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Intraoperative isotonic balanced versus hypotonic crystalloids on postoperative sodium homeostasis in small children undergoing major neurosurgery: a randomized controlled trial

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Abstract

Background Whether intraoperative isotonic balanced maintenance fluid is associated with less variation in sodium homeostasis in small children undergoing major neurosurgery remains unknown.

Methods Patients aged up to 6 years undergoing major neurosurgery were randomly assigned to receive either isotonic balanced solution (IB) or 0.2% hypotonic solution (H) as intraoperative maintenance fluid. Serum electrolyte levels were measured from preoperative baseline to 6 d following surgery.

Results Eighty patients were included in the primary analysis. Serum sodium change was significantly less in the IB patients from the end of surgery continuing to 24 h following surgery (at the end of surgery: -1.4 ± 3.6 versus −4.6 ± 3.5 mmol/l, $P < 0.001$; 24 h post: -1.2 ± 4.8 versus −3.4 ± 2.5 mmol/l, $P = 0.028$). Twenty (50%) of the IB patients and 25 (63%) of the H patients had serum sodium change > 2.5 mmol/l 24 h following surgery (6.0 ± 3.4 versus 4.8 ± 2.1 mmol/l), with 13 (33%) of the IB patients and 25 (63%) of the H patients having sodium decrease > 2.5 mmol/l (6.4 ± 3.7 versus 4.8 ± 2.1 mmol/l) ($P = 0.007$). Seven patients in group IB experienced an increase in blood sodium levels exceeding 2.5 mmol/l (median, 4.1 [range 2.7 ~ 9.2] mmol/l). Notably, 10 (25%) of the IB patients and 6 (15%) of the H patients had sodium variation > 5 mmol/l (median, 8.5 [range 5.1 ~ 14.6] versus 7.2 [range 5.5 ~ 11.1] mmol/l). Immediately following surgery till 24 h postoperatively, hyponatremia was less observed in the IB patients compared with that in the H patients. The IB patients had higher hemoglobin levels and less diuresis 48 h postoperatively. No symptoms including altered mental status, seizure, and circulatory overload were observed in all patients.

Conclusion Intraoperative isotonic balanced solution infusion resulted in statistically but not clinically minimal variation of sodium homeostasis and hemoglobin level postoperatively in small children undergoing major

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neurosurgery, compared to the use hypotonic solution. Potentially excessive sodium fluctuation following isotonic balanced maintenance fluid infusion should be cautioned, even for a brief period of infusion.

Trial registration Chinese Clinical Trial Registry (http://www.chictr.org.cn/). Registration number: ChiCTR2100046539. Registration date: May 21, 2021. Principal investigator: Lin-Lin Song.

Keywords Children, Homeostasis, Hyponatremia, Isotonic solutions, Neurosurgery

Introduction

The majority of prospective trials focused on tonicity of maintenance fluid did not include children with neurological disorders, especially small children. Patients with neurological disorders are at particularly high risk for developing hyponatremia, with mild hyponatremia occurring in half of the children and severe hyponatremia in approximately 12% of the children [1]. The prevalence of hyponatremia after neurosurgery in children was 4 ~ 88% depending on the process [2–4]. During major neurosurgery, stimulation of the antidiuretic hormone (ADH), the predominant cause of hyponatremia, may be due to hemodynamic causes such as intravascular depletion and hypotension, and nonhemodynamic causes such as stress, a postoperative state, mechanical ventilation, pain, nausea, vomiting and narcotic use. Elevated ADH leads to retention of free water and hyponatremia. Acute sodium derangement predisposes these patients to intracellular fluid shifts and brain edema, which potentially contribute to secondary neurological injury with seizure, encephalopathy, and even death [5]. Children of small age might be at greater risk of dysnatremia because of their reduced renal concentrating ability and limited sodium excretion function. Relatively small changes in serum sodium and extracellular free water will affect the pediatric brain to a much greater degree than the adult due to their immaturity of neural tissues and larger brain/skull size ratio.

Pediatric fluid management has changed over the last ten years with a shift from hypotonic intravenous fluids to predominantly isotonic intravenous fluids [6]. Recent studies involving perioperative neurosurgical children showed that 0.9% saline isotonic maintenance solution decreased the risk of hyponatremia when compared with 0.45% saline hypotonic fluid [7]. Saline use has been associated with increased hyperchloremic acidosis and nephrotoxicity [8, 9]. Previous studies demonstrated that balanced crystalloids are safe and cause less metabolic derangements than saline [10, 11]. Compared to lactate ringer's solution, acetate solution (Plasma-Lyte A) can be metabolized significantly faster with less oxygen demand and more independent of hepatic function [12].

However, some investigators have raised concerns about potential adverse outcomes from widespread use of isotonic intravenous fluids including hypernatremia, fluid overload, hyponatremia due to excessive sodium excretion, and hyperchloremic acidosis. For a major neurosurgery lasting 3 ~ 4 h, intraoperative isotonic fluid administration leads to a sudden 3-fold increase in sodium intake compared to general upper limit of daily salt requirement [13]. The excessive sodium intake must be balanced by appropriate renal wasting such that the serum sodium remains stable. The use of isotonic maintenance solutions may be less appropriate for small children with limited renal function such as infants. Inappropriate renal sodium loss has also been noted in neurosurgical children (e.g. a cerebral salt-wasting state). It is conceivable that small children undergoing neurosurgery might be predisposed to excessive sodium fluctuation during the postoperative period. In a 2021 randomized clinical trial in children presenting the emergency department, administration of gluconate/acetate solution resulted in higher incidence of electrolyte disorders compared with 0.45% saline [14].

In children undergoing major neurosurgery, there is a lack of clinically directive data on the optimal choice of intravenous maintenance solutions intraoperatively. Wide variation in routine practice exists with regard to the tonicity of intraoperative maintenance fluids in these patients. The primary aim of this assessor-blinded randomized controlled trial was to determine whether isotonic balanced fluid administered as intraoperative fluid regime to small children undergoing major neurosurgery was associated with less variation in electrolyte homeostasis compared to hypotonic fluid. The primary outcome was the variation in serum sodium level between baseline and 24 h following surgery. We hypothesized that intraoperative use of isotonic balanced fluids would be associated with less variation in sodium homeostasis perioperatively compared to hypotonic fluid in small children undergoing major neurosurgery.

