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The myocardial protective effect of monosodium phosphate cardioplegia in cardiopulmonary bypass in infants with an atrial septal defect

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Abstract

This study aimed to investigate the myocardial protective effect of liquid sodium phosphocreatine cardiac arrest in extracorporeal circulation surgery treating infants with atrial septal defects.

Eighty-four infants with atrial septal defects who required extracorporeal circulation surgery treatment at our hospital from January 2016 to June 2018 were divided into an observation group and a control group through a digitally randomized method, with 42 cases in each group. The control group adopted the conventional modified St Thomas II high potassium cold liquid crystal cardiac arrest, while the observation group adopted the liquid sodium phosphocreatine cardiac arrest.

The myocardial enzyme indexes of the 2 groups 3, 6, 12, and 24 hours postoperatively were higher than before establishing the cardiopulmonary bypass and the enzyme indexes of the control group at the same time were higher than that of the observation group; adenosine triphosphate, adenosine diphosphate, and other energy levels and the postoperative recovery rate energy levels of the observation group were higher than those in the control group, the difference was statistically significant ($P < .05$).

Liquid sodium phosphocreatine cardiac arrest used in extracorporeal circulation surgery treating infants with atrial septal defects can reduce myocardial ischemia-reperfusion injury, maintain energy supply during ischemia, strengthen the St Thomas II effect, and aid postoperative cardiac function recovery of high potassium cold liquid crystal cardiac arrest used in infants with atrial septal defects and treated with extracorporeal circulation surgery.

Abbreviations: ADP = adenosine diphosphate, AMP = adenosine monophosphate, AST = aspartate transaminase, ATP = adenosine triphosphate, CK-MB = creatine kinase - MB, CP = creatine phosphate, CPK = creatine-phosphokinase, CTnI = cardiac troponin I, CVP = central venous pressure, HR = heart rate, LDH = lactate dehydrogenase, MAP = mean arterial pressure.

Keywords: baby, during the operation, extracorporeal circulation, liquid sodium phosphocreatine cardiac arrest, myocardial protection, secondary groove pathogenesis

1. Introduction

A secundum atrial septal defect is a common congenital heart disease, the incidence rate of which accounts for about 10% of the incidence of congenital heart disease. The progress of the disease is slow, the clinical symptoms and signs are not obvious, and patients can be seriously affected in adulthood. The hemodynamic level of the patient and the occurrence of serious complications such as heart failure and pulmonary vascular occlusion seriously affect the health of the patient and can even endanger their lives. The secundum atrial septal defect was treated with intracardiac index surgery.[1,2] Cardiopulmonary bypass during open-heart surgery can cause myocardial ischemia and reperfusion injury, affecting the patient's cardiac function.[3] Surgical treatment of infants with a secundum atrial septal defect in the early stage is of great significance for the improvement of their prognosis. However, due to the immature development of the infant's body, myocardial damage and the prognosis of the child are more apparent.[4] Intraoperative myocardial protection in infants with secunduma-trial septal defect has significant implications for the improvement of the cardiac function and prognosis in infants. A cardioplegic solution is often used to protect the myocardial function during open-heart surgery.[5] However, there are few reports on the effect of monosodium phosphate cardioplegia on myocardial protection in infants with secundum atrial septal defect during

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cardiopulmonary bypass surgery. The purpose of this study was to analyze the myocardial enzyme index, hemodynamics, myocardial energy, and postoperative vasoactive drug use in cardiopulmonary bypass in infants with a secundum atrial septal defect with a conventional cardioplegic solution. The effect of this study provides a basis for myocardial function protection in infants undergoing cardiopulmonary bypass surgery for an atrial septal defect. The results are reported as following sections.

