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Original Article

Goal-Directed Fluid Therapy Using Normal Saline versus Ringer's Lactate in Pediatric Neurosurgical Patients: A Randomized Controlled Trial

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Abstract

Background Ringer's lactate (RL) and 0.9% sodium chloride (NS) are used intraoperatively in pediatric surgical patients. The fluid of choice in pediatric neurosurgical patients is still under research. Hence, we compared NS and RL intraoperatively with a primary objective of measuring the absolute difference in serum chloride concentrations (ΔCl^-) after surgery from baseline. Secondary objectives included changes in other electrolytes, osmolarity, pH, creatinine, brain relaxation score (BRS), and neurological outcome at discharge using a modified Rankin scale (mRS).

Methods This prospective randomized trial was conducted in American Society of Anesthesiologists status I to II children, aged 6 months to 14 years, after Institutional Ethical Committee approval and written informed consent. Forty patients were randomized in group-S (received 0.9% Saline) and group-R (received RL). The fluid administration was guided by Pleth Variability Index (target $<13\%$). Arterial blood samples were taken at the start of surgery, during tumor resection, and at the end of surgery.

Results Twenty-one patients in NS and 19 patients in RL were enrolled. ΔCl^- was 12 (9–16) mmol/L in NS group and 4 (2–15) mmol/L in RL group, $p = 0.03$. NS group developed more metabolic acidosis (6 [28.6%] vs. 0 [0.0%], $p = 0.021$). There was no difference in the other electrolytes, serum osmolarity, BRS, perioperative creatinine, and mRS between groups, $p = 0.36$, $p = 0.096$, $p = 0.658$, and $p = 0.168$, respectively.

Conclusion Intraoperative use of NS causes derangement in chloride balance, leading to metabolic acidosis compared to RL in children undergoing neurosurgical procedures. However, there was no difference in the other parameters, including serum osmolarity, BRS, and mRS.

Keywords
- neurosurgery
- normal saline
- pediatric
- Ringer's lactate

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Introduction

Fluid management during the perioperative phase poses unique challenges for pediatric neurosurgical patients. Perioperative fluid management aims to maintain or optimize cerebral physiology without disturbing systemic homeostasis. Cerebral physiology may get disturbed with the infusion of large volumes of nonphysiological fluids, that is, a fluid having composition varying largely from plasma. Fluid replacement during intracranial surgery should be done with glucose-free isotonic crystalloids. The choice between crystalloid and colloid solutions remains debatable.[1]

The osmotic gradient is the primary factor affecting water flow across a healthy blood–brain barrier.[2] Thus, fluid osmolarity is the most crucial element in preventing cerebral edema.[3,4] Normal saline (0.9% saline, NS) is a commonly used fluid in neurosurgical patients due to its mild hyperosmolarity (308 mOsm/L). However, there is a potential risk of hyperchloremic metabolic acidosis when NS is infused in large volume due to its supraphysiological chloride concentration (154 mEq/L) and low pH (5.0).[5] Previous studies observed that the balanced isotonic electrolyte solutions maintain the acid–base parameters.[3,6,7] Furthermore, these have been linked to side effects such as hyperkalemia, renal vasoconstriction, delayed micturition, acute kidney injury (AKI), and increased hospital mortality when used in higher quantity.[8]

Ringer's lactate (RL), being more physiological fluid, is favored in pediatric patients. Due to the lower serum osmolarity (273 mOsmols/L) and osmolality (255 mOsmols/kg), it is not studied extensively in neurosurgical cases as there may a theoretical risk of cerebral edema.[9] However, human studies have failed to show the change in serum osmolarity in healthy volunteers after infusion of two liters of RL.[10] Another study by Bhagat et al found that brain relaxation scores (BRS) were comparable in patients with supratentorial tumors receiving NS, RL, or a combination of the two fluids intraoperatively.[11]

In neurosurgical patients, major blood loss is quite common, and a large amount of fluid, blood, and blood products are frequently used. In pediatric patients, such major fluid shifts have a more significant effect than the adults, as the buffer and renal systems are not fully mature.[12] Hence, the type of fluid being used may cause major electrolytes and pH disturbances. There is very sparse literature on perioperative fluid management during pediatric neurosurgical procedures.