Materials and methods

This study was conducted at Peking University First Hospital, a tertiary teaching hospital and specialist referral center in Beijing between August 2021 and March 2022. The trial protocol was approved by the ethical committee of Peking University First Hospital (2021 – 269). Trial registration was completed at Chinese Clinical Trial Registry (http://www.chictr.org.cn; registration number: ChiCTR2100046539; registration date: May 21, 2021; principal investigator: Lin-Lin Song). Eligible participants were ASA physical status I or II children aged up to 6 years who were admitted for major neurosurgery under general anesthesia. Major neurosurgery was defined as surgery that involved an opening of the dura mater with a diameter exceeding 5 cm. Patients were excluded if they had pre-existing intracranial hypertension, significant renal and cardiorespiratory diseases, or preoperative dysnatremia. Written informed consent was obtained from legal guardians of all participants. This study adhered to CONSORT guidelines.

Before the surgery, eligible patients were randomly assigned in a 1:1 ratio to receive either isotonic balanced fluid (Plasma-Lyte A, Baxter Healthcare, Deerfield, IL) or 0.2% hypotonic fluid (Pediatric electrolyte supplements injection [3.75% glucose], Kelun, Sichuan, China) as intraoperative maintenance fluid. 0.2% hypotonic fluid was the routine maintenance fluid for general pediatric patients aged up to 6 years in our hospital including neurosurgical patients. Please refer to Additional file 1 for the compositions of both solutions. Randomization was done by an independent statistician using a computer-generated random sequence with blocks of 4 and 8. The allocation sequence was kept using sealed opaque envelopes.

Anesthesia management

Clear fluids were restricted for 2 h, breast milk for 4 h, and solid food for 6 h prior to surgery. No fluids were administered intravenously before the procedure. After standard monitoring was attached, general anesthesia was induced with propofol, sufentanil, remifentanil, cisatracurium, and maintained with a balanced anesthetic technique involving inhaled sevoflurane, intravenous administration of propofol and remifentanil, sufentanil, and cisatracurium. Radial artery and femoral vein catheterization were implemented following endotracheal intubation.

Children received either isotonic balanced or hypotonic fluids as maintenance fluid according to their group allocation from anesthesia induction until the end of surgery. The type of fluid administered was blinded to the attending surgeon but not blinded to the anesthetist in charge who was not involved in the postoperative assessment. Intraoperative hemodynamic management was left to the discretion of the anesthetist. Generally, systolic blood pressure variation was maintained within 20% baseline level. The maintenance fluid infusion was initiated with an initial infusion rate of 10 ml/kg/h and adjusted to the actual requirement. Blood loss was replaced by 3-fold volume crystalloid as allocated or same volume of packed red blood cells. Trigger for blood transfusion depended on age and actual hemoglobin level. In case of clinical signs of hypovolemia, blood product replacement or additional 10 ml/kg bolus of the same crystalloid as allocated could be administered as frequently as deemed necessary. Inotropes and vasopressors were allowed following adequate volume replacement with crystalloids and blood products if the hemodynamic status was deemed unsatisfactory. All medication were diluted with 0.9% saline.

Electrolytes determination and blood gas analyses were performed for study requirement, any intraoperative homeostasis maintenance, and hemoglobin replacement. The management of electrolyte disturbance was left to the discretion of the anesthetist. Generally, only severe hyponatremia was treated and replaced with 3% sodium chloride of 1 ml/kg for every mmol/l decrease of serum sodium below 130 mmol/l.

Postoperative period

Fluid regime during the postoperative period followed departmental routines. Both groups had the same hypotonic fluid ordered as the maintenance fluid until the patients tolerated enteral diets. Generally, the volume of maintenance fluid administered was calculated using the Holliday-Segar formula. Maintenance fluid was continued until more than 80% of daily fluid requirement was fulfilled with oral intake. Blood product administration was prescribed at the discretion of the attending surgeon. The attending surgeon referred to the clinical pathways for managing acute serum electrolyte level derangements if necessary.

Data collection

Baseline serum electrolyte levels were collected from laboratory reports one day before surgery. A sample with 2 ml of blood drawn from the femoral vein line was collected at 6 timepoints: (1) immediately following induction of anesthesia and femoral vein catheterization, (2) immediately at the end of surgery, (3) 24 (± 6 h) h after returning to the ward or intensive care unit, (4) 48 (± 6 h) h after returning to the ward or intensive care unit, (5) Day 4 following surgery, (6) Day 6 following surgery. Serum electrolytes, anion gap, glucose, and hemoglobin were measured by the central laboratory using the Beckman Coulter AU5800 (Beckman Coulter, California, US). Indirect potentiometry was employed to process serum electrolytes. Strong ion difference (SID) was calculated by subtracting the concentration of serum chloride from that of sodium and potassium.

Additional laboratory blood tests can be chosen by the anesthetist in charge and the attending surgeon based on individual clinical status. Among patients with multiple daily measurements, daily average was calculated and used as the patient's daily value to calculate the group average. All caregivers were blinded with respect to study-specific investigation results. To ensure patient safety, an independent safety staff reviewed all masked serum sodium level results and referred the anesthetist or surgeon to the clinical pathways for managing acute serum electrolyte level derangements if predefined thresholds were met.

Postoperatively, clinical adverse events potentially related to the use of trial maintenance fluids included (1) clinical evidence of circulatory overload defined as the presence of new-onset, generalized, peripheral edema associated with tachypnea, tachycardia, hypoxia, pulmonary crepitations, and pulmonary congestion on chest radiographs, (2) seizures ascribed to acute severe hyponatremia (serum sodium < 130 mmol/l), defined as seizure and concurrent severe hyponatremia, (3) altered level of consciousness ascribed to acute hyponatremia, defined as altered level of consciousness and concurrent severe hyponatremia. Cranial radiography was reviewed to reveal any clinically apparent cerebral swelling on postoperative Day 1. Postoperatively, other adverse events were also prospectively collected, including moderate and/or severe fever (> 38.5℃), bronchitis, pneumonia, intracranial infection, and wound infection.

