



# Comparison of intermittent versus continuous infusion of 3% hypertonic saline on intracranial pressure in traumatic brain injury using ultrasound assessment of optic nerve sheath

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## ABSTRACT

**Background:** The employment of hypertonic saline (HTS) in intracranial hypertension treatment has been effective when administered as a continuous infusion or bolus. However, the best route and concentration are undecided because of insufficient randomized controlled trials. This study aims to function the optic nerve sheath diameter (ONSD) ultrasonographic measurements to compare the effectiveness of 3% HTS continuous infusion and intermittent boluses in reducing elevated intracranial pressure (ICP) in traumatic brain injuries (TBIs).

**Methods:** This randomized study comprised 50 patients with TBI. In all patients examined by ultrasound, we employed a cutoff value of 5.5 mm for the ONSD to predict an increase in ICP of >20 mmHg. Patients with elevated ICP were divided into two groups: group A received continuous 3% HTS infusion (0.5 mL/kg/h), and group B received intermittent 3% HTS boluses (3 mL/kg). The primary endpoint was the ONSD at 48 h. The secondary outcomes included serum Na and serum K at 6, 12, 24, 48, and 72 h.

**Results:** The ONSDs in the continuous HTS infusion and intermittent bolus groups decreased significantly and steadily, with no significant variance between the two groups at 48 h ( $P = 0.449$ ). However, 3% HTS intermittent boluses caused a faster growth in sodium concentration at 6 and 12 h with noteworthy differences compared with continuous infusion ( $P = 0.013$  and  $0.001$ , respectively).

**Conclusions:** There were no differences in ONSD ultrasonographic values 48 h after treatment. Moreover, 3% HTS intermittent boluses caused an increase in sodium concentration at 6 and 12 h.

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## KEYWORDS

Hypertonic saline solution; intracranial hypertension; optic nerve; traumatic brain injury; ultrasonography

## 1. Introduction

In the developing world, traumatic brain injury (TBI) is one of the principal causes of death in young generations. The pathophysiology of TBI can be classified into primary and secondary injuries. In treating serious TBI, preventing secondary brain damage associated with elevated intracranial pressure (ICP) is crucial. One of the most common symptoms of several traumatic injuries and diseases is elevated ICP. Increased ICP to  $\geq 20$  mmHg can diminish brain perfusion, poor neurological outcomes, and even death [1,2].

There are numerous methods of adjusting ICP. Hyperosmolar therapy is the main pharmacological treatment for severe TBI. In controlling of elevated ICP after severe TBI, hypertonic solutions, including mannitol and hypertonic saline (HTS), are recommended [3].

They provide therapeutic benefits along with a wide therapeutic margin. ICP reduction has been demonstrated with both mannitol and HTS, although there is evidence that HTS has a stronger and longer-lasting effect in lowering ICP [4].

Mannitol is widely employed as a first-line agent, though numerous concerns are raised as mannitol might deliver hypotension. Because of the increased serum osmolality, hypotension is inherently noticed in patients with hypovolemia, rebound elevation of ICP, and renal injury [5].

Consequently, HTS has recently gained popularity as an alternative to mannitol and is more effective in lowering ICP than mannitol in patients with TBI. HTS reduces ICP by drawing fluid from the interstitial space and improving intracranial compliance, notably by preventing the accumulation of extracellular osmolytes in the brain that occurs when the blood-brain barrier is disrupted [6].

HTS is efficacious in treating elevated ICP when administered as a continuous infusion or bolus. However, the best route and concentration are uncertain due to a lack of randomized controlled trials.

ICP monitoring can be performed in both invasive and noninvasive methods. Clinicians have discovered several noninvasive approaches used as surrogates for invasive ICP measurement techniques, such as measuring the optic nerve sheath diameter (ONSD) [7].

Ocular ultrasound (US) can be used to assess ICP by measuring the ONSD before developing papilledema, which can consume several hours. The optic nerve sheath is continuous with the dura mater. The subarachnoid compartment of the optic nerve communicates with that of the brain; therefore, any increase in ICP causes optic nerve sheath expansion in the subarachnoid space around the optic nerve. The use of bedside US to measure the ONSD is gaining traction as a noninvasive technique to determine elevated ICP. ONSD assessment correlates with alternative observations of elevated ICP, such as clinical and radiological findings indicative of increased ICP, as noted in previous literature. An enlarged ONSD is highly correlated with direct ICP measurement with high specificity and sensitivity of >90% [8–10].

