[The experience of the application of ascorbinic acid as antioxidant after coronary artery surgery with use of cardiopulmonary bypass].
Rebrova TIu, Shipulin VM, Afanas'ev SA, Vorob'eva EV, Kiĭko OG.
Kardiologiia. 2012;52(7):73-6.

PubMed record: 22839718
http://www.ncbi.nlm.nih.gov/pubmed/22839718

Translation of this paper was arranged by Harri Hemilä in May 2015
harri.hemila@helsinki.fi
http://www.mv.helsinki.fi/home/hemila/
http://www.mv.helsinki.fi/home/hemila/CAF.htm (Cochrane review)
http://www.mv.helsinki.fi/home/hemila/CAF (Cochrane review references)

This translation is located at:
http://www.mv.helsinki.fi/home/hemila/T12.pdf
version 2015-10-27

The Russian paper:
http://www.medvestnik.ru/library/article/2904

TheRussian version is available also at:
http://www.mv.helsinki.fi/home/hemila/CAF/Rebrova_2012_Rus.pdf

Experience with Administration of Ascorbic Acid as Antioxidant After Coronary Artery Bypass Surgery With Cardiopulmonary Bypass

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Keywords: atrial fibrillation, aortocoronary bypass, lipid peroxidation.

One of the most common complications that occur after surgical treatment of coronary insufficiency in patients with ischemic heart disease (IHD) is arrhythmia [1, 2]. Also relevant in this regard is the finding by L.A. Bokeria that direct myocardial revascularization can cure arrhythmia only in a very small number of patients [3]. The primary peak of cardiac arrhythmia occurs during the first three days after operation [4], then a sinus rhythm is re-established. According to the literature data, patients with post-operative arrhythmia, in particular those with atrial fibrillation, have significantly lower 30-day and six-month survival rates than those without complications [5]. Antiarrhythmics, such as β-adrenoblockers, are recommended to prevent such complications. However, they are not always effective, because almost all antiarrhythmic agents are capable of proarrhythmic effect [6, 7].

The high frequency of arrhythmia in the post-operative period may reflect metabolic disorders that are occurring in cardiac muscle cells [4]. It has been established experimentally that one of the mechanisms of cardiac muscle damage as a result of ischemic and reperfusion stress is uncontrolled lipid peroxidation (LPO), which damages the structure and function of cell membranes [8, 9].

The aim of this study was to investigate the role of oxidant stress in the development of arrhythmia in the early post-operative period after coronary artery bypass surgery, as well as the possibility of preventing such arrhythmia with ascorbic acid.

Materials and methods

The study was conducted with 40 (male) patients suffering from chronic IHD, who were admitted to the Research Institute of Cardiology of the Siberian branch of the Russian Academy of Medical Sciences. All patients were recommended surgical treatment. Patients taking part in the study were divided into two comparable groups: the main group and the control group. A brief clinical profile of the observed patient groups is provided in Table 1. All the patients received standard basic treatment before and after operation, including β-adrenoblockers (metoprolol, bisoprolol, atenolol). For patients in the main group, basic treatment was supplemented with ascorbic acid. The ascorbic acid was administered as 1 g water-soluble tablets as follows: 2 g the evening before the operation and 1 g twice per day for the 5 days after the operation.

Arrhythmia was observed in patients during the pre- and post-operative period by ECG monitoring with a Siemens SC 9000 monitor.

Before administering ascorbic acid, as well as on the 1st and 5th days after surgery, venous blood samples were taken from all patients. Plasma taken from these samples was frozen and stored at the temperature of liquid nitrogen. The biosamples were used to evaluate the intensity of oxidative stress, which was assessed on the basis of the concentration of conjugated dienes (CD) [10] and the activity of the antioxidant enzyme catalase [11].

A comparison of the data was conducted using the Mann-Whitney U test and χ^2. The differences were considered statistically significant when $p<0.05$.

***Table 1*. Clinical profile of the observed groups of patients**

Parameter	Control group	Main group	*p*
Number of patients	20	20	
Male, %	100	100	
Mean age, years	61±6.6	56.4±6.7	0.68
Angina FC II, %	21	19	0.88
Angina FC III, %	79	81	0.88
Unstable angina, %	17	11	0.49
CHF FC II (NYHA classification), %	78	75	0.78
CHF FC III (NYHA classification), %	22	25	0.78
Postinfarction cardiosclerosis, %	61	57	0.79
Hypercholesterolemia, %	78	75	0.78
Class I-II obesity,%	30	32	0.89
Class II-III arterial hypertension, %	83	89	0.49
Diabetes, %	17	28	0.35
Smoking, %	39	53	0.31
Associated arteriopathies (stenoses >50%), %	43	46	0.83
Duration of CPB, min	104.7±27.9	107.3±39.9	0.67
Duration of ischemia, min	68.6±24.3	72.2±26.2	0.65
Number of bypasses	3.0±1.2	3.2±1.0	0.59

Note. FC — functional class; CHF — chronic heart failure; NYHA — New York Heart Association classification; CPB — cardiopulmonary bypass.