Hence, we aimed to compare NS and RL with a primary objective of comparing the absolute chloride difference in plasma immediately after surgery from baseline. The secondary objectives were to compare variations of other electrolytes and base deficit, incidence of hyperchloremic metabolic acidosis, BRS, serum osmolarity, serum creatinine at 24 hours, and neurological outcome at discharge.

Materials and Methods

This randomized, controlled, double-blind trial was conducted between August 2021 and April 2022 after getting the Ethical Committee approval NK/7299/DM/334 and obtaining written informed consent from the patient's next of kin. The children of age group from 6 months to 14 years having American Society of Anesthesiologists (ASA) physical status of 1 to 3, who were scheduled for elective craniotomy for intracranial space-occupying lesions, were enrolled. Patients with significant cardiorespiratory impairment, major end-organ dysfunction (kidney or liver failure), hematological abnormalities (malignancies), electrolyte abnormalities, and anticipated major blood loss were excluded.

The patients were randomized into two groups, group S (control group) and group R (intervention group). The randomization list was created by a computer-generated random number table, and a serially arranged sealed envelope ensured blinding. The envelope was opened, and the drug was prepared by the anesthesiologist who was involved in patient care. The study drug was prepared by pasting the opaque plaster over the label of the crystalloid bottle. The anesthesiologist collecting the data and the surgeon who assessed the surgical field condition were blinded to treatment group allocation.

Study Protocol

After ensuring adequate fasting as per ASA fasting guidelines, patients received intravenous midazolam (0.1 mg/kg) just before shifting the patient to the operation theatre. Preinduction monitoring included pulse oximetry (SpO_2), heart rate (HR), noninvasive arterial blood pressure, electrocardiography, and Pleth Variability Index (PVI) measurement probe (Masimo SET, Masimo Corporation, Irvine, California, United States). Patients were induced with fentanyl, propofol, and atracurium. Trachea was intubated with the appropriate size of an endotracheal tube. Postinduction monitors included arterial blood pressure, urinary output, temperature, and capnography (end-tidal carbon dioxide [$EtCO_2$]). The patients were ventilated with oxygen and nitrous oxide mixture (50:50) to obtain a target $EtCO_2$ between 35 and 40 mm Hg. The anesthesia was maintained with sevoflurane to target a combined minimum alveolar concentration of 1 to 1.2. Normothermia was maintained using warming blankets and warm fluids.

The intravenous fluid was administered by PVI-guided protocol to maintain PVI less than 13%. If the patient had hypotension with PVI more than 13%, a fluid bolus of 5 ml/kg was given. If hypotension occurs in patients with PVI less than 13%, we tried to look for the cause of the hypotension, such as blood loss exceeding maximum allowable blood loss (MABL), venous air embolism, and severe acidosis and managed accordingly. The patients in group S received NS, and group R received RL as the maintenance fluid calculated by Holliday and Segar formula.[13] Blood and blood products were given once the MABL was reached.[14] Hypotension was defined as blood pressure of less than 10% of the age-appropriate blood pressure values.

Various parameters, including demographic data, disease pathology, and vital parameters (HR, blood pressure, SpO_2, $EtCO_2$, and temperature), were recorded every 30 minutes or

during any events throughout the surgery. The arterial blood samples were taken for blood gas analysis at various time points; immediately after induction (baseline, T_0), at dural reflection (T_1), during tumor resection (T_2), and at the end of the surgery (T_3). The parameters recorded from blood gas analysis were pH, base deficits, sodium bicarbonate, electrolytes (Na^+, K^+, Cl^-, Ca^{++}), osmolarity, and hematocrit. After bone flap elevation, the BRS was graded by the surgeon blinded to the type of fluid being administered on a four-point scale.[15] The scores of 1 to 2 were considered clinically acceptable, while patients with grades 3 and 4 required rescue measures. At the end of the surgery, the total amount of fluid infused, urine output, blood loss, and blood products used was recorded. Preoperative and postoperative serum creatinine and hourly urine output (up to 24 hours) were recorded to rule out renal dysfunction. The neurological outcome was assessed using the modified Rankin scale (mRS) at discharge.[16] A score of 0 to 2 was considered good, while 3 to 6 was considered a poor neurological outcome.

