Clinical Study of the Protective Effect of Exogenous Creatine Phosphate on Ischemic Myocardium during Open Heart Surgery

Peiqing Dong, MD; Jing Yang, MD; Yuchun Pan, MD; Yulong Guan, MD; Meiling He

Department of Extracorporeal Circulation, Beijing Anzhen Hospital, Capital Medical University, Beijing

Keywords: cardiopulmonary bypass, cardioplegia, creatine phosphate, myocardial protection


ABSTRACT

This study was designed to evaluate the myocardial protective effect of exogenous creatine phosphate (CP) added to cardioplegic solution for use in open heart surgery.

Ninety-eight patients were divided into a control group (n = 44) and a CP group (n = 54). The spontaneous recovery rate of heart beat after aortic declamping was recorded and changes of serum enzymes including CPK, LDH, CPK-MB, HBDH, and AST were evaluated. The ultrastructural alterations of the myocardial tissue were observed in 4 patients (2 cases from each group) who had cardiac valve replacement.

The spontaneous recovery rate of heart beat in the CP group was significantly higher than the control group (39/54 versus 22/44), and the peak values of leakage of serum enzymes of the control group appeared earlier and receded later than those of the CP group. Electron microscope examination revealed better preservation of the ultrastructures of the myocardial tissue in the CP group than that of the control group. This data indicates that exogenous creatine phosphate added to the cardioplegic solution offers a better protective effect on the ischemic myocardium during open heart surgery.

Address correspondence to:
Peiqing Dong, MD
Beijing Anzhen Hospital
Capital Medical University
Beijing Heart Lung Blood Vessel Inst.
Beijing 100029, People’s Republic of China
INTRODUCTION

The efficacy of creatine phosphate (CP) has been widely documented both experimentally and clinically (1-5) in minimizing myocardial infarction and in enhancing myocardial preservation during open heart surgery.

Our present study was focused on the protective effect of CP added to cardioplegic solution on ischemic myocardium during open heart surgery.

MATERIALS AND METHODS

Ninety-eight patients who received open heart surgery were randomly divided into a control group (n=44) and CP group (n=54). The clinical profiles of patients in the groups are summarized in Table 1.

The control group was given conventional crystalloid cardioplegia (modified St. Thomas solution; Table 2), with an initial dose of 15-20 ml/kg, followed by a half dose every 20-30 min. In the other group, CP was added to the cardioplegia solution with a concentration of 2.5 g/L (10 mmol). In the CP group, 40 patients were given crystalloid cardioplegia containing CP: 14 patients were given CP blood cardioplegia (4:1), including one double valve replacement, one aortic valve replacement and 12 Marfans syndrome. The infusion dosage in the CP group was the same as that of the control group.

After releasing the aortic cross clamp, the heart's spontaneous recovery rate, the need for electrical defibrillation, sinus rhythm resumption, and the use of inotropic supportive agents in the recovery phase were recorded and observed.

Blood samples for assessment of the CPK, LDH, CPK-MB, HBDH, and AST levels were drawn at the following times: pre-operation, 6 and 12 h after aortic declamping, and 24 and 48 h after surgery. Data analysis was conducted on 36 patients who had all serum enzyme tests. Twelve patients were from the control group; their average cross clamp time was 78.82 ± 28.85 min. Twenty-four were from the CP group. According to the aortic cross clamp time, patients were further divided into 3 subgroups: cross clamp time less than 80 min, CP Group 1 (n=8); clamp time 80-120 min, CP Group 2 (n=10); over 120 min, CP Group 3 (n=6). Data was compared using the Students’ t-test and are presented as means.

RESULTS

The average aortic cross clamp times in the control group and the CP group were 83.22 ± 37.06 min and 99.5 ± 51.99 min, respectively (p < 0.05). For cross clamp times ranging from 60-120 min, there were 24 in the control group and 22 in the CP group. For cross clamp times greater than 120 min, there were 6 in the control group and 18 in the CP group.

After declamping, spontaneous defibrillation was significantly higher in the CP group (39/54 versus 22/44) and the need for electric shock was lower than that in the control group. Despite the longer cross clamp time, all CP patients showed higher spontaneous recovery rates (Figure 1).

As mentioned above, there were also 12 patients with Marfans syndrome who were given CP blood cardioplegia. The spontaneous resumption rate of these patients, as compared with 93 Marfans syndrome patients we reported on in 1995 (6), was remarkably increased, from 10/47 with crystalloid cardioplegia and 28/46 with blood cardioplegia to 11/12 with CP blood cardioplegia.

