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Comparison of 4.54% hypertonic saline and 20% mannitol for brain relaxation during auditory brainstem implantation in pediatric patients: a single-center retrospective observational cohort study

Hao Fan[1†], Linhong Zhong[1†], Huan Jia[2,3,4], Jinya Shi[1*] and Jingjie Li[1*]

Abstract

Background Mannitol is frequently utilized to achieve intracranial brain relaxation during the retrosigmoid approach for auditory brainstem implantation (ABI). Hypertonic saline (HS) is an alternative for reducing intracranial pressure; however, its application during ABI surgery remains under-investigated. We aimed to compare the efficacy and safety between HS and mannitol for maintaining brain relaxation.

Methods This single-center retrospective cohort study included pediatric patients undergoing ABI surgery from September 2020 to January 2022 who received only 4.54% HS or 20% mannitol for brain relaxation. The analysis involved initial doses, subsequent doses, and dosing intervals of the two hyperosmolar solutions, as well as the time elapsed from meningeal opening to the first ABI electrode placement attempt. Additionally, the analysis encompassed electrolyte testing, hemodynamic variables, urine output, blood transfusion, second surgeries, adverse events, intensive care unit length of stay, and 30-day mortality.

Results We analyzed 68 consecutive pediatric patients; 26 and 42 in the HS and mannitol groups, respectively. The HS group exhibited a reduced rate of supplementary use (7.7% vs. 31%) and lower total urine volume. Perioperative outcomes, mortality, and length of intensive care unit stay did not exhibit significant between-group differences, despite transient increases in blood sodium and chloride observed within 2 h after HS infusion.

Conclusions In pediatric ABI surgery, as an osmotherapy for cerebral relaxation, 4.54% HS demonstrated a lower likelihood of necessitating additional supplementation than 20% mannitol. Furthermore, the diuretic effect of HS was weak and the increase in electrolyte levels during surgery was temporary and slight.

†Hao Fan and Linhong Zhong contributed equally to this work and share first authorship.

*Correspondence:
Jinya Shi
drsjy0116@163.com
Jingjie Li
li_jingjie123@163.com

Full list of author information is available at the end of the article

Keywords Osmotherapy, Brain relaxation, Hypertonic saline, Mannitol, Auditory brainstem implantation, Pediatrics

Introduction

The inaugural World Hearing Report released by the World Health Organization in 2021 reported that more than 1.5 billion individuals worldwide experience hearing impairment and approximately 430 million people have moderate-to-severe hearing loss [1]. For individuals facing congenital deafness with bilateral cochlear malformations or cochlear nerve aplasia, auditory brainstem implantation (ABI) represents the final recourse for attaining the sense of hearing [2, 3]. ABI is an invasive brain–computer interface technology that directly stimulates the cochlear nucleus in the brainstem by bypassing the cochlea and auditory nerves [3]. The success of ABI hinges on the precise localization of the lateral recess of the fourth ventricle (Luschka hole), followed by the successful placement of the stimulation electrode. The retrosigmoid approach is the preferred approach for ABI surgery in patients without tumors [4]. After cutting the arachnoid over the foramen, retracting the flocculus and choroid plexus, the neurosurgeon need performe rostromedial retraction of the cerebellum [5]. However, the convexity of the cerebellum and narrow surgical corridor of the foramen of the Luschka hole obscure direct visualization of the auditory brainstem. Exposure of the cochlear nucleus and potential brain edema resulting from prolonged surgical procedures can complicate the surgery further. Achieving brain relaxation is crucial for optimizing the operating conditions during the retrosigmoid approach and safeguarding the brain against retraction injuries and ischemia caused by compression [6].

Brain relaxation, referring to the relationship between the cranial and brain content volumes when the surgeon opens the meninges [7], is an essential component of anesthesia for intracranial surgery and is a neuroprotective measure [8] that improves the quality of surgical exposure and reduces the brain retractor pressure [9]. The primary strategies for achieving brain relaxation and reducing intracranial pressure during and after craniotomy involved head elevation, optimizing anesthesia depth, avoiding positive end-expiratory pressure, moderate hyperventilation, and utilizing osmotherapy (such as mannitol or hypertonic saline) [10]. Osmotherapy acts by moving water across an osmotic gradient between the cerebral vasculature and cerebral interstitial space [11]. While both mannitol and HS are theoretically associated with similar brain relaxation, some studies suggest that hypertonic saline may offer advantages in achieving brain relaxation in patients undergoing surgery for brain tumors [12]. Furthermore, HS has become the only osmotic dehydration drug recommended by the relevant guidelines for craniocerebral injury in children [13]. The reported HS concentrations and dosages vary considerably, ranging from 3.0 to 23.4% [14, 15]. Qian et al. [16] measured serum and urine osmolality by means of freezing point depression and found that the real osmolality of 20% mannitol and 3.1% HS were approximately 1,378 and 972 mOsmol/kg, respectively. According to the formula used by the authors, the osmotic pressure of 4.54% HS is approximately 1,416 mOsm/L, close equimolar with 20% mannitol. At our institution, alternatively, 20% mannitol or 4.54% HS was used for brain relaxation.