We calculated the sample size based on the primary outcome (post-preoperative ΔCl^-) using the results of the previously published study by Lima et al.[17] We used Open Epi software and calculated that 32 participants (16 per group) would be required to detect a difference of 2.5 mmol/L (standard deviation [SD]: 3.0) between groups from baseline to after surgery, assuming a type I error of 0.05 and a power of 0.8. to account for possible losses during follow-up and missing data, we added 10% to the calculation, resulting in an estimate of 40 patients.

The data were analyzed using Statistical Package for Social Sciences (SPSS) version 25.0. The normality of continuous data, including age, weight, duration of surgery, anesthesia, the dose of the anesthetic agent, the total volume of intravenous fluids/blood loss/intraoperative urine output, blood gas parameters, and blood sugar were checked by using the Shapiro–Wilk test. Mean and SD were calculated for normally distributed continuous variables, whereas median and interquartile range were calculated for skewed data. The categorial data, including gender, ASA grading, Glasgow Coma Scale (GCS), diagnosis, BRS grading, and mRS, were represented in frequencies and percentages. A one-way analysis of variance (ANOVA) test was applied to compare means of normally distributed continuous variables (otherwise Kruskal–Wallis test). The chi-square/Fisher's exact test was applied to find any association between categorical variables and two study groups. Paired t-test was applied to analyze the absolute difference in plasma concentrations of chloride between baseline Cl^- and immediately after surgery (post-preop difference of Cl^-) and other normally distributed parameters within each group (otherwise Wilcoxon signed-rank test). The Kruskal–Wallis test was applied to find the median difference between the two study groups in BRS and GCS. Repeated measures ANOVA test (Friedman's test) at different time points within each group using Bonferroni correction as a post-hoc test for multiple comparisons. Two tabled *p*-value less than 0.005 was considered statistically significant with a 95% confidence interval.

Results

A total of 43 patients were assessed, out of which three patients were excluded from the study as they did not meet the inclusion criteria (►**Fig. 1**). A total of 40 patients, 21 in the NS group, and 19 in the RL group were analyzed. Demography, baseline characteristics, and case distribution were similar in both groups (►**Table 1**).

Arterial blood gas (ABG) parameters were comparable at all time points, baseline (►**Table 2**), dural reflection, post-tumor resection, and 24 hours after the surgery, except for Cl^- ions (►**Table 3**). The absolute chloride difference (post-tumor removal–baseline) was significantly elevated in the NS (11.24 ± 6.46) group as compared to RL (6.79 ± 7.78) with $p = 0.003$. The incidence of hyperchloremic metabolic acidosis was higher (28.6%) on the administration of NS than the RL group (0%), $p = 0.021$.

The BRS, total fluid administered, total blood loss, the volume of blood transfused, total urine output and preop, postop creatinine values, and the mRS at discharge were comparable (►**Table 4**).

Discussion

Effective fluid management is crucial during pediatric neurosurgical procedures as any disruption in electrolyte balance can affect cerebral homeostasis.[18,19]

This study found a statistically significant rise in serum chloride concentrations (post-preop ΔCl^-) in the NS group compared to the RL group in pediatric neurosurgical patients ($p = 0.003$). However, the two groups observed no significant differences in other electrolytes, base imbalance, serum osmolarity, glucose, hematocrit, and lactate. These results are consistent with a randomized control study by Lima et al.[17] They compared Plasmalyte-A and NS in 53 pediatric neurosurgical patients and observed that administration of NS led to increased serum chloride variation from before to after surgery. Plasmalyte-A was found to be more effective than NS in maintaining electrolyte balance. These findings can be explained by the higher chloride concentration in the NS (Cl^- =154 mmol/L) compared to RL (Cl^- = 109 mmol/L).[20]

