Comparable prognosis in different neonatal histidine-tryptophan-ketoglutarate dosage management

Li-Ting Bai[1], Yuan-Yuan Tong[2], Jin-Ping Liu[1,2], Zheng-Yi Feng[1,2], Ju Zhao[1,2], Sheng-Wen Guo[1,2], Yu Jin[1,2], Pei-Yao Zhang[1,2], Yi-Xuan Li[1,2]

[1]Department of Cardiopulmonary Bypass, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China;
[2]State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China

Abstract

Background: Histidine-tryptophan-ketoglutarate (HTK) is a solution commonly used for organ transplantation. However, there is no certified fixed regimen for on-pump heart surgery in neonates. We aimed to retrospectively evaluate the outcomes related to different HTK dosages and to analyze the safety of high-dosage perfusion.

Methods: A total of 146 neonates who underwent on-pump heart surgery with single-shot HTK perfusion were divided into two groups according to HTK dosages: a standard-dose (SD) group ($n = 63$, 40 mL/kg < HTK ≤ 60 mL/kg) and a high-dose (HD) group ($n = 83$, HTK >60 mL/kg). Propensity score matching (PSM) was performed to control confounding bias.

Results: The SD group had a higher weight (3.7 ± 0.4 *vs.* 3.4 ± 0.4 kg, $P < 0.0001$), a lower proportion of complete transposition of the great artery (69.8% *vs.* 85.5%, $P = 0.022$), a lower cardiopulmonary bypass (CPB) time (123.5 [108.0, 136.0] *vs.* 132.5 [114.8, 152.5] min, $P = 0.034$), and a lower aortic x-clamp time (82.9 ± 27.1 *vs.* 95.5 ± 26.0 min, $P = 0.005$). After PSM, 44 patients were assigned to each group; baseline characteristics and CPB parameters between the two groups were comparable. There were no significant differences in peri-CPB blood product consumption after PSM ($P > 0.05$). The incidences of post-operative complications were not significantly different between the two groups. There were no significant differences in ventilation time, intensive care unit stay, and post-operative hospital stay ($P > 0.05$). Follow-up echocardiography outcomes at 1 month, 3 to 6 months, and 1 year showed that left ventricular ejection fraction and end-diastolic dimension were comparable between the two groups.

Conclusions: In neonatal on-pump cardiac surgery patients, single-shot HD (>60 mL/kg) HTK perfusion had a comparable heart protection effect and short-term post-operative prognosis as standard dosage perfusion of 40 to 60 mL/kg. Thus, this study provides supporting evidence of the safety of HD HTK perfusion.

Keywords: Histidine-tryptophan-ketoglutarate; Neonate; Perfusion dosage; Cardiac recovery; Prognosis

Introduction

Cardioplegia solutions are essential for myocardial protection during cardiac surgery. Heart protection in the neonate population is especially difficult and important due to immature organ systems.[1] Histidine-tryptophan-ketoglutarate (HTK; Custodiol HTK solution; Koehler Chemi, Alsbach-Hähnlein, Germany) was initially proposed by Bretschneider[2] in the 1970s, and it is now widely used in clinical practice for long-duration cardiopulmonary bypass (CPB) surgeries. Many studies recommend a single shot of 40 to 60 mL/kg HTK perfused into the aortic root for 5 to 6 min, with an initial pressure of 80 to 100 mmHg. When the myocardium is at standstill, perfusion pressure should be reduced to 40 to 60 mmHg.[3-7] However, all these studies were based on adult or older pediatric patients. Due to the different physiology of neonatal patients, it is difficult to maintain perfusion time, pressure, and dosage simultaneously.

In our center, HTK perfusion in neonate on-pump cardiac surgery is generally based on two different considerations: (1) If the perfusion time and dosage of 40 to 60 mL/kg are used as the controlling factor according to HTK guidelines, the pump moves very slowly and the actual perfusion pressure is lower than the expected. (2) If initial perfusion pressure is increased, HTK dosage will increase to >60 mL/kg. Current research shows that aortic root perfusion pressure plays an important role by promoting penetration to poorly perfused tissue. Adequate infusion

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001643

Li-Ting Bai and Yuan-Yuan Tong contributed equally to this work.

Correspondence to: Jin-Ping Liu, Department of Cardiopulmonary Bypass, Fuwai Hospital, No. 167, North Lishi Road, Xicheng District, Beijing 100037, China
E-Mail: liujinping@fuwai.com

Chinese Medical Journal 2021;134(24)
Received: 26-11-2020 **Edited by:** Jing Ni

pressure improves penetration and provides rapid and complete cardioplegia.[8] High-dose HTK perfusion may result in hemodilution and blood ion fluctuation. Unfortunately, there is no early outcome data for neonatal congenital heart disease patients based on dose selection.

The purpose of this study is to retrospectively compare the short-term prognosis between standard-dose and high-dose HTK perfusion in neonatal cardiac surgery and evaluate the safety of HD HTK perfusion on heart protection and short-term clinical outcomes.

Methods

Ethics approval

The study was approved by the Ethics Committee of Fuwai Hospital (No. 2014-600), and all data were collected from electronic medical records.

Study population and design

We retrospectively reviewed neonates (aged ≤28 days at the time of surgery) who underwent on-pump congenital heart surgery in Fuwai Hospital from January 2012 to December 2018. All patients received single-shot HTK perfusion to achieve intra-operative cardioplegia. The patients were divided into two groups according to HTK dosage: a standard-dose group ($n = 63$, 40 mL/kg < HTK ≤60 mL/kg) and a high-dose group ($n = 83$, HTK >60 mL/kg) [Figure 1]. Exclusion criteria were: (1) non-HTK cardioplegia; (2) re-CPB during a single surgery which required secondary perfusion of cardioplegia solution; (3) reoperation patients; (4) heart transplantation patients; (5) pre-operative history of renal or hepatic dysfunction or coagulopathy; (6) failure to wean from CPB; and (7) missing data.