2. Methods

2.1. General information

Eighty-four infants who underwent extracorporeal circulation surgery for an atrial septal defect at our hospital from January 2016 to June 2018 were randomly divided into an observation group and a control group, with 42 cases in each group. Inclusion criteria[6]: All infants were diagnosed with secundum atrial septal defect through an imaging examination and the family members of the infants gave informed consent. Exclusion criteria[7]: Children with other congenital heart diseases, other severe organ dysfunction, or intraoperative death were excluded. The trial was approved by the hospital ethics committee and informed consent was given by the infants' parents. The observation group consisted of 20 males and 22 females, aged 0.8 to 2.5 years, mean age of 1.45 ± 0.45 years, a cardiothoracic ratio of 0.52 to 0.68, an average cardiothoracic ratio of 0.61 ± 0.03, an ejection fraction of 0.41 to 0.82, the mean ejection fraction was 0.71 ± 0.05, extracorporeal circulation time was 62 to 93 minutes, mean cardiopulmonary bypass time was 78.89 ± 12.75 minutes, myocardial block time was 36 to 57 minutes, and mean myocardial block time was 41.52 ± 6.48 minutes. The control group consisted of 21 males and 21 females, aged 0.6 to 2.4 years, mean age 1.41 ± 0.42 years, a cardiothoracic ratio of 0.55 to 0.67, an average cardiothoracic ratio of 0.62 ± 0.03, an ejection fraction of 0.40 to 0.82, the mean ejection fraction was 0.73 ± 0.06, extracorporeal circulation time was 60–95 minutes, mean cardiopulmonary bypass time was 78.95 ± 12.38 minutes, myocardial block time was 37 to 56 minutes, and the mean myocardial block time was 42.18 ± 6.87 minutes. There were no significant differences in gender, age, cardiothoracic ratio, mean ejection fraction, cardiopulmonary bypass time, or myocardial block time between the 2 groups ($P > .05$). The general data were comparable.

2.2. Treatment methods

Both groups received treatment for respiratory diseases, malnutrition, arrhythmia, and other complications or symptoms before surgery. In the control group, modified St Thomas II high-potassium cold crystal cardioplegia was routinely used. In the observation group, sodium creatine phosphate for the injection was added to the cardioplegia. The dosage of the myocardial protective solution was 10 mmol/L, which was equivalent to 2.5 g/L.[8] Both groups were treated with tracheal intubation according to anesthesia. Anesthesia induction and drug maintenance were essentially the same. Both the ascending aorta and superior and inferior vena cava were intubated to establish extracorporeal circulation, and the circulation was cooled to about 34°C to block the circulation. Both groups were injected with 15 mL/kg of their body weight of 2 cardiac arrests at 12°C through the aortic root. At the same time as the cardioplegia was injected, ice was placed on the surface of the heart to protect the myocardium and maintain the body temperature at about 30°C.

2.2.1. Infants with a polyester patch for secundum type interatrial septum. At the same time, the De Vega method or Kays method was used for tricuspid valvuloplasty. Postoperatively, the 2 groups were supported by different degrees of cardiopulmonary function according to the specific conditions. For patients with good preoperative cardiopulmonary function, the tracheal intubation was inserted according to the situation immediately. For patients with severe pulmonary hypertension, mechanical ventilation was appropriately extended.

2.2.2. Time. All the infants were treated with positive in otropic drugs and vasodilators according to their condition. Infants with arrhythmia still received antiarrhythmic drugs after treatment.

2.3. Detection methods

Before and 3, 6, 12, and 24 hours after the operation, the changes in the myocardial enzyme index, myocardial energy, and hemodynamic parameters were measured and vasoactive drugs were used within 2 days of the operation. On the day of the test, 3 mL of venous blood was taken from the 2 groups and centrifuged at 3500 rpm for 5 minutes, and then stored in a −20°C incubator for testing. Lactate dehydrogenase (LDH), creatine-phosphokinase (CPK), aspartate transaminase (AST), cardiac troponin I (CTnI), creatine kinase - MB (CK-MB), and other myocardial zymogram indicators: The detection kits for myocardial zymogram indicators were provided by Beckman Coulter. The enzyme-labeling instrument used was the ELx800 light-absorbing enzyme from Biotek, standard instrument. Myocardial energy substance detection: The levels of myocardial energy substances such as adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), and creatine phosphate (CP), were measured using a high-performance liquid phase method. Hemodynamic indicators: Hemodynamic observation indicators included heart rate (HR), central venous pressure (CVP), mean arterial pressure (MAP), etc. The detection instrument used FMS noninvasive hemodynamics provided by Beijing Baianji Technology Co, Ltd, monitor. Blood sample extraction operations were aseptic and all inspections were strictly performed according to the kit and instrument instructions.

2.4. Statistical methods

The SPSS19.0 software was used for statistical data processing. Measurement data were expressed as mean ± standard deviation and a 1-way analysis of variance was used for comparison between groups. Categorical data between the groups were compared using the Chi-squared test. Repeated measure analysis of variance was used for the comparison at multiple time points. $P < .05$ was considered statistically significant.

