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Background. **Despite potential benefits of histidine-tryptophan-ketoglutarate (HTK) solution as a cardioplegic solution, it can cause hyponatremia, especially in pediatric patients. Fluctuations in the sodium concentration during cardiopulmonary bypass (CPB) can adversely affect the central nervous system. We evaluated the relationship between the cardioplegic solution, the fluctuation of sodium concentration, and the incidence of postoperative seizure in pediatric cardiac patients.**

Methods. **The medical records of 628 patients were reviewed for the occurrence of a postoperative seizure, type of cardioplegic solution (HTK or del Nido solution), and intraoperative data. A change of sodium concentration exceeding 15 mmol/L (ΔNa>15) during CPB was defined as a significant fluctuation of sodium concentration.**

Results. **Postoperative seizures were detected in 18 patients (2.9%). The ΔNa>15 was detected in 63 of 189 patients (33.3%) who received the HTK solution and in 14 of 439 patients (3.2%) who received the del Nido solution ($p < 0.001$). The incidence of ΔNa>15 was strongly associated with postoperative seizure (odds ratio, 6.3; 95% confidence interval, 2.4 to 16.4, $p = 0.001$). After adjusting for potential confounders, the ΔNa>15 remained significantly associated with postoperative seizure (odds ratio, 3.9; 95% confidence interval, 1.3 to 12.3, $p = 0.018$).**

Conclusions. **Histidine-tryptophan-ketoglutarate solution during CPB frequently causes fluctuations of sodium concentration, usually combined with hyponatremia, which is associated with postoperative seizure. Special attention to sodium concentration is required, particularly when HTK solution is used in pediatric cardiac patients.**

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A seizure early after a cardiac operation is a marker for central nervous system injury and is associated with adverse neurodevelopmental sequelae [1–3]. A number of factors can cause seizure after pediatric cardiac operations and relate to both fixed and modifiable mechanisms [4]. However, the neurologic outcome can be improved by controlling the modifiable factors.

There are two types of cardioplegic solution, one based on extracellular components and the other based on intracellular electrolytes [5, 6]. Del Nido solution, based on extracellular sodium concentration and a high potassium level, has been used as pediatric cardioplegia with beneficial effect on myocardial protection [7, 8]. Histidine-tryptophan-ketoglutarate (HTK, Custodiol, Dr. F. Köhler Chemie, Alsbach, Germany) solution, based on the intracellular level of electrolytes, prolongs ischemia tolerance in the heart and decreases the incidence of arrhythmia, inotropic support, and intensive care unit length of stay [9, 10]. However, HTK solution can cause hyponatremia and hemodilution because of its low sodium concentration (15 mmol/liter) and relatively large volume of administration (50 mL/kg) if it is drawn into the cardiopulmonary bypass (CPB) circuit. When considering small intravascular and CPB priming volume, the risk of acute hyponatremia and normalization may be increased in pediatric patients.

Hyponatremia sometimes leads to seizure in clinical practice and results in a high morbidity, including permanent brain damage in children [11]. The most important factor for hospital-acquired hyponatremia is the administration of hypotonic fluid [12]. Hyponatremia during anesthesia can cause cerebral edema and affect the blood–brain barrier [13], and abrupt normalization of hyponatremia can cause more detrimental effects on the central nervous system. Accordingly, fluctuations of sodium concentration may provoke neurologic impairment, such as a seizure, after a car-

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diac operation. However, whether acute sodium concentration change induced by the cardioplegic solution during CPB is associated with the occurrence of postoperative seizure has not been well described. The purpose of this study was to determine the relationship between the cardioplegic solution, the fluctuation of sodium concentration, and postoperative seizure.

Material and Methods

After applying the exclusion criteria, the medical records of 628 pediatric patients who underwent open heart operations under CPB between 2008 and 2009 were reviewed retrospectively. The exclusion criteria were patients aged older than 18 years, use of a cardioplegic solution other than del Nido or HTK solution, procedures in which an aortic cross-clamp (ACC) was not used, and preoperative seizure.

Ethical approval was given by the local hospital ethics committee. The need for written informed consent was waived, because the data were collected as part of routine clinical care and the study caused no risk to patients.