Patient demographics, perioperative echocardiography parameters, blood routine, blood biochemistry test, intra-operative data, blood product consumption, ventilation time, length of intensive care unit (ICU) stay, post-operative hospitalization time, 30-day mortality, and incidences of early post-operative adverse events were collected from the clinical database. The complexity of surgeries was assessed by Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1).[9]

Anesthesia and CPB strategies

Intravenous anesthesia and oral endotracheal intubation were routinely performed in all patients. Radial or femoral artery catheterization was used to continuously monitor arterial blood pressure. An internal right jugular vein catheter was inserted to monitor central venous pressure.

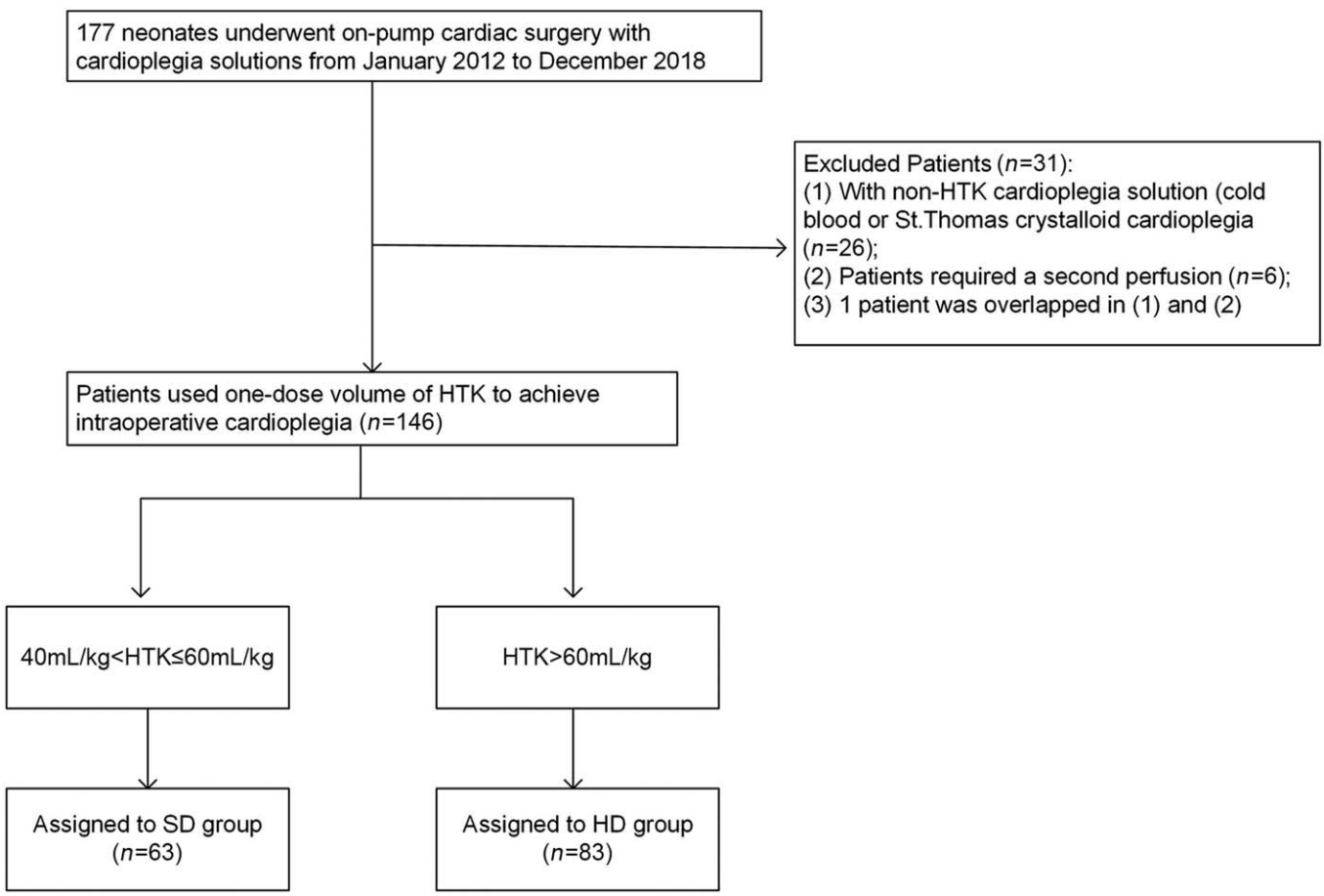

Figure 1: Flowchart for patients in different neonatal histidine-tryptophan-ketoglutarate dosage management included and exclued. HD: High-dose; HTK: Histidine-tryptophan-ketoglutarate; SD: Standard-dose.

Electrocardiogram, urethral catheterization, temperature, pulse oxygen saturation, and an arterial blood gas test were performed.

CPB was routinely established after the extracorporeal circulation pipeline fully heparinized and activated clotting time exceeded 410 s. All patients were perfused with a single shot of 4°C HTK to achieve cardioplegic arrest after the ascending aorta was x-clamped. Since there was no suitable and well-established HTK perfusion protocol for neonates regarding perfusion pressure, time, and dosage, we reviewed the clinical database. Some perfusionists chose to give a single dosage of 40 to 60 mL/kg HTK solution, while others preferred a single dosage of >60 mL/kg. A cell saver machine was used to remove HTK cardioplegia from the operative site, preventing it from entering the CPB blood storage chamber. During CPB, blood hematocrit and plasma colloid osmotic pressure were maintained between 24% and 27% (12–14 mmHg). After CPB, modified ultrafiltration was performed to ensure hematocrit >35%, and colloid osmotic pressure was kept between 15 and 18 mmHg.

Clinical outcomes

Clinical outcomes included post-operative heart function, early adverse events, and overall recovery indicators. Post-operative cardiac function was assessed by post-operative left ventricular ejection fraction, left ventricular end-diastolic dimension, cardiac enzymes, and cardiac complications. Cardiac enzymes including creatine kinase (CK), CK-MB, and lactate dehydrogenase were analyzed during the perioperative period. Delayed sternal closure, supraventricular tachycardia, cardiac arrest, hydropericardium, the use of a permanent pacemaker, and low cardiac output syndrome (LCOS)[10] were considered cardiac complications. Early adverse events included the incidence of in-hospital mortality, multiple organ dysfunction syndrome, re-intubation, pneumothorax, hydrothorax, infection, and peritoneal dialysis. Overall recovery indicators included ventilation duration, ICU stay, post-operative hospital stay, and hospital stay.

