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ORIGINAL ARTICLE

Modified del Nido cardioplegia is associated with low incidence of low main strong ion difference and hyperchloremia in pediatric patients after cardiac surgery

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Abstract

Purpose The aims of this study were (1) to determine the associations of cardioplegic solutions with postoperative main strong ion difference (mSID), which is the difference between sodium ion concentration and chloride ion concentration ($[Cl^-]$) and (2) to determine the associations of cardioplegic solutions with markers of organ dysfunction.

Methods In this retrospective cohort study, patients aged <5 years who underwent cardiac surgery in a tertiary teaching hospital were included. Patients were classified on the basis of the type of cardioplegic solution: modified del Nido cardioplegia (mDNC) and conventional cardioplegia (CC). The effects of mDNC on postoperative mSID and markers of organ functions were examined using propensity-matched analysis.

Results A total of 500 cases were included. mDNC solution was used in 163 patients (32.6%). After propensity score matching, patients in the mDNC group ($n = 152$) had significantly higher minimum mSID [28 (26, 30) mEq/L vs. 27 (25, 29) mEq/L, $p = 0.02$] and lower maximum $[Cl^-]$ [112 (109, 114) mEq/L vs. 113 (111, 117) mEq/L, $p < 0.001$] than patients in the CC group ($n = 304$). The incidences of low mSID and hyperchloremia in the mDNC group were significantly lower than those in the CC group (63.8 vs. 75.7%, $p = 0.01$ and 63.2 vs. 79.3%, $p < 0.001$, respectively). There was no significant difference in the incidence of postoperative acute kidney injury and B-type natriuretic peptide level between the two groups.

Conclusion The use of modified del Nido cardioplegia may reduce the incidence of abnormal mSID and hyperchloremia compared with the use of a chloride-rich cardioplegic solution.

Keywords Cardioplegia · Del Nido · Congenital heart disease · Chloride · Strong ion difference

Introduction

The use of a cardioplegic solution is very important for myocardial protection during cardiac surgery with cardiopulmonary bypass. Since the first report by Melrose and associates of elective cardiac arrest being achieved by injecting a potassium citrate solution into the aortic root [1], there have been many changes in the compositions of and methods for administering cardioplegic solutions. Although electrolytes are vital elements in the composition, there are many differences in cardioplegic solutions used worldwide.

According to the Stewart approach, electrolytes are classified into strong electrolytes, which are completely dissociated in physiologic conditions, and weak electrolytes, which are only partially dissociated when dissolved in water within the physiological pH range [2, 3]. The difference between strong cations and strong anions is called strong ion difference (SID). SID is to be considered as an independent variable that determines hydrogen ion concentration and it can be used to determine the presence of acidosis or alkalosis. Subsequent studies showed that "main strong iron difference" (mSID), the difference between sodium ion concentration ($[Na^+]$) and chloride ion concentration ($[Cl^-]$), can be used as a surrogate for SID [4–6]. Recently, many studies have shown associations of chloride ions and SID in plasma

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as well as in fluid with patients' outcomes including acute kidney injury and mortality [6–9].

Although there have been many studies on an appropriate cardioplegic solution for myocardial protection, there has been no study focusing on mSID and chloride ion concentration of a cardioplegic solution, and currently used cardioplegic solutions differ greatly in mSID and chloride ion concentration. For instance, mSID in St. Thomas' Hospital cardioplegic solution No. 2 [10], which has been widely used for both adult and pediatric patients, has an mSID of negative 40.4 and 160.4 mEq/L of chloride ions. On the other hand, del Nido cardioplegia, which has been in common use in pediatrics [11] and has recently been used for adults [12], has an mSID of positive 34.4 and 115.2 mEq/L of chloride ions. However, there is lack of information on the effects of mSID and chloride ions in cardioplegic solutions on patients' outcomes.

A modified del Nido cardioplegia has recently been used in our institution. There are large differences in mSID and chloride ion concentrations in the conventional cardioplegia we used before and the modified del Nido cardioplegia. We hypothesized that the two cardioplegic solutions have different effects on the serum concentrations of major extracellular ions, sodium and chloride ions, and on the difference (mSID). Thus, the aims of this study were (1) to determine the associations of each type of cardioplegic solution with postoperative mSID and concentrations of strong ions and (2) to determine the associations of each type of cardioplegic solution with other patients' outcomes including kidney dysfunction and with surrogates of cardiac outcomes in pediatric patients with congenital heart disease who needed cardiopulmonary bypass.

Methods

Design and study population

This study was a retrospective study of pediatric patients with congenital heart disease (CHD) who underwent cardiac surgery with cardiopulmonary bypass (CPB) at a tertiary teaching hospital (Okayama University Hospital, Japan) during the period from May 2018 to December 2021. We included patients who met the following criteria: (1) younger than 15 years of age, (2) use of cardioplegia and aortic cross clamp, and (3) admission to the pediatric cardiac intensive care unit (PCICU) after cardiac surgery. Patients who underwent circulatory arrest and regional perfusion with additional cannulation, patients without data on measurements of chloride ions and/or sodium ions, and patients who underwent a second or subsequent cardiac operation(s) during the study period were excluded from this study. The study was approved by the Okayama University Hospital Ethics Committee (Institutional Review Board Approval Number 2301-021; approval date, December 2, 2022; title, Associations between Types of Cardioplegia and Postoperative Electrolyte abnormalities and Organ Functions in Pediatric Patients), and the need for informed consent was waived. All regulations and measures of ethics and confidentiality were handled in accordance with the Declaration of Helsinki.