Previous brain relaxation studies have predominantly focused on adult patients with conditions involving intracranial hypertension, such as supratentorial tumors and traumatic brain injury (TBI) [2, 9, 12, 15, 17–22]. However, there is a lack of research on brain relaxation in pediatric patients undergoing ABI surgery with normal preoperative intracranial pressure (ICP). Additionally, the stringent patient eligibility criteria, limited applicability, and the requirement for multidisciplinary collaborations further contribute to the selectivity of centers [23], resulting in a scarcity of research on ABI. We conducted this retrospective study to compare the effectiveness and safety of 4.54% HS and 20% mannitol for achieving brain relaxation during ABI surgery in children, aiming to provide a reference for further research and elucidate the potential advantages of these treatments in optimizing intraoperative conditions.

Materials and methods

Study population and study design

This study was conducted in accordance with the 2013 Declaration of Helsinki. The Ethics Committee of the Shanghai Ninth People's Hospital approved this study (SH9H-2021-T154-2) on January 28, 2022, and waived the requirement for written informed consent due to the retrospective nature of the study. This retrospective, observational study complied with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (S1 checklist).

This study included consecutive pediatric patients who underwent ABI surgery under general anesthesia between September 2020 and January 2022 at our institution, which is currently the only medical institution that performs ABI surgery in China. The inclusion criteria were (1) pediatric patients (age < 12 years) who underwent ABI surgery; (2) surgery using a retrosigmoid approach; and (3) administration of only one of the following hyperosmotic solutions during surgery—4.54% HS or 20% mannitol—typically determined by the attending anesthesiologist of the subspecialty anesthesia team, often randomly. The exclusion criteria were

(1) Perioperative American Society of Anesthesiologists physical status classification of ≥III; (2) preoperative hyponatremia or hypernatremia, defined as a serum sodium concentration of <130 or >150 mmol/L; (3) perioperative treatment involving a hyperosmotic agent, such as mannitol or HS; (4) medical conditions including congestive heart failure (ejection fraction<20%) or renal failure (creatinine clearance<30 mL/kg); (5) preoperative anemia (hemoglobin<10 g/L); (6) crossover use of 2 hyperosmolar solutions; and (7) intraoperative administration of furosemide. The study design and flowchart are shown in Fig. 1.

Data collection

Based on the hyperosmolar medication administered during surgery, as indicated on the anesthesia record sheet, the individuals were classified into either a mannitol or HS group. The primary outcome measured in the study was the proportion of patients requiring a supplementary infusion of hyperosmotic solution beyond the initial dose. In addition, time from initial hypertonic solution infusion to opening the meninges, time from initial hyperosmotic solution infusion to additional administration, and time elapsed from meningeal opening to the first placement of the ABI electrode were also measured. The secondary outcomes included urine output, electrolyte testing, heart rate, mean arterial pressure, and body temperature. Intraoperative outcomes were measured before (T0) and 15 (T15), 30 (T30), 60 (T60), 120 (T120), and 180 (T180) minutes after the hyperosmolar solution infusion, and at the time of admission to the post-anesthesia care unit (PACU). Serum creatinine and blood urea nitrogen levels were recorded preoperatively (D0) and on the first (D1) and third (D3) days