Statistical analysis

As a retrospective observational study comparing the prognosis of two different HTK dosage perfusion groups, some baseline variables were not comparable. Therefore, it was necessary to use propensity score matching (PSM) to control confounding bias. PSM produced a balanced match of standard-dose to high-dose HTK perfusion cases in a 1:1 ratio with a caliper (match tolerance) of 0.02. The propensity score was calculated from the following baseline characteristics: weight, age, RACHS-1, CPB time, and aortic x-clamp (AC) time. All of these variables were statistically different between the two groups before PSM. A total of 88 patients were propensity-score–matched, and 44 pairs of patients were generated. All the data extraction and analyses were performed using Statistical Package for Social Sciences 26.0 software (SPSS Inc., Chicago, IL, USA). Quantitative variables were presented as mean ± standard deviation using a *t*-test, or median and interquartile range, and Mann-Whitney *U* test. Categorical variables were compared with the Chi-squared test and Fisher exact test. For all calculations, statistical significance was defined as $P < 0.05$.

Results

Baseline characteristics and CPB parameters

A total of 146 neonates were included in this study: 63 standard-dose and 83 high-dose HTK recipients. Forty-four pairs were found through PSM analysis. Baseline characteristics and CPB parameters are shown in Table 1. The median dosage of HTK was 54.4 (51.3, 57.1) mL/kg in the standard-dose group, while it was 70.3 (66.7, 78.1) mL/kg in the high-dose group ($Z = -10.333$, $P < 0.0001$). There were several statistically significant differences between the two groups before PSM. The standard-dose group had a higher body weight (3.7 ± 0.4 *vs.* 3.4 ± 0.4 kg, $t = 3.219$, $P < 0.0001$) and a lower incidence of complete transposition of the great artery (69.8% *vs.* 85.5%, $\chi^2 = 5.279$, $P = 0.022$). CPB time (123.5 [108.0, 136.0] *vs.* 132.5 [114.8, 152.5] min, $Z = -2.120$, $P = 0.034$) and AC time (82.9 ± 27.1 *vs.* 95.5 ± 26.0 min, $t = 2.862$, $P = 0.005$) were both statistically lower in the standard-dose group compared with the high-dose group. After PSM, all baseline characteristics, as well as CPB parameters, were comparable between the two groups.

Cardiac protection indicators

As shown in Table 2, there were no significant pre-operative and early post-operative differences in cardiac enzyme release, for CK, CK-MB, and lactic dehydrogenase ($P > 0.05$). Pre-discharge cardiac enzymes were also comparable between the two groups ($P > 0.05$). There were no significant differences in early cardiac complications, such as delayed sternal closure, supraventricular tachycardia, cardiac arrest, hydropericardium, LCOS, and the usage of a permanent pacemaker ($P > 0.05$).

Peri-CPB blood gas monitoring

The differences in peri-CPB concentration of Na^+ (mmol/L), K^+ (mmol/L), CI^- (mmol/L), Ca^{2+} (mmol/L), hematocrit (%), glucose (mg/dL), and lactic acid (mmol/L) between the two groups were not significant before and after PSM ($P > 0.050$) [Figure 2]. The only significant difference of peri-CPB ion concentrations between the two groups before PSM was the glucose level during the re-warming period (178.7 ± 49.5 *vs.* 153.0 ± 44.6 mg/dL, $t = 2.223$, $P = 0.030$). The concentration of Mg^{2+} in the SD group was lower at pediatric intensive care unit (PICU) arrival (0.7 ± 0.1 *vs.* 0.8 ± 0.2 mmol/L, $t = -2.487$, $P = 0.015$) [Supplementary Table 1, http://links.lww.com/CM9/A669].

Peri-CPB blood products consumption

Blood product consumption during the peri-CPB period is shown in Table 3. Before PSM, intra-operative platelet usage was higher for the SD group (56.6 ± 107.1 *vs.*

Table 1: Baseline characteristics of neonates with different HTK dose management and their cardiopulmonary bypass parameters ($n = 146$).

Variables	Before PSM				After PSM			
	SD group ($n = 63$)	HD group ($n = 83$)	Statistics	*P* value	SD group ($n = 44$)	HD group ($n = 44$)	Statistics	*P* value
HTK, mL/kg	54.4 (51.3, 57.1)	70.3 (66.7, 78.1)	−10.333*	<0.0001	54.5 (50.3, 56.6)	67.6 (64.7, 71.4)	−8.084*	<0.0001
Male, *n* (%)	52 (82.5)	61 (73.5)	1.675†	0.196	35 (79.5)	31 (70.5)	0.970†	0.325
Age, days	16.7 ± 6.3	16.9 ± 6.6	0.169‡	0.866	15.3 ± 5.9	16.0 ± 6.4	−0.540‡	0.887
Weight, kg	3.7 ± 0.4	3.4 ± 0.4	−3.219‡	0.000	3.6 ± 0.4	3.6 ± 0.364	0.350‡	0.727
Body length, cm	50.8 ± 2.8	50.0 ± 3.1	−1.592‡	0.114	50.6 ± 2.9	51.0 ± 2.2	−0.701‡	0.485
RACHS-1	3 (3, 4)	3 (3, 4)	1.586*	0.742	3 (3, 4)	3 (3, 4)	1.000*	<0.0001
Diagnosis, *n* (%)								
Aortic coarctation	3 (4.8)	2 (2.4)	–¶	0.652	3 (6.8)	2 (4.5)	–¶	1.000
Interrupted aortic arch	3 (4.8)	3 (3.6)	–¶	1.000	2 (4.5)	3 (6.8)	–¶	1.000
Complete transposition of great artery	44 (69.8)	71 (85.5)	5.279†	0.022	31 (70.5)	34 (77.3)	0.530†	0.467
Patent foramen ovale	16 (25.4)	21 (25.3)	<0.0001†	0.990	9 (20.5)	12 (27.3)	0.563†	0.453
Patent ductus arteriosus	48 (76.2)	64 (77.1)	0.017†	0.897	31 (70.5)	32 (72.7)	0.056†	0.813
Atrial septal defect	39 (61.9)	58 (69.9)	1.022†	0.312	29(65.9)	31 (70.5)	0.210†	0.647
Ventricular septal defect	21 (33.3)	27 (32.9)	0.003†	0.959	16 (36.4)	14 (32.6)	0.139†	0.709
Pulmonary artery hypertension	17 (27.0)	31 (37.3)	1.744†	0.187	10 (22.7)	14 (31.8)	0.917†	0.338
Anomalous pulmonary venous connection	12 (19.0)	8 (9.6)	2.682†	0.101	7 (15.9)	6 (13.6)	0.090†	0.764
Preoperative ICU entrance	13 (20.6)	14 (16.9)	0.337†	0.668	10 (22.7)	9 (20.5)	0.067†	0.796
Preoperative intubation	7 (11.1)	7 (8.4)	0.296†	0.586	4 (9.1)	5 (11.4)	–¶	1.000
CPB parameters								
CPB time, min	123.5 (108.0, 136.0)	132.5 (114.8, 152.5)	−2.120*	0.034	128.4 ± 31.0	129.3 ± 30.5	−0.142‡	0.887
AC time, min	82.9 ± 27.1	95.5 ± 26.0	2.862‡	0.005	86.0 ± 27.0	85.5 ± 25.4	0.098‡	0.923
Lowest nasopharyngeal temperature,°C	27.8 ± 1.7	27.6 ± 1.7	−0.543‡	0.588	27.7 ± 1.5	27.6 ± 2.0	0.381‡	0.704
Lowest rectal temperature, °C	29.1 ± 1.7	28.9 ± 1.8	−0.687‡	0.493	29.0 ± 1.2	28.8 ± 2.1	0.552‡	0.582
Mean arterial pressure, mmHg	42.0 ± 9.8	39.9 ± 8.4	−1.401‡	0.163	42.9 ± 10.1	39.9 ± 9.4	1.421‡	0.159
Spontaneous re-beating, *n* (%)	62 (98.4)	83 (100.0)	1.327†	0.432	44 (100.0)	44 (100.0)	–	–