Cardiopulmonary bypass technique and perioperative management

All of the patients were treated with mildly to moderately hypothermic CPB. The CPB prime consisted of 25% albumin and acetate Ringer's solution with the ratio of amounts of albumin and Ringer's fluid depending on each patient. Red blood cells (RBC) were also added to achieve a hematocrit level of >30% if the body weight was <8 kg and of >25% if the body weight was ≥8 kg. Sodium bicarbonate and mannitol were added to the prime based on the patient's body weight. Priming volumes in CPB circuits were approximately 350, 500, 700, 1000, and 1200 mL for patients with body weights of approximately <8, 8–15, 15–25, 25–35, and >35 kg, respectively.

In Oct 2020, we adopted modified del Nido cardioplegia (mDNC) in addition to the conventionalcardioplegia (CC). The reason for the modification was that Plasma-Lyte, the base solution of original del Nido cardioplegia, was unavailable in Japan. The mDNC includes normal saline and sodium lactate instead of Plasma-Lyte; however, it retains components such as sodium bicarbonate, potassium chloride, mannitol, lidocaine, and magnesium sulfate, similar to the original del Nido cardioplegia. The CC was cold crystalloid cardioplegia at an induction dose of 20 mL/kg with subsequent doses of 10 mL/kg every 20 min. The mDNC was a 1:4 ratio of cold blood cardioplegia at an induction dose of 20 mL/kg with subsequent doses of 10 mL/kg every 60 min. The detailed components of each cardioplegic solution are shown in Table 1.

Before the initiation of CPB, each patient received 20 mg furosemide through the CPB circuit. A roller pump was used, and the target pump flow rates were 150 mL/kg min for patients with a body weight of 10 kg or less and 2.4 L/min/m^2 for patients with a body weight 10 kg or more. All of the patients received conventional ultrafiltration during CPB and modified ultrafiltration at the end of CPB. Postoperative indication for peritoneal dialysis is (1) oliguria (<0.5 mL/kg/h) for more than 2 h or (2) hyperkalemia (more than 5.5 mEq/L) despite aggressive diuretic therapy, optimization of inotropic support, and adjustment of fluid status. Other additional management and laboratory measurements in the operating room and PCICU were dependent on the cardiac surgeons and anesthesiologists who were responsible for each patient.

Table 1 Components of conventional cardioplegia and modified del Nido cardioplegia

Components			CC			mDNC		
	Na (mEq/L)	Cl (mEq/L)	Solution (ml)	Na (mEq)	Cl (mEq)	Solution (ml)	Na (mEq)	Cl (mEq)
Blood: cardioplegia ratio			0:1			1:4		
Normal saline	154	154	1000	154	154	1468	226	226
Plasma-Lyte	140	98	0	0	0	0	0	0
KCL	0	1000	20	0	20	62	0	62
8.4%, $NaHCO_3$	1000	0	2	2	0	26	26	0
Sodium lactate	1000	0	0	0	0	54	54	0
20%, mannitol	0	0	0	0	0	32.6	0	0
2%, procaine	0	0	13.6	0	0	0	0	0
2%, lidocaine	0	0	0	0	0	26	0	0
MgSO4	0	0	40	0	0	38.6	0	0
50%, glucose	0	0	4	0	0	0	0	0
8.5%, calcium gluconate	0	0	6	0	0	0	0	0
Water	0	0	0	0	0	462	0	0
Total	–	–	1085.6	156 (143.7 mEq/L)	174 (160.3 mEq/L)	2169.2	306 (141.1 mEq/L)	288 (132.8 mEq/L)

mDNC modified del Nido cardioplegia, *CC* conventional cardioplegia

Study variables and data sources

Patients' information and laboratory data were stored in a central server and subsequently exported for further analyses through a medical data recording system, Prescient CDM (FUJIFILM Medical IT Solutions Co., Ltd., Tokyo, Japan), and additional information was obtained from electronic patient medical records. Preoperative data included patient demographics, baseline chloride concentration ($[Cl^-]_{base}$), baseline sodium concentration ($[Na^+]_{base}$), and baseline serum creatinine level. Patients were labeled by average SpO_2 before starting CPB: pre-CPB average $SpO_2 \leq 92\%$ (cyanotic CHD) and pre-CPB average $SpO_2 > 92\%$ (non-cyanotic CHD). Data in the operation room included type of surgery, which was classified on the basis of the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) category [13], and CPB duration. Postoperative chloride and sodium concentrations, pH, base excess (BE), and lactate concentration were measured by an arterial blood gas analyzer (ABL 800, Radiometer Co., Copenhagen, Denmark). Other postoperative data included peak serum creatinine level and total duration of mechanical ventilation for the first 30 days after surgery. Imputation for missing values was conducted by forward filling from the last non-missing value.