This study compares the effectiveness of continuous infusion of 3% HTS and intermittent boluses in reducing increased ICP in TBIs using ultrasonographic measurements of ONSD.

## 2. Materials and methods

### 2.1. Study population

This prospective, double-blind study was performed from December 2020 to February 2022 at the neurosurgery intensive care unit (N-ICU) at University Hospital after receiving the Research Ethical Committee of the Faculty of Medicine Cairo University's approval according to the ethical standards of the latest revision of the Declaration of Helsinki with registration at ClinicalTrials.gov.

This study's objective was clarified to all patients' legal representatives in full detail, along with the details of the management protocol. Written informed consent was signed before enrollment in this study, which was designed to recruit 50 patients who had isolated TBI (defined as an abbreviated injury score [AIS] for the head of  $\geq 3$  without significant injury in other regions defined as an AIS of  $> 2$ ), from both genders, between 18 and 60 years of age, with a Glasgow Coma Scale (GCS) score between 4 and 12, and had a mean ONSD of  $\geq 5.5$  mm for three times of measurement to predict an increase in ICP of  $> 20$  mmHg. Patients were excluded from the study if they had contraindications to HTS (pregnancy, renal failure, coagulopathy, and cardiac dysfunction), a GCS score of  $> 12$  or 3, a serum sodium [Na] level of  $\geq 150$  mmol/L at admission to the ICU, hypotension that necessitates the use of vasopressors to maintain the mean arterial pressure (MAP) of  $> 60$  mmHg, and age of  $< 18$  or  $> 60$  years. Patients with patients' legal representatives who refused to sign the consent or had multiorgan affection were also excluded. Before the beginning of the study, 50 opaque envelopes had been prepared and numbered sequentially.

A computer-generated random-number table assigned each consecutive envelope to receive a sheet indicating either continuous HTS infusion group (group A) or intermittent bolus group

(group B). Envelopes were then sealed. The sealed envelopes were opened sequentially throughout the study when a patient fulfilled the inclusion criteria.

Five physicians were involved in the research: one physician responsible for performing the randomization procedure, two physicians experienced in performing ONSD measurement, and two attending physicians assigned for data collection. Meanwhile, ONSD measurement data were not sent to the attending physician, thus preventing these results from affecting the clinical judgment. The physicians who performed US examinations were not aware of patient allocation.

#### Management protocol

After full resuscitation, all patients were admitted to the N-ICU, a complete physical examination with a comprehensive neurological examination at the emergency department (ED) by the neurologist during the primary survey. Examination results and the GCS scores were recorded in the local trauma database. Intubation was performed if patients had a GCS score of  $< 9$ . In addition, all patients presenting with head trauma underwent head computed tomography (CT) within 30 min after arrival at the ED. An experienced neuroradiologist evaluated the CT results in every patient.

On admission to N-ICU, the baseline characteristic data of patients were collected from the medical records of the local trauma database (e.g., age, sex, weight, body mass index [BMI], comorbidity, Injury Severity Score, AIS, and injury diagnosis). Hemodynamics (mean heart rate [HR], MAP, temperature, and oxygen saturation [SpO<sub>2</sub>]) were then evaluated, and routine laboratory tests (complete blood count, Na, potassium [K], serum urea, serum creatinine, alanine transaminase, aspartate transaminase, international normalized ratio, prothrombin concentration, lactate, bilirubin, plasma osmolarity, and blood gases) were performed. A central venous catheter was inserted. Additionally, at this time, the GCS scores, Simplified Acute Physiology Score (SAPS II), and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were measured.

All patients received standard ICU care: the MAP was maintained at  $> 90$  mmHg, and SpO<sub>2</sub> was maintained at  $> 95\%$ . With paracetamol and/or active cooling, the temperature was kept at  $< 37.5^\circ\text{C}$ . The blood sugar level was maintained at  $< 180$  mg/dl. The head of the bed was elevated to  $30^\circ$ – $45^\circ$  with the patient's head and neck in a neutral position. Agitation was avoided by adequate sedation with fentanyl. Prophylactic broad-spectrum antibiotics and antiseizure medications, such as phenytoin (5 mg/kg/day) or

valproate (15 mg/kg/day), should be administered to all patients for at least a week. Others included early feeding with adequate caloric intake (30–50 kcal/kg/day) and protein intake of 2 g/kg/day, unless enteral feeding (EN) is contraindicated or cannot tolerate, in which case the parenteral nutrition would be substituted within 24 to 48 hours. If the hemoglobin concentration is <10 g/dL within the first 48 h after an injury, the packed RBCs are required with deep venous thrombosis prophylaxis, which can be pharmacological or nonpharmacological. Subsequently, patients underwent US examinations to assess the ONSD.