Data are presented as median (Q1, Q3) or mean ± standard deviation. *Z values. †χ^2 values. ‡t test. ¶Fisher exact test. –: Not applicable; AC: Aortic x-clamp; CPB: Cardiopulmonary bypass; HD: High-dose; HTK: Histidine-tryptophan-ketoglutarate; ICU: Intensive care unit; PSM: Propensity score matching; RACHS-1: Risk Adjustment for Congenital Heart Surgery-1; SD: Standard-dose.

26.8 ± 25.4 mL, $t = 2.162$, $P = 0.034$). However, there were no significant differences in peri-CPB blood product consumption in the two groups after PSM.

Recovery parameters and extracardiac complications

Between the two groups, ventilation duration, ICU stay, and post-operative hospital stay before and after PSM were similar ($P > 0.05$), as was the incidence of extracardiac complications ($P > 0.05$) [Table 4].

Post-operative follow-up echocardiography parameters

Post-operative follow-up echocardiography parameters are shown in Figure 3. The follow-up echocardiography frequency between the two groups was comparable

Table 2: Cardiac protection indicators measurement for neonates in different HTK dose management group before and after PSM ($n = 146$).

Variables	Before PSM				After PSM			
	SD group ($n = 63$)	HD group ($n = 83$)	Statistics	*P* value	SD group ($n = 44$)	HD group ($n = 44$)	Statistics	*P* value
Cardiac function enzymes								
Pre-operative								
CK (IU/L)	199 (125, 366)	191 (104, 374)	−0.464*	0.642	171 (121, 239)	208 (128, 548)	−0.700*	0.484
CK-MB (IU/L)	37 (24, 55)	34 (25, 60)	−0.177*	0.860	39 (26, 57)	36 (25, 56)	−0.099*	0.921
LDH (IU/L)	407 (345, 507)	447 (350, 637)	−1.561*	0.118	431 (351, 532)	468 (352, 654)	−0.821*	0.412
Post-operative day 1								
CK (IU/L)	833 (660, 1002)	877 (691, 1120)	−1.215*	0.224	898 ± 345	938 ± 374	−0.604*	0.611
CK-MB (IU/L)	69 (46, 99)	58 (49, 77)	−1.160*	0.246	78 (51, 105)	55 (45, 67)	−1.571*	0.116
LDH (IU/L)	652 (549, 848)	667 (518, 823)	−0.487*	0.626	676 (562, 899)	643 (519, 851)	−0.148*	0.883
Pre-discharge								
CK (IU/L)	47 (33, 67)	40 (28, 59)	−0.820*	0.412	44 (29, 65)	36 (27, 62)	−0.685*	0.493
CK-MB (IU/L)	16 (11, 28)	14 (11, 26)	−0.719*	0.472	15 (11, 32)	14 (11, 24)	−0.314*	0.754
LDH (IU/L)	334 (257, 412)	333 (268, 393)	−0.413*	0.680	371 ± 123	328 ± 90	1.598*	0.110
Cardiac complications, *n* (%)								
Delayed sternal closure	5 (7.9)	9 (10.8)	0.349†	0.778	4 (9.1)	7 (15.9)	0.935†	0.521
Supraventricular tachycardia	3 (4.8)	7 (8.4)	0.757†	0.515	1 (2.3)	5 (11.4)	–	0.202
Cardiac arrest	0 (0.0)	1 (1.2)	–	1.000	0 (0.0)	0 (0.0)	–	–
Hydropericardium	1 (1.6)	1 (1.2)	–	1.000	0 (0.0)	1 (2.3)	–	1.000
Permanent pacemaker	0 (0.0)	1 (1.2)	–	1.000	0 (0.0)	1 (2.3)	–	1.000
LCOS	4 (6.3)	7 (8.4)	0.223†	0.758	2 (4.5)	5 (11.4)	–	0.434
Echocardiology parameters								
Pre-operative EF (%)	65.1 (65.0, 75.2)	65.0 (63.0, 71.2)	−1.134*	0.257	66.2 (61.2, 70.2)	64.5 (60.0, 67.7)	−1.165*	0.244
Pre-operative LVEDD (mm)	18.4 ± 4.5	17.7 ± 3.9	0.849‡	0.397	18.1 ± 4.5	17.7 ± 3.9	0.479‡	0.633
Pre-discharge EF (%)	65.5 ± 5.5	65.0 ± 6.2	0.485‡	0.629	66.0 ± 5.4	63.9 ± 6.5	1.552‡	0.125
Pre-discharge LVEDD (mm)	18.2 ± 2.5	18.1 ± 2.4	0.329‡	0.742	17.8 ± 2.4	18.7 ± 2.2	−1.739‡	0.086