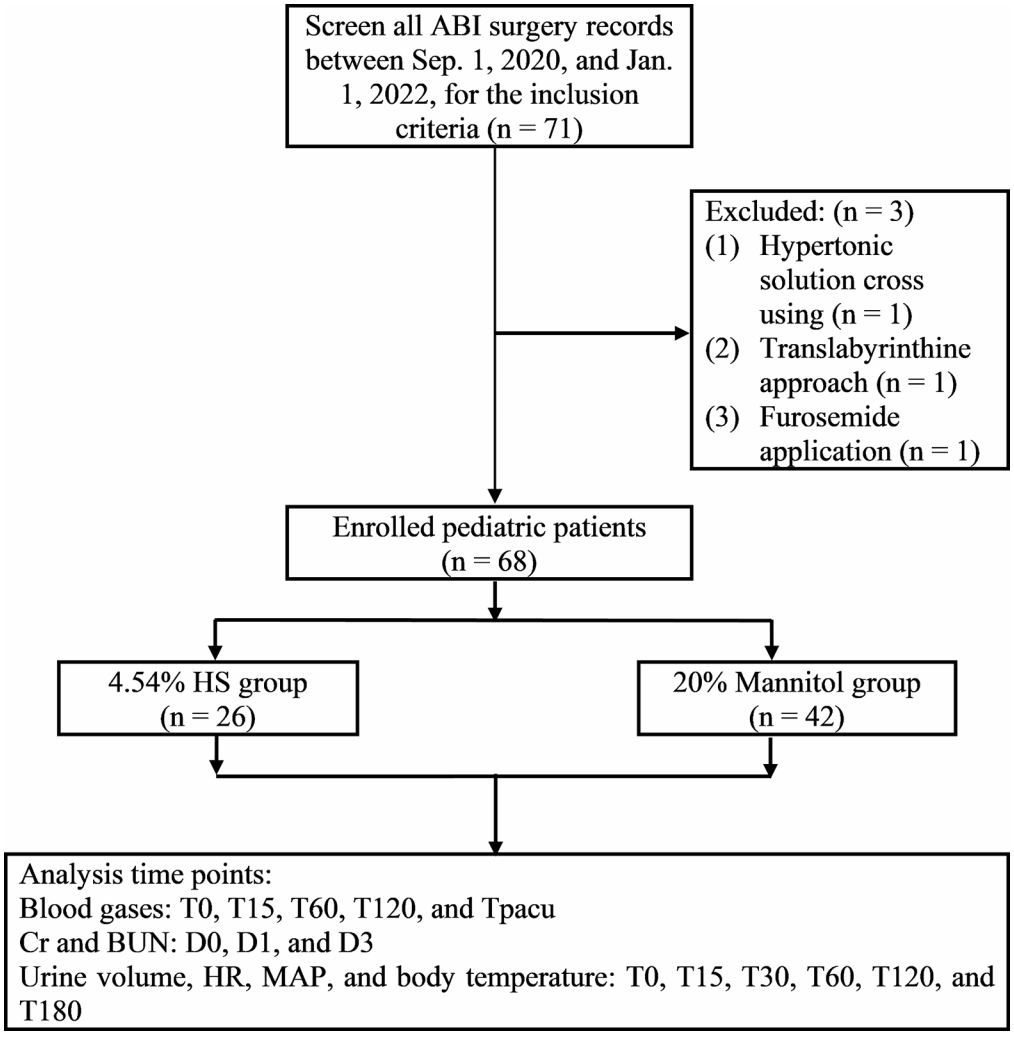

Fig. 1 The retrospective cohort study design and flowchart. ABI, auditory brainstem implantation, T0, prior to infusion of osmotherapy; T15, 15 min after starting the infusion; T30, 30 min after starting the infusion; T60, 60 min after starting the infusion; T120, 120 min after starting the infusion; T180, 180 min after starting the infusion; Tpacu, time of admission to the post-anesthesia care unit; Cr, serum creatinine; BUN, blood urea nitrogen; D0, preoperative; D1, postoperative day 1; D3, postoperative day 3; HR, heart rate; MAP, mean arterial pressure

postoperatively. Bleeding, blood transfusion, second operations, adverse events in the PACU, length of stay in the intensive care unit (ICU), and 30-day mortality data were also recorded.

This surgical approach involves cutting the arachnoid over the foramen, retracting the flocculus and choroid plexus, and performing rostromedial retraction of the cerebellum [5].

Table 1 Characteristics of the study population

Parameters	HS ($n=26$)	Mannitol ($n=42$)	*P*-value
Sex (n [%])			1.000
Male	14 (53.8)	23 (54.8)	
Female	12 (46.2)	19 (45.2)	
Age (months)	40.21 ± 16.10	41.28 ± 17.39	0.748
Weight (kg)	15.46 ± 3.16	15.14 ± 3.45	0.697
Height (cm)	96.04 ± 10.83	96.96 ± 11.87	0.082
ASA (n [%])			0.206
I	16 (61.5)	33 (78.6)	
II	9 (34.6)	7 (16.7)	
III	1 (3.8)	2 (4.8)	
Anesthetic duration (min)	313.35 ± 60.73	334.79 ± 76.15	0.229
Surgery duration (min)	293.31 ± 72.93	311.67 ± 61.06	0.268
Midazolam premedication (mg)	0.23 ± 0.40	0.31 ± 0.45	0.460
Fentanyl induction (μg)	54.62 ± 19.22	44.98 ± 20.22	0.056
Propofol maintenance (mg)	320.26 ± 113.18	321.31 ± 138.31	0.974
Remifentanil maintenance (μg)	795.08 ± 262.22	723.78 ± 223.88	0.236
Dexmedetomidine (μg)	26.91 ± 19.57	33.30 ± 19.35	0.245
Dexamethasone (mg)	4.50 ± 0.98	4.44 ± 1.10	0.824
Vasoactive drugs administration for cardiovascular reflexes(n [%])	4 (15.38)	13 (30.9)	0.15
Crystal amount (mL)	219.40 ± 63.07	184.75 ± 96.20	0.115
Colloid amount (mL)	155.82 ± 64.42	152.17 ± 59.27	0.815
First dose of mannitol or HS (mL)	42.00 [35.00, 50.00]	44.50 [38.00, 50.00]	0.594
First dose of mannitol or HS adjusted weight (mL)	2.91 [2.50, 3.07]	2.96 [2.68, 3.17]	0.557
Total dose of mannitol or HS (mL)	43.50 [35.00, 50.00]	50.00 [40.00, 54.00]	0.2053
Total dose of mannitol or HS adjusted weight (mL)	3.00 [2.55, 3.15]	3.07 [2.82, 3.67]	0.165
Total urine output (mL)	281.92 ± 165.820	550.48 ± 262.520	< 0.001

Values are presented as mean ± standard deviation, n (%), or median (quartiles 25–75), as appropriate

ASA, American Society of Anesthesiologists status; HS, hypertonic saline solution

Statistical analyses

Statistical analyses were performed using SPSS (version 20.0; SPSS Inc., Armonk, NY, USA). A P value < 0.05 was considered statistically significant.

Baseline characteristics

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables and as frequency or percentage for categorical variables. Normally distributed continuous variables were analyzed using the Kolmogorov–Smirnov test. Differences between groups were analyzed using one-way analysis of variance (ANOVA), the Chi-square test, or Mann–Whitney U test.

Primary outcome

The primary outcome data are presented in the same way as the baseline characteristics.

Based on different types of endings (binary or continuous variables), logistic regression or linear regression were used to further assess the primary outcomes. For logistic regression, results are presented as the odds ratio (OR) and 95% confidence interval (CI). For linear regression, results are presented as the β and 95% (CI). All logistic/linear regression analyses included 4 covariates: sex (male or female), age (continuous variable), American Society of Anesthesiologists classification (grade variable), and time to surgery (continuous variable).

Secondary outcomes

For secondary outcomes recorded only once, data are presented in the same way as the baseline characteristics.