The "exposure" was the use of mDNC. The primary outcome was postoperative main strong ion difference (mSID): $[Na^+] - [Cl^-]$. Maximum mSID ($mSID_{max}$) and minimum mSID ($mSID_{min}$) within 48 h after surgery were used for the outcome. Low mSID and high mSID were defined as mSID < 30 and >37 mEq/L, respectively. The secondary outcomes were chloride ion concentration, sodium ion concentration, lactate concentration, B-type natriuretic peptide (BNP) level, postoperative acute kidney injury (AKI), and total duration of mechanical ventilation for the first 30 days after surgery. Maximum and minimum chloride ion concentrations within 48 h after surgery ($[Cl^-]_{max}$ and $[Cl^-]_{min}$, respectively), maximum and minimum sodium ion concentrations within 48 h after surgery ($[Na^+]_{max}$ and $[Na^+]_{min}$, respectively), maximum lactate concentration within 48 h after surgery (Lac_{max}), maximum creatine kinase-myoglobin binding (CK-MB) within 7 days after surgery ($CK\text{-}MB_{max}$), maximum troponin T (TnT) within 7 days after surgery (TnT_{max}), and maximum BNP level for a 30-day period after surgery (BNP_{max}) were used for the outcomes. Hypochloremia and hyperchloremia were defined as $[Cl^-] < 98$ and >110 mEq/L, respectively. AKI was diagnosed and classified within 48 h after surgery by Kidney Disease Improving Global Outcomes (KDIGO) criteria [14].

Statistical analysis

Data are presented as frequency and proportion or median (IQR, interquartile range; 25% quartile, 75% quartile) as appropriate. For group-wise comparisons of continuous variables, the Wilcoxon rank sum test (two groups) or Kruskal–Wallis test (more than two groups) was used. For categorical variables, Fisher's exact test or the Chi-square test was used as appropriate.

To examine the impact of the use of mDNC, we selected subsets of patients in whom mDNC was used and in whom CC was used who were matched for baseline characteristics before surgery and types of surgery that were possibly associated with the selection of cardioplegic solution and outcomes. The variables were weight, cyanotic CHD, baseline mSID ($mSID_{base}$), $[Cl^-]_{base}$, and STAT score. Matching was based on propensity scores obtained by logistic regression and using one-to-two nearest neighbor matching without replacement with the use of mDNC as the dependent variable. The standardized differences were computed after matching to evaluate the strength of the match.

We conducted a sensitivity analysis to assess the association of the number of cardioplegia administrations with mSID and $[Cl^-]$. Patients were classified into four categories based on the number of cardioplegia administrations: one, two, three, and four or more. In both the mDNC and CC groups, mSID and $[Cl^-]$ were compared among these categories.

All statistical comparisons were two-sided and a significance level was defined as a p value of less than 0.05. All statistical analyses were performed using R 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants

A total of 642 patients who underwent cardiac surgery were considered to be eligible for this study. After excluding 142 patients based on the exclusion criteria, 500 patients were included and analyzed in a cohort (Fig. 1). Within 48 h after surgery, 363 patients (72.6%) had low mSID, 220 patients