Data are presented as median (Q1, Q3) or mean ± standard deviation. *Z values. †χ^2 values. ‡*t* values. ¶Fisher exact test. –: Not applicable; CK: Creatine kinase; CK-MB: Creatine kinase-MB; EF: Ejection fraction; HD: High-dose; LCOS: Low cardiac output syndrome; LDH: Lactic dehydrogenase; LVEDD: Left ventricular end-diastolic dimension; POD: Post-operative day; PSM: Propensity score matching; SD: Standard-dose.

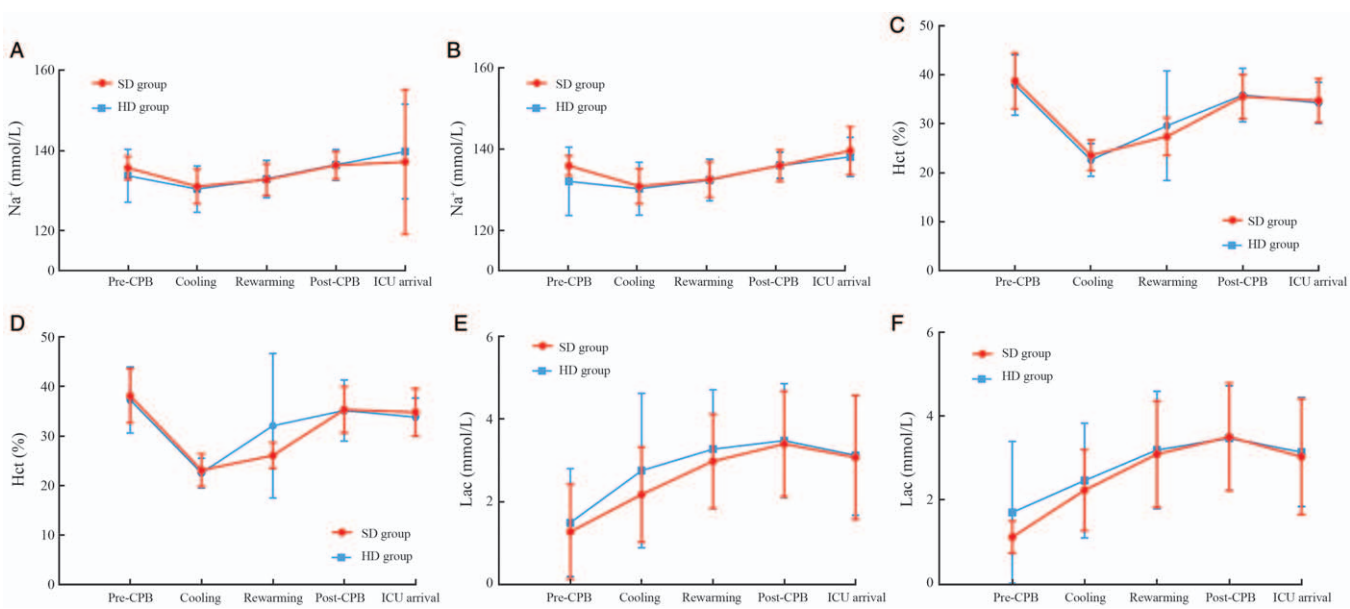

Figure 2: Perioperative blood gas monitoring between the two groups. (A) Na^+ before PSM; (B) Na^+ after PSM; (C) Hct before PSM; (D) Hct after PSM; (E) Lac before PSM; (F) Lac after PSM. CPB: Cardiopulmonary bypass; Hct: Hematocrit; HD: High-dose; ICU: Intensive care unit; Lac: Lactate; PSM: Propensity score matching; SD: Standard-dose.

Table 3: Peri-CPB blood products consumption for neonates in different HTK dose management group before and after PSM ($n = 146$).

