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Prevention of systemic inflammatory response syndrome after emergency on-pump coronary artery bypass grafting with high-dose ascorbic acid: a prospective randomized controlled trial

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Abstract

INTRODUCTION: Emergency coronary artery bypass grafting (CABG) surgery carries a risk of postperfusion systemic inflammatory response syndrome (SIRS). The prophylactic use of high doses of ascorbic acid, which possesses an antioxidant and immunomodulatory effect, may be justified, but has not been sufficiently studied in this clinical scenario. **OBJECTIVE:** To determine the possibilities of preventing the systemic inflammatory response with ascorbic acid (AA) during emergency coronary artery bypass grafting under cardiopulmonary bypass (CPB). **MATERIALS AND METHODS:** We prospectively examined 60 patients (32 men and 28 women, aged 63 (59; 70) years who underwent CABG (3 ± 1 bypass), performed for emergency indications under CPB 95 (77; 122) min. Patients were randomly divided into two groups: patients in the main group (n = 30) were given 4 grams of AA intravenously 1 hour before the skin incision, patients in the control group (n = 30) received standard pre-operative prevention of SIRS. **RESULTS:** The use of AA (n = 30) was accompanied by a decrease in the incidence of SIRS (20 and 47 %; p = 0.048) and a reduction in postoperative hospitalization

Профилактика постперфузионного воспалительного ответа высокими дозировками аскорбиновой кислоты при экстренных операциях коронарного шунтирования: проспективное рандомизированное контролируемое исследование

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Реферат

АКТУАЛЬНОСТЬ: Экстренные операции аортокоронарного шунтирования (АКШ) сопряжены с риском постперфузионного системного воспалительного ответа (СВО). Профилактическое применение высоких дозировок аскорбиновой кислоты, обладающей антиоксидантным и иммуномодулирующим эффектом, может быть обоснованным, но в данной клинической ситуации недостаточно изучено. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Определить возможности профилактики аскорбиновой кислотой СВО при экстренном АКШ в условиях искусственного кровообращения. **МАТЕРИАЛЫ И МЕТОДЫ:** В проспективное ранодомизированное исследование было включено 60 пациентов (32 мужчины и 28 женщин, средний возраст 63 (59; 70) года, перенесших операцию АКШ (3 ± 1 шунт), выполненную по экстренным показаниям в условиях искусственного кровообращения 95 (77; 122) мин. Пациентов рандомизированно разделили на две группы. Пациентам основной группы (n = 30) превентивно за 1 ч до кожного разреза внутривенно вводили 4 г аскорбиновой кислоты, пациентам контрольной группы (n = 30) про-

(9 [8; 10] and 11 [10; 16] days; $p = 0.013$). **CONCLUSIONS:** Prophylactic use of AA is safe and can reduce the frequency of individual manifestations of SIRS and the duration of postoperative hospitalization.

KEYWORDS: cardiac surgical procedures, cardiopulmonary bypass, systemic inflammatory response syndrome, ascorbic acid

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водили стандартную предоперационную профилактику СВО. **РЕЗУЛЬТАТЫ:** Применение аскорбиновой кислоты ($n = 30$) сопровождалось снижением частоты проявлений СВО (20 и 47 %; $p = 0,048$) и сокращением сроков послеоперационной госпитализации (9 [8; 10] и 11 [10; 16] сут; $p = 0,013$). **ВЫВОДЫ:** Профилактическое применение аскорбиновой кислоты безопасно, позволяет снизить частоту отдельных проявлений СВО и длительность послеоперационной госпитализации.

КЛЮЧЕВЫЕ СЛОВА: кардиохирургия, искусственное кровообращение, синдром системного воспалительного ответа, аскорбиновая кислота

