally occurring sugar alcohol used clinically as an osmotic diuretic. Various theories and mechanisms have described the effects produced by mannitol in the CNS and other organs. According to the osmotic theory, at the higher end of clinically relevant doses, mannitol generates a substantial blood-brain osmotic gradient and exerts at least some of its ICP lowering effect by direct removal of water from the parenchyma.[12] Mannitol is believed to induce a decrease in total cerebral blood volume not only by decreasing hematocrit, but by decreasing the volume, rigidity and cohesiveness of RBC membranes and thereby decreasing mechanical resistance to passage through microvasculature.[12,13] Through its osmotic diuretic effect, it contributes to a reduction in the total circulating blood volume.[12,13]

A rebound elevation in the ICP is seen sometimes following accumulation of osmotically active particles in the brain parenchyma with prolonged use of mannitol.[12]

This study was designed to evaluate the effect of intravenous administration of 20% mannitol on the ONSD in patients with raised ICP. In order to do so, we compared the changes in the ONSD from baseline and at 30, 60 and 120 minutes. Additionally, we compared and correlated the changes in between right and left eye, in relation to the dose of mannitol and the mean arterial pressure (MAP). Also compared were the changes in ONSD in patients on mechanical ventilation against those not on mechanical ventilation. We hypothesized that serial ONSD monitoring with a cut-off value of 5.0 mm can reflect changes following IV administration of 20% mannitol in patients with raised ICP.

METHODS

Study Design and Setting

The was a prospective cohort observational study of patients receiving osmotherapy for increased ICP presenting to the multidisciplinary Intensive Care Unit (ICU) of Tribhuvan University Teaching Hospital. The study was conducted following approval by the Institutional Review Committee.

Participants

Adult patients more than 18 years of age, diagnosed with traumatic brain injury or intracranial hemorrhage or acute stroke with a mean optic nerve sheath diameter of more than 5mm and receiving osmotherapy with 20% mannitol were included in the study.

Patients with a history of ocular surgery, ocular pathology at baseline and who had undergone a decompressive cranial surgery were excluded from the study.

The IRC waived the requirement for written informed consent given the observational nature of the study. A verbal informed consent, however, was taken from the legal guardian.

Variables

Demographic parameters and diagnosis were documented. The baseline (T1) ONSD measurement of the right eye, left eye and MAP were recorded. The dose of 20% mannitol was noted. In patients on mechanical ventilation, the peak inspiratory pressure (PIP) and PEEP were documented. Thereafter, the prescribed dose of 20% mannitol was administered intravenously via a dedicated line over 20 minutes.

ONSD measurements of both eyes at 30 (T2), 60 (T3) and 120 (T4) minutes after the completion of administration of the prescribed dose of 20% mannitol were recorded along with the corresponding MAP at each examination. Each measurement of ONSD was performed by a single investigator using a 6-10 Hz linear array USG probe (SonoSite M-Turbo®) with the head of the patient elevated at 30 degrees, in supine position. A transparent dressing and adequate jelly coupling the ultrasound probe was placed over both eyes. Measures were taken to ensure hygiene and safety during all examinations.

Sample size determination

The sample size was determined based on a previous study which showed a mean difference (δ) and standard deviation of difference (σ) of ONSD at baseline and 60 minutes to be 0.24 and 0.49 respectively. In order to detect a significant difference in ONSD at T1 and T3 with a power of 80% (β=0.2) at a significance level of $p < 0.05$ ($\alpha = 0.05$), the minimal sample size required was calculated to be 35. A sample size of 40 patients was taken to account for an assumed dropout of 10%.

RESULTS

A total of 48 patients admitted to the ICU of TUTH were screened for eligibility and 40 patients were enrolled as they fulfilled the inclusion criteria. The flow of participants in the study is shown in Figure 1.