### 3. US measurement of the ONSD

US-ONSD measurements were performed after admitting the patient to the ICU by an experienced physician. Before the study, the physician was intensely trained by performing ONSD measurements no less than 20 times. These were performed on a high-frequency linear probe (5–10 MHz) of the US machine (Mindray®, China) linear US probe. It was calibrated to provide a suitable angle for viewing it, and the depth was set to 5–6 cm. The probe was covered with gloves easily available with gel placed in it to prevent gel contact with the eyes, which prohibited any reaction or possible infection within the eye. The probe was gently positioned over the closed eye, over the patient's upper eyelid in a supine position, with the head end elevated at 20°–30° in the axial plane to avoid pressing the eyeball. The ONSD appeared as a linear, well-defined hypoechoic region. Almost 3 mm behind the papilla, which suggested the best dispensability, maximum US contrast, and high reproducibility was the point of measurement of the outer limit of the hyperechoic line using electronic calipers. The right and left ONSDs were measured in the transverse direction, with the probe rotated slightly to visualize the optic nerve better. The ONSD was measured three times in each eye, and the mean ONSD was calculated [10].

We used a cutoff value of 5.5 mm for the ONSD to predict an increase in ICP of >20 mmHg. Patients with elevated ICP were separated into two groups. Group A received general care plus 3% HTS continuous infusion at a dose of 0.5 mL/kg/h intravenously over 48 h through a central venous catheter. Group B received standard care and 3% HTS intermittent boluses at a 3 mL/kg dose every 6 h over 30 min for 48 h via a central venous catheter. The target serum Na concentration was between 150 and 159 mmol/L, and serum osmolarity of >320 mOsm/kg was identified as the target therapeutic level. When the Na level in the blood reached >160 mmol/L, HTS administration was stopped, and the patient was excluded.

### 4. Data collection

The ONSD defined the primary outcome as an assessment tool for ICP after 48 h. The secondary outcomes included a rebound increase in ICP after the discontinuation of HTS at 72 h. Moreover, the ultrasonographic measurements of the ONSD were obtained at 6, 12, 24, and 72 h, whereas the serum Na and serum K levels, plasma osmolarity, and GCS scores were obtained at 6, 12, 24, 48, and 72 h. The SAPS II and APACHE II scores were evaluated after 48 h of admission.

### 5. Statistical analysis

Statistical analyses were performed using SPSS version 25.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive analysis was performed for qualitative data using frequency and percentage; for quantitative data consistent with the normal distribution, the mean and SD were used for analysis; for data that did not meet the criteria for a normal distribution, the analysis involved the median with IQR. The chi-square or Fisher's exact test evaluated categorical variables with normally distributed data. Continuous variables with abnormal distribution were compared using the Mann–Whitney U test. A P-value of <0.05 indicated statistical significance.

### 6. Sample size

The sample size was calculated using the G\*Power program (version 3.1.9.2, Universität Düsseldorf, Düsseldorf, Germany) to measure the ONSD after 48 h, as an assessment tool for ICP as it was the primary outcome in the current study based on a previous study [11] reporting that the ONSD after 48 h following intermittent boluses of 3% HTS in patients with TBI was  $4.5 \pm 0.6$ . If a difference of 10% in the ONSD following 3% HTS continuous infusion was clinically significant, a minimal sample size of 21 patients in each group was required with a 90% power at the  $\alpha = 0.05$  level. The number was increased to 50 patients (25 per group) to compensate for possible dropouts.

### 7. Results

In the current study, 62 patients were assessed for eligibility. We excluded six patients who met the exclusion criteria or declined to participate. Only 56 patients with TBIs were enrolled in the study and randomly assigned to one of two groups: continuous infusion (group A) and intermittent bolus (group B). Group A received a continuous infusion of 3% HTS ( $n = 27$ ), whereas group B received intermittent boluses of 3% HTS ( $n = 29$ ). Two patients in group A were dropped

from the study because of loss of follow-up and discontinuation of intervention, whereas four patients in group B were dropped for the same reasons. Only 50 patients completed the study, and their data were analyzed as shown in the Consolidated Standards of Reporting Trials flowchart (Figure 1). There was no statistically significant difference between the two groups regarding age, BMI, sex, ISS, AIS head, mode of injury, predominant lesion on CT scan, ONSD, and GCS, SAPS II, or APACHE II scores on admission (Table 1).