3. Results

3.1. The comparison of the changes in myocardial zymogram index before and after the operation

In both the control and observation groups, the preoperative values of myocardial zymograms indexes were significantly increased compared to those measured after the operation ($P < .05$, Table 1). By comparing the indexes between the 2 groups, we found that there were no significant preoperative differences in LDH, CPK, AST, CTnI, and CK-MB between them ($P > .05$), whereas the changes in myocardial zymograms at 3, 6,

Table 1

Comparison of changes in myocardial zymogram indexes before and after surgery in both groups (n = 42).

Time	Group	LDH, IU/L	CPK, IU/L	AST, IU/L	CTnI, μg/L	CK-MB, IU/L
Before transfer	Observation group	227.62 ± 53.24	188.93 ± 42.26	32.26 ± 4.75	0.66 ± 0.21	133.58 ± 78.52
	Control group	233.48 ± 50.75	194.75 ± 40.48	33.78 ± 3.98	0.68 ± 0.19	130.75 ± 70.44
	P	>.05	>.05	>.05	>.05	>.05
3 h postoperation	Observation group	358.85 ± 42.52*	213.65 ± 44.52*	45.52 ± 5.77*	2.24 ± 0.26*	159.85 ± 81.52*
	Control group	426.63 ± 53.78†	328.52 ± 46.25†	126.53 ± 13.58†	4.85 ± 0.48†	211.78 ± 80.26†
	P	<.05	<.01	<.01	<.05	<.05
6 h postoperation	Observation group	411.75 ± 65.98*	341.57 ± 51.75*	48.75 ± 5.82*	2.98 ± 0.32*	186.48 ± 82.42*
	Control group	563.75 ± 76.78†	456.98 ± 62.84†	154.27 ± 22.48†	5.78 ± 0.58†	287.42 ± 89.92†
	P	<.05	<.05	<.05	<.05	<.05
12 h postoperation	Observation group	486.78 ± 70.62*	368.87 ± 64.58*	52.29 ± 6.62*	3.42 ± 0.38*	240.65 ± 75.44*
	Control group	675.62 ± 81.16†	495.75 ± 68.55†	242.75 ± 28.75†	6.82 ± 0.74†	355.58 ± 73.62†
	P	<.01	<.01	<.01	<.05	<.01
24 h postoperation	Observation group	533.79 ± 73.44*	380.75 ± 72.26*	61.87 ± 7.92*	4.52 ± 0.62*	254.78 ± 82.57*
	Control group	816.27 ± 96.68†	567.42 ± 73.52†	288.92 ± 33.46†	8.66 ± 1.29†	443.62 ± 85.49†
	P	<.01	<.01	<.01	<.01	<.01

P values in the table indicate statistical significance between observation group and control group.

AST = aspartate transaminase, CK-MB = creatine kinase – MB, CPK = creatine-phosphokinase, CTnI = cardiac troponin I, LDH = lactate dehydrogenase.

* Comparison of myocardial enzyme indexes with observation group before treatment, $P < .05$.

† Comparison of myocardial enzyme indexes with control group before treatment, $P < .05$.

12, and 24 hours after the operation were significantly higher in the observation group when compared to the control group ($P < .05$, Table 1, Fig. 1).

3.2. The comparison of the myocardial energy level and recovery rate before and after the operation

The preoperative and postoperative levels of ATP, ADP, AMP, and CP in both groups were measured. There were no significant differences in the preoperative concentrations of ATP, ADP, AMP, and CP between the 2 groups ($P > .05$, Table 2). The levels of ATP, ADP, AMP, and CP in the observation group were significantly higher than those in the control group in the postoperative period ($P < .05$, Table 2). The recovery rate was also significantly increased in the group treated with phosphate cardioplegia compared with the controls (Table 2).

3.3. The comparison of the hemodynamic changes between the 2 groups

In both groups, the hemodynamic parameters were significantly improved after the surgery compared to those measured before