Variables	Before PSM				After PSM			
	SD group ($n = 63$)	HD group ($n = 83$)	*t* value	*P* value	SD group ($n = 44$)	HD group ($n = 44$)	*t* value	*P* value
RBC, mL								
Intra-operation	303.8 ± 118.0	301.7 ± 172.2	0.162	0.871	300.5 ± 112.5	327.7 ± 195.1	−0.803	0.425
Priming	184.1 ± 54.5	173.5 ± 68.2	1.047	0.297	186.4 ± 51.0	181.8 ± 58.2	0.390	0.698
During CPB	69.8 ± 108.7	81.9 ± 103.8	−0.683	0.496	63.6 ± 103.6	81.8 ± 99.5	−0.840	0.403
Anesthesia	1.0 ± 56.6	6.5 ± 26.4	−1.836	0.070	0.5 ± 3.0	9.6 ± 34.2	−1.755	0.086
POD 0	34.9 ± 69.9	19.3 ± 78.8	1.246	0.215	34.1 ± 68.0	27.3 ± 99.7	0.375	0.709
POD 1	15.9 ± 44.7	20.5 ± 55.8	−0.537	0.592	15.9 ± 48.0	27.3 ± 62.4	−0.958	0.341
FFP, mL								
Intra-operation	26.8 ± 64.7	14.109 ± 39.9	1.455	0.148	22.7 ± 64.9	13.1 ± 44.6	0.814	0.418
Priming	0.0 ± 0.0	1.0 ± 6.4	−1.379	0.172	0.0 ± 0.0	0.0 ± 0.0	–	–
During CPB	1.6 ± 12.6	1.8 ± 12.2	0.474	0.636	2.3 ± 15.1	0.0 ± 0.0	1.000	0.323
Anesthesia	7.7 ± 39.2	1.5 ± 7.2	1.248	0.216	9.1 ± 45.7	1.7 ± 8.4	1.054	0.295
POD 0	15.9 ± 44.7	7.2 ± 26.1	1.367	0.175	11.4 ± 38.7	4.6 ± 21.1	1.027	0.308
POD 1	1.6 ± 12.6	3.6 ± 24.4	−0.601	0.549	0.0 ± 0.0	6.8 ± 33.4	−1.354	0.183
Platelet, mL								
Intra-operation	56.6 ± 107.1	26.8 ± 25.4	2.162	0.034	52.6 ± 108.6	23.1 ± 17.5	1.782	0.082
Anesthesia	42.3 ± 92.4	26.8 ± 25.4	1.294	0.200	45.8 ± 101.9	23.1 ± 17.5	1.458	0.152
POD 0	4.8 ± 37.8	0.0 ± 0.0	1.000	0.321	0.0 ± 0.0	0.0 ± 0.0	–	–
POD 1	9.5 ± 53.0	0.0 ± 0.0	1.426	0.159	6.8 ± 45.2	0.0 ± 0.0	1.000	0.323
Fibrinogen (g)								
Intra-operation	0.3 ± 0.3	0.3 ± 0.2	0.250	0.803	0.3 ± 0.3	0.3 ± 0.2	−0.022	0.982
Anesthesia	0.3 ± 0.2	0.3 ± 0.2	0.049	0.961	0.3 ± 0.2	0.3 ± 0.2	−0.256	0.798
POD 0	0.0 ± 0.1	0.0 ± 0.0	1.149	0.252	0.0 ± 0.1	0.0 ± 0.0	1.000	0.323
Prothrombin complex, IU								
Intra-operation	133.7 ± 111.3	138.3 ± 107.5	1.000	0.321	131.8 ± 118.2	153.3 ± 105.6	−0.899	0.371
Anesthesia	133.7 ± 111.3	138.3 ± 107.5	−0.252	0.801	131.8 ± 118.2	153.3 ± 105.6	−0.899	0.371
POD 0	0.0 ± 0.0	0.0 ± 0.0	−0.252	0.801	0.0 ± 0.0	0.0 ± 0.0	–	–

Data are presented as mean ± standard deviation. CPB: Cardiopulmonary bypass; FFP: Fresh frozen plasma; HD: High-dose; POD: Post-operative day; PSM: Propensity score matching; RBC: Red blood cell; SD: Standard-dose; –: Not applicable.

Table 4: Recovery parameters and extracardiac complications for neonates in different HTK dose management group before and after PSM ($n = 146$).

Variables	Before PSM				After PSM			
	SD group ($n = 63$)	HD group ($n = 83$)	Statistics	*P* value	SD group ($n = 44$)	HD group ($n = 44$)	Statistics	*P* value
Recovery parameters								
Ventilation duration, h	51.0 (27.6, 89.8)	48.1 (27.0, 76.3)	−0.235*	0.814	51.2 (27.8, 95.9)	47.4 (27.2, 92.7)	−0.296*	0.767
ICU stay, days	5.9 (3.9, 9.9)	4.9 (3.0, 7.8)	−1.148*	0.251	5.9 (3.9, 9.4)	5.6 (2.9, 9.7)	−0.551*	0.582
Post-operative hospital stay, days	14 (10, 19)	13 (10, 15)	−1.201*	0.230	14 (11, 19)	13 (10, 16)	−0.971*	0.311
Extracardiac complications, *n* (%)								
Re-intubation	6 (9.5)	5 (6.0)	0.603†	0.427	4 (9.1)	4 (9.1)	–	1.000
Pneumothorax	1 (1.6)	6 (7.2)	–	0.141	0	2 (4.5)	–	0.494
Hydrothorax	3 (4.8)	1 (1.2)	–	0.315	3 (6.80)	1 (2.3)	–	0.616
Infection	2 (3.2)	0	–	0.185	1 (2.3)	0	–	1.000
Peritoneal dialysis	6 (9.5)	11 (13.3)	0.484†	0.487	5 (11.4)	6 (13.6)	0.104†	0.747
Multiple organ dysfunction syndrome	2 (3.2)	2 (2.4)	–	1.000	1 (2.3)	2 (4.5)	–	1.000
In-hospital death	4 (6.4)	4 (4.8)	–	0.726	2 (4.5)	2 (4.5)	–	1.000

Data are presented as median (Q1, Q3). *Z values. †χ^2 values. ‡t values. ¶Fisher exact test. HD: High-dose; ICU: Intensive care unit; PSM: Propensity score matching; SD: Standard-dose.

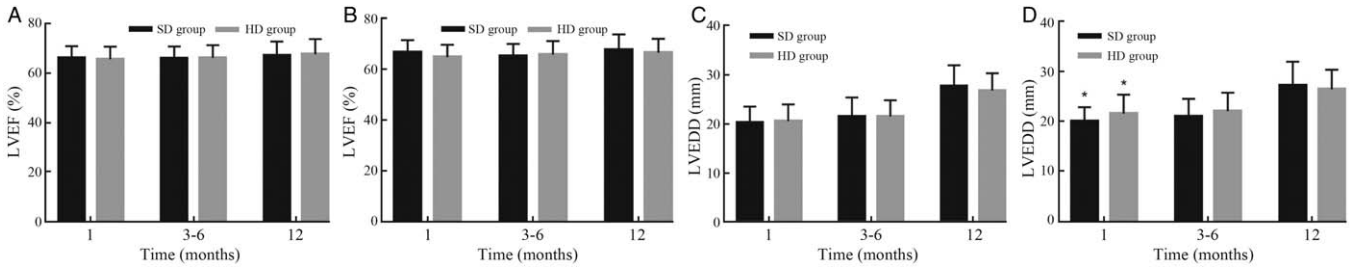

Figure 3: Comparison of LVEF and LVEDD between groups during the post-operative follow-up period. (A) LVEF before PSM; (B) LVEF after PSM; (C) LVEDD before PSM; (D) LVEDD after PSM. *The difference of LVEDD at 1-month post-discharge was significant between SD group and HD group. HD: High-dose; LVEDD: Left ventricular end-diastolic dimension; LVEF: Left ventricular ejection fraction; PSM: Propensity score matching; SD: Standard-dose.