Baseline demographic data, the surgical procedures performed, anesthesia and surgery duration, laboratory data, any fluids and blood product given during the surgery and the postoperative period, input and output volume within 48 h following surgery, and duration of postoperative hospital stay were documented. A research staff who was blinded to group allocation independently collected data and assessed outcomes.

Outcomes

Primary outcome

The primary outcome was the variation of serum sodium level between 24 h following surgery and baseline ($\Delta Na_{24h-pre}$), reflecting the derangement of sodium hemostasis.

Secondary outcomes

Secondary outcomes were classified into laboratory and patient-centered outcomes.

Laboratory outcomes included the variations of serum electrolytes between postoperative pre-specified timepoints and baseline ($\Delta Na_{timepoints-pre}$), the occurrence of electrolyte derangements including hyponatremia (serum sodium < 135 mmol/l), severe hyponatremia (serum sodium < 130 mmol/l), hypernatremia (serum sodium > 145 mmol/l), hypokalemia (serum potassium < 3.5 mmol/l), hyperkalemia (serum potassium > 4.5 mmol/l), hypomagnesemia (serum magnesium < 0.75 mmol/l), hypochloremia (serum chloride < 97 mmol/l), hyperchloremia (serum chloride > 110 mmol/l), non-anion gap acidosis (serum bicarbonate < 20 mmol/l and anion gap < 20 mmol/l), hypoglycemia (blood glucose < 2.8 mmol/l), hyperglycemia (blood glucose > 6.1 mmol/l) within 48 h following surgery. The level of radiographical brain swelling is recorded on a 4-point scale based on postoperative computed tomography reports (0 = no, 1 = mild, 2 = moderate, 3 = severe).

Patient-centered outcomes included the amount of input (fluids and oral intake) and output (urine and drain loss), the occurrence of seizures or altered mental status related to hyponatremia, circulatory overload related to trial maintenance fluid, and other postoperative adverse events as well as length of postoperative hospital stay.

Sample size calculation

The critically significant change between two serum sodium results is 2.5 mmol/l (for a 1-tailed test, the percentage change of the reference change value is $1.645 \times \sqrt{2} \times \sqrt{\mathrm{CVA}^2 \times \mathrm{CVI}^2}$, wherein CVA the laboratory analytical coefficient of variation of 0.8% and CVI is the within-individual coefficient of 1% for serum sodium [15]). Assuming $\Delta Na_{24h-pre}$ in the isotonic balanced fluid group were 2.5 mmol/l less than that in the hypotonic fluid group, a sample of 37 participants in each group would be required to achieve the desired power of 90% at a 5% level of significance. Considering the potential dropout, the total sample size was 80 pts in both groups.

Statistical analysis

Categorical data were reported as numbers, proportions and continuous data as means (standard deviations) or medians (interquartile ranges), depending on the distribution of the variables. Categorical data were compared using one or two-tailed χ^2 test or Fisher's exact test where appropriate. Continuous data were compared using independent *t* test or Mann-Whitney *U* test based on the distribution. ANOVA for repeated measures was used to compare $\Delta Na_{timpoints-pre}$ at individual timepoints. Multivariate ANOVA was used to compare serum sodium change between both groups. Univariate logistic regression was used to compare demographic and clinical characteristics between patients with clinically significant change in serum sodium or hyponatremia 24 h following surgery and those who did not, with a predefined $P < 0.1$. Identified variables from these analyses were included in the multivariate logistic regression model to analyze potential predictors. A P value of < 0.05 was considered statistically significant. All data were analyzed using SPSS statistics 26.

Results

Of 102 consecutive patients who were screened, 83 were eligible and 82 were approached for consent. Among them, one refused the consent and one changed the operation plan to conservation treatment on operation day, leaving 80 patients enrolled and included in the primary analysis [Fig. 1].

Baseline characteristics

Table 1 summarizes patient demographic characteristics, baseline and intraoperative clinical data according to group allocation. Both groups were similar in terms of demographic data and details of the surgical procedures. Intraoperatively, the mean amount of trial fluid received by the isotonic balanced and hypotonic solution patients was 7.3 ± 3.7 versus 8.2 ± 4.1 ml/kg/h, respectively ($P = 0.290$). Of the total fluid infused by volume intraoperatively, 56% (± 17%) and 65% (± 14%) were from trial maintenance fluids. Total volume of fluids infused, packed red cell transfusion and vasopressor support were comparable between both groups.