Multivariate ANOVA was used to assess differences in the secondary outcomes recorded at multiple time points (hemodynamic and laboratory variables) between groups and across time points. A Bonferroni correction was used as a post hoc analysis for pairwise comparisons.

Results

Demographic and clinical characteristics

In total, 71 pediatric patients underwent ABI at our institution during the study time period. The following patients were excluded: one patient due to conversion to a retrolabyrinthine approach, one patient due to crossover with a hypertonic agent, and one patient due to furosemide administration. Consequently, the final analysis comprised 68 patients who met the inclusion criteria. The HS and mannitol groups included 26 and 42 patients, respectively (Fig. 1). The demographic, anesthetic, and surgical variables were comparable between the groups (Table 1).

Hyperosmotic solutions for brain relaxation

The recorded additional hyperosmolar drugs were all the same as initially administered. There was no significant difference observed in the total administration of hyperosmotic solutions between the two groups, including total administration adjusted for weight (Table 1). There was no significant difference between the two groups in the time from hypertonic solution infusion to opening the meninges (47.38±5.10 in the HS group vs. 43.62±3.37 in the Mannitol group, P=0.567) and the time elapsed from meningeal opening to the first placement of the ABI electrode (17.00 [14.00, 22.00] in the HS group vs. 19.00 [15.50, 24.50] in the Mannitol group, P=0.2154) (Table 2). However, the number of additional administrations of the hypertonic solution was significantly lower in the HS group than in the Mannitol group (7.7% vs. 31%, P=0.034; OR: 0.17, 95% CI: 0.02–0.81, P=0.047) (Tables 2 and 3). There was no difference in the time interval between initial and additional administration between the two groups (97.50±10.61 in the HS group vs. 72.15±41.46 in the Mannitol group, P=0.419) (Table 2).

Table 2 Brain relaxation scores and additional hypertonic solution requirements

Variable	HS (n=26)	Mannitol (n=42)	P-value
Need for additional hyperosmotic solution (n [%])	2 (7.7)	13 (31.0)	0.034
Time from initial hypertonic solution infusion to opening the meninges (min)	47.38±5.10	43.62±3.37	0.567
Time from initial hyperosmotic solution infusion to additional administration (min)	97.50±10.61	72.15±41.46	0.419
Time elapsed from meningeal opening to the first placement of the ABI electrode (min)	17.00 [14.00, 22.00]	19.00 [15.50, 24.50]	0.2154

Values are presented as mean±standard deviation, n (%), or median (quartiles 25–75), as appropriate

HS, hypertonic saline solution

Table 3 Logistic regression analysis of the primary outcomes

Outcome	OR/β (95% CI)	P value
Need for additional hyperosmotic solution (%)	0.17 (0.02, 0.81)	0.047
Time elapsed from meningeal opening to the first placement of the ABI electrode (min)	-2.322 (-6.650, 2.006)	0.300

OR, odds ratio; CI, confidence interval. The results of outcome "Need for additional hyperosmotic solution" were shown as OR value. The results of outcome "Time elapsed from meningeal opening to the first placement of the ABI electrode" were shown as β value

Blood gas analysis

Figure 2 presents the blood gas analysis results. The serum sodium levels (Na^+) were significantly higher in the HS group at T15 (145.2±2.57 vs. 136.47±3.34, P<0.001), T60 (145.2±2.57 vs. 136.47±3.34, P<0.001), and T120 (142.82±1.94 vs. 139.06±2.93, P<0.001), and the interaction P-value was significant (P<0.001) (Fig. 2A). The serum potassium level (K^+) was significantly lower in the HS group only at T15 (3.66±0.34 vs. 4.05±0.55, P<0.01) (Fig. 2B). There was a significant difference in pH between the two groups at T60 (7.4±0.04 vs. 7.45±0.06, P<0.01) and T120 (7.39±0.05 vs. 7.43±0.07, P<0.05) (Fig. 2C). Arterial carbon dioxide pressure ($PaCO_2$) and lactate (Lac) did not show any difference between the two groups (Fig. 2D and E). The hemoglobin levels in the HS group were significantly lower than those in the Mannitol group at T60 (92.35±10.59 vs. 97.58±12.8, P<0.05) and T120 (91.9±15.17 vs. 100.11±13.54, P<0.05) (Fig. 2F). The serum creatinine levels (Cr) did not differ between the two groups on D0, D1, and D3 (Fig. 2G). Blood urea nitrogen (BUN) differed between the HS and Mannitol groups only on D1 (3.74±0.81 vs. 4.31±1.00, P<0.05) (Fig. 2H). More detailed data can be found in Table S1.

Intraoperative urine output, hemodynamic variables, and body temperature

The total urine volume was significantly lower in the HS than in the Mannitol group (281.92±165.82 mL vs. 550.48±262.52 mL, P<0.001; Table 1). Furthermore, the cumulative urine output at each time point in the Mannitol group was significantly higher than that in the HS group, except at T0 (Fig. 3A). Within 1 h following the infusion of hypertonic solution, the variations in urine output at each observation time point were significantly higher in the Mannitol group than those in the HS group. (T15–T10, T30–T15, T60–30, P<0.01, < 0.01, and <0.01, respectively, Fig. 3B). However, there was no longer a difference between the two groups regarding changes in urine output after 1 h (Fig. 3B). Mean arterial pressure did not differ between the groups at any observation time point (Fig. 4A). The heart rate at T60 (82.19±9.26 vs. 91.04±9.31, P<0.05 in the HS group), T120 (84.69±9.16 vs. 91.79±10.35, P<0.05 in the mannitol group and 82.19±9.26 vs. 92.54±6.57, P<0.01 in the HS group), and T180 (84.69±9.16 vs. 92.59±12.89, P<0.05 in the mannitol group and 82.19±9.26 vs. 95.44±11.03, P<0.001 in the HS group) showed significant increases compared with that at T0 (Fig. 4B). The body temperature of the two groups showed a significant difference only at T180 compared with that at T0 (35.9±0.58 vs. 36.56±0.91, P<0.05 in the Mannitol group and 35.97±0.44 vs. 36.91±0.53, P<0.05 in the HS group, Fig. 4C). More detailed data can found in Table S2.