In this study, we observed that the hyperchloremic metabolic acidosis at the time of post-tumor removal (pH< 7.35 and Cl- >110 mEq/L) was higher (28.6%) in the NS group compared to RL group (0%), $p = 0.02$. Zunini et al retrospectively compared NS and RL in 122 pediatric patients of less than 5 years undergoing craniofacial surgeries. They found that severe acidosis (pH < 7.25) was more frequently observed in the patients who received NS (39%) as compared to RL (8%), and there was no significant hyponatremia (Na^+ <135 mEq) in the RL group.[21] These findings may occur because of the acidotic pH of NS (pH = 5.0, Cl^-154 mEq/L) and high chloride concentration compared to RL (pH = 6.5, Cl^-109 mEq/L). From the existing literature, we can conclude that using NS may cause significant metabolic acidosis in pediatric surgical patients. These changes may not be clinically relevant when used in limited volumes. Still, when

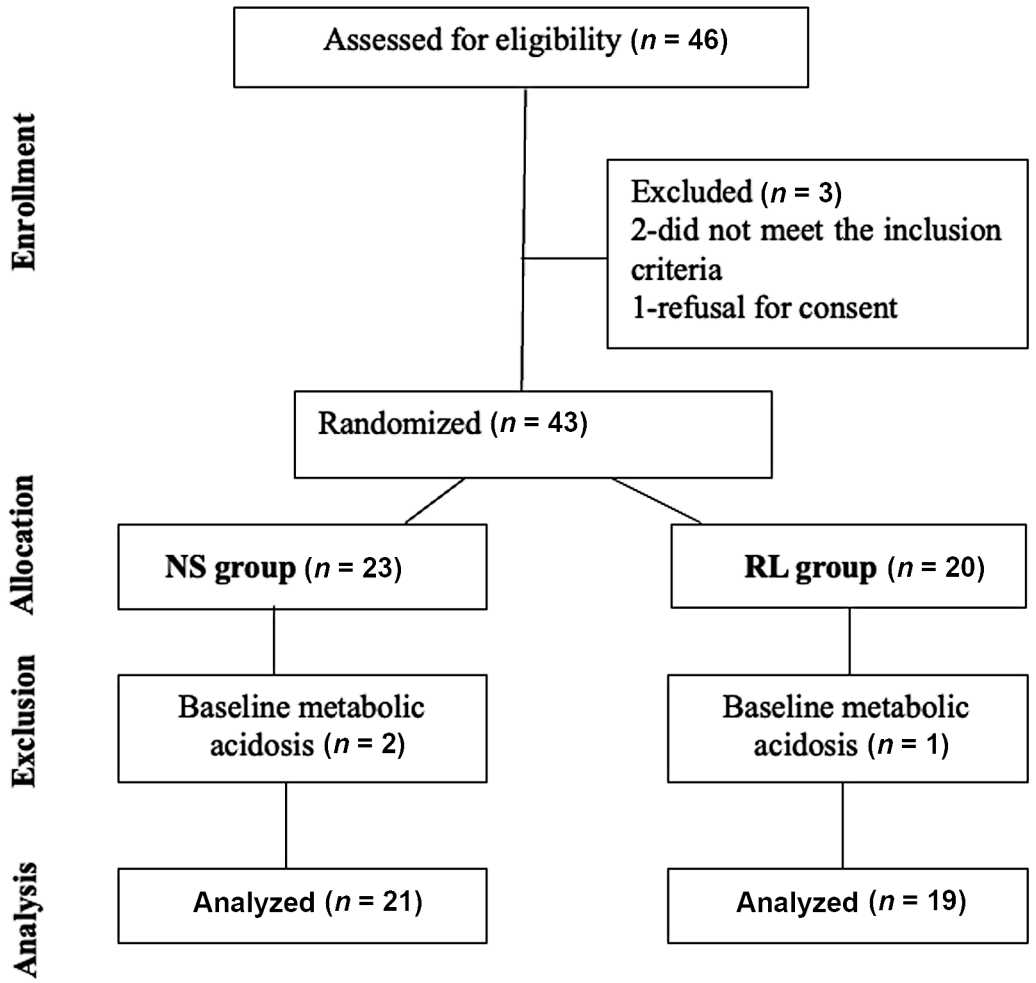

Fig. 1 Consort diagram. NS, normal saline; RL, Ringer's lactate.

Table 1 Descriptive characteristics of the study groups

Parameters	NS ($n = 21$)	RL ($n = 19$)	*p*-Value
Age (years)	8.67 ± 4.31	8.11 ± 3.78	0.624
Age groups, years, *n* (%)			
1–5 6–10 11–14	8 (38.1%) 4 (19.0%) 9 (42.9%)	6 (31.6%) 7 (36.8%) 6 (31.6%)	0.448
Gender, *n* (%)			0.987
Male Female	10 (47.6%) 11 (52.4%)	9 (47.4%) 10 (52.6%)	
Weight (kg)	26.14 ± 11.86	26.11 ± 10.84	0.992
Duration of surgery, hours, mean ± SD	3.29 ± 0.92	3.34 ± 0.67	0.549
