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Effectiveness of a novel 1% glucose isotonic electrolyte solution for intraoperative fluid therapy in children: a randomized controlled trial

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Abstract

Background: An appropriate electrolyte solution is important for safe intraoperative anesthesia management in children. This trial assessed the effectiveness of a novel 1% glucose isotonic electrolyte solution in intraoperative fluid therapy in children.

Methods: This trial analyzed data from 100 patients aged older than 1 month with an ASA score of I to II who received general anesthesia. Patients were randomly assigned to receive either the novel electrolyte solution (containing glucose, sodium, potassium, chloride, and bicarbonate) or lactated Ringer's solution intraoperatively as a maintenance fluid. Patient demographics and the results of blood gas analysis at 1, 2, and 3 hours were documented, and changes in glucose and electrolyte concentrations and the acid–base status were analyzed.

Results: During infusion of the novel solution, the glucose and potassium concentrations were stable. Conversely, the solution was linked to increased sodium levels but decreased bicarbonate levels, although both changes were within the physiological ranges. In addition, pH remained stable during the intraoperative period. Hypoglycemia, hyperglycemia, hyponatremia, or hypernatremia was not detected.

Conclusions: The novel 1% glucose isotonic electrolyte solution helped to maintain glucose and electrolyte concentrations and acid–base stability, and it may therefore improve children's safety during the intraoperative period.

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Fluid therapy, glucose, isotonic solution, electrolyte, pediatric surgery, anesthesia management, glycemic control, hypotonic solution

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Introduction

Fluid therapy is fundamental for safe intraoperative anesthesia management in children. Inappropriate fluid management can result in several serious complications, including brain damage and mortality. Wider intraoperative glycemic fluctuation is associated with an increased incidence of postoperative acute kidney injury after pediatric cardiac surgery.[1] Perioperative hyperglycemia is associated with poor outcomes, including surgical site infections and increased length of hospital stay; hence, glycemic control remains an important consideration in patients undergoing surgery.[2–5] Hypotonic fluids can cause hyperglycemia and hyponatremia; thus, they should be avoided intraoperatively.[6] Numerous studies and reports stated that physiologically composed isotonic electrolyte solutions containing 1% to 2% glucose are safe for intraoperative maintenance infusion in children.[7] Isotonic solutions are better than hypotonic solutions in children requiring maintenance intravenous infusion in terms of their sodium content.[8] Administration of an isotonic fluid can prevent a reduction of blood sodium levels and elevation of glucose in infants, thereby leading to enhanced safety in comparison with hypotonic fluids.[9] At present, these isotonic solutions are not available at our hospital, and consequently, pediatric anesthesiologists tend to use a hypotonic solution containing 3.75% or 8% glucose. To address this issue, a pre-packed 1% glucose isotonic electrolyte solution was used. This study examined the ability of this novel solution to stabilize blood glucose concentrations during surgery. The secondary endpoints were changes in the acid–base status and electrolyte levels following intraoperative fluid therapy using the novel solution in children.

Methods

Study design

This was a single-center, double-blind, parallel-group, randomized controlled study. The procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Declaration of Helsinki of 1964, as revised in 2000. The study protocol was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University, National Center for Children's Health (2019-k-394). The study was performed at Beijing Children's Hospital (Beijing, China) from February to August 2020. Written informed consent was obtained from the parents or legal guardians of the children before any study procedures were performed. The study was registered with the Chinese Clinical Trial Registry under the number ChiCTR2 00029053 (12/01/2020). This article adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Patient cohort

The inclusion criteria were as follows: age >1 month, ASA score of I to II, receipt of

general anesthesia for more than 3 hours, and expected to require an arterial line to analyze arterial blood gas during surgery. The exclusion criteria were as follows: (1) presence of diabetes and/or other endocrine metabolic diseases; (2) receipt of steroids, such as glucocorticoids and catecholamines; and (3) hyperglycemia before surgery (the first blood sample test after inserting the arterial line). Patients were randomly assigned to treatment group (1% glucose isotonic electrolyte solution, Otsuka, Tokyo, Japan) or control group (lactated Ringer's solution). The composition of both solutions is presented in Table 1. The allocation order was generated by permuted block randomization with a block size of four and was concealed with sequentially numbered sealed envelopes. The caregivers of patients as well as the clinical investigators who collected the clinical information were blinded to the patient grouping until the final data analysis.