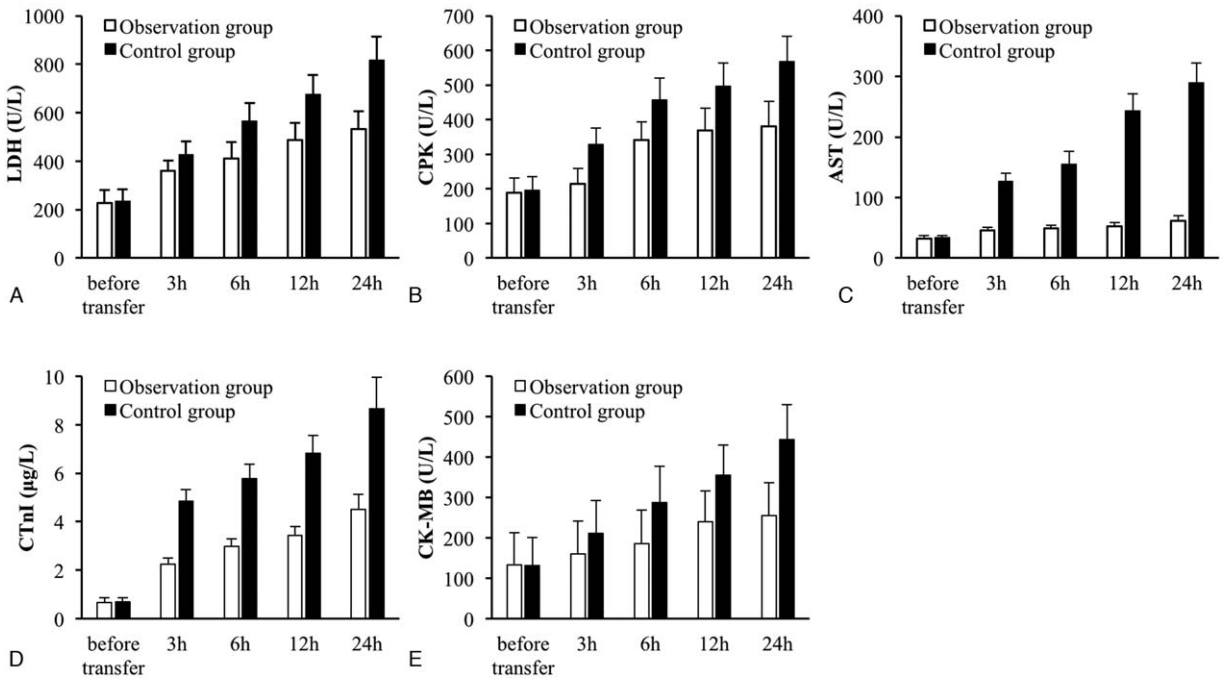

Figure 1. The comparison of the myocardial zymogram indexes in both groups before and after surgery. The concentrations of (A) lactate dehydrogenase (LDH), (B) creatine-phosphokinase (CPK), (C) aspartate transaminase (AST), (D) cardiac troponin I (CTnI), and (E) creatine kinase - MB (CK-MB) in the control and observation groups were measured before the operation and at 3, 6, 12, and 24 hours after the surgery.

Table 2

Comparison of myocardial energy levels and recovery rates before and after surgery in both groups (n = 42, mmol/g).

Myocardial energy substance	Group	Preoperative	Postoperative	Recovery rate
Adenosine triphosphate	Observation group	0.31 ± 0.06	0.24 ± 0.08	77.42%
	Control group	0.32 ± 0.07	0.11 ± 0.04	34.38%
	P	> .05	< .05	< .05
Adenosine diphosphate	Observation group	0.20 ± 0.08	0.17 ± 0.06	85.00%
	Control group	0.19 ± 0.06	0.13 ± 0.03	68.42%
	P	> .05	< .05	< .05
Adenosine monophosphate	Observation group	0.05 ± 0.02	0.13 ± 0.04	260.00%
	Control group	0.04 ± 0.01	0.06 ± 0.02	150.00%
	P	> .05	< .05	< .01
Creatine phosphate	Observation group	0.41 ± 0.12	0.55 ± 0.12	134.15%
	Control group	0.42 ± 0.13	0.34 ± 0.13	80.95%
	P	> .05	< .05	< .01

P values indicate statistical significance between observation group and control group.

Table 3

Comparison of hemodynamic changes between the 2 groups (n = 42).