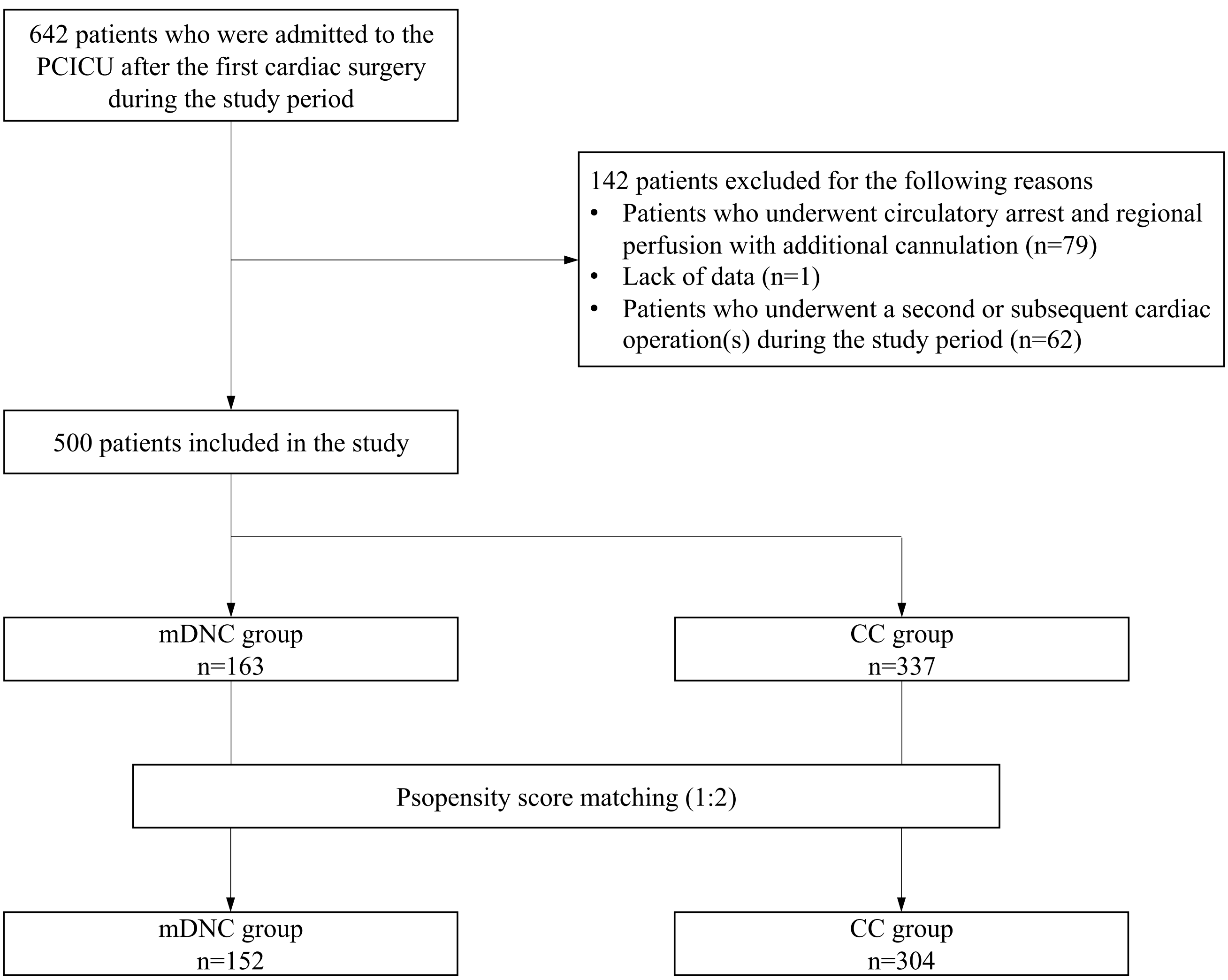

Fig. 1 Flow chart. *PCICU* pediatric cardiac intensive care unit, *mDNC* modified del Nido cardioplegia, *CC* conventional cardioplegia

(44.0%) had high mSID, 372 patients (74.4%) had hyperchloremia, and 27 patients (5.4%) had hypochloremia.

mDNC solution was used in 163 patients (32.6%). The two groups were balanced at baseline with few differences. Before matching, characteristics that were found to be significantly different included $[Cl^{-}]_{base}$. The number of cardioplegia administrations was 1 [1, 2] in the mDNC group and 2 [2, 4] in the CC group ($p < 0.001$). Comparison of demographics of the patients and outcomes in the patients in the cohort and comparison of those between the mDNC group and CC group are shown in Tables 2 and 3, respectively.

Postoperative main strong ion difference, chloride ion concentration, and sodium ion concentration

In the unmatched analysis, there were significant differences in $mSID_{min}$ [28 (26, 30) mEq/L vs. 27 (24.5, 29) mEq/L, $p = 0.001$], $[Cl^{-}]_{max}$ [112 (109, 114) mEq/L vs. 114 (111, 117) mEq/L, $p < 0.001$], $[Cl^{-}]_{min}$ [104 (101, 106) mEq/L vs. 105 (102, 108) mEq/L, $p < 0.001$], $[Na+]_{max}$ [144 (141.5, 146) mEq/L vs. 145 (143, 148) mEq/L, $p < 0.001$], and $[Na+]_{min}$ [137 (135, 139) mEq/L vs. 138 (136, 140) mEq/L, $p = 0.009$] between the mDNC group and CC group (Table 3). The incidences of low mSID and hyperchloremia in the mDNC group were significantly lower than those in the CC group (62.6 vs. 77.4%, $p = 0.001$ and 61.3 vs. 80.7%, $p < 0.001$, respectively).

Propensity score matching yielded 152 patients in the mDNC group and 304 patients in the CC group with adequate balance (Table 2). After the propensity score matching, patients in the mDNC group had significantly higher $mSID_{min}$ [28 (26, 30) mEq/L vs. 27 (25, 29) mEq/L, $p = 0.02$] than that in patients in the CC group. Patients in the mDNC group had significantly lower $[Cl^{-}]_{max}$ [112 (109, 114) mEq/L vs. 113 (111, 117) mEq/L, $p < 0.001$] and $[Cl^{-}]_{min}$ [104 (101.8, 106) mEq/L vs. 105 (102, 108) mEq/L, $p = 0.001$] than those in patients in the CC group. The incidences of low mSID and hyperchloremia in the mDNC group were also significantly lower than those in the CC group (63.8 vs. 75.7%, $p = 0.01$ and 63.2 vs. 79.3%, $p < 0.001$, respectively) (Table 3).

Association of the number of cardioplegia administrations with main strong ion difference and chloride ion concentration

In the CC group, there was a significant difference in $mSID_{min}$ among patients categorized by the