Study procedure

According to current recommendations, infants were allowed to drink milk up to 4 hours before surgery and clear fluids up to 2 hours before surgery. Older children were not permitted to have solid food and milk for 6 hours prior to surgery. After induction and arterial line insertion, the first blood sample was collected (T0). If hyperglycemia was not detected, then administration of the randomly selected fluid was initiated. Samples were subsequently collected after 1, 2, and 3 hours (T1, T2, and T3, respectively). All samples were tested for arterial blood gas levels using the i-STAT handheld device (Abbott, Abbott Park, IL, USA). The infusion rate was $10\,mL/kg \cdot hour$, which was subsequently adjusted according to the estimated fluid requirement during surgery. Normal glucose concentrations were defined as levels of 4 to 10 mmol/L. Hyperglycemia was treated by halting the infusion of the study fluid and infusing glucose-free fluid. Hypoglycemia was treated by halting the infusion of the study fluid and infusing a 10% glucose intravenous injection. The total volume and duration of infusion were also recorded. The primary outcome was the glucose concentration, and additional analyses were performed on the acid–base status and electrolyte levels.

Table 1. Composition of the novel solution and lactated Ringer's solution.

	1% glucose isotonic electrolyte solution	Lactated Ringer's solution
Sodium, mmol/L	140	132
Potassium, mmol/L	3	4
Calcium, mmol/L	–	2
Chloride, mmol/L	118	113
Bicarbonate, mmol/L	25	–
Lactate, mmol/L	–	27
Glucose, mmol/L	56	–
Osmolarity[a], mOsmol/L	286	278

[a]Without glucose.

Statistical analysis

Based on the change in blood glucose concentrations in our preliminary study, the proportion of patients with significant changes in blood glucose versus baseline was 25% in the control group, and we supposed that a reduction of the glucose change incidence rate of >20% in the treatment group would indicate a significant effect. Furthermore, the sample size was calculated by testing for a two-proportion design model (two-sided, $\alpha = 0.05$, $\beta = 0.8$, 10% dropout rate, 1:1 group allocation) using PASS (NCSS, Kaysville, UT, USA). This resulted in a required sample size of 50 patients per group. All continuous data were presented as the mean ± standard deviation or median (interquartile range).

To assess differences between the two groups, the *t*-test was used for normally distributed continuous variables, whereas the Mann–Whitney U test was used for non-normally distributed continuous variables. For categorical variables, the χ^2 test and Fisher's exact test were used. Repeated-measures analysis of variance with the post-hoc Tukey's multiple comparison test was used to compare outcome variables between different time points in the same group. $P < 0.05$ indicated a significant difference. Statistical analysis was performed using IBM SPSS Statistics 19.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.0 (GraphPad Software Company, San Diego, CA, USA).

Results

Patient demographics

Between February and August 2020, 116 patients were enrolled in the study. Among them, the caregivers of four patients declined participation, and 12 patients were ineligible. Finally, 100 patients (57 boys, 43 girls) were enrolled and analyzed (Figure 1). The patients' ages ranged from 1 month to 13 years, and the mean weight was 16.9 ± 10.6 kg. The demographic and clinical characteristics of the patients are summarized in Table 2, and no statistical differences were noted between the two groups. The glucose concentrations, acid–base status, and electrolyte data are presented in Table 3.