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Introduction

Systemic inflammatory response (SIRS) is common for everyday cardiologic and anesthetic practice. According to Kirklin et al., its incidence rate can reach 30 % among all patients who underwent cardiac surgeries performed under cardiopulmonary bypass (CPB) [1]. SIRS triggers in the given clinical model have been studied comprehensively and described in literature. The main ones involve contact of blood cells with the surface of extracorporeal circuit, ischemia and reperfusion of myocardium and lungs, surgical traumatization of tissues, lung ventilation, systemic anticoagulation, etc. [2–5]. Despite the development and improvement of various pharmacological and technical strategies aimed at minimizing the periperfusion inflammatory response, most of these solutions are focused on combating the already developed SIRS. The use of some technical devices and techniques is often laborious, not always possible and associated with high economic expenditures [6]. These circumstances determine the relevance of SIRS problem in cardiac surgery and dictate the necessity to develop approaches to its solution. The identification of a methodology aimed at preventing the development of SIRS and implemented before CPB onset — a highly probable risk factor of SIRS development, is of special significance. In this regard, our attention was drawn to ascorbic acid, which shows evident antioxidant and immunomodulatory activity, and is also an essential cofactor of endogenous catecholamines biosynthesis [7].

High-dose ascorbic acid therapy used for SIRS prevention and treatment, both in case of sepsis [8, 9] and surgery performed under CPB conditions [10, 11], has been actively studied and discussed in recent years. However, we took the fundamental differences of given clinical situations into account. Surgery under CPB, as opposed to sepsis, admits the possibility of using any given preventive measure as pointed out above, whereas etiological factor is time critical. These circumstances allowed us to rely on the effectiveness of ascorbic acid therapy in cardiologic and anesthetic practice, despite the current disappointment with ascorbic acid therapy in sepsis case [9]. Emergency cardiac surgery itself has become the field of our interest due to its continuing need and high risk.

Objective

Determine the possibilities of preventing the systemic inflammatory response with ascorbic acid during emergency coronary artery bypass grafting under cardiopulmonary bypass.

Materials and methods

A prospective randomized study included 60 patients (men, $n = 32$, women, $n = 28$), who underwent emergency coronary artery bypass grafting under CPB and cold blood cardioplegia. The study was approved by the Local Ethics Committee of Russian National Research Medical University named after N.I. Pirogov (meeting No 181 dated January, 28 2019).

Intravenous injection of midazolam 0.05–0.08 mg/kg, propofol 0.5–2 mg/kg, fentanyl 2.5–3.5 mcg/kg and rocuronium bromide 1 mg/kg was used to induce general anesthesia of all operated patients. Anesthesia was maintained by means of sevoflurane 0.5–1.0 of minimum alveolar concentration, whereas propofol at a dose of 3–4 mg/kg/h was used during CPB. Fentanyl was infused intravenously at a dose of 3–4 mcg/kg/h, and was also added fractionally at traumatic stages of surgery at a dose of 2–4 mcg/kg. Myoplegia was maintained by fractional intravenous injection of rocuronium bromide.

CPB was always performed in the normothermy mode with a perfusion index of 2.4 l/min/m^2 by means of Jostra-20 device (Maquet). Balanced crystalloid (700 ml) and colloidal solutions (500 ml gelatin solution), 4 % sodium bicarbonate solution (100 ml) were used for primary filling of CPB line. Cold blood cardioplegia was always used to protect the myocardium during aortic compression. Systematic heparinization was performed in an amount of 300 units/kg to achieve the targeted activated coagulation time > 450 s.

The criteria of perioperative inflammatory response involved at least two of the following factors developed within 24 hours after surgery: 1) leukocytes level increase > 20×10^9/L; 2) body temperature rise > 38.0 °C; 3) development of vasoplegia requiring vasoconstrictor therapy with norepinephrine for more than 24 hours.

A prospective randomized study was carried out to analyze the effectiveness of high-dose ascorbic acid therapy for preventing postperfusion SIRS after emergency cardiac surgeries performed under CPB due to acute coronary syndrome development. 60 patients were examined in the early period after cardiac surgery performed under CPB. Patients of the control group ($n = 30$) underwent standard pre-surgery SIRS preventive treatment. In addition to standard preventive treatment of SIRS, one hour before skin incision patients of the main group ($n = 30$) underwent 5-minute intravenous infusion of ascorbic acid at a dose of 4 grams. When analyzing the data obtained, special attention was paid to identification of perioperative SIRS symptoms. Randomization was performed by means of closed-envelope method. All prospectively examined patients signed an informed consent to participate in the study during pre-surgery examination conducted by anesthesiologist. Vasoactive and inotropic indices were used to assess the severity of inotropic and vasopressor therapy at all stages of study. When calculating inotropic index, commonly-accepted formula was used: dopamine dosage (mcg/kg/min) + dobutamine (mcg/kg/min) + epinephrine 100×(mcg/kg/min), when calculating vasoactive index: dopamine dosage (mcg/kg/min) + dobutamine (mcg/kg/min) + epinephrine 100×(mcg/kg/min) + norepinephrine 100×(mcg/kg/min).