Table 2 Baseline characteristics before matching and after matching

Characteristics	All ($n = 500$)	Before matching				After matching		
		CC ($n = 337$)	mDNC ($n = 163$)	p value	Standardized mean difference	CC ($n = 304$)	mDNC ($n = 152$)	Standardized mean difference
Age, months, [IQR]	1.00 [0.00, 4.00]	1.00 [0.00, 4.00]	0.00 [0.00, 5.00]	0.937	0.004	1.00 [0.00, 4.00]	0.00 [0.00, 5.00]	0.047
Weight, kg [IQR]	7.99 [5.00, 15.10]	8.10 [5.04, 14.55]	7.98 [4.92, 16.88]	0.811	0.003	8.04 [4.81, 14.95]	7.91 [4.79, 16.43]	0.054
Male, n (%)	269 (53.8)	177 (52.5)	92 (56.4)	0.466	0.079	159 (52.3)	86 (56.6)	0.086
Cyanosis, n (%)	158 (31.7)	111 (33.0)	47 (28.8)	0.399	0.091	91 (29.9)	43 (28.3)	0.036
STAT score [IQR]	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	0.08	0.183	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	0.103
Baseline serum creatinine level, mg/dL [IQR]	0.31 [0.26, 0.39]	0.32 [0.26, 0.38]	0.31 [0.26, 0.39]	0.986	0.005	0.32 [0.26, 0.38]	0.31 [0.26, 0.39]	0.002
$mSID_{base}$, mEq/L [IQR]	33.00 [31.00, 35.00]	33.00 [31.00, 35.00]	33.00 [31.00, 35.00]	0.351	0.117	33.00 [31.75, 35.00]	33.00 [31.00, 35.00]	0.116
$[Cl^{-}]_{base}$, mEq/L [IQR]	106.00 [104.00, 108.00]	106.00 [104.00, 108.00]	106.00 [103.00, 107.00]	0.005	0.246	106.00 [104.00, 108.00]	105.50 [103.00, 107.00]	0.178
$[Na^{+}]_{base}$, mEq/L [IQR]	139.00 [137.00, 140.00]	139.00 [137.00, 140.00]	138.00 [137.00, 140.00]	0.113	0.227	139.00 [137.00, 140.00]	138.50 [137.00, 140.00]	0.133

mDNC modified del Nido cardioplegia, *CC* conventional cardioplegia, *IQR* interquartile range, *STAT* Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery, *mSIDbase* main strong ion difference at baseline, $[Cl^{-}]_{base}$ serum chloride ion concentration at baseline, $[Na+]_{base}$ serum sodium ion concentration at baseline

Table 3 Outcomes before matching and after matching

Characteristics	All ($n = 500$)	Before matching			After matching		
		CC ($n = 337$)	mDNC ($n = 163$)	p value	CC ($n = 304$)	mDNC ($n = 152$)	p value
Duration of CPB (minutes)	105.00 [76.00, 148.00]	106.00 [76.00, 144.00]	105.00 [75.50, 159.50]	0.471	103.00 [74.00, 142.00]	100.00 [74.00, 153.25]	0.557
$mSID_{max}$, mEq/L [IQR]	37.00 [35.00, 39.00]	37.00 [35.00, 39.00]	37.00 [35.00, 39.00]	0.341	37.00 [35.00, 39.00]	37.00 [35.00, 39.00]	0.344
$mSID_{min}$, mEq/L [IQR]	27.00 [25.00, 30.00]	27.00 [24.50, 29.00]	28.00 [26.00, 30.00]	0.001	27.00 [25.00, 29.00]	28.00 [26.00, 30.00]	0.022
High mSID, n (%)	220 (44.0)	143 (42.4)	77 (47.2)	0.358	128 (42.1)	72 (47.4)	0.333
Low mSID, n (%)	363 (72.6)	261 (77.4)	102 (62.6)	0.001	230 (75.7)	97 (63.8)	0.011
$[Cl^-]_{max}$, mEq/L [IQR]	113.00 [111.00, 116.00]	114.00 [111.00, 117.00]	112.00 [109.00, 114.00]	<0.001	113.00 [111.00, 117.00]	112.00 [109.00, 114.00]	<0.001
$[Cl^-]_{min}$, mEq/L [IQR]	105.00 [102.00, 107.00]	105.00 [102.00, 108.00]	104.00 [101.00, 106.00]	<0.001	105.00 [102.00, 108.00]	104.00 [101.75, 106.00]	0.001
Hyperchloremia, n (%)	372 (74.4)	272 (80.7)	100 (61.3)	<0.001	241 (79.3)	96 (63.2)	<0.001
Hypochloremia, n (%)	27 (5.4)	21 (6.2)	6 (3.7)	0.331	16 (5.3)	5 (3.3)	0.477
$[Na^+]_{max}$, mEq/L [IQR]	144.00 [142.00, 147.00]	145.00 [143.00, 148.00]	144.00 [141.50, 146.00]	< 0.001	145.00 [143.00, 148.00]	144.00 [141.00, 146.00]	<0.001
$[Na^+]_{min}$, mEq/L [IQR]	137.00 [135.00, 140.00]	138.00 [136.00, 140.00]	137.00 [135.00, 139.00]	0.009	138.00 [136.00, 140.00]	137.00 [135.00, 139.00]	0.009
Lac_{max}, mmol/L [IQR]	2.60 [1.80, 4.30]	2.60 [1.90, 4.10]	2.70 [1.70, 5.05]	0.767	2.60 [1.90, 4.20]	2.65 [1.70, 4.93]	0.922
AKI, n (%)	156 (32.6)	110 (33.7)	46 (30.1)	0.486	99 (32.6)	45 (29.6)	0.593
$CK\text{-}MB_{max}$, U/L [IQR]	62.00 [38.00, 117.25]	61.00 [37.00, 118.00]	70.00 [42.50, 116.00]	0.564	61.00 [37.00, 115.50]	74.00 [41.75, 122.25]	0.351
TnT_{max}, ng/mL [IQR]	2.30 [1.29, 3.82]	2.15 [1.26, 3.33]	2.56 [1.31, 4.09]	0.163	2.17 [1.32, 3.36]	2.56 [1.30, 4.56]	0.225
BNP_{max}, pg/mL [IQR]	217.00 [108.90, 459.07]	226.30 [112.75, 505.10]	198.10 [103.50, 387.10]	0.168	214.80 [108.03, 435.93]	197.10 [99.62, 384.30]	0.422
Duration of mechanical ventilation, days [IQR]	0.97 [0.20, 2.79]	0.93 [0.20, 2.79]	1.02 [0.22, 2.86]	0.73	0.89 [0.20, 2.59]	1.04 [0.21, 3.04]	0.441