Glucose concentration

The changes in blood glucose levels are presented in Figure 2a and Table 3. The time effect was statistically significant ($P = 0.001$), and the glucose concentration changed over time in both groups. The group effect was not statistically significant ($P = 0.111$), but the blood glucose concentration at T1 differed between the two groups ($P = 0.001$). Tukey's multiple comparisons test in the treatment group illustrated that the blood glucose

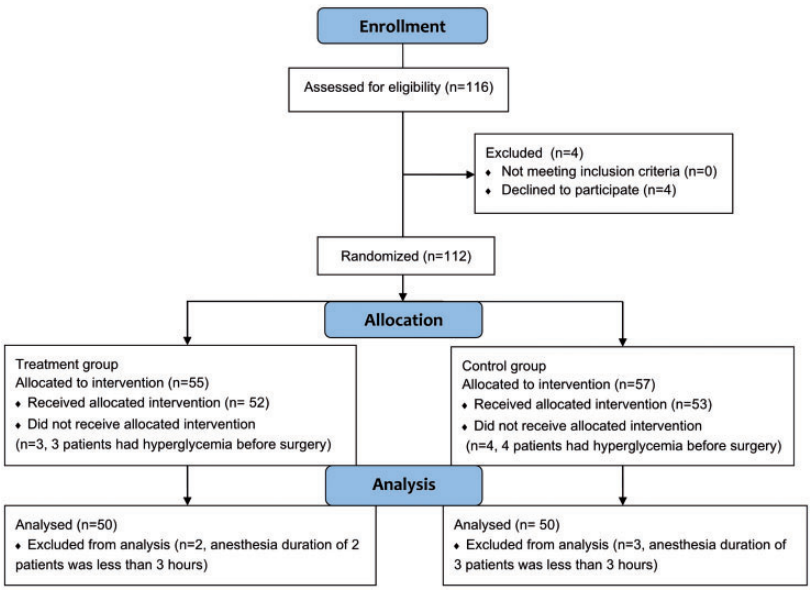

Figure 1. Flow diagram of patients in the study.

Table 2. Demographic and clinic characteristics of the participants.

	Treatment group (n = 50)	Control group (n = 50)	*P*
Male	27	30	0.55
Female	23	20	
Age (years)	3.6 ± 3.5	4.5 ± 3.9	0.24
Weight (kg)	15.1 ± 9.7	18.7 ± 11.2	0.09
Fluid volume (mL/kg·h)	11.7 ± 3.8	11.4 ± 2.4	0.65
Duration of anesthesia (min)	233.0 (205.0–307.0)	272.5 (225.0–323.0)	0.06
Baseline data (T0)			
Glucose, mmol/L	7.3 ± 1.6	7.1 ± 1.9	0.60
pH	7.35 ± 0.06	7.37 ± 0.06	0.11
Sodium, mmol/L	137.0 ± 2.8	137.9 ± 2.0	0.06
Potassium, mmol/L	3.7 ± 0.4	3.7 ± 0.3	0.62
Bicarbonate, mmol/L	23.7 ± 2.6	23.4 ± 2.9	0.58

Data are expressed as the mean ± standard deviation or median (interquartile range).

concentration was different between T2 and T3 ($P = 0.021$); however, this change had little clinical significance. In the control group, the blood glucose concentration was significantly different between T1 and T0 ($P = 0.001$), between T1 and T2 ($P = 0.001$), and between T1 and T3 ($P < 0.001$). The blood glucose level was lowest at T1 in the control group, whereas its level was more stable in the treatment group. In both groups, hyperglycemia and hypoglycemia were not detected.

pH

The changes in pH are presented in Figure 2b and Table 3. The time and group effects were not statistically significant ($P = 0.080$ and $P = 0.066$, respectively). pH was relatively stable over time in both groups.

Sodium

The changes in sodium concentrations are shown in Figure 2c and Table 3. The time effect was statistically significant ($P < 0.001$), and the sodium concentrations increased over time, albeit within the physiological range, in both groups. The group effect was not statistically significant ($P = 0.444$), and both infusion fluids had the same influence on the sodium concentrations. Tukey's multiple comparisons test illustrated that the sodium concentration was significantly different in T0 versus T1, T2, and T3 (all $P < 0.001$) in the treatment group and in T0 versus T2 and T3 ($P = 0.012$ and $P = 0.002$, respectively) in the control group. At the end of the study, neither hyponatremia nor hypernatremia was observed in any patients.

