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Myocardial Protective Effect of Exogenous Creatine Phosphate in Children Undergoing Open Heart Surgery

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Abstract

Objective: To explore the protective role of exogenous Creatine Phosphate (PCr) in the postoperative cardiac muscle recovery in children undergoing open heart surgery.

Material and methods: 63 cases of congenital heart disease were randomly divided into 3 groups; A, B and C; 21 cases in each group. Myocardial perfusion fluids were made of the same amount of blood in the St, Thomas Hospital cardioplegic solution type 2 (STH 2). In B and C group, intraoperative myocardial perfusion solution added with exogenous CP. All the groups were postoperatively treated with general fluid therapy, while group C was given postoperative intravenous exogenous CP. Trends of myocardial enzyme at different time points were monitored.

Results: At the end of surgery (T2), enzyme levels in the plasma were significantly increased, no difference between the groups B and C but were significantly lower than that in group A ($P<0.05$); after surgery myocardial enzyme levels recovered fastest in Group C, slowest in A group, the differences between each group were significant ($P<0.05$).

Conclusions: Perioperative and postoperative exogenous PCr have myocardial protective effect and accelerate the repair of injured myocardium due to ischemia during open heart surgery in children.

Keywords: Creatine-phosphate (PCr); Congenital heart disease; Cardiopulmonary bypass

Introduction

To obtain a bloodless operating field during open-heart surgery, aortic cross-clamping is deliberately introduced leading to a period of myocardial ischemia. As a consequence, an unbalance between demand and supply of cellular high-energy phosphates is created. This results in a rapid fall of creatine phosphate levels, followed by a decrease in the tissue content of ATP. Low levels of ATP are related to the loss of cellular function and the onset of cell injury and death. The precise mechanism of action is, however, still unclear.

Most protective measures taken during open-heart surgery aimed at the conservation of cardiac high-energy phosphate pools in the ischemic tissues. To this end, commonly electro-mechanical activity is abolished rapidly by intracoronary infusion of an ice-cold crystalloid or sanguineous cardioplegic solution immediately after aortic cross-clamping.

The clinical application of creatine phosphate (PCr) for cardioprotection during heart surgery and myocardial ischaemia is based on the results of a series of pharmacological studies in animal models. Its application as a cardioplegic additive and for intravenous infusion leads to significantly better functional recovery following ischaemia, during the postinfarction period and upon reperfusion.

Material and Methods

Clinical data

From August 2015-February 2016, 63 cases of congenital heart disease (CHD) were performed open heart surgery under CPB, including 39 cases of ventricular septal defect, 24 cases of atrial septal defects. Cases were randomly divided into three groups, each 21 cases. A group of 9 males and 12 females, age (6.4 ± 2.3) years, body mass (13.7 ± 5.3) kg, ejection fraction (63 ± 8)%; group B, 11 males and 10 females, age (6.8 ± 2.4) years, body mass (14.3 ± 5.7) kg, ejection fraction (65 ± 7)%; group C, 11 males and 10 females, age (6.5 ± 2.4) years, body mass (13.9 ± 5.2) kg , ejection fraction (62 ± 5)%. 3 groups were comparable clinical data.

Method of treatment

Three groups were adopted general anesthesia. All the maintenance drugs were basically the same. Conventional CPB was established with moderate hypothermia (28 ~ 32). During the surgery, Hct. 20% to 30%, Systemic infusion flow rate 1.6 ~ 2.8 L / (m^2/ min) and mean aortic pressure 40 ~ 60 mmHg were maintained. All the patients in three groups were given cardioplegic solution (the same amount of blood in the STH 2 solution), but group B and group C were added with exogenous PCr (10 mmol/ L) into intraoperative cardioplegic solution. The first dose of 20 ml / kg then added half dose (10 ml/kg) after each 30 min. After surgery, patients in group A and B were treated with conventional fluid therapy, however group C was treated with intravenous PCr at dose of (1.0 g / once/day) continuously up to

postoperative 5 days. Venous blood were collected to detect plasma level of Creatine kinases (CK), CK-MB, cardiac troponin I (cTnI) on one day before surgery, preoperative (T1), the end of operation (T2), postoperative 1st day (T3), 2nd day (T4), 3rd day (T5) and 5th day (T6) respectively.

Statistical method

Statistical analysis was done by using SPSS 13.0 software. Datas were expressed as mean ± standard deviation ($\bar{x} \pm s$), the groups were compared using ANOVA or t-test. $P \leq 0.05$ assumed statistically significant.

Results

Duration of Circulation and aortic clamping in each group did not reach statistical significant difference (P>0.05). Comparisons of Myocardial enzymes in 3 groups at different time points are shown in Table 1. As Seen from Table 1, preoperative myocardial enzymes in three groups of children showed no significant difference (P>0.05); at the end of surgery each index level were elevated, no difference between group B and C but were lower than that in group A (P<0.05); after surgery, the fastest recovery of myocardial enzyme levels was found in group C while group A was found to be the slowest, difference between the groups was statistically significant (P<0.05).