Time	Group	HR, beats/min	CVP, mH_2O	MAP, mm Hg
Before transfer	Observation group	118.52 ± 8.45	9.38 ± 2.65	65.59 ± 6.85
	Control group	119.42 ± 8.97	9.42 ± 2.37	65.42 ± 6.42
	P	> .05	> .05	> .05
3 h postoperation	Observation group	94.45 ± 8.11*	6.75 ± 2.29*	74.45 ± 7.54*
	Control group	118.25 ± 8.79†	9.40 ± 2.48†	65.98 ± 6.84†
	P	< .05	< .05	< .05
6 h postoperation	Observation group	92.78 ± 7.45*	6.27 ± 2.03*	78.59 ± 7.87*
	Control group	116.45 ± 8.69†	9.26 ± 2.64†	66.47 ± 6.26†
	P	< .05	< .05	< .05
12 h postoperation	Observation group	91.26 ± 7.12*	6.18 ± 1.84*	84.62 ± 7.94*
	Control group	115.78 ± 8.87†	9.18 ± 2.61†	66.82 ± 6.37†
	P	< .05	< .05	< .05
24 h postoperation	Observation group	90.42 ± 6.94*	6.02 ± 1.81*	85.74 ± 7.88*
	Control group	111.56 ± 7.95†	9.04 ± 2.54†	67.87 ± 6.69†
	P	< .05	< .05	< .05

P values in the table indicate statistical significance between observation group and control group.
CVP = central venous pressure, HR = heart rate, MAP = mean arterial pressure.
* Comparison of myocardial enzyme indexes with observation group before treatment, $P < .05$.
† Comparison of myocardial enzyme indexes with control group before treatment, $P < .05$.

the operation (Table 3). The preoperative hemodynamic parameters, including HR, CVP, and MAP, were not statistically significant between the 2 groups ($P > .05$, Table 3, Fig. 2). The HR and CVP in the observation group measured at 3, 6, 12, and 24-hour postoperation were significantly higher than those in the control group, whereas the MAP was lower when compared to the control group ($P < .05$, Table 3, Fig. 2).

3.4. The comparison of postoperative vasoactive drug use in the 2 groups

The doses of vasoactive drugs such as dopamine, adrenaline, and milrinone in the observation group were lower than those in the control group on days 1 and 2 after the operation, the difference was statistically significant ($P < .05$, Table 4).

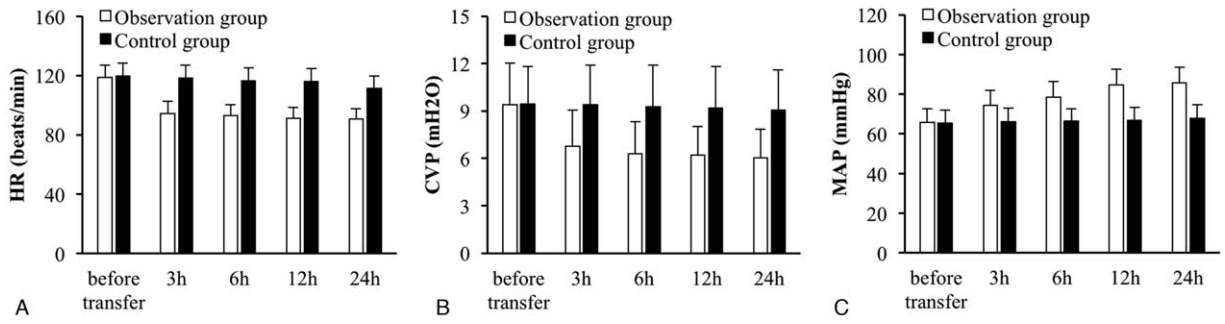

Figure 2. The comparison of the hemodynamic indicator indexes in both groups before and after surgery. The (A) heart rate (HR), (B) central venous pressure (CVP), and (C) mean arterial pressure (MAP) in the control and observation groups were measured before and at 3, 6, 12, and 24 hours after the surgery.

Table 4

Comparison of postoperative vasoactive drug use between the 2 groups (n = 42, mg/kg).

Time	Group	Adrenalin	Dopamine	Milrinone
Postoperative 1 d	Observation group	0.03 ± 0.01	5.87 ± 2.14	0.28 ± 0.12
	Control group	0.06 ± 0.02	3.15 ± 1.79	0.61 ± 0.18
	P	<.05	<.05	<.05
Postoperative 2 d	Observation group	0.05 ± 0.02	6.42 ± 2.87	0.64 ± 0.18
	Control group	0.12 ± 0.04	10.52 ± 3.04	0.85 ± 0.27
	P	<.05	<.05	<.05

P values in the table indicate statistical significance between observation group and control group.