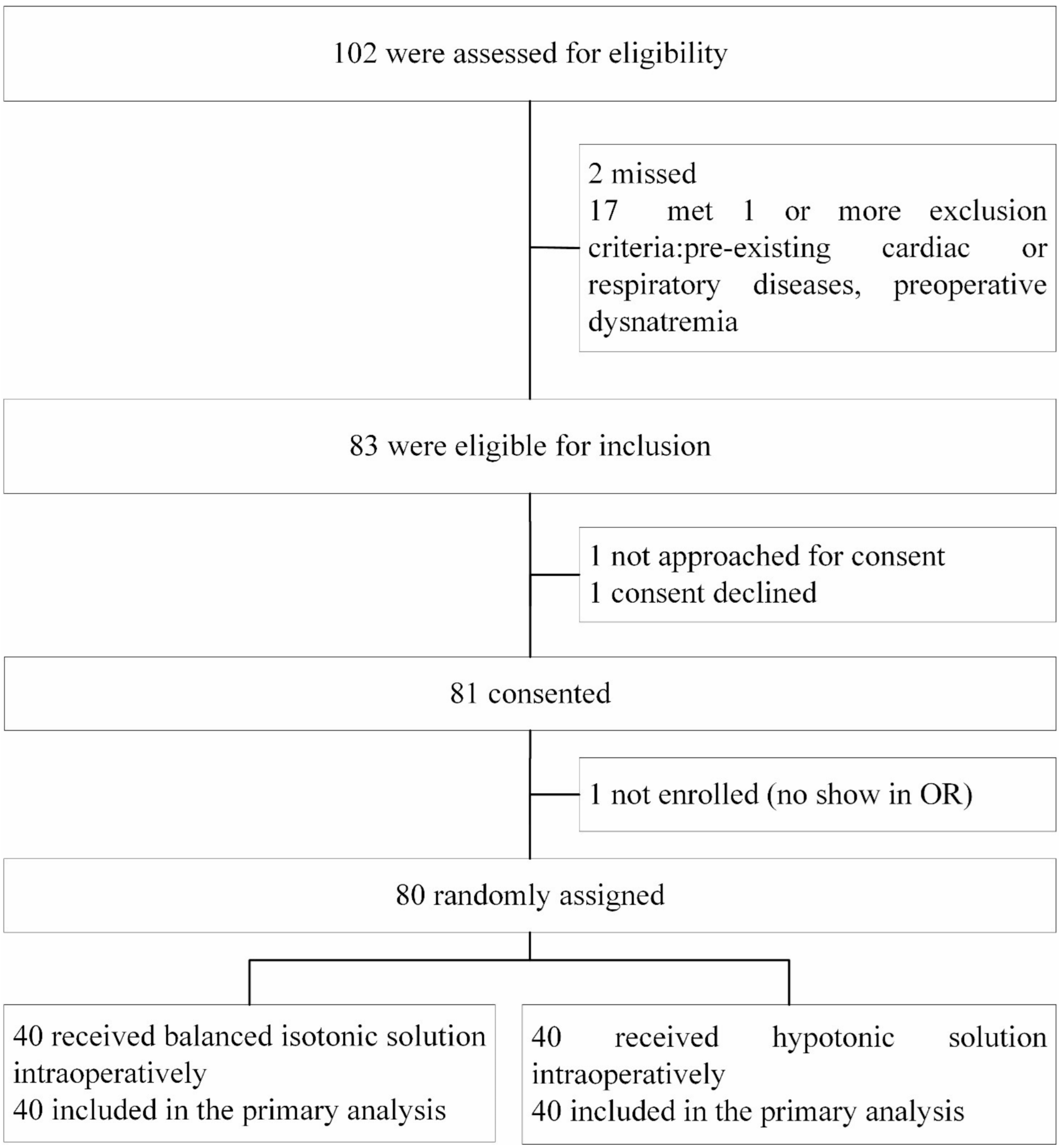

Fig. 1 Participant flow through the trial. OR, operating room

Table 1 Patient characteristics and clinical data

Characteristics and clinical data	Isotonic balanced	Hypotonic	*P* value
Age, month	28(18～42)	36(22～50)	0.229
Male, *n* (%)	22(55)	26(65)	0.494
Weight, kg	13.0(11.1～16.8)	13.4(11.8～19.8)	0.423
Height, cm	92(83～102)	95(85～108)	0.301
Body weight index	15.9(14.6～16.9)	15.7(14.8～16.9)	0.954
ASA I, *n* (%)	27(67.5)	27(67.5)	1.000
Surgery reason, *n* (%)			0.675
Epilepsy	38(95)	36(90)	
Tumor*	2(5)	3(7.5)	
Craniosynostosis	0(0)	1(2.5)	
Duration of surgery, min	184 ± 49	175 ± 38	0.371
Duration of anesthesia, min	243 ± 55	240 ± 42	0.790
Fluid input, ml/kg/h	12.8 ± 4.8	12.6 ± 5.3	0.893
Trial maintenance fluid, ml/kg/h	7.3 ± 3.7	8.2 ± 4.1	0.122
Normal saline, ml	100(0～115)	100(0～100)	0.647
Blood product, ml	200(200～200)	200(200～200)	0.183
Red blood cell transfusion, ml	200(100～200)	200(175～200)	0.183
Blood loss, ml	150(100～150)	150(100～150)	0.698
Urine output, ml/kg/h	4.1(2.3～6.6)	3.9(2.3～8.4)	0.840
Vasoactive agents, *n* (%)	12(30)	16(40)	0.348
Fluid balance, ml/kg/h	-0.1 ± 3.1	0.9 ± 4.2	0.303
Postoperative admission location			
ICU, *n* (%)	9(22.5)	7(17.5)	0.576
Fluid input within first 24 h post, ml	1553 ± 464	1467 ± 359	0.365
Blood product within first 24 h post, ml	0(0～200)	0(0～0)	0.581
Drain output within first 24 h post			
Subdual drainage, *n* (%)	16 (40)	11 (27.5)	0.237
Subdural, ml	247(159～305)	265(203～334)	0.577
Epidural drainage, *n* (%)	35 (87.5)	31 (77.5)	0.239
Epidural, ml	159(80～204)	158(142～200)	0.928
Subdural or epidural drainage, *n* (%)	38 (95)	34 (85)	0.263
Total, ml	247(170～354)	180(149～296)	0.179
Urine output within first 24 h post, ml	834 ± 411	864 ± 388	0.838
Fluid balance within first 24 h post, ml	468(292～721)	421(131～660)	0.397

*One temporal tumor and one lateral ventricular tumor in the isotonic balanced patients as well as one ependymoma and two fourth ventricle tumors in the hypotonic patients. Data are *n* (%), mean (± standard deviation), median (interquartile range). ICU, intensive care unit

Laboratory outcomes

Serum sodium level showed a consistent decrease in both groups following induction, which stabilized within 48 h following surgery [Table 2; Fig. 2, and Additional file 2]. Immediately following induction, a fall in serum sodium level was −4.0 ± 2.6 versus −4.5 ± 2.6 mmol/l in the isotonic balanced and hypotonic patients, respectively ($P = 0.230$). The differences in sodium change between both groups were significant from the end of surgery to 24 h following surgery. Intraoperative isotonic balanced maintenance fluid infusion did not prevent sodium homeostasis derangement but exhibited an early onset stabilization of serum sodium.