On admission, the mean GCS score for the patients who received continuous infusion (group A) was 7 (3), and that for the patients who received intermittent boluses (group B) was 8 (5) ( $P = 0.567$ ). In the examination of the effect of both groups on GCS change after 48 h, it was noted that the mean GCS scores were 8 (6) for group A and 7 (6) for group B. There was no statistically significant difference between both study groups regarding GCS on admission and 12, 24, and 48 h after treatment (Figure 2) ( $P = 0.567$ ,  $P = 0.412$ ,  $P = 0.708$ , and  $P = 0.681$ , respectively).

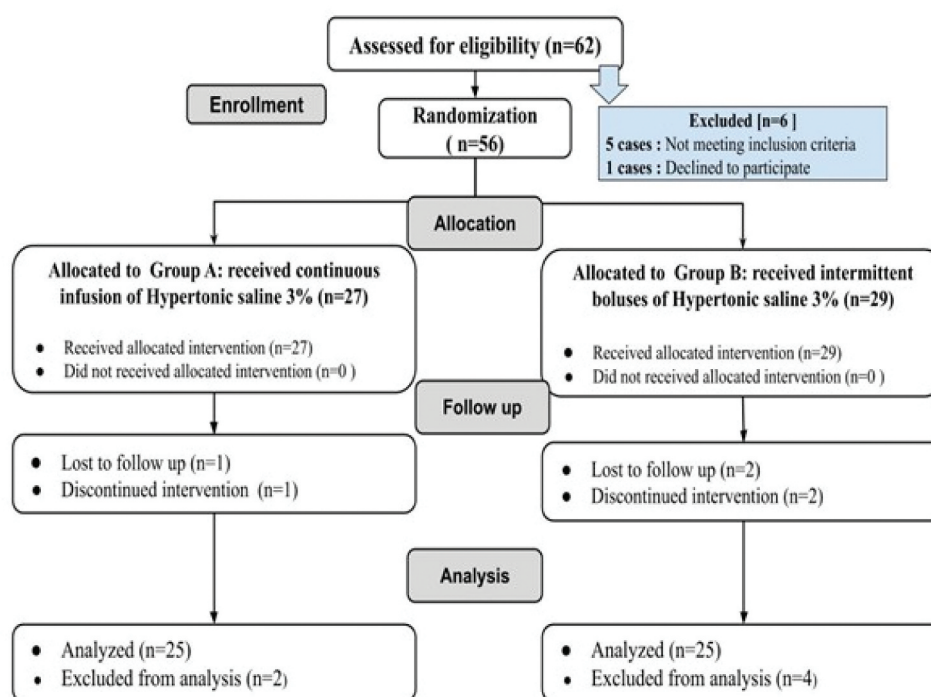


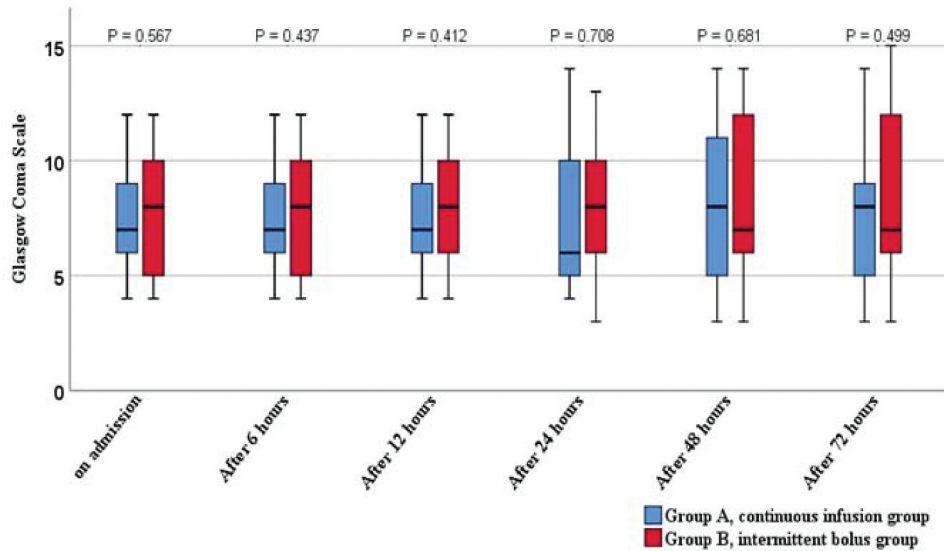
Figure 1. Consort flow diagram.