Postoperative clinical seizure was identified and recorded by the nurses or physicians in the pediatric intensive care unit. Seizures were identified using established clinical criteria of tonic clonic, or myoclonic activity of a limb, trunk, or cranial muscle that was not interruptible by manipulation of the body part involved. A computed tomography scan, electroencephalography (EEG), and a neurologic examination by a neurologist were performed in patients with seizure.

Anesthetic management was standardized for all patients. General anesthesia was induced using thiopental, midazolam, and fentanyl, and was maintained with the continuous infusion of sufentanil and midazolam. Sevoflurane was sometimes administered at the discretion of the attending anesthesiologist. Neuromuscular relaxation was achieved with vecuronium. Hemodynamic monitoring was performed with electrocardiography, pulse oximetry, continuous arterial blood pressure, and central venous pressure.

All patients received methylprednisolone (1 mg/kg) 6 hours before the operation and dexamethasone (0.5 mg/kg; maximum, 20 mg) at the onset of CPB. Three pediatric cardiac surgeons performed the operations. Cardioplegic arrest was induced under CPB and ACC using del Nido or HTK solution (Table 1). The HTK solution (50 mL/kg) was cooled to 4°C and perfused at an initial pressure of 100 mm Hg until asystole, and then the perfusion pressure was maintained at 40 mm Hg. The del Nido solution (30 mL/kg) was infused at a pressure of 30 to 40 mm Hg every 30 minutes.

Arterial blood gas and electrolytes were routinely measured at baseline, within 30 minutes of administering the cardioplegic solution, and every 1 or 2 hours. In patients who received the HTK solution, 1 mmol/kg sodium bicarbonate was administered after the cardioplegic solution was perfused, according to the institutional protocol. Modified ultrafiltration was performed in all patients after weaning from CPB.

Table 1. Composition of Histidine-Tryptophan-Ketoglutarate and Modified del Nido Solution

Substrate (mmol)	HTK Solution[a]	del Nido Solution[b]
Na+	15	141.7
K+	9	29.7
Ca_2+	0.02	0
Mg_2+	4	16.7
Bicarbonate	0	13
Histidine · HCl · H_2O	18	0
Histidine	180	0
Tryptophan	2	0
Ketoglutarate	1	0
Mannitol	30	16.5

[a] HTK is histidine-tryptophan-ketoglutarate (Custodiol, Dr F. Köhler Chemie, Alsbach, Germany) solution.

[b] The del Nido solution was prepared with 1000 mL plasma solution A (CJ Pharmaceutical, Seoul, Korea), 26 mmol KCL, 13 mmol bicarbonate, 13 mg lidocaine, 2 g $MgSO_4$, and 3.25 g mannitol. Plasma solution A (1000 mL) included Na (3.22 g), Cl (3.48 g), K (0.19 g), and Mg (0.036 g).

A change of sodium concentration more than 15 mmol/L (ΔNa>15) during bypass is defined as a significant fluctuation of sodium concentration.

Statistics

Data are presented as median (ranges) or mean ± standard deviation, where appropriate. Associations between categoric variables were evaluated using the χ^2 and Fisher exact tests. The differences between patients with and without seizure were analyzed using the *t* test or Mann-Whitney *U* test. Examined risk factors were age, weight, occurrence of ΔNa>15, type of cardioplegic solution, surgeon, priming volume, the volume of cardioplegic solution administered, ACC time, CPB time, highest and lowest sodium and glucose concentrations, use of regional cerebral perfusion, duration of regional cerebral perfusion, lowest nasopharyngeal temperature, and operative risk (risk adjustment for congenital heart operations which allow comparisons of in-hospital mortality for groups of children undergoing operations for congenital heart disease) [14].

The variables were tested by univariate logistic regression for their association with seizure. Any risk factors with a value of $p \leq 0.2$ were considered in a multivariate stepwise logistic regression to determine their association with seizure. If multicollinearity existed between possible risk factors, some adjustments were made. Confounders were adjusted for the evaluation of relationship between ΔNa>15 and postoperative seizure. A value of $p < 0.05$ was considered significant. All analyses used SPSS 17.0 software (SPSS Inc, Chicago, IL).