Serum sodium change at the end of surgery was clinically significantly less in group IB compared with that in group H (-1.4 ± 3.6 versus −4.6 ± 3.5 mmol/l, $P < 0.001$). With regard to the primary outcome, $\Delta Na_{24h-pre}$ was statistically but not clinically less in the isotonic balanced patients compared with that in the hypotonic patients (-1.2 ± 4.8 versus −3.4 ± 2.5 mmol/l, $P = 0.028$) [Table 2]. Twenty (50%) in the isotonic balanced patients and 25 (63%) in the hypotonic patients had $\Delta Na_{24h-pre}$>2.5 mmol/l (6.0 ± 3.4 versus 4.8 ± 2.1 mmol/l) ($P = 0.260$). Among them, 13 (33%) in the isotonic balanced patients and 25 (63%) in the hypotonic patients had serum sodium decrease > 2.5 mmol/l (6.4 ± 3.7 versus 4.8 ± 2.1 mmol/l) compared with baseline ($P = 0.007$), and 7 in group IB and none in group H exhibited serum sodium increase > 2.5 mmol/l (median, 4.1 [range 2.7～9.2] mmol/l). Notably, 10 (25%) in the isotonic balanced patients and 6 (15%) in the hypotonic patients had $\Delta Na_{24h-pre}$ > 5mmol/l (median, 8.5 [5.1～14.6] mmol/l versus 7.2

Table 2 Comparisons of changes in serum electrolytes, acid-base parameters, and blood hemoglobin

	End of surgery-baseline		24 h post-baseline		48 h post-baseline	
	Isotonic balanced	Hypotonic	Isotonic balanced	Hypotonic	Isotonic balanced	Hypotonic
Sodium, mmol/l	-1.4 ± 3.6*	-4.6 ± 3.5	-1.2 ± 4.8*	-3.4 ± 2.5	0.0 ± 2.9	-0.2 ± 2.5
Potassium, mmol/l	-0.3 ± 0.6	-0.1 ± 0.5	-0.6 ± 0.4	-0.6 ± 0.4	-0.2 ± 0.4	-0.2 ± 0.4
Calcium, mmol/l	0.1 ± 0.1	0 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.2
Magnesium, mmol/l	0.1 ± 0.2	0.1 ± 0.1	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.1	0.1 ± 0.1
Chloride, mmol/l	-1.3 ± 3.9	-2.6 ± 3.4	0.5 ± 3.1	1.0 ± 2.4	-0.1 ± 3.9	-0.4 ± 3.5
Glucose, mmol/l	0.7 ± 1.6*	3.1 ± 3.3	1.7 ± 2.1	2.2 ± 2.2	0.7 ± 0.9	0.3 ± 0.7
Bicarbonate, mmol/l	2.6 ± 2.0	2.4 ± 2.8	-1.5 ± 3.1	-1.9 ± 3.5	2.0 ± 3.0	1.8 ± 3.4
Anion gap, mmol/l	-3.2 ± 4.7	-4.6 ± 6.0	0.1 ± 3.6	-0.3 ± 3.5	-2.1 ± 3.2	-1.8 ± 4.2
Strong ion difference, mmol/l	-0.6 ± 4.2	-1.9 ± 5.2	-1.4 ± 3.1	-2.3 ± 2.4	-0.1 ± 2.6	0.0 ± 3.2
Hemoglobin, g/l	-10 ± 19	-9 ± 16	-9 ± 15	-14 ± 14	-20 ± 13*	-27 ± 17

*$P < 0.05$, isotonic balanced fluid versus hypotonic fluid

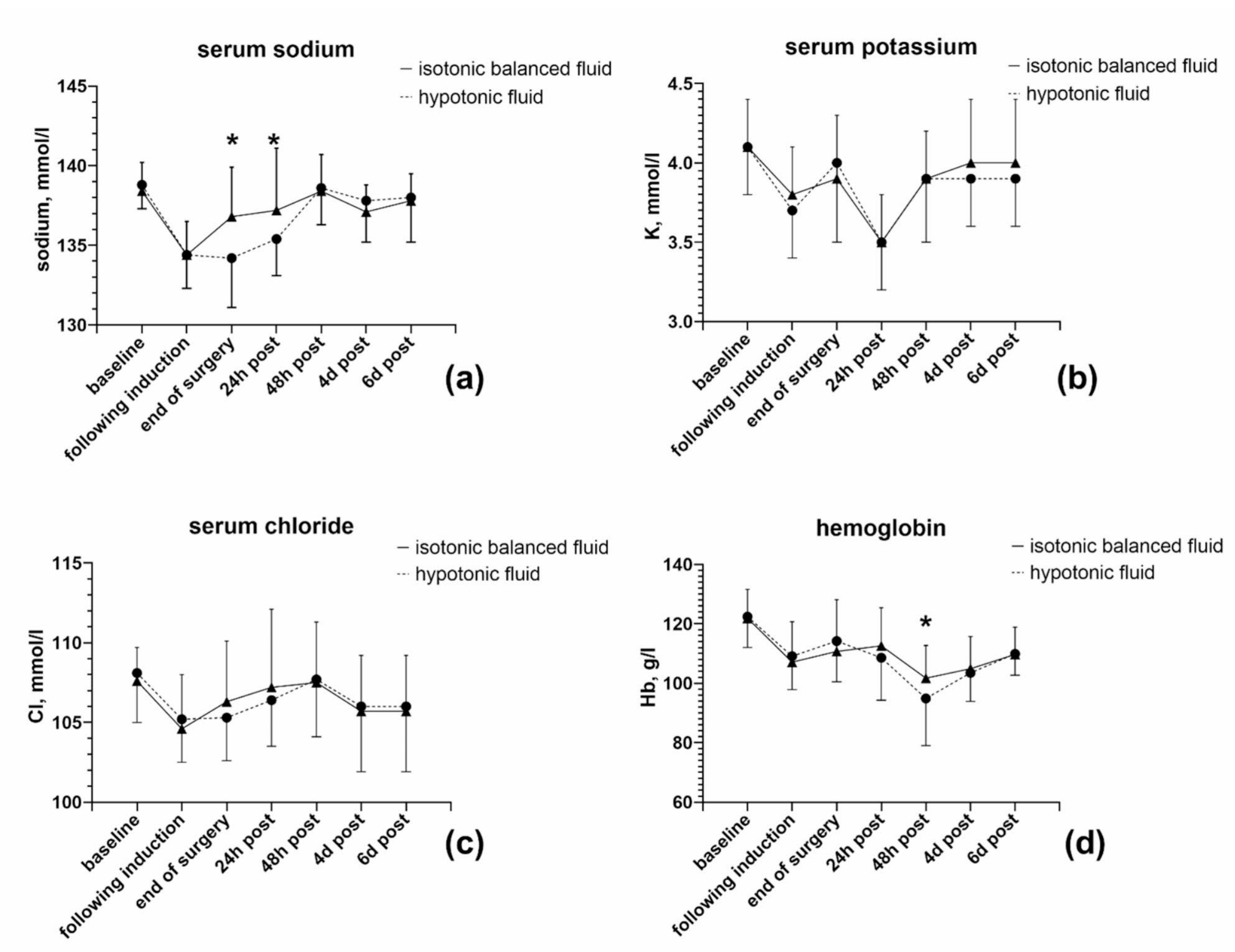

Fig. 2 Mean measurements in serum electrolyte and blood hemoglobin levels by intraoperative maintenance fluid types during the study period **(a)** serum sodium, **(b)** serum potassium, **(c)** serum chloride, **(d)** blood hemoglobin. Ends of whiskers represented standard deviations. *$P < 0.05$, isotonic balanced fluid versus hypotonic fluid