Table 1. Demographic and neurological condition data.

|                                     |                         | Group A<br>(n=25) | Group B<br>(n=25) | P-value |
|-------------------------------------|-------------------------|-------------------|-------------------|---------|
| Age (year)                          |                         | 39.6 ± 11.8       | 35.3 ± 10.8       | 0.186   |
| Sex                                 | Male / Female; n        | 16 / 9            | 15 / 10           | 0.771   |
| BMI (kg/m <sup>2</sup> )            |                         | 28.1 ± 4.8        | 27.3 ± 4.1        | 0.553   |
| ISS                                 |                         | 24 (9)            | 26 (7)            | 0.958   |
| AIS head                            |                         | 4 (1)             | 5 (1)             | 0.580   |
| Mode of injury: n(%)                | Road traffic accident   | 16 (64%)          | 17 (68%)          | 0.941   |
|                                     | Fall from height        | 6 (24%)           | 5 (20%)           |         |
|                                     | Other                   | 3(12%)            | 3 (12%)           |         |
| Initial GCS at hospital admission   |                         | 8 (2)             | 8 (4)             | 0.705   |
| Predominant lesion on CT scan: n(%) | Subarachnoid hemorrhage | 5(20%)            | 5(20%)            | 0.931   |
|                                     | Cerebral contusion      | 15(60%)           | 16(64%)           |         |
|                                     | Diffuse axonal injury   | 5(20%)            | 4(16%)            |         |
| GCS at ICU admission                |                         | 7 (3)             | 8 (5)             | 0.567   |
| Baseline SAPS II                    |                         | 33 (20)           | 28 (25)           | 0.628   |
| Baseline APACHE II                  |                         | 11 (4)            | 11 (4)            | 0.503   |
| Patient outcome ; n (%)             | Survival                | 19 (76%)          | 18 (72%)          | 0.747   |
|                                     | Death in ICU; n (%)     | 6 (24.0%)         | 7 (28.0%)         |         |
| GCS at time of discharge from ICU   |                         | 13 (1)            | 14 (2)            | 0.064   |
| ICU stay (day)                      |                         | 17.5 ± 11.8       | 17.2 ± 12.9       | 0.936   |

Data are presented as mean ± SD, No. (%) and median (IQR); Group A, continuous infusion group; Group B, intermittent boluses group; SD, standard deviation; BMI, body mass index; AIS, Abbreviated injury Score; ISS, injury severity score; GCS, Glasgow Coma Scale; SAPS II, Simplified Acute Physiology Score; APACHE II, Acute Physiology and Chronic Health Evaluation Score.





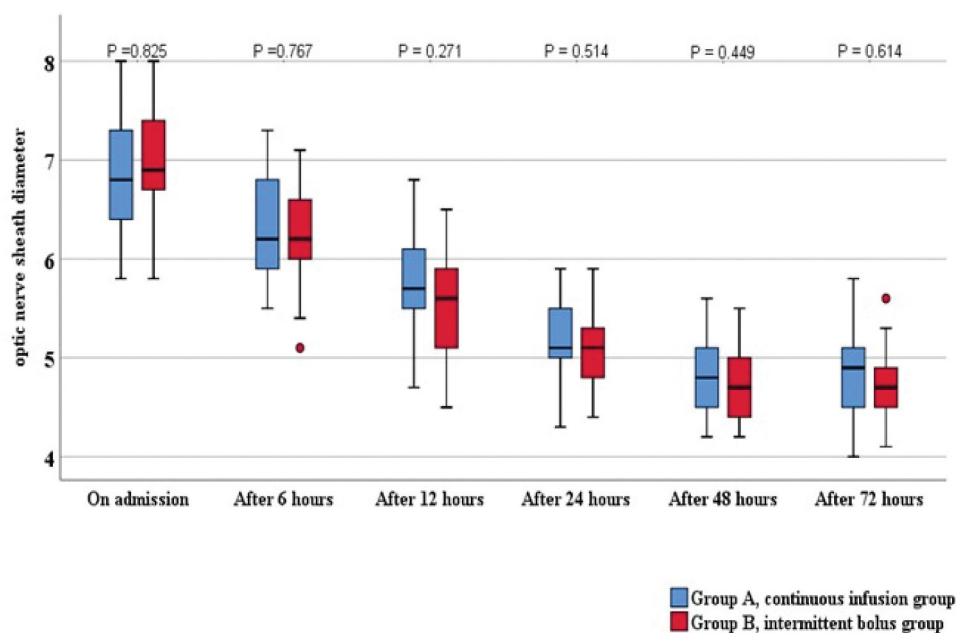
**Figure 2.** Boxplot chart for Glasgow coma scale between the two studied groups. Data are presented as medians, quartiles, and ranges.