Results and discussion

The results for CD concentration and catalase activity in the blood plasma of the observed patient groups are shown in Table 2. The data shows that there were no significant differences in the initial parameters between the groups. This is entirely consistent with the data shown in Table 1 and the fact that IHD development is accompanied by the activation of LPO in the cardiac muscle and blood of patients [12]. However, in the post-operative period, CD concentration and catalase activity were different between the observed patient groups. For example, the CD concentration in the blood plasma of the control group patients had not changed to a statistically significant extent 24 hours and 5 days after surgery. In patients taking ascorbic acid, a statistically significant decrease in CD concentration from the initial values for the group was observed 24 hours after the operation. Given that CDs are primary products of LPO [13], the decrease in concentration may be interpreted as an indication that ascorbic acid blocks the development of oxidant stress during its initial stages. Under normal conditions, the LPO process is constantly controlled by the body's antioxidant system. Under the conditions of chronic IHD with repeated episodes of ischemia and reperfusion, exhaustion of some antioxidants occurs [8], which can negatively impact the effectiveness of LPO suppression under acute ischemic stress. Indeed, as shown above, patients suffering from IHD with severe heart failure have a significantly lower level of endogenous lipid-soluble antioxidants [14].

In order to evaluate the status of the antioxidant system in patients of the observed groups and the responsiveness of the system during treatment with ascorbic acid, we assessed the activity of catalase, the major enzyme of antioxidant protection.

As shown in Table 2, there were no statistically significant differences in catalase activity in the pre-operative period between patients in the observed groups. However, 24 hours after surgery we identified a statistically significant increase (greater than 2.1) in the activity of this enzyme in the patients of the control group. On the 5^{th} day, catalase activity had fallen, but still remained higher than before the surgery.This pattern of activity in one of the major antioxidant enzymes can be interpreted as an indicator of the compensatory effort of the antioxidant system in response to ischemic and reperfusion stress, to which the cardiac muscle has been exposed during surgical intervention. At the same time, an increase in catalase activity suggests that the endogenous antioxidant system of patients in the study group, or at least its enzyme component, maintains a functional reserve.

We did not notice any significant changes in catalase activity in patients of the main group during the entire period of the study. The pattern of catalase enzyme activity in this group may be the result of

antioxidant stability in the body as a result of taking ascorbic acid.

At present, the pathogenesis of reperfusion arrhythmias, including those occurring after surgical treatment of IHD with the use of cardiopulmonary bypass, is believed to be related to the "oxygen paradox" and consequently to the pathological activation of LPO processes [1, 2, 4].

The presented data suggests that ascorbic acid does significantly reduce LPO activation in the case of ischemic and reperfusion stress on cardiac muscle, although it does not fully prevent activation. In these circumstances, we rightly expect less pronounced arrhythmia associated with heart failure. Indeed, according to our data, recovery of the coronary flow in the control group in 20% of cases (4 patients) was accompanied by the development of atrial fibrillation in the post-operative period. In the group of patients receiving ascorbic acid, the occurrence rate of atrial fibrillation was significantly lower ($\chi 2$=4.11; p=0.04) and was observed only in 5% of cases (one patient). Such a clear fall in arrhythmia rate in patients of the main group indicates that the electric stability of the heart muscle increased in the post-operative period.

It appears that a decrease in the intensity of free-radical processes as a result of taking ascorbic acid has a positive effect on the structure and function of cardiac cell membranes. Therefore, according to current understanding, the cardio-protective effect of antioxidants is related to preservation of the chemical composition of the lipid bilayer and the functioning of the ionic channels of cell membranes [15].

Table 2. **Parameters for catalase activity and conjugated diene concentration in blood plasma of cardiac surgery patients**

Phase of study	Control group (n=20)	Main group (n=20)	*p*
Catalase			
Pre-operative (1)	16.7±6.8 p_{1-2}=0.009	17.7±9.1 p_{1-2}=0.78	0.24
24 hours after operation (2)	36.1±6.7 p_{2-3}=0.003	23.8±6.4 p_{2-3}=0.31	0.02
5 days after operation (3)	25.8±5.6 p_{3-1}=0.53	18.0±4.1 p_{3-1}=0.39	0.36
Conjugated dienes			
Pre-operative (1)	2.7 ±0.87 p_{1-2}=0.041	2.96 ±1.09 p_{1-2}=0.0007	0.49
24 hours after operation (2)	2.16±0.58 p_{2-3}=0.87	1.77 ±0.97 p_{2-3}=0.13	0.08
5 days after operation (3)	2.15±0.59 p_{3-1}=0.41	2.2±1.31 p_{3-1}=0.001	0.51

Note. p_{1-2} — significance of differences between the parameters in the group before operation and 24 hours after operation;
p_{2-3} — significance of differences between the parameters in the group 24 hours and on the 5th day after operation;
p_{3-1} — significance of differences between the parameters in the group before operation and on the 5th day after operation.

Conclusion

The results of the study show that prescribing ascorbic acid can effectively suppress the development of oxidant stress for surgical treatment of ischemic heart disease using a cardiopulmonary bypass machine. However, further clinical and laboratory investigations must be conducted to determine whether including ascorbic acid in the medication for this kind of patient to prevent arrhythmia in the post-operative period is appropriate.

References, see:
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