[range 5.5 ~ 11.1] mmol/l) ($P = 0.264$). Among them, 7 (18%) in the isotonic balanced patients and 6 (15%) in the hypotonic patients experienced sodium decrease > 5 mmol/l (median, 8.1 [range 5.1 ~ 14.6] versus 7.2 [range 5.5 ~ 11.1] mmol/l) ($P = 0.762$), while 3 in the isotonic balanced patients had sodium increase > 5 mmol/l (median, 8.9 [range 6.2 ~ 9.2] mmol/l). Both serum nadir sodium of 126.8 mmol/l and maximum sodium of 145.0 mmol/l in all patients were observed in those receiving intraoperative isotonic balanced maintenance fluids, and the hypotonic patients had the minimum and maximum sodium levels at 128.6 and 139.2 mmol/l, respectively. No significant differences with respect to $\Delta Na_{48h-pre}$ were noted between both groups (0.0 ± 2.9 versus −0.2 ± 2.5 mmol/l, $P = 0.364$). Fifteen (38%) in the isotonic balanced patients and 14 (35%) in the hypotonic patients had $\Delta Na_{48h-pre}$ > 2.5 mmol/l ($P = 0.816$). Furthermore, the change in serum levels of potassium, chloride, calcium, and magnesium were similar between both groups at pre-specified postoperative timepoints [Table 2].

Episodes of laboratory-defined hyper-/hyponatremia, hyper-/hypokalemia, hyper-/hypochloremia during the postoperative period were summarized in Table 3. Immediately following surgery, 9 (23%) versus 18 (45%) had hyponatremia in the isotonic balanced patients and the hypotonic patients, respectively ($P = 0.033$). Severe hyponatremia was not seen in the isotonic balanced patients but noted in 3 hypotonic patients. Five of 19 (26%) in the isotonic balanced patients demonstrating hyponatremia following induction continued to experience hyponatremia at the end of surgery compared to 13 of 18 (72%) in the hypotonic patients. Twenty-four h following surgery, hyponatremia remained less seen in the isotonic balanced patients compared with that in the hypotonic patients (20% versus 43%, $P = 0.030$). However, 3 isotonic balanced patients had severe hyponatremia compared to 1 hypotonic patient having it. Two (25%) of 8 hyponatremic patients 24 h postoperatively in group IB continued to experience hyponatremia 48 h postoperatively compared to 3 (17.6%) of 17 hyponatremic patients in group H. No significant differences were noted between both groups in the rates of hypernatremia, hyper- or hypokalemia, hyper- or hypochloremia, or non-anion gap acidosis.

Patient demographics and clinical data (variables in Table 1) along with laboratory data collected within 24 h postoperatively, were compared using univariate logistic regression with a $P < 0.1$ between patients with serum sodium change > 2.5 mmol/l or hyponatremia 24 h following surgery and those who did not. Identified variables were included in the multivariate logistic regression model. $\Delta Na_{24h-pre}$ > 2.5 mmol/l was significantly associated with serum sodium level at the end of surgery (odd ratio 0.754, 95% confidence interval 0.627 ~ 0.906, $P = 0.003$) as demonstrated by the logistic regression model. For hyponatremia occurring 24 h following surgery, intraoperative maintenance fluid amount was identified as a significant predictive variable (odd ratio 1.265, 95% confidence interval 1.053 ~ 1.519, $P = 0.012$).

Radiographically, the grade of brain swelling on postoperative Day 1 was comparable between the isotonic balanced patients and the hypotonic patients (2[1 ~ 3] versus 2[1 ~ 3], $P = 0.580$). The grade of brain swelling being 3 was seen in 18 (45%) of the isotonic balanced patients and 14 (35%) of the hypotonic patients ($P = 0.361$).

Higher blood hemoglobin level 48 h following surgery was noted in the isotonic balanced patients compared with that in the hypotonic patients (102 ± 11 versus 95 ± 16 g/l, $P = 0.029$). During surgery, neither hypoglycemia nor blood glucose level > 10 mmol/l were documented. Glucose concentrations increased significantly at the end of surgery in the hypotonic patients compared with the isotonic balanced patients (3.1 ± 3.3 versus

Table 3 Postoperative electrolyte outcomes based on clinical reference thresholds

Laboratory outcomes, *n*(%)	Isotonic balanced	Hypotonic	*P* value
Hyponatremia 24 h post	8(20)	17(43)	0.030*
Severe hyponatremia 24 h post	3(8)	1(3)	0.615
Hyponatremia 48 h post	2(5)	3(8)	1.000
Severe hyponatremia 48 h post	0(0)	0(0)	1.000
Hyponatremia within 48 h post	8(20)	17(43)	0.030*
Severe hyponatremia within 48 h post	3(8)	1(3)	0.615
Hypernatremia within 48 h post	0(0)	0(0)	1.000
Hyperchloremia 24 h post	9(23)	5(13)	0.239
Hypochloremia 24 h post	1(3)	0(0)	1.000
Hyperchloremia 48 h post	11(28)	10(25)	0.799
Hypochloremia 48 h post	0	0	1.000
Hypokalemia within 48 h post	23(58)	23(58)	1.000
Hypocalemia within 48 h post	3(8)	4(10)	1.000
Hypomagnesemia within 48 h post	0(0)	1(3)	1.000
NAG			
NAG acidosis 24 h post	27(68)	33(83)	0.121
NAG acidosis 48 h post	17(43)	15(38)	0.452
Brain swelling grade in cranial CT on postoperative Day 1	2(1 ~ 3)	2(1 ~ 3)	0.580

*$P < 0.05$, isotonic balanced fluid versus hypotonic fluid. CT, computed tomography; NAG, non-anion gap