At 6, 12, 24, and 48 h after treatment, the ultrasonographic ONSDs in the continuous infusion and intermittent bolus groups were statistically significantly lower than the admission values. There was no statistically significant difference between the two groups at 6, 12, 24, and 48 h. There was no statistically significant difference in the percentage decrease in ONSD ultrasonographic values at 48 h after treatment between the two groups. There was no rebound increase in the ONSDs at 72 h (Figure 3).

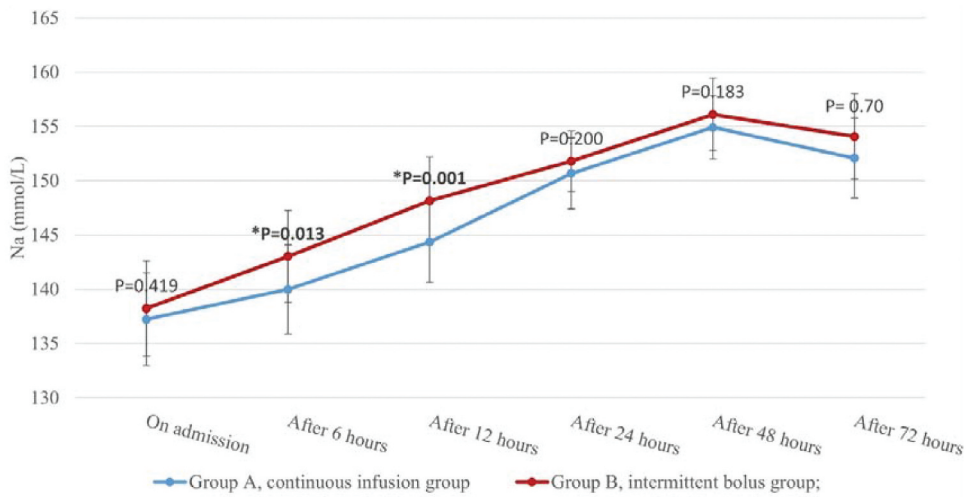
At 6, 12, 24, and 48 h after admission, the mean serum Na<sup>+</sup> values, and plasma osmolality in both groups statistically significantly increased at 6 and 12 h. Moreover, 3% saline intermittent boluses induced

a faster increase in Na concentration and plasma osmolality. Still, there were no significant differences in the percentage of decrease in ultrasonographic ONSDs between both groups ( $P = 0.767$  and  $P = 0.271$ ). There was no significant difference between both groups in reaching the target therapeutic level of serum Na and plasma osmolality at 24 and 48 h after treatment (Figures 4, 5).

The mean serum K<sup>+</sup> values were statistically significantly decreased from the admission values at 6, 12, 24, and 48 h in both study groups. There was no statistically significant difference between the two study groups in the entire study period ( $P = 0.08$ ,  $P = 0.102$ ,  $P = 0.091$ , and  $P = 0.242$ , respectively)



**Figure 3.** Boxplot chart for optic nerve sheath diameter between the two studied groups. Data are presented as medians, quartiles, and ranges.