Statistical analysis was performed with the benefit of commercial programs — Microsoft Excel and Medcalc. Kolmogorov-Smirnov method was used to determine the shape of distribution. In case of normal distribution, data was presented as ($M \pm \sigma$), Student's t-test was used to compare the data; in the event of abnormal distribution, data was presented as Me (Q1; Q3), Wilcoxon and Mann-Whitney criteria were used to compare the data. Spearman (for abnormally distributed data) and Pearson correlation analyses (for normal distribution) were carried out to determine the relationship between studied parameters. Fisher's criterion was used for intergroup frequency comparison. The differences and relationships between parameters were considered as valid at $p < 0.05$.

Results

The effectiveness of SIRS preventive treatment has been studied with the help of preventive pre-surgery high-dose ascorbic acid therapy.

The parameters of pre-surgery laboratory screening, general clinical status as well as characteristics of surgical intervention did not significantly differ in both groups (Table 1) and reflected the presence of pre-existing myocardial damage. Also, patients of both groups were comparable in terms of time passed after acute myocardial infarction (AMI) and characteristics of acute coronary syndrome (Table 1).

A comparative analysis of post-surgery data received 24 hours after intervention (Table 2) has shown that leukocytes, C-reactive protein and procalcitonin levels did not differ a lot in the groups of patients with and without ascorbic acid therapy ($p > 0.1$). There were also no significant intergroup differences in the severity and duration of inotropic and vasopressor support, assessed by means of inotropic and vasoactive indices ($p > 0.1$). Despite this fact, reduction of fever incidence rate and severity was noted within 24 hours after surgical intervention in the groups of patients who underwent ascorbic acid therapy (see Table 2). Also, the severity of inotropic and vasopressor support immediately after surgical treatment did not differ in the groups of patients with and without ascorbic acid therapy: inotropic index — 2 (1; 4) and 2 (1; 5), respectively, $p = 0.978$; vasopressor index — 4 (2; 13) and 4 (2; 12), respectively, $p = 0.555$.

Table 1. General clinical and laboratory parameters of the initial state of patients and operations performed

Parameters	Group 1, with ascorbic acid	Group 2 without ascorbic acid	*p*
EuroSCORE, points	7.9 ± 2.4	7.3 ± 2.5	0.729
Age, years	64 (59; 68)	61 (60; 71)	0.299
LVEF, %	51 ± 9	48 ± 10	0.671
Artery bypass grafting, *n*	3 ± 1	3 ± 1	0.825
CPB, min	98 (77; 115)	92 (76; 129)	0.619
MI, min	48 (42; 66)	50 (38; 67)	0.992
Leukocytes, ×10⁹/L	5.3 (4.5; 6.4)	5.7 (5; 7.3)	0.966
Troponin, before surgery ng/ml	0.9 (0.2; 1.9)	1.3 (0.2; 2.1)	0.804
AMI with ST rise, *n* (%)	3 (10 %)	2 (7 %)	1
AMI without ST rise, *n* (%)	7 (23 %)	9 (30 %)	0.771
Unstable angina pectoris with a risk of lethality according to GRACE scale > 6 %, *n* (%)	20 (67 %)	19 (63 %)	1
Patients operated within 48 hours after AMI *n* (%)	5 (17 %)	3 (10 %)	0.706
Patients operated within 3–7 days, *n* (%)	25 (83 %)	27 (90 %)	0.706

AA — ascorbic acid; AMI — acute myocardial infarction; CPB — cardiopulmonary bypass; EuroSCORE — European System for Cardiac Operative Risk Evaluation — a scale for assessing the risk of cardiac surgery; GRACE — Global Registry of Acute Coronary Events — a scale for assessing the risk of mortality and development of myocardial infarction; LVEF — left ventricular ejection fraction; MI — myocardial ischemia.