Potassium

The changes in potassium concentrations are presented in Figure 2d and Table 3. The time effect was statistically significant ($P < 0.001$), and the potassium concentration changed over time within the physiological range in both groups. The potassium concentration was significantly different at each subsequent time point between the two groups ($P_{T1} = 0.005$, $P_{T2} = 0.020$, $P_{T3} = 0.011$). The group effect was statistically significant ($P = 0.002$), and the two infusion fluids had different effects on the potassium concentration. Tukey's multiple comparisons test in the control group illustrated that the potassium concentration was significantly higher at T1, T2, and T3 than at T0 ($P = 0.007$, $P = 0.001$, and $P = 0.001$,

Table 3. Glucose concentrations, acid–base status, and electrolytes at different time points in the two groups.

Time points		T0		T1		T2		T3	
Group		Treatment group	Control group	Treatment group	Control group	Treatment group	Control group	Treatment group	Control group
Glucose	Mean ± SD	7.3 ± 1.6	7.1 ± 1.9	7.1 ± 1.5	6.1 ± 1.1*	7.0 ± 1.3	7.0 ± 1.8	7.2 ± 1.2	6.7 ± 1.2
mmol/L	t, P	0.53	0.60	3.80	<0.001	0.07	0.94	1.30	0.20
pH	Mean ± SD	7.35 ± 0.06	7.37 ± 0.06	7.35 ± 0.07	7.37 ± 0.07	7.34 ± 0.05	7.36 ± 0.07	7.33 ± 0.06	7.36 ± 0.07
	t, P	−1.6	0.11	−1.21	0.23	−1.56	0.12	−2.4	0.02
Sodium	Mean ± SD	137.0 ± 2.8	137.9 ± 2.0	139.1 ± 3.4*	139.0 ± 2.9	139.9 ± 3.1*	140.2 ± 3.6*	140.0 ± 3.0*	141.0 ± 4.1*
mmol/L	t, P	−2.0	0.06	0.19	0.85	−0.48	0.63	−0.03	0.98
Potassium	Mean ± SD	3.7 ± 0.4	3.7 ± 0.3	3.6 ± 0.5	4.0 ± 0.6*	3.8 ± 0.6	4.1 ± 0.7*	3.8 ± 0.5	4.1 ± 0.7*
mmol/L	t, P	0.50	0.62	3.34	0.01	2.11	0.04	2.87	0.01
Bicarbonate	Mean ± SD	23.7 ± 2.6	23.4 ± 2.9	22.6 ± 2.6*	21.7 ± 2.5*	22.1 ± 2.6*	21.9 ± 2.5*	21.9 ± 2.7*	22.4 ± 2.5*
mmol/L	t, P	0.55	0.58	1.79	0.08	0.45	0.66	−0.91	0.36

Data are presented as the mean ± SD. * indicates a significant difference in the group compared with T0.

respectively). The potassium concentration was lower at T1, T2, and T3 in the treatment group than in the control group. The potassium concentration increased over time within the physiological range in the control group, whereas it was relatively stable in the treatment group.

Bicarbonate

The changes in bicarbonate concentrations are presented in Figure 2e and Table 3. The time effect was statistically significant ($P < 0.001$), and the bicarbonate concentration decreased over time, albeit within the physiological range, in both groups. The group effect was not statistically significant ($P = 0.591$), and the bicarbonate concentration was not significantly different at each subsequent time point between the two groups. Meanwhile, the two infusion fluids had the same influence on the bicarbonate concentration. Tukey's multiple comparisons test illustrated that the bicarbonate concentration was significantly different at T0 versus T1, T2, and T3 (all $P < 0.001$) in the treatment group and at T0 versus T1, T2, and T3 ($P < 0.001$, $P = 0.004$, and $P = 0.041$, respectively) in the control group. The two groups displayed the same variations of bicarbonate concentrations, and the changes were all within the physiological range.