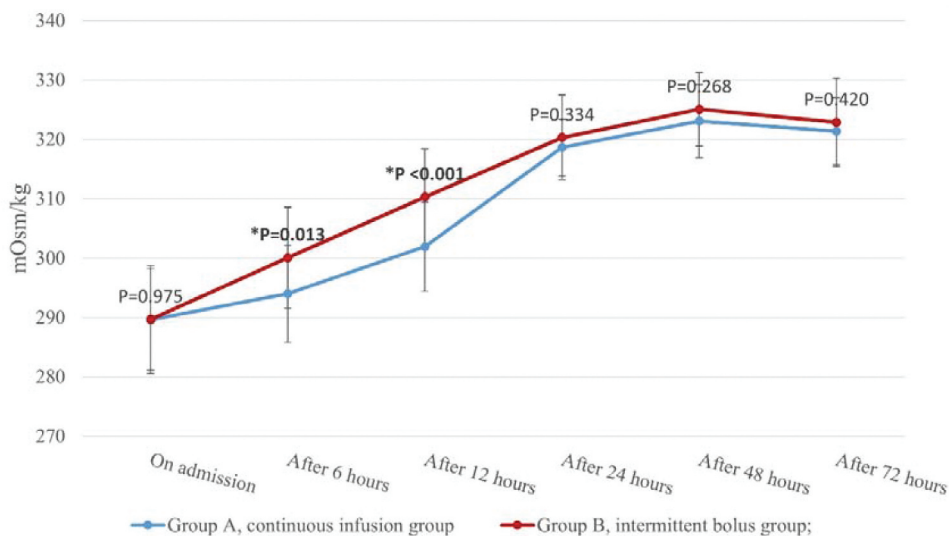
**Figure 4.** Comparison between the two studied groups regarding serum Na<sup>+</sup> level. Data are presented as mean ± SD.\*Statistically significantly higher in group B compared to group A.

(Figure 6). There was no statistically significant difference in the mean HR, MAP, body temperature, or SpO<sub>2</sub> values via study period between the two study groups. At the end of 48 h, there was no statistically significant difference between the two groups regarding clinical and biochemical outcomes (Table 1).

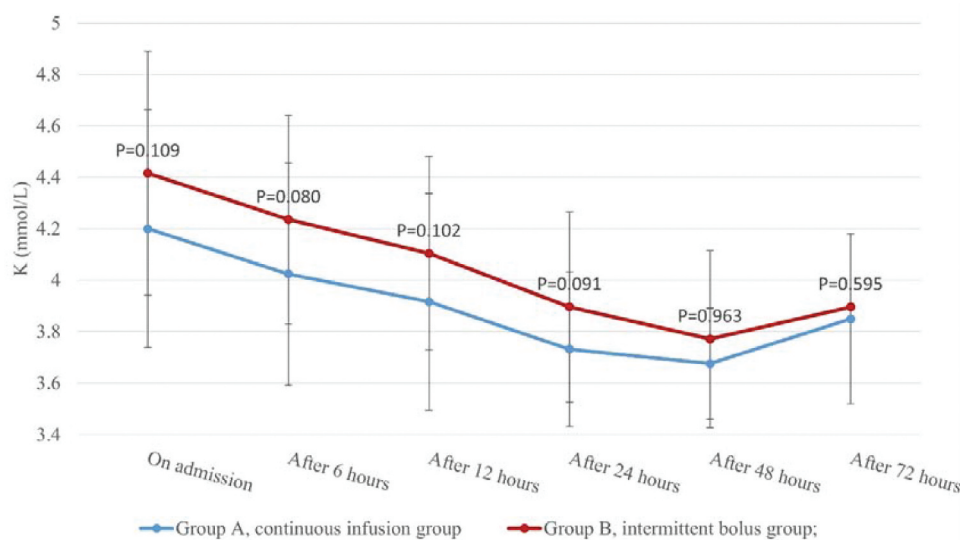
### 8. Discussion

This study showed that ultrasonographic ONSDs significantly and gradually decreased at 6, 12, 24, and 48 h after the start of HTS therapy in the two groups, with no significant difference in these values. There was no rebound increase in the ONSDs at 72 h.

Moreover, intermittent boluses of 3% saline induced a faster increase in Na concentration at 6 and 12 h, but no significant changes in the percentage of decrease in ultrasonographic ONSD were noted compared with the continuous infusion group. There was no significant difference between both groups in reaching the target therapeutic serum Na level and osmolality at 48 h after treatment. Both groups showed a substantial decrease in the serum K level at 6, 12, 24, and 48 h after treatment. Furthermore, no significant differences in the GCS scores were found at the end of treatment, and no significant hemodynamic changes were found between the two groups. Moreover, the method of HTS administration (continuous infusion or intermittent boluses) does not affect the length of ICU stay and ICU mortality rate.



**Figure 5.** Comparison between the two studied groups regarding plasma osmolality. Data are presented as mean ± SD.\*Statistically significantly higher in group B compared to group A.



**Figure 6.** Comparison between the two studied groups regarding serum K<sup>+</sup> level. Data are presented as mean  $\pm$  SD.

ICP is a significant indicator of neurological deterioration in patients with TBI, and post-traumatic ICH is related to poor neurological outcomes. An ICP of 5–15 mmHg is considered normal in healthy adults, and an ICP of >20 mmHg indicates intracranial hypertension in TBI [12].