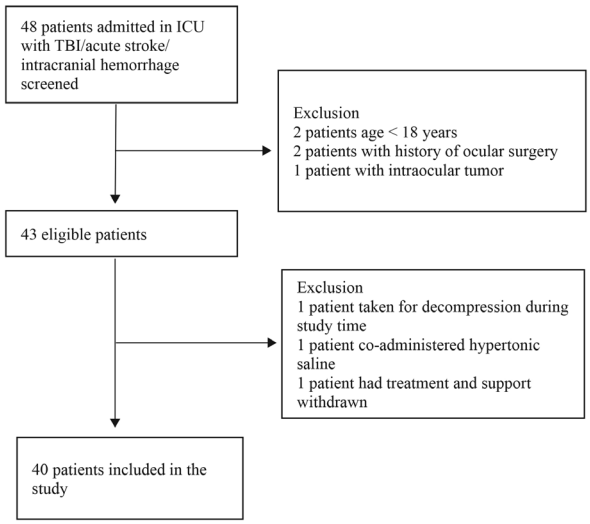

Figure 1: Flow of patients in the study

Baseline characteristics along with the dose of mannitol are described in Table 1. Table 2 shows the ONSD values and MAP values at baseline (T1), 30 (T2), 60 (T3) and 120 (T4) minutes. Compared to the baseline values of 6.1 ± 0.74 mm, the mean ONSDs at T2, T3 and T4 were significantly lower after administration of 20% mannitol with all p values < 0.001. The mean ONSD was lowest at T3, 60 minutes after administration of 20% mannitol.

Table 1. Baseline characteristics of patients, data presented as mean ± SD or number of patients.

Variables	Values
Age	54.03 ±19.15
Sex (M/F)	25 (62.5%) / 15 (37.5%)
Weight (kgs)	62.58 ±11.30
BMI (kg/m^2)	23.28 ± 3.31
Mechanically ventilated/non-ventilated	26/14
Dose of 20% mannitol (gm/kg)	0.5 ± 0.13

Table 2 : ONSD values at different time points, p value < 0.05 considered statistically significant compared to baseline. Data presented as mean ± SD

Variables	T1 (baseline)	T2 (30 minutes)	T3 (60 minutes)	T4 (120 minutes)
MAP (mmHg)	96.4±12.7	101.5 (p < 0.001)	104.3 (p <0.05)	97.7 (p > 0.05)
RT ONSD (mm)	6.13 ± 0.74	5.72 ± 0.73 (p < 0.001)	5.54 ± 0.71 (p < 0.001)	5.83 ± 0.72 (p < 0.001)
LT ONSD (mm)	6.08 ± 0.77	5.63 ± 0.75 (p < 0.001)	5.49 ± 0.74 (p < 0.001)	5.82 ± 0.77 (p < 0.001)
Mean ONSD (mm)	6.10 ± 0.74	5.68 ± 0.73 (p < 0.001)	5.51 ± 0.71 (p < 0.001)	5.82 ± 0.73 (p < 0.001)

Comparison of right ONSD and left ONSDs showed no statistically significant difference at any point of the study time as shown in Figure 2. Compared to the baseline value, mean arterial pressure was significantly raised at 30 minutes (T2) and 60 minutes (T3). Though significantly lowered compared to T3 (p < 0.05), MAP at 120 minutes (T4) was non-significantly changed while compared to baseline (T1). Analysis showed no statistically significant correlation between MAP and change in ONSD at any time point in the study.

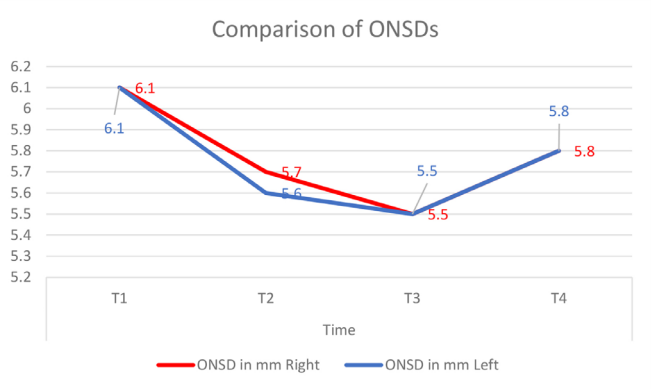

Figure 2: Comparison of ONSD at different time points

There was a statistically significant correlation between change in ONSD (ΔONSD) at each time point to the dose of mannitol administered. ΔONSD was positively correlated with dose of mannitol at 30 minutes (Pearson's correlation, r= 0.359, p < 0.05), 60 minutes (r= 0.424, p < 0.01) and 120 minutes (r= 0.582, p < 0.001) (Figure 3).