Infusion rate

The infusion rates in the two groups are presented in Figure 3. In the treatment group, the infusion rates were 12.3 ± 2.3, 10.2 ± 1.4, and 9.9 ± 1.5 mL/kg · hour in the first, second, and third hours, respectively, in the treatment group, versus 12.4 ± 1.3, 10.6 ± 0.9, and 10.4 ± 0.9 mL/kg · hour, respectively, in the control group. There was no difference in the infusion rate at any time point between the two groups ($P = 0.769$, $P = 0.368$, and $P = 0.083$,

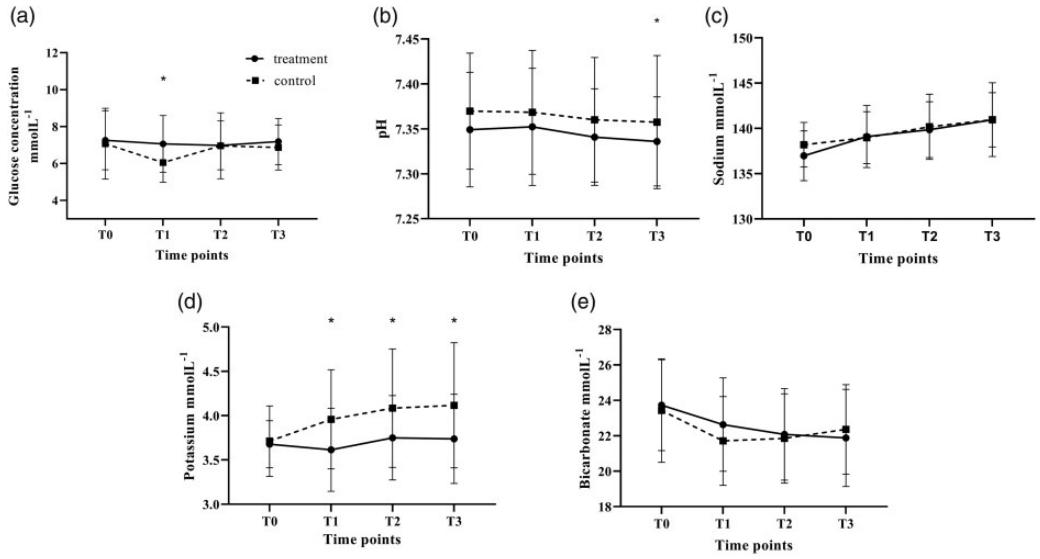

Figure 2. The changes in glucose concentrations, the acid–base status, and electrolyte levels. (a) The changes in glucose concentrations in the two groups. (b) The pH remained relatively stable in both groups. (c) The sodium concentration increased within the physiological range in both groups. (d) The potassium concentration increased within the physiological range in the control group and remained relatively stable in the treatment group. (e) The bicarbonate concentration decreased within the physiological range in both groups. $^{*}P < 0.05$ indicates a significant difference between the two groups.

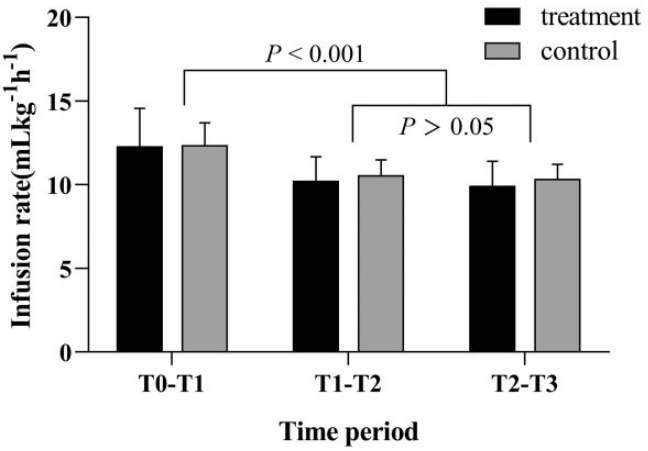

Figure 3. Comparison of the infusion rate in the first 3 hours of surgery between the treatment and control groups. The infusion rates were higher in the first hour in both groups.

respectively). In a comparison of the infusion rate by treatment period, the infusion rate was higher in the first hour than in the second and third hours (both $P < 0.001$).

Discussion

Our study compared two isotonic electrolyte fluids for intraoperative infusion and found that a 1% glucose isotonic electrolyte solution was better than lactated Ringer's solution in maintaining stable blood glucose and potassium concentrations in our studied cohort. Furthermore, we found that the 1% glucose isotonic electrolyte solution could maintain the levels of other electrolytes and the acid–base status within the normal physiological range.