One of the CP patients had intermittent ventricular arrhythmia but was successfully treated with lidocaine and dobutamine on the day of operation. Three patients in the control group who had severe ventricular arrhythmias were given multiple doses of antiarrhythmic agents up to 48 to 72 h post operation, and one of them needed an intra-aortic balloon pump. There were no deaths in either group.

Serum CPK began to rise on the 6th hour after operation, with the peak value at the 12th hour, then leakage in both the CP and control groups came down gradually towards the baseline in all the 3 CP groups. But the value of the control group at 48 hours after operation was still higher than that of the three CP groups (Figure 2).

LDH level increased in all groups and reached peak values at the 12th hour. But among the three CP groups, the value of Groups 1 and 2 were lower than that of Group 3, which was, in turn, still lower than the value of the control group (p < 0.05).
Forty-eight hours after operation, the LDH level in all CP groups decreased to normal value. However, the level of the control group decreased slowly and was still above the baseline at this time (Figure 3).

CPK-MB, in the control group, increased steeply to its peak value at the 6th hour, in sharp contrast, the value of the three CP groups increased moderately with peak values much lower than that of the control group (p < 0.01) and showed a delay until the 12th hour (Figure 4).

There was not much difference between groups, as the value began to rise at the 6th hour after operation and reached peak values at the 12th hour. HBDH in the control group was a bit higher than all CP groups (p < 0.05), but all returned to normal range at 48 hours after operation (Figure 5).

The changes in AST were similar to those of HBDH (Figure 6).

When viewed with the electron microscope, there was mild swelling of the myocardial cells, well laid out myofibrillae, intact mitochondria with homogeneous matrix and without definite crest fragmentation in the CP patients. However, there was marked dropsy and vacuolation of mitochondria, prominent fragmentation and disarrangement of their crest, reduced matrix-density, and ill laid out myofibrillae in control patients (Figures 7 and 8).
DISCUSSION

During open heart surgery, ischemia may induce quick consumption of high energy phosphate and produce ionic, biochemical and morphological changes that sometimes greatly undermine the activity and contraction.

Ruda (2) reported the reduction of ventricular arrhythmias by giving CP intravenously in patients with acute myocardial infarction. Sharov and Semenovsky (1) reported on the ultrastructural changes in both isolated myocardium and clinically with infusion of CP cardioplegia and showed remarkable protection against ischemic injury. Sharov (4) also found exogenous CP could reduce infarction size, stabilize the sarcolemma of ischemic cardiomyocytes, and protect antithrombotic action.

The addition of exogenous CP to cardioplegia solution could provide an energy supply during the ischemia phase. As Robinson (3) confirmed, exogenous CP was an additive myocardial protective and antiarrhythmic agent in cardioplegia. In our study, the beneficial effects are as follows:

1. Higher spontaneous recovery rate of the CP groups than that of the control group, despite longer cross clamping time. Significant reduction of DC shocks for defibrillation and better
resumption of sinus rhythm.

2. Higher spontaneous recovery rate of the CP blood cardioplegic group than both the control and the blood cardioplegia group without CP administration.

3. The general tendency of the changes in the 5 serum enzymes are similar to those reported in the literature (7), but in the three CP groups, the leakage of the enzymes was much slower than the control group. In CP Group 3, the increase was higher than that in CP Groups 1 and 2, but it was still lower than the control group. This is contradictory to that reported in the literature (8) stating that the longer the cross clamping time (over 30 min), the higher the level of enzymes and the quicker the leakage tendency. The same author also pointed out that the rate of the serum enzymes leakage is related to the rate of myocardium resumption. But our study shows that there is a protective effect and a quicker recovery when CP is added in.

4. Mitochondria, where ATP is produced, are the energy resources of living cells; therefore, keeping them intact is associated with the normal function of the cells. In this study, the ultrastructural changes have shown that, under the same conditions of myocardial damage, administration of CP could protect the myocardial cell ultrastructure better.

CONCLUSION

Exogenous CP as a component of cardioplegia will produce a protective effect on ischemic hearts, increase the rate of spontaneous defibrillation, and reduce postoperative arrhythmias, as well as preserve the ultrastructure of the myocardial cells.

Exogenous CP as an additive to blood cardioplegia increases the protection of the ischemic heart over that offered by blood cardioplegia alone.

ACKNOWLEDGEMENT

We would like to thank ALFA-WASSERMANN SPA (Italy) for supplying creatine phosphate (Neoton).

REFERENCES