Duration of anesthesia, hours, mean ± SD	3.77 ± 0.93	3.79 ± 0.73	0.638
ASA grade I, *n* (%)	21 (100%)	19 (100%)	1.000
GCS, mean ± SD	14.81 ± 0.68	15.00 ± 0.00	0.185
Distribution of cases, *n* (%)			0.366
Supratentorial Infratentorial	7 (33.3%) 14 (66.7%)	9 (47.4%) 10 (52.6%)	

Abbreviations: ASA, American Society of Anesthesiologists; GCS, Glasgow Coma Scale; NS, normal saline; RL, Ringer's lactate; SD, standard deviation.
Data are presented as *n* (%) and mean ± SD.

Table 2 Baseline ABG parameters (T0)

Parameters	NS ($n = 21$)	RL ($n = 19$)	*p*-Value
pH	7.37 ± 0.10	7.40 ± 0.05	0.117
PO_2 (mm Hg)	256.23 ± 46.38	261.39 ± 79.60	0.903
PCO_2 (mm Hg)	34.70 ± 4.28	33.02 ± 1.62	0.342
HCO_3^- (mEq/L)	20.95 ± 1.90	20.51 ± 1.76	0.724
Base excess	−3.29 ± 1.87	−3.15 ± 1.58	0.801
SpO_2 (%)	99.58 ± 0.27	99.61 ± 0.34	0.369
Potassium (mEq/L)	3.52 ± 0.23	3.57 ± 0.22	0.526
Sodium (mEq/L)	138.95 ± 3.29	140.14 ± 2.87	0.147
Chloride (mEq/L)	96.43 ± 1.72	96.37 ± 2.11	0.587
Calcium (mEq/L)	0.96 ± 0.10	0.97 ± 0.11	0.545
Hematocrit (%)	31.08 ± 7.29	29.31 ± 10.30	0.902
Hemoglobin (mg%)	10.61 ± 1.14	10.91 ± 1.13	0.406
Glucose (mg/dL)	134.10 ± 12.31	137.32 ± 22.65	0.586
Lactate (mEq/L)	0.91 ± 0.11	0.91 ± 0.11	0.977
Osmolarity (mOsm/L)	284.43 ± 11.75	286.68 ± 8.04	0.293

Abbreviations: HCO_3^-, bicarbonate; NS, normal saline; PCO2, partial pressure of carbon dioxide; PO2, partial pressure of oxygen; RL, Ringer's lactate; SD, standard deviation; SpO2, pulse oximetry.
Data are presented as *n* (%) and mean ± SD.