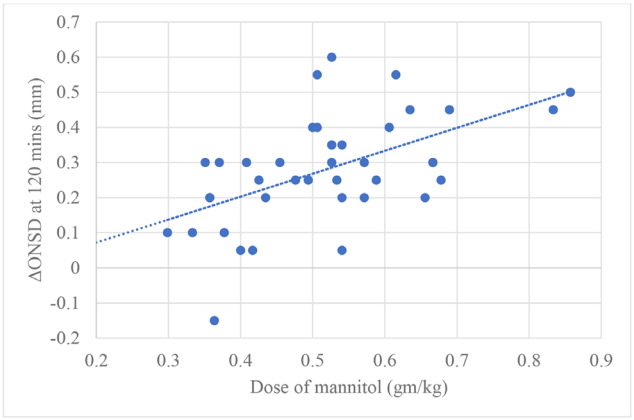

Figure 3: Correlation between dose of mannitol to ΔONSD at 120 minutes

DISCUSSION

Our study showed significant changes in ONSD values after administration of mannitol at 30, 60 and 120 minutes from baseline (6.1 ± 0.7mm) with the highest changes at 60 minutes (5.51 ± 0.7 mm, p < 0.001).

In congruity with our study, a study by Jun et al. observed similar changes in ONSD after administration of mannitol to patients undergoing robot assisted laparoscopic prostatectomy.[14] The highest changes occurred at 90 minutes, well under the time to peak action of mannitol. However, the rise in ICP among these patients was attributed to positioning and establishment of pneumo-peritoneum under anaesthesia rather than TBI, intracranial hemorrhage or acute stroke.

Similar changes were shown in the study by Launey et al. where changes in ONSD were compared to invasively measured ICP prior to and after osmotherapy with 20% mannitol in 13 cohorts similar to our study population.[10] There was a significant decrease in ONSD values after only 20 minutes following administration of 20% mannitol. On the basis of the correlation established by this study between ONSD and invasively measured ICP (R2 = 0.54, p < 0.002) and several other studies it can be assumed that the changes in ONSD in our study were reflective of the concomitant change in ICP brought about by the administration of 20% mannitol.[11,15]

Another study has also studied the changes in ONSD brought about by osmotherapy.[16] Though this study aimed at comparing change in ONSD with the use of mannitol and hypertonic saline at various time points different than those used in our studies, it found significant decrease in ONSD, reflecting a reduction in ICP.

Our study showed a statistically significant positive correlation between dose of mannitol administered and ΔONSD at 30 minutes (r = 0.359, p = 0.023) 60 minutes (r = 0.424, p = 0.006) and at 120 minutes (r = 0.582, p < 0.001).

In a subgroup analysis, variation of the dose of mannitol was studied and an analysis on change in ONSD (ΔONSD) in correlation with the dose administered was done in

two groups with a cut-off value of 0.5gm/kg. ΔONSD was significantly higher among patients in the dose > 0.5gm/kg group at 60 minutes ($p < 0.05$) and 120 minutes ($p < 0.001$). On linear regression analysis a significant positive correlation was found between change in mannitol ONSD and dose of mannitol. There are no studies directly comparing these variables. However, taking the strong correlation between ICP and ONSD into consideration, our results are similar to the results of the study by Sorani et al.[17] In their study they explored the dose-response relation in patients with TBI and found a linear relation between dose of mannitol and change in ICP indicating that an additional 7 g of mannitol (0.1 g/kg for 70-kg person) achieves an additional reduction of approximately 1.0 mmHg in ICP. Though our study did not explore such parameters, a higher degree of decrease in ONSD values were sustained for a longer period of time in patients with doses higher than 0.5 mg/kg as compared to those receiving lower doses.