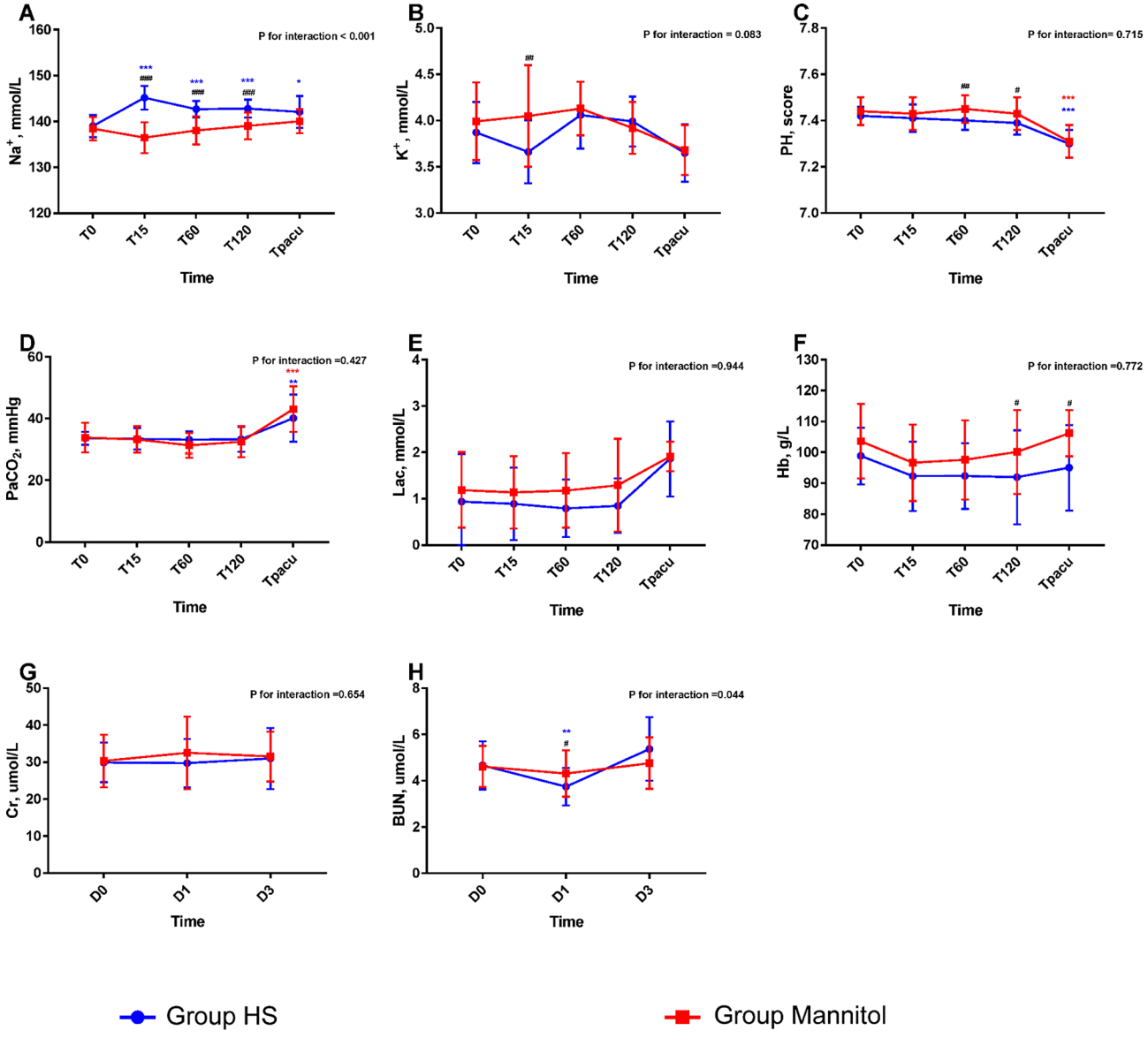

Fig. 2 Blood gases, Cr, and BUN levels over time in pediatric patients undergoing auditory brainstem implantation receiving 4.54% HS or 20% mannitol for brain relaxation. A: serum sodium; B: serum potassium; C: PH; D: $PaCO_2$; E: Lac; F: Hb; G: Cr; H: BUN. Cr, serum creatinine; BUN, blood urea nitrogen; HS, Hypertonic saline; T0, prior to infusion of osmotherapy; T15, 15 min after starting the infusion; T30, 30 min after starting the infusion; T60, 60 min after starting the infusion; T120, 120 min after starting the infusion; T180, 180 min after starting the infusion; Tpacu, time of admission to the post-anesthesia care unit; D0, preoperative; D1, postoperative day 1; D3, postoperative day 3; Na^+, serum sodium; Cl^-, serum chloride; K^+, serum potassium; pH, hydrogen ion concentration; $PaCO_2$, arterial carbon dioxide partial pressure; Lac, lactic acid; Hb, hemoglobin. # Significant between-group differences: #$P<0.05$; ##$P<0.01$; ###$P<0.001$. * Significant differences compared to T0: *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$

Adverse events

The number of recorded postoperative complications did not differ between the two groups. In the HS group, there was 1 case each of a second operation, delayed tracheal extubation, and emergence agitation. In the Mannitol group, there were 2 cases each of postoperative nausea and vomiting and emergence agitation. In each group, 2 patients required a blood transfusion. Finally, no deaths in the hospital or at 30 days postoperatively were recorded in either group (Table 4).