Table 4 Patient-centered outcomes during the postoperative period

Patient-centered outcomes	Isotonic balanced	Hypotonic	*P* value
Fluid input within second 24 h post, ml	1671 ± 364	1791 ± 457	0.204
Blood product within second 24 h post, ml	0(0 ~ 0)	0(0 ~ 0)	0.347
Drain output within second 24 h post			
Subdual drainage, *n* (%)	16 (40)	11 (27.5)	0.237
Subdural, ml	206(137 ~ 263)	308(113 ~ 362)	0.056
Epidural drainage, *n* (%)	35 (87.5)	28 (77.5)	0.056
Epidural, ml	101(43 ~ 191)	79(48 ~ 124)	0.274
Subdural or epidural drainage, *n* (%)	38 (95)	34 (85)	0.263
Total, ml	202(116 ~ 277)	107(61 ~ 236)	0.057
Urine output within second 24 h post, ml	1154 ± 420	1444 ± 512	0.008*
Fluid balance within second 24 h post. ml	321(47 ~ 572)	291(-75 ~ 485)	0.355
Length of postoperative hospital stay, d	11(8 ~ 14)	11(10 ~ 14)	0.530
Circulatory overload, *n* (%)	0(0)	0(0)	1.000
Hyponatremic seizure, *n* (%)	0(0)	0(0)	1.000
Altered mental status ascribed to hyponatremia, *n* (%)	0(0)	0(0)	1.000
Fever (> 38.5℃) within 6d post, *n* (%)	31(77.5)	31(77.5)	1.000
Fever (> 38.5℃) within 6d post, d	2(1 ~ 3)	1(1 ~ 3)	0.410
Bronchitis, *n* (%)	8(20)	9(22.5)	0.785
Pneumonia, *n* (%)	2(5)	2(5)	1.000
Intracranial infection, *n* (%)	0(0)	0(0)	1.000
Wound infection, *n* (%)	2(5)	3(7.5)	1.000
More than 2 sodium measurements within 48 h post, *n* (%)	2(5)	1(2.5)	1.000

*$P < 0.05$, isotonic balanced fluid versus hypotonic fluid

0.7 ± 1.6 mmol/l, $P < 0.001$), which showed stabilization 24 h following surgery.

3. Patient-centered outcomes.

Patient-centered outcomes including volume of fluid intake and output as well as postoperative adverse events are presented in Table 4. There were no differences in the fluid intake volume between the isotonic balanced patients and the hypotonic patients within 48 h following surgery. Less diuresis was observed in the isotonic balanced patients compared with that in the hypotonic patients 48 h following surgery (1154 ± 420 versus 1444 ± 512 ml, $P = 0.008$).

None of the patients developed any signs of circulatory overload, hyponatremic seizures and altered mental status documented by the care team. The patients who had severe hyponatremia postoperatively recovered with sodium correction and no subsequent neurological damage was reported. There were no significant differences in postoperative adverse events (bronchitis, pneumonia, intracranial infection, wound infection), days with moderate and/or severe fever, and duration of postoperative hospital stay between both groups.

Discussion

This randomized controlled trial involving children aged up to 6 years undergoing major neurosurgery provided prospective evidence for a statistically but not clinically decreased odds of postoperative sodium homeostasis derangement with the isotonic balanced solution administration as an intraoperative maintenance fluid, compared with the hypotonic solution. The present study is focused on those of the most vulnerable population to be affected by acute electrolyte disequilibrium. Although the data in this specific pediatric population added support to the known literature demonstrating that isotonic balanced crystalloids are associated with less sodium derangement in general pediatric population, excessive sodium fluctuation following isotonic balanced fluid infusion was evident in this vulnerable population. This study focused two important periods following the initial neurosurgical procedure for risk of hyponatremia (postoperative Day 0 ~ 1 and Day 5 ~ 6) [1] to assess the impact of intraoperative isotonic balanced maintenance fluid on postoperative sodium homeostasis. Intraoperative isotonic balanced maintenance fluid infusion reduced the incidence of hyponatremia by approximately 50% on postoperative Day 0 ~ 1, compared to hypotonic fluid maintenance, and had no significant effect on sodium homeostasis on postoperative Day 5 ~ 6.

The results from this trial with Plasma-Lyte A is consistent with the previous investigations in pediatric population. McNab et al. compared Plasma-Lyte A and 0.45% saline in the pediatric population who needed intravenous maintenance hydration for 6 h and above and demonstrated a lower rate of hyponatremia without an increase in adverse events in those receiving plasma-Lyte A [16]. Serum $\Delta Na_{end-induction}$ in this study was similar to a recent neurosurgical pediatric trial which administered

Plasma-Lyte A during and (24 h) after brain tumor resection in patients aged 6 months to 12 years (the median $\Delta Na_{end-induction}$: 2 [0～4.5] versus 3 [-1～3] mmol/l, respectively) [8].

The safe utilization of isotonic balanced solutions and the impact on electrolytes in small children undergoing major neurosurgery deserve special attention by the care team. The American Academy of Pediatrics recently recommends patients 28 days to 18 years of age requiring maintenance intravenous fluids should receive isotonic solutions with appropriate potassium and dextrose as they significantly decrease the risk of developing hyponatremia [17]. However, prescribing practice of perioperative fluids in children still varies. Use of hypotonic fluids remains the standard of care in small neurosurgical patients in some medical centers around the world, just as the departmental routines in our hospital. Glomerular filtration rate (GFR) in a neonate reaches adult levels only by two years of age [18]. The low GFR is because of decreased glomerular capillary surface area, low systemic arterial pressure, and high renal vascular resistance. The concentrating ability is low because of hypotonicity of renal medulla. The variability in coping with a sodium burden is reflected by dramatic $\Delta Na_{24h-pre}$ (-14.62～9.22 mmol/l) following intraoperative isotonic fluid infusion in our patients. Small children receiving isotonic fluid therapy have an increased risk for hypernatremia due to the limited ability to deal with an abrupt massive sodium load by the immature kidney. Seven isotonic balanced patients (18%) demonstrated increased serum sodium of >2.5 mmol/l 24 h following surgery compared with none of the hypotonic patients in this study. Desalination was also observed in a study wherein patients who developed hyponatremia had a higher urine sodium loss and greater diuresis [19]. This is also termed "cerebral salt wasting syndrome", which might be related to overexpansion of the extracellular fluid compartment from fluids infused during surgery in combination with increased ADH, natriuretic peptide, and GFR. We noted severe hyponatremia 24 h following surgery in 3 isotonic balanced patients and 1 hypotonic patient, although mild hyponatremia was less observed in isotonic balanced patients. Isotonic balanced fluids produce an additional sodium burden, which is potentially associated with a positive fluid balance and respiratory complications [20–22]. This study provides safe evidence that intraoperative isotonic maintenance fluid lasting approximately 4 h was not associated with signs of circulatory overload, postoperative positive fluid balance, and increased respiratory complications compared to the hypotonic fluid. Perioperative safe infusion duration limit for isotonic balanced maintenance fluid in this vulnerable population still needs to be investigated in future trials.