Results

The study population was a median age of 6 months (range, 0.3 to 216 months) and a median weight of 7.5 kg

Table 2. Data for Patients With Postoperative Seizure

Pt	Cardioplegic Solution	ΔNa>15	Hyponatremia	Diagnosis	Operation	Day	Weight (kg)	Comments
1	HTK	Yes	Yes	VSD	Patch closure	POD1	7.8	Small SDH
2	HTK	Yes	Yes	VSD, PS	Patch closure, infundibulectomy	POD1	6.5	Small SDH
3	HTK	Yes	Yes	TOF	Total correction	POD2	7.8	Small SDH
4	HTK	Yes	Yes	TOF	Total correction	POD1	7.4	SDH
5	HTK	Yes	Yes	VSD, MR	Patch closure, MVP	POD1	7.8	
6	HTK	Yes	Yes	VSD	Patch closure	POD1, 2	6.6	
7	HTK	Yes	No	VSD	Patch closure	POD2	8	R/O acute cerebellar infarct
8	HTK	Yes	No	TGA	ASO	POD1	3.2	
9	HTK	No	Yes	DORV, AVSD	Biventricular repair	POD2	8.3	
10	HTK	No	No	VSD, PS	Patch closure Infundibulectomy	POD1	3.7	R/O ICH
11	HTK	No	No	VSD, TR	Patch closure, TVP	POD1	10.4	R/O massive air embolism, death
12	Del	No	No	CoA, VSD, ASD, PDA	Total correction	POD3	2.2	CPR on arrival at PICU, poor cardiac function
13	Del	No	No	VSD, PA	Total correction	POD14	3.3	Failure in weaning from CPB, ECMO, death
14	Del	No	No	VSD, ASD	Patch closure	POD2	3.9	
15	Del	No	No	CoA, VSD	Total correction	POD6	6	R/O multifocal infarct, SDH
16	Del	No	No	Shone's complex	Total correction	POD2	33	Open sternum, unstable vital sign
17	Del	No	No	VSD, ASD	Patch closure	POD2	5.8	
18	Del	No	No	VSD, PA, MAPCA	Creation of conduit between RV and PA	POD3	3.6	

ASD = atrial septal defect; ASO = arterial switch operation; AVSD = atrioventricular septal defect; CoA = coarctation of aorta; CPB = cardiopulmonary bypass; CPR = cardiopulmonary resuscitation; Del = del Nido solution; ΔNa>15 = change in sodium exceeding 15 mmol/L; DORV = double-outlet right ventricle; ECMO = extracorporeal membrane oxygenation; HTK = histidine-tryptophan-ketoglutarate solution; ICH = intracranial hemorrhage; MAPCA = major aortopulmonary collateral artery; MR = mitral regurgitation; MVP = mitral valve prolapse; PA = pulmonary artery; PICU = pediatric intensive care unit; POD = the postoperative day when the first seizure occur; PS = pulmonary stenosis; R/O = ruled out; RV = right ventricle; SDH = subdural hematoma; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; TR = tricuspid regurgitation; TVP = tricuspid valvuloplasty; VSD = ventricular septal defect.

(range, 1.4 to 72.5 kg). HTK solution was used in 189 patients, and del Nido solution was used in 439.

Seizure was identified in 18 of 628 patients (2.9%), and the ΔNa>15 was observed in 8 of 18 patients with seizure. Table 2 presents the data for patients who were documented to have postoperative seizure. Of all seizures, 72% occurred in the first and second days after the operation. Seizure occurrence was not correlated with grade of surgical risk. There were differences in age, ACC time, the lowest serum sodium concentration, and a change of intraoperative sodium concentration between the patients with and without seizure (Table 3).

The ΔNa>15 occurred in 77 patients (63 received HTK solution and 14 del Nido solution) during CPB. The use of HTK solution was significantly associated with ΔNa>15 and hyponatremia (<125 mmol/L) compared with del Nido solution, with an odds ratio (OR) of 15.1 (95% confidence interval [CI], 8.2 to 27.8; $p < 0.001$) and 125 (95% CI 18.2 to 1000, $p < 0.001$), respectively. The incidence of ΔNa>15 was strongly associated with postoperative seizure (OR, 6.3; 95% CI, 2.4 to 16.4, $p = 0.001$).