Discussion

In this retrospective observational cohort study, we found that in temporary cerebral parenchymal dehydration induced by hypertonic dehydration infusion to achieve and sustain intraoperative cerebral relaxation in children undergoing ABI surgery, 4.54% HS was less likely to require additional supplementation than 20% mannitol and had a lower diuretic effect. It is essential to highlight that after the infusion of 4.54% HS, some children experienced transient mild hypernatremia and hyperchloremia.

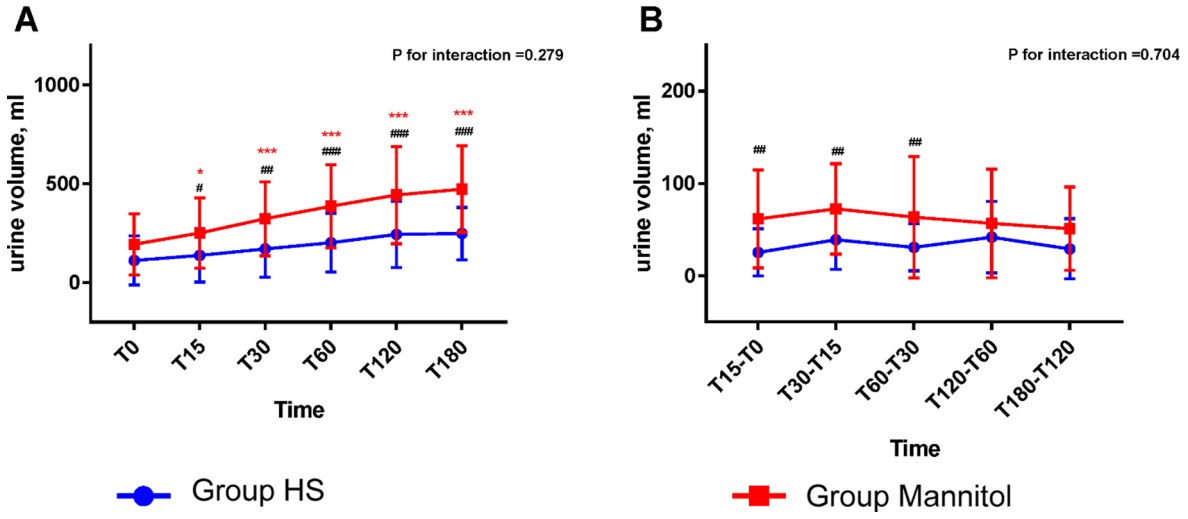

Fig. 3 Cumulative (**A**) and changes (**B**) in urine volume over time in pediatric patients undergoing auditory brainstem implantation receiving 4.54% HS or 20% mannitol for brain relaxation. HS, Hypertonic saline; T0, prior to infusion of osmotherapy; T15, 15 min after starting the infusion; T30, 30 min after starting the infusion; T60, 60 min after starting the infusion; T120, 120 min after starting the infusion; T180, 180 min after starting the infusion. # Significant between-group differences: #$P<0.05$; ##$P<0.01$; ###$P<0.001$. * Significant differences compared to T0: *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$

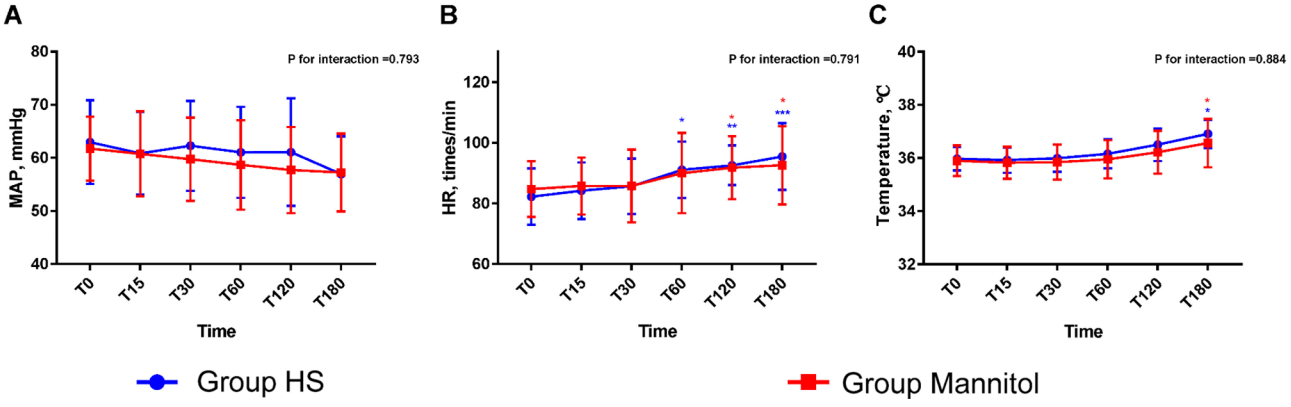

Fig. 4 MAP (**A**), HR (**B**), and body temperature (**C**) over time in pediatric patients undergoing auditory brainstem implantation receiving 4.54% HS or 20% mannitol for brain relaxation. HS, Hypertonic saline; T0, prior to infusion of osmotherapy; T15, 15 min after starting the infusion; T30, 30 min after starting the infusion; T60, 60 min after starting the infusion; T120, 120 min after starting the infusion; T180, 180 min after starting the infusion. HR, heart rate; MAP, mean arterial pressure; HS, Hypertonic solution. * Significant differences compared to T0: *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$

However, these levels were slightly above average and returned to normal within 2 h after infusion.