Table 3 Change in blood gas parameters at various time points

Parameters	NS ($n = 21$)	RL ($n = 19$)	*p*-Value
ΔSerum sodium			
T1	-0.69 ± 2.27	-0.13 ± 3.49	0.614
T2	-0.30 ± 2.63	-0.54 ± 3.61	0.892
T3	0.48 ± 2.11	-0.62 ± 2.65	0.174
ΔSerum potassium			
T1	0.08 ± 0.15	0.01 ± 0.23	0.259
T2	0.09 ± 0.22	0.05 ± 0.20	0.523
T3	0.07 ± 0.22	−0.01 ± 0.31	0.107
ΔSerum chloride			
T1	13.57 ± 3.53	14.52 ± 4.46	0.390
T2	11.24 ± 6.46	6.79 ± 7.78	0.037*
T3	12.05 ± 8.22	8.32 ± 8.57	0.132
ΔSerum HCO_3^-			
T1	0.04 ± 0.11	−0.02 ± 0.12	0.202
T2	0.01 (0.15)	0.02 ± 0.13	0.703
T3	0.03 ± 0.15	0.03 ± 0.15	1.000
ΔSerum base deficit			
T1	−0.46 ± 1.12	−0.88 ± 2.33	0.348
T2	−0.56 ± 1.92	−0.05 ± 1.56	0.277
T3	−0.84 ± 2.01	0.21 ± 2.12	0.116
ΔSerum calcium			
T1	−0.58 ± 1.30	−0.86 ± 1.48	0.472
T2	−0.41 ± 1.35	−0.25 ± 1.41	0.578
T3	−0.63 ± 1.59	−0.17 ± 2.20	0.693
ΔSerum glucose			
T1	−2.43 ± 15.47	−10.11 ± 19.66	0.184
T2	1.05 ± 15.72	4.74 ± 18.40	0.524
T3	4.81 ± 15.77	0.68 ± 21.55	0.489

(*Continued*)

Table 3 (*Continued*)

Parameters	NS ($n = 21$)	RL ($n = 19$)	*p*-Value
ΔSerum lactate			
T1	0.02 ± 0.14	0.01 ± 0.16	0.402
T2	0.00 ± 0.14	0.04 ± 0.13	0.352
T3	0.00 ± 0.14	0.06 ± 0.10	0.053
ΔSerum osmolarity			
T1	5.67 ± 9.69	1.42 ± 5.90	0.168
T2	4.38 ± 9.82	1.21 ± 7.21	0.586
T3	2.90 ± 10.43	1.95 ± 6.20	0.860
ΔSerum hematocrit			
T1	0.60 ± 7.54	3.21 ± 9.98	0.124
T2	0.87 ± 7.53	2.48 ± 10.73	0.644
T3	0.27 ± 6.89)	2.19 ± 10.35	0.480
ΔSerum hemoglobin			
T1	−2.43 ± 15.47	−10.11 ± 19.66	0.184
T2	1.05 ± 15.72	4.74 ± 18.40	0.524
T3	4.81 ± 15.77	0.68 ± 21.55	0.489

Abbreviations: HCO_3^-, bicarbonate; NS, normal saline; RL, Ringer's lactate; SD, standard deviation; T1, At dural reflection; T2, Post-tumor-removal; T3, At the end of surgery.
Data are presented as mean ± SD.
* signifies that $p < 0.05$, statistically significant.