Group	CK	CK-MB	cTnI
Group A			
T1	71.0 ± 42.9	13.4 ± 6.1	0.24 ± 0.17
T2	787.9 ± 97.6	38.5 ± 6.8	1.42 ± 0.52
T3	1745.7 ± 133.6	44.7 ± 7.3	4.54 ± 1.71
T4	1032.1 ± 89.3	41.7 ± 7.7	3.79 ± 1.33
T5	415.7 ± 52.9	34.9 ± 6.9	2.97 ± 1.56
T6	99.5 ± 42.1	24.5 ± 8.9	2.21 ± 0.67
Group B			
T1	73.5 ± 39.8	12.9 ± 5.9	0.21 ± 0.18
T2	654.3 ± 84.8*	35.4 ± 6.8*	0.79 ± 0.26*
T3	1598.1 ± 123.4*	41.3 ± 7.1*	4.13 ± 1.54*
T4	807.4 ± 82.2*	37.9 ± 7.4*	3.43 ± 1.41*
T5	349.8 ± 62.1*	31.5 ± 7.1*	2.25 ± 1.35*
T6	283.4 ± 44.3*	23.5 ± 8.4*	1.18 ± 0.41*
Group C			
T1	69.8 ± 43.4	15.3 ± 6.2	0.22 ± 0.19
T2	661.4 ± 90.2*	35.9 ± 6.6*	0.81 ± 0.29*
T3	1407.3 ± 109.9*Δ	38.9 ± 6.9*Δ	3.77 ± 1.51*Δ
T4	659.1 ± 76.5*Δ	34.2 ± 6.7*Δ	3.11 ± 1.21*Δ
T5	303.5 ± 47.6*Δ	28.7 ± 6.4*Δ	1.67 ± 0.59*Δ
T6	227.6 ± 39.8*Δ	18.6 ± 6.4*Δ	1.09 ± 0.39*

*Δ

Table 1: Comparative index level of myocardial enzymes of 3 groups at different time points (U / L, x ± s).

Discussions

Creatine Phosphate (PCr) is one of the important substances involved in cellular energy metabolism. It is also an important source of energy supply for the cells to replenish energy in the form of adenosine triphosphate (ATP). ATP is the main source of energy in any metabolic processes of cells. Creatinephosphate provides phosphate to the ADP and prepares ATP in anaerobic condition with the help of enzyme creatine kinase. Its pharmacological effects include: to maintain the high-energy phosphate level of cells; stability of membrane phospholipids. Exogenous Creatine Phosphate have a protecting and stabilizing role of the cell structure in myocardial ischemia by inhibiting lipid membrane of muscle fibers but also to stabilize the electrophysiological state ischemic myocardial cells. Zucchi et al. [1] found that Creatinephosphate can also protect the body from damaging effect of free radical peroxidation and provide a stabilizing effect on the membrane. Cardiac surgery will often block the ascending aorta followed by a state of myocardial ischemia and hypoxia causing myocardial ischemic injury.

A key component in the development of ischemic functional and structural myocardial injury during open heart procedures is an inadequate cellular energy supply which occurs as a consequence of the cessation of oxidative metabolism. In such conditions high energy phosphates are rapidly depleted. As they play a critical role in the maintenance of cell viability and postischemic recovery of contractile function, their conservation is therefore a primary objective in any procedure designed to reduce ischemic injury. Exogenous administration of phosphocreatine (CP) has been suggested as being beneficial to the ischemic heart.

Many complications of improper myocardial protection are closely associated with increased postoperative mortality in cardiac surgery, thus perioperative protection of myocardium in cardiac surgery to reduce the damage and speed up the recovery of myocardial injury, has become one of the core subjects studied in cardiac surgery.

St. Thomas' Hospital cardioplegic solution No. 2 [STH2]), commercially known as plegisol solution was approved by the Food and Drug Administration for use in the United States and remains the most widely used crystalloid cardioplegic solution in the world. Continuing experimental studies have shown that STH2 is substantially more eficacious than STH1 in terms of both myocardial protection and antiarrhythmic effects [2].

Addition of exogenous high-energy phosphate compounds, like many other metabolic additives, has been shown to confer beneficial effects, despite controversy regarding the ability of these compounds to enter the cell. Thus, creatine phosphate (CP) alone or in combination with adenosine triphosphate (ATP) when used as an additive to STH2 enhanced the protective properties of STH2 in terms of both function and antiarrhythmic effects [3,4]; these experimental studies were confirmed clinically [5] but only at the cellular level and not on clinically measurable variables. Exogenous CP, as the energy matrix added in cardioplegic solution in myocardial perfusion, can replenish energy of ischemic myocardial cells. Mitochondrial and cell membrane function are maintained, can avoid damage due to anaerobic

metabolism, thus the myocardial protection has been strengthened [6,7]. Creatine- phosphate can also dilate coronary artery, increase coronary blood flow, and improve myocardial oxygen supply [8]. In our study, we added exogenous Creatine-phosphate in cardioplegic solution and post-operative intravenous solution. We found that CP plays a positive role to improve post-ischemic myocardial energy metabolism.

Postoperative changes of myocardial enzymes reflect myocardial injury and recovery situations. Especially cTnI, regardless of age, gender and site of myocardial injury, as long as there is a small amount of myocardial necrosis, the blood levels will rise relatively quickly [9]. cTnI is widely recognized as specific biochemical indicators of myocardial injury [10,11]. The results of this study shows that, in the immediate postoperative period, CK, CK-MB and cT-nI level in 3 groups were higher, while B, C groups were lower when compared with group A, confirmed that exogenous CP in children undergoing open heart surgery for repairing septal defects under cardiopulmonary bypass can provide myocardial protection; post-operative rate of decreased myocardial enzymes was found to be fastest in Group C, while group A was the slowest, suggesting that CP can speed up the recovery of myocardial reperfusion injury.

Conclusion

Perioperative and post-operative use of exogenous creatine phosphate can speed up the recovery of the injured myocardium after the open heart surgery in children with congenital heart diseases.

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