($P > 0.05$). After PSM, LVEDD at 1-month post-discharge showed a difference between the standard-dose and high-dose groups (20.0 ± 2.8 *vs.* 21.5 ± 3.8 mm, $t = -2.085$, $P = 0.041$), but other post-operative echocardiography parameters were comparable ($P > 0.05$).

Discussion

HTK is increasingly used for the protection of neonatal hearts during the cardioplegic arrest.[11,12] It protects the organs by removing extracellular sodium and calcium ions, while a highly concentrated buffer histidine/histidine hydrochloride solution strengthens the extracellular environment to prolong the organ's resistance to blood oxygenation interruptions.[13] The buffer captures H^+ ions, which are produced during ischemia by anaerobic glycolysis. Consequently, the development of myocardial acidosis is reduced, and the myocardium needs less frequent cardioplegically re-perfusion. A single-dose HTK perfusion regimen is becoming more frequent in technically complex heart surgeries requiring a long AC. The median AC time in this study cohort was above 80 min, which is consistent with previous studies where AC time exceeded 60 min.[5,14] This retrospective study aimed to investigate the clinical influence of high dosage HTK perfusion on neonatal patients. The HTK dosage in the high-dose group was significantly higher than in previous studies.

Perioperative heart-related events and parameters were thoroughly compared between the two groups. One of the most commonly reported complications of HTK protection is related to intra-operative and post-operative arrhythmias. One prospective randomized study found a higher frequency of spontaneous ventricular fibrillation after aortic clamp removal in the single-dose HTK (30 mL/kg) group compared with repetitive cold blood cardioplegia in adults.[15] The result was confirmed by Gaudino *et al*[3] when they compared the same dosage of HTK solution with warm blood cardioplegia. However, HTK solution perfusion did show a higher spontaneous resumption rate when compared with St Thomas crystalloid cardioplegia.[13] The resumption rate in our study reached 100% after the PSM adjustment of both groups. A post-operative arrhythmia study by Scrascia *et al*[16] reported comparable rates between a single-dose HTK perfusion (20–25 mL/kg) and cold blood cardioplegia during aortic surgery. The incidence of supraventricular tachycardia, as well as post-operative ventricular function by echocardiography, showed no differences in either group, indicating that standard dosage *vs.* higher dosage showed comparable cardiac protective effects. Additionally, the blood lactate concentrations at different periods during CPB showed no differences between either group, which indicates that perfusion was comparable between the two groups, and gave adequate protection. Early post-operative echocardiography parameters and myocardial enzyme fluctuation were all no different in low and high perfusion volume patients. Follow-up echocardiography parameters showed no differences in either group, indicating that the cardiac function recovery of the late post-operative period was comparable.

Previous studies suggested that HTK cardioplegia may cause electrolyte imbalances and their related adverse outcomes in pediatric cardiac surgery, especially hyponatremia that may result from large perfusion volume.[17,18] Kim *et al*[18] reported that the use of HTK in pediatric patients during CPB frequently causes fluctuations of sodium concentration, and hyponatremia, which is associated with post-operative seizure. However, Lueck *et al*[19] found that only non-physiological hyponatremia together with low osmotic pressure will cause cerebral swelling, by shifting water from extracellular spaces to intracellular spaces. HTK is an iso-permeable low sodium solution[20] and has no negative impact on patients' osmotic pressure-related results. Overtreatment of hyponatremia in pediatrics must be avoided[19] due to poor post-operative outcomes from increased serum sodium concentration (≥145 mmol/L) at the end of CPB.[21] In our cohort study, intra-operative serum sodium concentration was comparable in the two groups; a high dose of HTK did not result in a significant intra-operative low sodium level. Compared with the sodium concentration range in a previous study,[20] we can demonstrate that peri-CPB serum sodium concentration did not fluctuate significantly in our cohort, and it returned to normal by the time patients arrived at PICU. Furthermore, no neurologic complications were reported after surgery in either group.

Hemodilution is another common concern when crystalloid cardioplegia is used. In this study, hematocrit was <35% during the cooling and re-warming period and elevated to a normal level at the end of CPB. Hematocrit in both groups was comparable despite the higher HTK perfusion levels in the HD group. Perioperative blood consumption did not indicate any different hemodilution effects between the two groups. Hemodilution can be reduced by pumping cardioplegic solution from the

coronary sinus, spontaneous diuresis, or ultrafiltration.[22] In our center, we routinely open the right atrium during HTK perfusion. Extra cardioplegia is collected by blood salvage through the coronary sinus to avoid hemodilution. All neonates who underwent surgery received routine ultrafiltration during the rewarming period and modified ultrafiltration before CPB weaning.

A comprehensive comparison of post-operative systemic organ recovery and extracardiac complications was investigated in this cohort study to reveal any possible potential risks in long-term prognosis between the two groups. There were no significant differences found in ICU stay, post-operative hospital stay, and extracardiac complications between the two groups. These results provide supporting evidence that standard-dose and high-dose HTK perfusion regimens are equally effective.

There are some limitations to our study. Since this study was not a randomized controlled trial (RCT), patient selection criteria are not completely random; thus, the inherent bias associated with a retrospective study exists. Although we applied PSM to balance the influence of selection bias and potential confounding factors, bias associated with pre-operative factors could not be completely excluded. An RCT study comparing standard-dose and high-dose HTK perfusion in neonates is necessary. Second, limited data restricted us from comparing the exact perfusion time and pressure between the two groups. Third, this study was a single-center study and the sample size was not large. The conclusions of our study need to be verified in a larger population and/or multiple-center study.

Funding

This study was supported by a grant from the National Natural Science Foundation of China (No. 81670375).

Conflicts of interest

None.