Table 4 Other secondary outcome parameters

Parameters	NS ($n = 21$)	RL ($n = 19$)	*p*-Value
Hyperchloremic metabolic acidosis, n (%)	6 (28.6%)	0 (0.0%)	0.021*
BRS grades			
1 2 3 4	8 (38.1%) 12 (57.1%) 1 (4.8%) 0	6 (31.6%) 8 (42.1%) 5 (26.3%) 0	0.184
Total blood loss (mL)	340.48 ± 177.92	296.32 ± 194.46	0.287
PRBC (mL)	264.00 ± 158.34	232.00 ± 52.15	1.000
Total IV fluids (mL)	1075.71 ± 490.43)	947.37 ± 350.58	0.349
Total urine output (mL)	449.05 ± 331.39	328.95 ± 190.99	0.302
Creatinine (mg/dL) Preop At 24 hours	0.84 ± 0.12 0.91 ± 0.09	0.90 ± 0.10 0.87 ± 0.10	0.087 0.087
mRS at discharge, *n* (%) Good (0–2) Bad (3–6)	19(90.50) 2(9.50%)	19 (100) 0 (0)	0.179

Abbreviations: BRS, brain relaxation score; IV, intravenous; mRS, modified Rankin Score; NS, normal saline; PRBC, packed red blood cells; RL, Ringer's lactate; SD, standard deviation.
Data are presented as *n* (%) and mean ± SD.
* signifies that $p < 0.05$, statistically significant.

administered in larger volume, as during major blood losses, severe acidosis may occur leading to adverse outcomes.[22]

The factors described above contribute to homeostatic disruption and thus result in metabolic acidosis.[23] RL being multielectrolyte solution with buffering agents appears to be a more promising agent than NS for maintaining the acid–base balance. To troubleshoot these homeostatic alterations, we used goal-directed fluid therapy and limited the total fluid volume to 44.11 ± 16.03 mL/kg in the NS group and 40.68 ± 17.05 mL/kg in the RL group. Previous studies conducted on kidney transplant recipients and neurosurgical patients also observed a higher incidence of hyperchloremic metabolic acidosis in patients receiving NS, intraoperatively.[11,24]

We found no discernible changes in BRS between the two groups, despite the potential risks of hypo-osmolarity and greater brain bulge as demonstrated in animal studies by Williams et al.[10] This did not find any clinically significant increase in intracranial pressures in healthy volunteers who

received large-volume infusions (2 L) of NS or RL. However, their study was conducted on healthy individuals without intracranial pathology. Similarly, Bhagat et al also observed no difference in BRS among the patients receiving either RL or NS or mixture of these two fluids in neurosurgical patients.[16] These findings may be explained by the buffering mechanisms of the body that may not allow the osmolarity to fall with mild hypo-osmolar fluids.

Under normal conditions, administration of NS has little impact on our physiology as the kidney can retain bicarbonate and eliminate chloride ions.[25] Administration of large volumes of NS has been associated with impaired renal function, resulting from splanchnic vasoconstriction and a reduction in glomerular filtration rate. However, our study found that routine use of limited amounts of NS was not associated with renal dysfunction.

Intraoperative fluid management is crucial for achieving desirable postoperative outcomes. We found that the mRS was similar in both the groups. As neurological outcome is affected by multiple factors, intraoperative fluid therapy may not have a direct influence. However, if nonphysiological fluids are given in larger amounts, they may affect the outcome.

This study observed that the use of RL was associated with a safer electrolyte and acid–base profile when compared to NS. However, there are certain limitations to this study. The sample size is small for getting more significant results. We excluded the patients with massive blood loss that would have affected the results. The study groups were heterogeneous as we have included the patients with both supratentorial and infratentorial lesions. The assessment of brain relaxation was done using a subjective score. Intracranial pressure monitoring could have been a more valid tool. This study was conducted on patients undergoing elective neurosurgery. Hence, the study results cannot be extrapolated to neurosurgical patients with severely deranged cerebral physiology. These potential limitations may be addressed in future studies.

Conclusion

We conclude that intraoperative use of NS leads to significant hyperchloremic metabolic acidosis compared to RL. Other outcome parameters, including serum osmolarity, BRS, AKI, and mRS at discharge, were comparable in both groups. Hence, it may be used safely in pediatric neurosurgical patients without severely raised intracranial pressure. However, patients receiving massive fluid therapy are yet to be evaluated. These results must be confirmed with the larger multicentric clinical trials.

Conflict of Interest
None declared.

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