Compared with the findings attained using an invasive intraparenchymal catheter, Soldatos et al. concluded that an ONSD of >5.7 mm can be exploited to noninvasively assess ICP with 74% sensitivity and 100% specificity [13]. Similarly, Toscano et al. demonstrated that the ONSD is a powerful marker of intracranial hypertension. It is simple to perform with minimal training. Regular ONSD daily monitoring may be benefit ICUs when invasive ICP monitoring is unavailable [14].

The use of osmotic agents is an important component of nonsurgical TBI management. HTS is used in osmotic therapy to treat both ICP and cerebral perfusion pressure (CPP) increase. The effectiveness is determined by the integrity of the blood-brain barrier, the reflection coefficient of the osmotic agent, and created osmotic gradient. The effect of lowering ICP is referred to its ability to reduce brain water content. HTS also causes a variation in blood viscosity, which is believed to impact cerebral blood flow by increasing CPP in previously hypoperfused areas [15,16]. Studies illustrated that repeated boluses of HTS reduce ICP and increase CPP [17]. In patients with TBI, continuous infusion of HTS has been shown to improve CPP by increasing natremia and osmolarity and decreasing intracranial hypertension [18–20].

This study realized that using ultrasound to measure the ONSD as an additional assessment tool has several benefits concerning early detection of elevated ICP and the prevention of associated hazards. Our findings are consistent with previous works. Fahmy et al. conducted a study that used US to measure the ONSD to compare the effectiveness of

3% HTS and 20% mannitol in reducing elevated ICP in severe TBIs. This study elucidated that both 3% HTS and 20% mannitol significantly decreased the ONSD from the admission values. Patients who received 3% HTS had a significant decrease in the ONSD than other patients who received 20% mannitol [11].

In the present study, there was an increase in Na concentration at 6 and 12 h after intermittent boluses of 3% saline, which matches observations made by Garrahy et al., who compared boluses versus continuous HTS infusion in the treatment of symptomatic hyponatremia. The result showed that the bolus of 3% saline resulted in a faster elevation of the serum Na level at 6 and 12 h. Still, there was no difference at 24 h [21].

Our results are similar to a study conducted by Wells et al. [22], who studied the association between serum Na and ICP using HTS to target mild hypernatremia in patients with TBI. These conclusions support the results of our study, which revealed that there were no significant differences in the percentage of decrease in the ultrasonographic ONSDs concomitant with a rapid elevation of the serum Na level in the intermittent bolus group compared with that in the continuous infusion group at 6 and 12 h after HTS treatment.

Furthermore, the results of this study are similar to the findings of a retrospective study carried out by Roquilly et al., who found that after discontinuing the continuous HTS infusion, there was no rebound ICP elevation. However, this study only assessed a rebound increase in ICP in the continuous HTS infusion group [18].

The findings of this study coincide with the observations of Rozet et al., who compared the effect of mannitol and HTS on brain relaxation and electrolyte balance. The result reveals the HTS induced a 6-h increase in blood Na level and acute yet transient hypokalemia. Hypokalemia

can occur with HTS because Na is reabsorbed in exchange for K during HTS therapy to maintain the osmotic gradients needed for urinary concentration [17].

With all these previous studies, the current study may be considered the first prospective, randomized study that compared the effectiveness of 3% HTS continuous infusion and intermittent boluses in lowering elevated ICP in TBIs using ONSD ultrasonographic measurements. Although the study met its objectives, it has some limitations. Our analysis had a 6-month time limit, one of its drawbacks. Another limitation is that our study only focused on TBI as a cause of increased ICP, excluding other factors such as ischemic stroke and tumors, which could lead to different outcomes if studied. Another limitation related to the study is its single-center design. However, because our research was conducted in a major tertiary care hospital, we believe that our findings can be replicated. We believe that these limitations should be considered in future studies. We conclude that the route of delivery of HTS in the treatment of patients with TBI has no impact on the outcome. To determine the best route of administration for HTS and the most efficient and safest concentration to use, further research with larger sample size is required.

## 9. Conclusions

When comparing intermittent boluses and continuous infusion of HTS in patients with TBI, there was no difference in ONSD ultrasonographic values 48 h after treatment. Moreover, HTS was associated with a rapid elevation of the serum Na levels at 6 and 12 h after treatment initiation in intermittent boluses. There was no significant difference in the length of ICU stay and ICU mortality rate between both groups.


## Disclosure statement

No potential conflict of interest was reported by the author(s).

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