4. Discussion

A secundum atrial septal defect is a common congenital disease with no apparent clinical symptoms or signs in the early stages while the patient has obvious clinical features in adulthood, or even in old age.[9] Patients with secundum atrial septal defect often have serious complications such as hemodynamic changes, heart failure, and pulmonary artery dysfunction in adulthood, affecting the health and normal life of patients, and even causing poor prognosis such as death.[10] Secundum atrial septal defect is often treated with cardiopulmonary bypass surgery.[11] Early detection and treatment of secundum atrial septal defect is important for the improvement of their prognosis and quality of life. However, in infants with secundum atrial septal defect, due to immature development, their postoperative recovery is slow and intraoperative myocardial function protection is even more important.[12,13] The search for myocardial function protection in infants with a secundum atrial septal defect is of great significance in improving surgical outcomes and prognosis.

Cardiac cardioplegia has a high protective effect on myocardial function during open-heart surgery.[14] Sodium creatine phosphate can enhance the intracardiac protective effect of conventional cardioplegia in animal heart surgery.[15,16] However, there are few reports on myocardial protection in infants with secundum atrial septal defect enhanced with sodium phosphate locally and abroad. Cardiac cardioplegia using sodium creatine phosphate has secondary effects in infants with an atrial septal defect. The effects on intraoperative myocardial enzymes, myocardial energy, hemodynamics, and vasoactive substances may guide the protection of myocardial function during cardiopulmonary bypass in infants with an atrial septal defect.

During a myocardial ischemia-reperfusion injury, the permeability of the myocardial muscle cell membrane is increased, resulting in the release of myocardial enzymes into the blood. LDH, CPK, AST, CTnI, and CK-MB are key myocardial enzymes used to estimate the degree of myocardial injury.[17] The results of this study showed that cardiac cardioplegia containing sodium creatine phosphate effectively reduced myocardial enzymes, such as LDH, CPK, AST, CTnI, and CK-MB, in infants with an atrial septal defect, indicating reduced myocardial damage during cardiopulmonary bypass. ATP, ADP, AMP, and CP are the key myocardial energetic indexes.[18] In this study, we showed that cardioplegia with sodium creatine phosphate improved the postoperative levels of ATP, ADP, AMP, and CP in infants receiving a cardiopulmonary bypass. The level of energy substances prevents myocardial damage caused by insufficient intraoperative myocardial energy supply. Cardioplegia containing sodium creatine phosphate is used in infants with a secundum atrial septal defect for cardiopulmonary bypass. The hemodynamic indicators including HR, CVP, and MAP were commonly used to evaluate cardiac function in patients.[19] We further observed that phosphate cardioplegia improved the average arterial pressure, reduced the heart rate and central venous pressure of the infant, and maintained the blood flow of the child. Stable kinetic levels prevent myocardial damage caused by myocardial reperfusion and hemodynamic abnormalities. In the extracorporeal circulation, in a secundum atrial septal defect requiring cardiac cardioplegia, sodium creatine phosphate is used including a small number of vasoactive drugs such as dopamine, adrenaline, and milrinone in infants. At the same time, it may reduce the side effects of the vasoactive drugs used on the function and development of the child's body, which is conducive to postoperative recovery. Cardioplegia with sodium creatine phosphate increases the possible cardio-protection mechanism in conventional cardioplegia in patients undergoing cardiac surgery: 1 sodium creatine phosphate enhances the stability of phospholipid bilayer results and prevents cardiomyocytes from passing through oxidation and degradation; sodium creatine 2 can inhibit 5′-N to protect the adenylate pool[20–22]; sodium creatine 3 can slowly enter the ischemic cells and increase the level of high-energy phosphate compounds[23,24]; Myocardial ischemia occurs when sodium creatine phosphate promotes the influx of calcium ions into cells and promotes the contraction of the myocardium. Because of the small sample size and short postoperative observation time, the effect of cardiac cardioplegia with sodium creatine phosphate on myocardial protection in infants with secundum atrial septal defect requiring cardiopulmonary bypass remains unclear. Therefore, it is evident that the application of cardioplegia with sodium creatine phosphate for the myocardial protection of infants with secundum atrial septal defect requiring cardiopulmonary bypass requires a larger sample size with long-term experiments and comprehensive research.

5. Conclusion

In summary, cardiac cardioplegia with sodium creatine phosphate is used in infants with a secundum atrial septal defect requiring a cardiopulmonary bypass to reduce myocardial ischemia-reperfusion injury, maintain energy supply during ischemia, and enhance the St Thomas II effect. The protective effect of high-potassium cold crystal cardioplegia is beneficial to the recovery of cardiac function in infants with a secundum atrial septal defect after cardiopulmonary bypass.

Author contributions

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Writing – original draft: Fang Yang, Bo Zhai.
Writing – review & editing: Fang Yang, Bo Zhai.

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