References

1. Turkoz R. Myocardial protection in pediatric cardiac surgery. Artif Organs 2013;37:16–20. doi: 10.1111/aor.12029.
2. Bretschneider HJ. Myocardial protection. Thorac Cardiovasc Surg 1980;28:295–302. doi: 10.1055/s-2007-1022099.
3. Gaudino M, Pragliola C, Anselmi A, Pieroni M, De Paulis S, Leone A, *et al*. Randomized trial of HTK versus warm blood cardioplegia for right ventricular protection in mitral surgery. Scand Cardiovasc J 2013;47:359–367. doi: 10.3109/14017431.2013.836241.
4. Pérez-Andreu J, Fernández-Doblas J, Sao Avilés A, de la Torre Garcia T, Roses Noguer F, Abella RF. Myocardial protection in the arterial switch operation: custodiol versus cold blood cardioplegia. Interact Cardiovasc Thorac Surg 2020;30:136–143. doi: 10.1093/icvts/ivz216.
5. Valente AS, Lustosa GP, Mota LAM, Lima A, Mesquita FA, Gondim A, *et al*. Comparative analysis of myocardial protection with HTK solution and hypothermic hyperkalemic blood solution in the correction of acyanogenic congenital cardiopathies - a randomized study. Braz J Cardiovasc Surg 2019;34:271–278. doi: 10.21470/1678-9741-2018-0243.
6. Angeli E. The crystalloid cardioplegia: advantages with a word of caution. Ann Fr Anesth Réanim 2011;30:S17–S19. doi: 10.1016/s0750-7658(11)70003-x.
7. Viana FF, Shi WY, Hayward PA, Larobina ME, Liskaser F, Matalanis G. Custodiol versus blood cardioplegia in complex cardiac operations: an Australian experience. Eur J Cardiothorac Surg 2013;43:526–531. doi: 10.1093/ejcts/ezs319.
8. Takach TJ, Glassman LR, Milewicz AL, Clark RE. Continuous measurement of intramyocardial pH: relative importance of hypothermia and cardioplegic perfusion pressure and temperature. Ann Thorac Surg 1986;42:365–371. doi: 10.1016/s0003-4975(10)60537-1.
9. Nakayama Y, Shibasaki M, Shime N, Nakajima Y, Mizobe T, Sawa T. The RACHS-1 risk category can be a predictor of perioperative recovery in Asian pediatric cardiac surgery patients. J Anesth 2013;27:850–854. doi: 10.1007/s00540-013-1645-1.
10. Burkhardt BE, Rücker G, Stiller B. Prophylactic milrinone for the prevention of low cardiac output syndrome and mortality in children undergoing surgery for congenital heart disease. Cochrane Database Syst Rev 2015;3:Cd009515. doi: 10.1002/14651858.CD009515.pub2.
11. Edelman JJ, Seco M, Dunne B, Matzelle SJ, Murphy M, Joshi P, *et al*. Custodiol for myocardial protection and preservation: a systematic review. Ann Cardiothorac Surg 2013;2:717–728. doi: 10.3978/j.issn.2225-319X.2013.11.10.
12. Lin YZ, Huang JB, Li XW, Tang XM, Lu WJ, Wen ZK, *et al*. Clinical comparative analysis of histidine-tryptophan-ketoglutarate solution and St. Thomas crystalloid cardioplegia: a 12-year study from a single institution. Exp Ther Med 2017;14:2677–2682. doi: 10.3892/etm.2017.4814.
13. Liu J, Feng Z, Zhao J, Li B, Long C. The myocardial protection of HTK cardioplegic solution on the long-term ischemic period in pediatric heart surgery. ASAIO J 2008;54:470–473. doi: 10.1097/MAT.0b013e318188b86c.
14. Bibevski S, Mendoza L, Ruzmetov M, Tayon K, Alkon J, Vandale B, *et al*. Custodiol cardioplegia solution compared to cold blood cardioplegia in pediatric cardiac surgery: a single-institution experience. Perfusion 2020;35:316–322. doi: 10.1177/0267659119878006.
15. Braathen B, Jeppsson A, Schersten H, Hagen OM, Vengen O, Rexius H, *et al*. One single dose of histidine-tryptophan-ketoglutarate solution gives equally good myocardial protection in elective mitral valve surgery as repetitive cold blood cardioplegia: a prospective randomized study. J Thorac Cardiovasc Surg 2011;141:995–1001. doi: 10.1016/j.jtcvs.2010.07.011.
16. Scrascia G, Guida P, Rotunno C, De Palo M, Mastro F, Pignatelli A, *et al*. Myocardial protection during aortic surgery: comparison between bretschneider-HTK and cold blood cardioplegia. Perfusion 2011;26:427–433. doi: 10.1177/0267659111409276.
17. Ji B, Liu J, Long C, Yang K, Zheng Z. Potential risk of hyponatremia using histidine-tryptophan-ketoglutarate solution during pediatric cardiopulmonary bypass. Ann Thorac Surg 2012;93:2120–2121. doi: 10.1016/j.athoracsur.2011.12.007.
18. Kim JT, Park YH, Chang YE, Byon HJ, Kim HS, Kim CS, *et al*. The effect of cardioplegic solution-induced sodium concentration fluctuation on postoperative seizure in pediatric cardiac patients. Ann Thorac Surg 2011;91:1943–1948. doi: 10.1016/j.athoracsur.2011.02.003.
19. Lueck S, Preusse CJ, Welz A. Clinical relevance of HTK-induced hyponatremia. Ann Thorac Surg 2013;95:1844–1845. doi: 10.1016/j.athoracsur.2013.01.026.
20. Lindner G, Zapletal B, Schwarz C, Wisser W, Hiesmayr M, Lassnigg A. Acute hyponatremia after cardioplegia by histidine-tryptophane-ketoglutarate — a retrospective study. J Cardiothorac Surg 2012;7:52. doi: 10.1186/1749-8090-7-52.
21. Lee JJ, Kim YS, Jung HH. Acute serum sodium concentration changes in pediatric patients undergoing cardiopulmonary bypass and the association with postoperative outcomes. Springerplus 2015;4:641. doi: 10.1186/s40064-015-1436-2.
22. Boettcher W, Dehmel F, Redlin M, Sinzobahamvya N, Photiadis J. Cardiopulmonary bypass strategy to facilitate transfusion-free congenital heart surgery in neonates and infants. Thorac Cardiovasc Surg 2020;68:2–14. doi: 10.1055/s-0039-1700529.

How to cite this article: Bai LT, Tong YY, Liu JP, Feng ZY, Zhao J, Guo SW, Jin Y, Zhang PY, Li YX. Comparable prognosis in different neonatal histidine-tryptophan-ketoglutarate dosage management. Chin Med J 2021;134:2968–2975. doi: 10.1097/CM9.0000000000001643