mDNC modified del Nido cardioplegia, *CC* conventional cardioplegia, *IQR* interquartile range, *CPB* cardiopulmonary bypass, $mSID_{max}$ maximum main strong ion difference, $mSID_{min}$ minimum main strong ion difference, *mSID* main strong ion difference, $[Cl^-]_{max}$ maximum serum chloride ion concentration, $[Cl^-]_{min}$ minimum serum chloride ion concentration, $[Na+]_{max}$ maximum serum sodium ion concentration, $[Na+]_{min}$ minimum serum sodium ion concentration, Lac_{max} maximum lactate concentration, *AKI* acute kidney injury, $CK\text{-}MB_{max}$ maximum creatine kinase-myoglobin binding, TnT_{max} troponin T, BNP_{max} maximum BNP level

number of cardioplegia administrations ($p = 0.03$). Compared to $mSID_{min}$ in patients with single-shot CC [28 (26, 30) mEq/L], patients with three administrations of CC [27 (24, 29) mEq/L] and patients with four or more administrations of CC [26 (24, 29) mEq/L] had significantly lower $mSID_{min}$ ($p = 0.02$ and $p = 0.009$, respectively) (Fig. 2). Similarly, in the CC group, there was also a significant difference in $[Cl^-]_{max}$ among patients categorized by the number of cardioplegia administrations ($p < 0.001$). Compared to $[Cl^-]_{max}$ in patients with single-shot CC [111 (109, 113) mEq/L], patients with two administrations of CC [114 (111, 117) mEq/L], patients with three administrations of CC [114.5 (112, 118) mEq/L], and patients with four or more administrations of CC [115 (113, 118.5) mEq/L] had significantly higher $[Cl^-]_{max}$ ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively) (Fig. 3). In contrast, in the mDNC group, there was no significant difference in $mSID_{min}$ and $[Cl^-]_{max}$ (Figs. 2 and 3).

Other secondary outcomes

In the unmatched analysis, there was no significant difference in Lac_{max}, $CK\text{-}MB_{max}$, TnT_{max}, BNP_{max}, or the duration of mechanical ventilation between the two groups. After

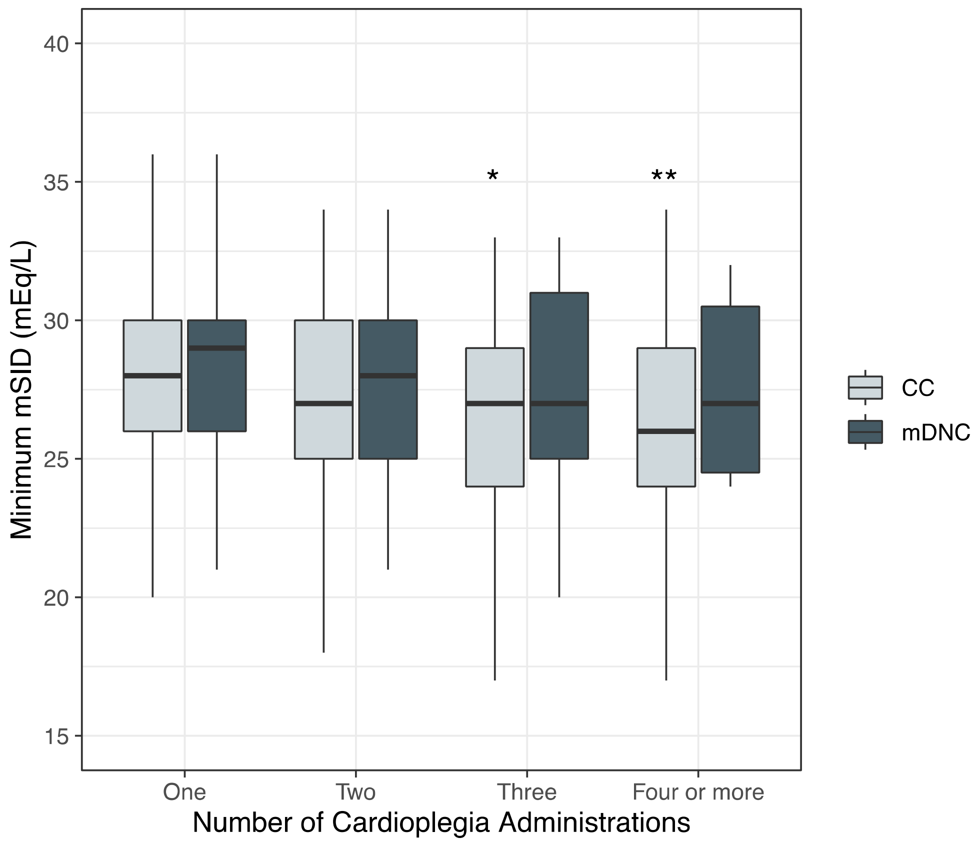

Fig. 2 Minimum main strong ion difference and number of cardioplegia administrations. *Asterisks* indicate statistical significance compared to $mSID_{min}$ in patients receiving single-shot cardioplegia within each group. *$mSID_{min}$* minimum main strong ion difference, *CC* conventional cardioplegia, *mDNC* modified del Nido cardioplegia. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