Univariate analysis revealed that marginal predictors of seizure included ΔNa>15, age, weight, type of cardioplegic solution, ACC time, CPB time, highest glucose concentration, and lowest sodium concentration. The lowest sodium concentration was not included in a multiple logistic regression analysis because there was multicollienarity between ΔNa>15. A stepwise logistic regression analysis showed that age, ΔNa>15, ACC time, and cardioplegic solution were independent predictors of postoperative seizure. After

Table 3. Characteristics of Patients With and Without Seizure

Variable	With Seizure (n = 18) Mean ± SD	Without Seizure (n = 610) Mean ± SD	*p* Value
Age, mon	9 ± 22	25 ± 43	0.045
Weight, kg	7.5 ± 6.8	11.0 ± 11.0	0.084
Priming volume, mL	378 ± 265	437 ± 336	0.617
Cardioplegics volume, mL	633 ± 783	536 ± 468	0.780
ACC time, min	102 ± 59	76 ± 49	0.017
CPB time, min	170 ± 113	144 ± 77	0.349
Na concentration, mmol/L			
Highest	144 ± 5	142 ± 5	0.144
Lowest	131 ± 8	134 ± 5	0.043
ΔNa, mmol/L	13.1 ± 7.3	8.1 ± 5.1	0.003
Glucose concentration, mg/dL			
Highest	214 ± 71	194 ± 59	0.251
Lowest	116 ± 28	112 ± 34	0.066
Lowest nasopharyngeal temp, °C	24.9 ± 3.5	25.7 ± 3.2	0.312
Regional cerebral perfusion time, min	21 (n = 1)	28 ± 13 (n = 32)	0.674

ACC = aortic cross clamping; CPB = cardiopulmonary bypass; ΔNa = a change of intraoperative sodium concentration.

adjusting the potential confounders of age, ACC time, and cardioplegic solution in association between ΔNa>15 and postoperative seizure, we found that ΔNa>15 was significantly associated with postoperative seizure (OR, 3.9; 95% CI, 1.3 to 12.2; $p = 0.018$).

A subgroup analysis for those patients who received HTK solution indicated that seizure was detected more frequently in patients with ΔNa>15 (8 of 63) than those without ΔNa>15 (3 of 126), with an OR of 6.0 (95% CI, 1.5 to 23.3; $p = 0.007$). The incidence of ΔNa>15 was strongly associated with postoperative seizure (OR, 6.0; 95% CI, 1.5 to 23.3, $p = 0.01$). There were differences in age, ACC time, CPB time, the lowest serum sodium concentration, and a change of intraoperative sodium concentration between patients with and without seizure (Table 4).

Univariate analysis revealed that marginal predictors of seizure included ΔNa>15, age, weight, surgical risk, priming volume, ACC time, CPB time, and lowest sodium concentration. Lowest sodium concentration was not included in multiple logistic regression analysis because there was a multicollienarity between ΔNa>15. Age, ACC time, and ΔNa>15 were finally included in the model for a stepwise logistic regression analysis. The ΔNa>15 was marginally significantly associated with postoperative seizure after adjusting the effect of age and ACC time in patients who received HTK solution (OR, 4.3; 95% CI, 1.0 to 19.0; $p = 0.053$).

Table 4. Characteristics of Histidine-Tryptophan-Ketoglutarate Solution in Patients With and Without Seizure

Variable	With Seizure (n = 11)	Without Seizure n = 178)	*p* Value
Age, mon	4.6 ± 3.7	37 ± 52.8	0.020
Weight, kg	7.0 ± 2.1	14.2 ± 13.8	0.089
Priming volume, mL	409 ± 157	555 ± 330	0.237
Cardioplegics volume, mL	546 ± 286	694 ± 577	0.648
ACC time, min	90 ± 38	58 ± 28	0.004
CPB time, min	131 ± 52	104 ± 54	0.046
Na concentration, mmol/L			
Highest	143 ± 6	141 ± 6	0.434
Lowest	126 ± 5	130 ± 6	0.023
ΔNa, mmol/L	17.1 ± 6.3	11.2 ± 7.0	0.007
Glucose concentration, mg/dL			
Highest	200 ± 62	187 ± 52	0.453
Lowest	125 ± 19	117 ± 22	0.115
Lowest nasopharyngeal temp (°C)	26.0 ± 2.3	26.9 ± 2.9	0.410

ACC = aortic cross clamp; CPB = cardiopulmonary bypass; ΔNa = a change of intraoperative sodium concentration.