During ABI surgery, the retrosigmoid approach to access the fourth ventricle requires cutting the arachnoid over the foramen, retracting the flocculus and choroid plexus, and performing rostromedial retraction of the cerebellum [5]. Cerebellar over-retraction may cause complications such as cerebellar edema [24], cerebellar contusion [25], or cerebellar clots [26]. Osmotherapy with either mannitol or HS is the recommended first-line medical intervention for optimizing cerebral perfusion through brain relaxation [27]. During craniotomy, brain relaxation is usually evaluated by the chief surgeon using 3-, 4- or 5-point scales and reported as dichotomized outcomes (good and poor) [28]. In this retrospective study, we relied on the medical records to assess brain relaxation indirectly by considering the time elapsed from meningeal opening to the first attempt to place the ABI stimulation electrode. The infusion of hypertonic solutions and other conventional strategies typically occurs approximately 30 min before the opening of the meninges, roughly coinciding with the initiation of mastoid grinding. Our study revealed no difference in the duration from meningeal opening to the first attempt at electrode placement between the two groups, suggesting that both hypertonic treatments provided essentially similar brain relaxation conditions for surgical exposure. This conclusion is consistent previous reports [29]. When significant cerebral swelling or insufficient space in the lateral recess was observed after opening the meninges, the chief neurosurgeon could request a second dose of the hyperosmolar solution to improve surgical exposure.

Table 4 Secondary outcomes

Outcome	HS (*n* = 26)	Mannitol (*n* = 42)	*P*-value
Bleeding amount (mL)	44.62 ± 36.27	34.40 ± 30.02	0.213
Blood transfusion (n [%])	2 (7.7)	2 (4.8)	0.634
Second operation (n [%])	1 (3.8)	0 (0.0)	0.382
PACU adverse events (n [%])			0.085
None	17 (65.4)	18 (42.9)	
Delayed tracheal extubation	1 (3.8)	0 (0.0)	
Emergence agitation	1 (3.8)	2 (4.8)	
PONV	0 (0.0)	2 (4.8)	
Fever (T > 37.3 ℃)	8(30.7)	22(52.4)	
ICU stay (days)	3.42 ± 2.16	3.24 ± 0.58	0.599
ICU exceeding 3 days (n [%])	1 (3.8)	7 (16.7)	0.14
Thirty-day mortality	0 (0.0)	0 (0.0)	

Values are presented as mean ± standard deviation and n (%), as appropriate

HS, hypertonic saline; ICU, intensive care unit; PACU, post-anesthesia care unit; PONV, postoperative nausea and vomiting

This study revealed that the number of additional administrations of hypertonic agent was significantly lower in the HS group. The reflection coefficient values, which represent the effectiveness of the hypertonic agent, were 1 for HS and 0.9 for mannitol. This theoretically suggests that HS can provide a more substantial osmotic pressure gradient and lead to superior brain relaxation effects [9, 17, 20, 22]. Our findings suggest that HS elicited a more sustained effect on brain relaxation, consistent with the results reported by Liu et al. [30] and Rozet et al. [31]. A meta-analysis also indicated that hypertonic saline, compared to mannitol, can maintain lower intracranial pressure even after 90–120 min and has a more sustained effect in children with TBI [32]. HS exhibited a more prolonged effect, which may be related to the participation of a non-permeable mechanism in addition to its permeable dehydration mechanism [14, 30].

Mannitol has a more potent effect on urine output increase than HS [29]; in our study, the difference in total urine output between the two groups was nearly 2-fold. Although all hypertonic solutions induce diuresis, the mechanisms are considerably different. In contrast to the osmotic diuretic effect caused by intravenous mannitol injections, HS mainly produces a delayed mild diuretic effect by stimulating the release of atrial natriuretic peptide, which does not lead to rapid or massive dehydration. HS stimulates vasopressin release from the pituitary gland, which decreases water loss through the kidneys [33]. After HS infusion, urine output increased less in the first hour compared to that in the Mannitol group. However, there was no significant difference between the groups beyond the first hour in this study. In addition, as in previous studies [19], we observed a plasma volume expansion effect in the HS group, indicated by a mild decrease in hematocrit and lactic acid levels. However, some studies [9, 22, 30] have shown that the expansion effect of HS has a low probability of secondary ischemic brain injury caused by low blood volume. Conversely, in this study, mannitol infusion was promptly followed by a profound diuresis, which some authors suggest leads to hypovolemia [34]. The heart rate and mean arterial pressure did not differ between the two groups. This may be problematic in patients with trauma who typically require fluid resuscitation to increase blood volume [35]. There was no difference in MAP between the groups. However, HR increased in both groups 1–2 h after infusion compared to pre-infusion levels, with a more significant increase observed in the HS group based on the review data available for this study. We speculate that circulatory stability in children depends more on changes in HR than on BP changes. Typically, we pre-supplement with 6% hydroxyethyl starch at 10 mL/kg, considering factors such as urine output, fasting times in pediatric patients, and limited use of crystalloid fluid during craniotomy surgery. Hence, caution may be warranted regarding routine use or the amount of colloids in non-hypovolemic osmotherapy with HS.