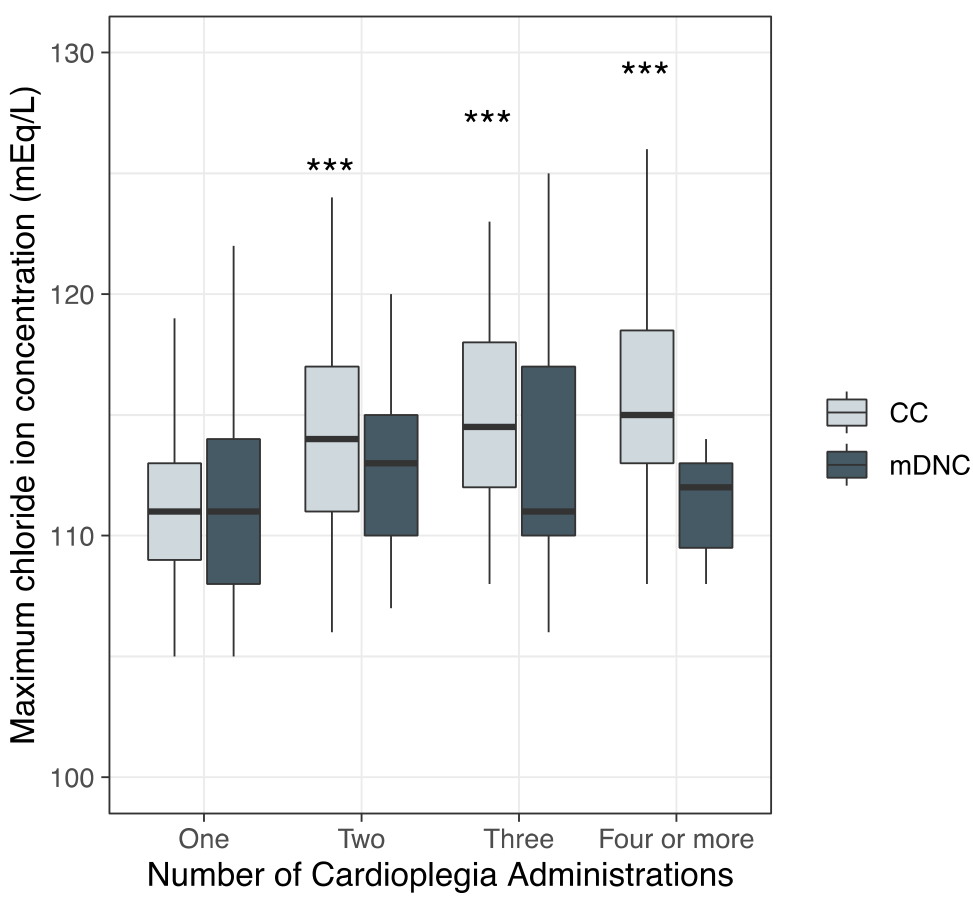

Fig. 3 Maximum chloride ion concentration and number of cardioplegia administrations. *Asterisks* indicate statistical significance compared to $[Cl^-]_{max}$ in patients receiving single-shot cardioplegia within each group. *$[Cl^-]_{max}$* maximum chloride ion concentration, *CC* conventional cardioplegia, *mDNC* modified del Nido cardioplegia. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

the propensity score matching, there was still no significant difference in those secondary outcomes between the two groups. Comparisons of the secondary outcomes before and after propensity score matching are shown in Table 3.

Discussion

In this retrospective study, we found that derangements of mSID and chloride ions were common (incidences of low mSID, high mSID, and hyperchloremia: 72.6, 44.0, and 74.4%, respectively) in pediatric patients after cardiac surgery. Both before and after propensity score matching $mSID_{min}$ and $mSID_{max}$ in the mDNC group were significantly lower than those in the CC group, and $[Cl^-]_{max}$ in the mDNC group was significantly lower than that in the CC group. There was no significant difference between the two groups in other clinical outcomes including serum lactate level, markers of myocardial injury, kidney dysfunction, and duration of mechanical ventilation.

While there are large differences in the concentrations of strong ions, especially sodium and chloride ions, which are the main extracellular strong cations and anions, among different types of cardioplegic solutions, there has been no study, to our knowledge, in which the effects of different types of cardioplegic solutions on postoperative strong ions were assessed. mSID in the CC, one of the extracellular types of cardioplegic solutions causing depolarization, is negative 16.6 mEq/L. On the other hand, mSID in the mDNC is positive 8.3 mEq/L before blood additive. The positive mSID due to relatively low chloride concentration in the mDNC may explain the close-to-normal mSID and $[Cl^-]$ in the mDNC group after propensity score matching in our study. It is noted that while there is a statistically significant difference in mSID and $[Cl^-]$ between the mDNC group and CC group, the difference is only one unit (mEq/L), which might not have a significant clinical impact. However, multiple administrations of cardioplegia, especially CC, could have a more pronounced effect on mSID and $[Cl^-]$, as demonstrated in Figs. 2 and 3. In this context, patients who require prolonged and/or multiple aortic cross clamps may benefit from mDNC, which has a positive mSID and requires fewer administrations. Further prospective investigation is necessary to assess the effect of multiple cardioplegia solutions with different strong ions on mSID and $[Cl^-]$ in pediatric patients.