Comment

We investigated whether fluctuations in sodium concentration during CPB was associated with early postoperative seizure in pediatric cardiac patients. The HTK solution frequently induced acute sodium concentration changes, and this increased the incidence of postoperative seizure.

Hyponatremia, defined as a sodium level of less than 130 mmol/L, is the most common electrolyte disturbance in hospitalized patients. Severe hyponatremia (<125 mmol/L) can cause various symptoms, such as nausea, vomiting, cramps, an altered level of consciousness, and seizure. Previous studies have suggested that this threshold is associated with increased seizure susceptibility [15, 16]. Fluctuation of the sodium concentration during CPB may cause a worse effect on the central nervous system. Therefore, we focused on changes in sodium concentration and defined $\Delta Na>15$ as a significant change of sodium concentration.

Hypoxia and ischemia during CPB may impair the brain's adaptive mechanisms against acute sodium concentration changes and worsen brain injury [17]. Although fluctuating sodium levels during CPB can be postulated to adversely affect neurologic outcome, we found no report providing evidence of a relationship between a fluctuation in sodium concentration during CPB and postoperative seizure.

At the cellular level, changes and restoration of cell volume occur quickly after tonicity is altered [18]. This means that acute hyponatremia abruptly increases cellular volume, and regulatory volume decrease occurs by compensatory loss of solutes over a period of minutes. This reverse process may occur when hyponatremia is restored to the normal range. Returning volume-regulated cells to a normotonic condition thus causes shrinkage or swelling. Although hyponatremia itself is harmful due to cerebral edema or increased intracranial pressure, the acute normalization of sodium concentration can also induce brain shrinkage, which may damage delicate cerebral vessels and lead to subdural hematoma, subcortical parenchymal hemorrhage, or subarachnoid hemorrhage. Interestingly, the current study detected subdural hematoma in 4 of 8 patients who experienced seizure and $\Delta Na>15$. However, the association between the subdural hematoma, fluctuations in sodium concentration, and seizure remained to be determined.

Our subgroup analysis of the patients in HTK group to rule out possible factors associated with the cardioplegic solution enabled the assessment of the effect of the fluctuation of sodium concentration itself on postoperative seizure.

Duration of deep hypothermic cardiac arrest (DHCA) is a predictor of seizure [19]. However, we did not include DHCA in our study because regional cerebral perfusion was used rather than DHCA in our institution. Regional cerebral perfusion was not associated with postoperative seizure in the present study.

This study has several limitations. Seizures were identified on clinical grounds, and the incidence of seizure activity detected by continuous EEG monitoring can be much higher. Electrographic neonatal seizures are relatively common after heart operations [20]. In addition, other variables associated with seizure, such as hemodynamic variables, hematocrit, and genetic condition, were not fully investigated. Furthermore, the long-term outcomes of patients with seizure and fluctuation of sodium concentration were not validated.

Clinical seizure after operations for transposition of the great vessels is significantly associated with subsequent neurodevelopmental outcome and abnormalities in brain magnetic resonance imaging [21]. However, seizure associated with sodium concentration may be different, because no patients with $\Delta Na>15$ and seizure continued to have seizures after hospital discharge.

Lastly, this study cannot provide definite evidence regarding the effect of rapidity of occurrence of hyponatremia or its normalization on postoperative seizure. Because HTK solution is administered in a short time, we can infer that hyponatremia induced by the HTK solution occurs rapidly. However, we cannot determine the rate of its normalization.

In conclusion, HTK cardioplegic solution is related to hyponatremia during CPB. Fluctuation of sodium concentration was associated with postoperative seizure in pediatric cardiac patients. Special attention to sodium concentration is required, particularly when HTK solution is used in pediatric cardiac patients.

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