Electrolyte abnormalities are the adverse effects most commonly encountered in osmotherapy with a clinical importance equivalent to its brain relaxation properties [36]. The arterial sodium and chloride levels were consistently higher than those at baseline after HS administration throughout our recorded period. Although the serum sodium levels in the HS group were higher than those in the Mannitol group and baseline values, they remained within the range of mild hyponatremia (below 150 mmol/L) after infusion prioperatively, fluctuating between 139 and 149 mmol/L. HS exacerbates hypernatremia through renal tubular sodium-potassium exchange, increasing potassium excretion and causing hypokalemia [35]. This may explain the significant difference between the two groups in pH values at T60 and T120 and potassium levels at T15. Research indicates that electrolyte abnormalities following HS infusion, primarily hypernatremia and hyperchloremia [37], which can lead to renal vasoconstriction and decreased renal perfusion [38], were transient and did not result in adverse consequences [21, 31]. In contrast, mannitol decreases sodium levels due to the inflow of water-diluted serum electrolytes [19]. Mannitol infusion-induced diuresis, hypovolemia, and renal vasoconstriction can decrease renal blood flow [34], and its direct damage to renal tubular epithelial cells, potentially leads to acute renal failure or nephropathy [39]. Therefore, administering mannitol in children should be performed with caution [40]. In contrast, HS is less prone to induce nephrotoxicity due to the presence of the sodium-potassium pump. Renal damage should be suspected if blood sodium concentration exceeds 160 mmol/L [18, 19, 40]. Under close monitoring, when moderate to severe hypernatremia is detected,

a glucose solution should be used for rehydration, and sodium-excreting diuretics, such as furosemide, may be considered to promote sodium excretion and prevent excessive blood sodium levels. In our study, there was no difference in electrolyte levels in the PACU between the two groups, and renal function indices remained within normal ranges in both groups at all time points. Additionally, the length of ICU stay, blood loss, blood transfusion, perioperative complications, and 30-day mortality were similar between the two groups.

This study has some limitations. First, pediatric ABI surgery is conducted in a limited number of centers globally. Due to marketing access reasons, pediatric ABI surgery has only been performed in mainland China since January 2019 [41]. Consequently, the sample size of the cohort was small. Given the rarity of the disease, multicenter prospective studies to verify these conclusions are required. Second, because this was a retrospective study, direct cerebral relaxation scores could not be determined due to an inability to determine blindness and due to data missing from the medical records. As a result, we could only use other indirect indicators for evaluation. However, our study focused solely on a single disease, ensured that the same surgical approach was applied, and followed a largely uniform anesthesia regimen, controlling for bias between the groups. Third, some data regarding the electrolyte levels were missing owing to the challenges of obtaining blood samples from children. However, the missing data did not introduce bias in this study. Forth, hemodynamic monitoring was limited to arterial blood pressure and heart rate, while parameters such as central venous pressure, cardiac output, and stroke volume variability were not monitored. Additionally, the significant difference in urine output between the two groups suggests that monitoring of circulatory indicators may be insufficient. Further studies are needed to investigate the effects of the two hypertonic solutions on circulation in young children.

In conclusion, this is the first study to explore the efficacy and safety of 20% mannitol and 4.54% HS for brain relaxation during ABI in children. Both agents offer comparable brain relaxation conditions for surgical exposure, with HS potentially necessitating less supplementation and posing a lower risk of hypovolemia. Additionally, HS induced only minimal transient changes in electrolytes during the perioperative period. Further high-quality randomized controlled trials are required to confirm these results.

Abbreviations: ABI, auditory brainstem implantation; ICP, intracranial pressure; OR, odds ratio; CI, confidence interval (CI); PACU, post-anesthesia care unit; HS, Hypertonic saline; ICU, intensive care unit; MAP, mean arterial pressure.

Abbreviations

ABI	Auditory brainstem implantation
ICP	Intracranial pressure
OR	Odds ratio
CI	Confidence interval (CI)
PACU	Post-anesthesia care unit
HS	Hypertonic saline
ICU	Intensive care unit
MAP	mean arterial pressure

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Author contributions
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Data availability
The data supporting the findings can obtained from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The Ethics Committee of the Shanghai Ninth People's Hospital approved this study (SH9H-2021-T154-2) on January 28, 2022, and waived the requirement for written informed consent due to the retrospective nature of the study.

Consent for publication
Not applicable. The article contains no individual-level data.

Competing interests
The authors declare no competing interests.

Author details
[1]Anesthesiology Department, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, No. 639 Zhizaoju Road, Shanghai 200011, China
[2]Department of Otolaryngology Head and Neck Surgery, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiao Tong University, No. 639 Zhizaoju Road, Shanghai 200011, China
[3]Ear Institute, Shanghai Jiao Tong University School of Medicine, No. 390 Yanqiao Road, Shanghai 200125, China
[4]Shanghai Key Laboratory of Translational Medicine on Ear and Nose Diseases, No. 390 Yanqiao Road, Shanghai 200125, China

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