A meta-analysis analyzed 18 studies which explored the correlation between the dose of mannitol and changes in ICP.[18] The aggregated data analysis showed that mannitol invariably reduced ICP, however the quantitative relationship between dose and response was inconsistent. This inconsistency was credited to the variations among protocols and patients included in those studies. Similar to the studies included in the meta-analysis, a weak linear dose-response relation was found in our study. This highlights the need for a consensus of methods and results required to determine this relationship. However, it can be concluded that sonographic measurement of ONSD is sensitive to detect the subtle changes attributed to the dose-response relationship.

Although differences were present among individual patients, our study did not find significant difference in left and right eye measurements of mean ONSD at baseline or at any point of time after administration of mannitol. Significant difference between right and left eye ONSD were noted in a study by Skoloudik et al.[19] They reported a statistically significant difference in ONSD on the side ipsilateral to the lesion among 31 patients presenting in the hyperacute phase of intracranial hemorrhage. The findings in our study can be attributed to the heterogenous pathology involved and timing of evaluation and is consistent with various other studies.[10,11,20]

Our study did not find a significant correlation between the MAP and ONSD. Correlation analysis was also performed between changes in MAP and ONSD which showed no significant statistical correlation (p value > 0.05 at every time point). Our study result is in concordance with the findings of various studies where investigators have failed to show any significant correlation between MAP (ΔMAP) and ONSD (ΔONSD) or ICP. [10,14,21]

A subgroup analysis in our study compared the changes in ONSD between mechanically ventilated patients and those not on mechanical ventilation. Comparison of means using the independent t-test showed no significant difference in ONSD among these groups. Change in ONSD in relation to PEEP/PIP was not found to be significant at any point ($p > 0.05$ at every time point).

In a study performed on 33 patients with TBI by Cooper et al., the application of a PEEP of 10 cm H2O raised ICP from a baseline of 13.2 ± 7.7 mmHg to 14.5 ± 7.5 mmHg ($p < 0.005$).[22] However, this rise in ICP was considered to be clinically non-significant. Similar result was obtained among a pediatric patient cohort with TBI in a study by Khandelwal et al.[23] Application of PEEP ranging from 0-3 cm of H2O was not associated with any rise in ICP. But when PEEP was raised from 3 to 5 cm H2O there was a statistically significant but clinically non-significant rise in ICP.

Similarly, in a study by Bala et al. which evaluated the effects of variable PEEP and EtCO2 in non-brain injured patients undergoing surgery under general anaesthesia, a statistically significant increase in ONSD following stepwise increment in PEEP from 0 cm H_2O at baseline to 8, 12 and 15 cm H_2O was found.[24]

Our study did not detect a significant difference in change in ONSD in mechanically ventilated patients with various values of PEEP when compared to non-ventilated patients. This can be attributed to use of minimal PEEP (median: 5 cm H_2O) among most patients in our study. Further studies with adequate power will be required to establish a relation between PEEP and its effects on ONSD.

There are certain limitations of our study. The decision to use mannitol and the dose were decided on the judgment of raised ICP by the treating physician rather than with the use of invasive monitoring. Another limitation is attributable to the inherent limitation of using the ONSD to detect an elevation in ICP. It is an operator dependent entity but, in our study, only one investigator was responsible for all measurements which would have circumvented this limitation to a certain degree. Measurements of serum osmolality was not done.

CONCLUSION

In patients with an acutely elevated ICP, administration of 20% mannitol caused a significant change in the sonographically measured ONSD which can be correlated with concomitant change in ICP among patients with raised ICP. ONSD can be used for monitoring such changes and effectiveness of osmotherapy on a point of care basis. However, larger studies are warranted to validate the use of ONSD as a reliable surrogate to invasively monitored ICP.

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