Prior studies have shown less hyperchloremic acidosis and kidney injury in adult patients in whom chloride-restrictive fluids were used [15–17]. Several studies have also shown associations of abnormal mSID and/or $[Cl^-]$ with the development of AKI in critically ill patients [6, 18–20]. One of the suggested mechanisms is that high serum chloride can result in afferent arteriolar vasoconstriction, decreased renal artery blood flow, and reduced glomerular filtration rate, leading to salt and water retention [21, 22]. High intravenous chloride loads reduced renal blood flow, glomerular filtration rate, and renal cortical tissue perfusion [22, 23] and increased the incidence of AKI [24]. Metabolic acidosis caused by low strong ion difference may have detrimental effects on, or an adverse association with, renal function by augmenting the proinflammatory response through the release of inflammatory mediators [25–27]. However, our study showed no significant difference in the incidence of AKI between the group in which CC, which is a chloride-rich cardioplegia, was administered and the group in which mDNC, which is a chloride-restrictive cardioplegia, was administered despite the significant differences in mSID and $[Cl^-]$. One possible explanation is the difference in targeted populations. It is possible that low SID and hyperchloremia after cardiac surgery are common but not deleterious [27, 28]. The evidence obtained in previous studies might not apply to cardioplegic solutions and pediatric cardiac patients. Second, there is a possibility of small sample size and lack of power, although the incidence of AKI in the mDNC group after propensity score matching tended to be high. Third, the inconsistency can be attributed to the relatively small difference in mSID and $[Cl^-]$ between the mDNC group and CC group in our study. However, multiple administrations of cardioplegia, as shown in Figs. 2 and 3, may have a more significant impact on postoperative mSID and $[Cl^-]$. The effect of multiple cardioplegia administrations on postoperative AKI in pediatric cardiac patients remains unknown.

Although del Nido cardioplegia is a well-established cardioplegic solution for myocardial protection, especially in pediatric patients, there is little evidence for the efficacy of a modification of the original del Nido cardioplegia. Kantathut et al. used lactated Ringer's as a base solution for del Nido cardioplegia in 89 adult patients and reported lower troponin T levels, decreased incidence of arrhythmia, and less vasopressor and inotropic support than those in patients administered the standard cardioplegic solution with similar mortality rates in the two groups [29]. Nakao et al. also reported similar systolic function, diastolic function, and cardiac enzyme levels after CPB when using a modified del Nido cardioplegia in piglets [30]. Our study showed no significant differences in postoperative CK-MB and TnT as markers of myocardial injury between the two groups and no significant differences in postoperative serum lactate level and BNP level as surrogates of systemic perfusion and cardiac function. In this sense, the findings of non-inferiority of our modification of del Nido cardioplegia in terms of myocardial protection are consistent with the results of those previous studies, even though different base solutions and different amounts of core components such as mannitol, magnesium sulfate, sodium bicarbonate, potassium chloride, and lidocaine were used in the studies.

The findings of this study suggested that a cardioplegic solution with high mSID has an advantage for reduction in the risk of derangements of postoperative mSID and [Cl^-]. Considering that the St. Thomas' Hospital cardioplegic solution No. 2, one of the most widely used cardioplegic solutions, has much higher concentration of chloride ions and lower mSID [10] than those in the CC in this study and considering evidence of a negative impact of chloride-rich fluid on kidney function [15–17], the effect of a chloride-rich cardioplegic solution on postoperative AKI warrants further investigation. Future research with a sufficient sample size should be conducted to determine an ideal cardioplegic solution, taking into account strong ions in solutions, to achieve better outcomes in patients. The findings of this study also suggested that modification of del Nido cardioplegia can be an option when Plasma-Lyte is unavailable, having an acceptable effect on myocardial protection.

There are several limitations in this study. First, this study was a single center, retrospective study focusing on pediatric patients and the findings cannot be generalized to other populations. However, since, to our knowledge, there has been no report focusing on main extracellular strong ions in cardioplegic solutions even for pediatric patients, for whom the original del Nido cardioplegia has been well established [11], this retrospective study is worth reporting. Second, the two cardioplegic solutions used in this study are not commercially available. Although the CC could be "categorized" to St. Thomas cardioplegic solution in terms of an extracellular type causing depolarization and the mDNC could be "categorized" to del Nido cardioplegia in terms of core components in the solution, the cardioplegic solutions used in this study are not the same as widely used cardioplegic solutions. In this sense, generalizability of our findings is not satisfactory. Third, mSID is not equivalent to the more rigorous form of SID, which is calculated based on sodium ion and chloride ion as well as potassium ion, magnesium ion, calcium ion, and lactate [31]. Since sodium ion and chloride ion are the two major extracellular ions, the difference in their concentrations has been recently proposed as a useful surrogate for SID [6, 32, 33]. However, the more comprehensive form of SID may yield different results from our findings using mSID.

Conclusion

Derangements of mSID and chloride ions are common in pediatric patients after cardiac surgery. The use of modified del Nido cardioplegia may reduce the incidence of abnormal mSID and hyperchloremia without a negative impact on cardiac and kidney functions compared with the use of a chloride-rich cardioplegic solution.

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

Declarations

Conflict of interest There are no conflicts of interest to declare.

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