The characteristics of suitable maintenance intravenous fluids include the fluid composition needed to maintain a child's extracellular volume while minimizing the risks of volume depletion, fluid overload, and glucose and electrolyte imbalance. A lack of glucose supply increases the risk of lipolysis leading to ketogenesis, especially after prolonged preoperative starvation; therefore, intraoperative glucose infusion should be considered in all pediatric patients. The main outcome of the study was that intraoperative infusion of the novel 1% glucose isotonic electrolyte solution helped to maintain a stable and physiologically appropriate glucose concentration. In the control group, the blood glucose concentration was slightly lower 1 hour after the infusion, and it returned to the preoperative level in the second hour. The changes in the blood glucose concentration during the first hour are probably attributable to the ability of the fluid infusion to supplement fluid losses in the fasting period, considering that a high-dose infusion of a glucose-free solution lowers the blood glucose concentration in children (Figure 3). Neither hyperglycemia nor hypoglycemia was detected in the two groups. Additionally, the effects of the 1% glucose solution on blood glucose stabilization are based on a normal infusion rate ($10\,mL/kg \cdot hour$). Regular and close monitoring of the blood glucose concentration is important when using a glucose-containing solution for intraoperative fluid therapy in children, especially when the infusion rate is increased.

Children have historically been administered hypotonic maintenance intravenous fluids.[10] A study indicated that hyponatremia is the most common electrolyte abnormality in hospitalized patients, affecting approximately 15% to 30% of children and adults.[11] Perioperatively, stress-induced antidiuretic hormone secretion increases the risk of hyponatremia. Consequently, an increasing number of associations of pediatric anesthesiologist associations have recommended the intraoperative use of isotonic electrolyte fluids.[12,13] In our study, the sodium concentration increased within the physiological range during the infusion of both solutions. No serious hyponatremia or hypernatremia was detected, and infusion of our novel 1% glucose isotonic electrolyte solution helped to maintain the sodium concentration at an appropriate level.

Physiologically composed isotonic electrolyte solutions are beneficial for maintaining homeostasis and shifting the status more toward the normal range in patients with pre-existing imbalances.[14] An intraoperative infusion of glucose containing electrolyte solution is more important in young children. During infusion of the 1% glucose isotonic electrolyte solution, the potassium concentration and pH remained stable, and the bicarbonate concentration decreased within the physiological range. This is the result of the electrolyte pattern of the novel fluid. The rise in the potassium concentration in the control group is potentially alarming. The bicarbonate concentration was lower in both fluids, and thus,

additional bicarbonate supplementation might be needed during long surgeries. Close intraoperative monitoring is essential, especially with long operative times.

This study had some limitations. First, because most pediatric surgeries are completed within 3 hours, only parameters assessed during this period were analyzed. Second, the sample size was not sufficient for non-inferiority testing. Furthermore, the infusion rate was fixed at 10 mL/kg · hour rather than based on the 4-2-1 rule. Another limitation was that the study did not include neonates and premature infants. Future research should include these groups as study participants.

In summary, the present study illustrated that a novel 1% glucose isotonic electrolyte solution could maintain normal blood glucose concentrations, a normal acid–base status, and normal electrolyte concentrations in our studied cohort. Despite the superiority of isotonic electrolyte solutions, strict glucose monitoring and an appropriate infusion rate are critical during surgery in children, especially those with a high metabolic rate, hepatic dysfunction, parenteral nutrition, metabolic disorders, and long surgery times.

Author contributions

ZZG was responsible for study conception, data acquisition, the inclusion and exclusion of studies, data extraction, data analysis, and writing the manuscript. FW was responsible for the inclusion and exclusion of studies, data extraction, and writing the manuscript. LH, XHC, and JX were responsible for data acquisition, supervision, and review of the manuscript for important intellectual content. WYF and HZC were responsible for checking the data of the outcomes, data analysis and interpretation, and drafting the article. All authors approved the manuscript.

Data availability statement

The datasets for this study are available from the corresponding author upon request.

Declaration of conflicting interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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