Despite significant variations in sodium levels postoperatively compared to baseline in both groups, no signs of circulatory overload or severe neurological sequalae, such as hyponatremic seizures and altered mental status, were observed. Acute hyponatremia causes an osmotic water shift from the hypotonic plasma to the relatively hypertonic brain, promoting cerebral edema and associated morbidities. However, previous studies on the relationship between hyponatremia and postoperative morbidities in various neurological conditions have yielded inconsistent results. Two of the largest prospective studies found no association between hyponatremia and acute inpatient mortality in patients with traumatic brain injury or subarachnoid hemorrhage [23, 24]. In contrast, a retrospective study in neurologically ill children with external ventricular drains showed that greater serum sodium fluctuations were significantly associated with a higher risk of mortality [25]. Similarly, Williams reported that postoperative hyponatremia was associated with more complicated and significantly worse neurological outcomes in children with intracranial neoplasms [26].The negative findings of hyponatremic encephalopathy in our study might be attributed to the fact that neurological patients typically adapt hyponatremic conditions preoperatively. In a retrospective study on pediatric brain tumor surgery, 43% of patients exhibited hyponatremia upon admission, even though their sodium levels were normal immediately before surgery [1]. Additionally, the presence of concomitant neurosurgical conditions and antiepileptic medications complicated the assessment of the exact impact of hyponatremia on patients' overall status [27]. Regarding other clinical outcomes, despite the potential influence of various factors, the higher hemoglobin levels and reduced diuresis observed 48 h following surgery as well as a weak trend towards less subdural drainage (medians of 206 and 308 ml) in isotonic balanced patients, might indicate a lower accumulation of intravascular fluids and brain edema associated with intraoperative use of isotonic balanced maintenance fluid compared to hypotonic fluid.

Even with intraoperative isotonic balanced fluid infusion, 20% of patients still developed postoperative hyponatremia. ADH levels are often elevated in postoperative patients. Choong's study demonstrated that mean ADH levels were elevated on postoperative Day 1 and normalized the next day [28]. This study investigated children admitted for neurosurgical surgery, a particular group subjected to several non-osmotic stimuli for ADH secretion such as neural tissue manipulation, pain, stress, and certain medications. Clinically significant decrease in serum sodium level 24 h following surgery was related to intraoperative hypotonic maintenance fluid and low serum sodium level following induction as evidenced by the Logistic regression model in this study.

Avoiding excessive volume replacement during induction and active correction of serum sodium decrease following induction intraoperatively deserved further consideration.

We noted comparably high rates of postoperative hypokalemia in both groups. Despite the contribution of K from Plasma-Lyte A, hypokalemia occurs when this contribution is minimal and generally insufficient as a general rule.

The limitations of the current study were its relatively small sample size and the resultant inability to detect some clinically important secondary outcomes. Our findings were limited to one center with departmental routines applied and hence may not be generalizable. Complete transition to a hypotonic fluid administration strategy during the postoperative period reduced the impact of a brief duration of intraoperative isotonic fluids administration. Nonetheless, we observed that a higher percentage of the isotonic balanced patients experienced a sodium fluctuation greater than 5 mmol/l, compared to the hypotonic patients, over a mean infusion period of approximately 4 h. The primary reason for surgery was epilepsy, which may not be fully representative of other types of neurosurgeries. Further research on major neurosurgeries for conditions such as traumatic brain injury and neoplasms is needed to validate our findings. We excluded several diagnostic groups of children such as patients with baseline hyponatremia, limiting the generalizability of our findings. We are aware that there are regional differences to the availability of isotonic balanced solutions, and this may be the primary influence on prescription practices. Safe and effective fluid composition regimen for small children with neurological compromise remains to be investigated in prospective trials with large sample size. Brain edema following neurosurgery is common and expected immediately postoperatively. The effect of the serum sodium changes on brain edema may be minimal in neurosurgical patients, particularly when the alteration in serum sodium levels is not substantial.

Conclusion

In small children undergoing major neurosurgery, intraoperative isotonic balanced solution infusion resulted in statistically but not clinically minimal variations in serum sodium and hemoglobin levels postoperatively, compared to the use of hypotonic fluid. Our findings suggested that the potential risk of excessive sodium fluctuation following the use of isotonic balanced solution in small children undergoing major neurosurgery should be cautioned, even for a brief period of infusion. This randomized controlled trial contributes to more comprehensive practice recommendations for safe fluid administration in pediatric neurosurgery.

Abbreviation

$\Delta Na_{timepoints-pre}$	the variations of serum electrolytes between postoperative pre-specified timepoints and baseline
$\Delta Na_{24h-pre}$	the variation of serum sodium level between 24 h following surgery and baseline
ADH	Antidiuretic hormone
H	Hypotonic solution
GFR	Glomerular filtration rate
IB	Isotonic balanced solution
SID	Strong ion difference

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
XMW wrote the original draft and performed formal analysis.ZY acquired data, performed formal analysis, and wrote the original draft.XMW and ZY contributed equally to this work.ZHT acquired data and wrote the original draft.LC acquired data.GZY reviewed and edited the original draft. SLL conceptualized the study, established the methodology, administered the project, and edited the original draft.WDX conceptualized the study, established the methodology, and edited the original draft.

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Data availability
The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The trial protocol was approved by the ethical committee of Peking University First Hospital (2021 – 269). Written informed consent was obtained from legal guardians of all participants. This study was conducted in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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