Table 2. Hemodynamic, general clinical and laboratory parameters in the emergency group of patients with and without the use of AA 24 hours after transfer to the intensive care unit

Parameters	Group 1 (*n* = 30) with ascorbic acid	Group 1 (*n* = 30) without ascorbic acid	*p*
Leukocytes, ×10⁹/L	12 (9; 13)	12 (11; 14)	0.427
Patients with leukocyte level > 20 × 10⁹/L, *n* (%)	6 (20 %)	4 (13 %)	0.73
C-reactive protein, mg/l	108 (56; 145)	127 (89; 162)	0.995
Procalcitonin, ng/ml	0.02 (0; 3.4)	0.09 (0; 1.4)	0.499
Fibrinogen, g/l	3.6 (2.8; 4)	3.6 (2.8; 5)	0.453
Temperature (max. during 1st day), °C	37 (36.7; 37.4)	37.5 (37; 38)	0.041
Patients with fever > 38 °C during 1st post-surgery day, *n* (%)	5 (17 %)	12 (40 %)	0.084
II, points	0 (0; 1)	0 (0; 2)	0.383
VI, points	0 (0; 1.5)	0 (0; 2)	0.279
SVRI, dyne/s/sm^{-5}m^2	1891 (1799; 2081)	1681 (1598; 2247)	0.85

Data is presented as (M ± σ), Me (Q1; Q3).
II — inotropic index; SVRI — systemic vascular resistance index; VI — vasoactive index.

Further, when analyzing combined endpoints — combinations of several systematic inflammatory process symptoms (need for vasoconstrictors > 24 hours, fever > 38 °C, leukocytosis > 20 × 10^9/L) and respiratory disorders (pneumonia, atelectasis, effusion in pleural cavity of more than 500 ml) (Table 3), we have revealed more frequent ($p = 0.048$) manifestation of one or several SIRS signs in the groups of patients without ascorbic acid therapy. However, the incidence rate of respiratory disorders as well as its combination with SIRS symptoms did not differ in the study groups ($p > 0.1$).

Further, it was revealed that the duration of hospitalization in the groups of patients with ascorbic acid therapy was significantly lower than with a standard allowance ($p = 0.013$), although the duration of post-surgery intensive care measures, frequency of repeated hospitalization in intensive care unit (ICU) as well as lethality did not differ in the study groups ($p > 0.1$) (Table 4).

Discussion

The results of this study rather did not confirm the obvious effectiveness of preventive infusion of ascorbic acid before emergency CABG, since this therapeutic measure did not affect neither the results of surgeries nor the duration of post-surgery intensive care, however, it turned out to be associated with a reduction in the duration of post-surgery hospitalization, probably due to fever incidence rate decrease in post-surgery period. Similar data on reducing the duration of hospitalization was obtained in a number of single-center researches, which were studying the effectiveness of high-dose ascorbic acid therapy in cardiac surgery [12, 13].

In a well-known research conducted by Marik et al., the use of high-dose ascorbic acid as a cocktail component (ascorbic acid + hydrocortisone + thiamine) significantly reduced lethality in the group of terminal patients (8.5 and 40.4 %, $p < 0.01$), decreased the incidence rate of progressive multiple organ failure, and provided faster dosage lowering and reduction of vasopressor support when using ascorbic acid [8]. However, further multicenter randomized placebo-controlled CITRIS-ALI study showed that a 96-hour ascorbic acid infusion in patients with sepsis and acute respiratory distress syndrome did not reduce the severity of organ dysfunction and had no effect on inflammatory markers level (C-reactive protein) as well as vascular damage (thrombomodulin) within 168 hours. Nevertheless, the authors revealed significant decrease in 28-day lethality and reduction of hospitalization duration in a group of patients undergoing ascorbic acid therapy [9].

Table 3. Combined criteria (endpoints) of systemic inflammatory response syndrome and/or respiratory system disorders after surgery in groups of patients, *n* (%)

Endpoints	Group 1 (*n* = 30), with ascorbic acid	Group 2 (*n* = 30), without ascorbic acid	*p*
Respiratory disorders*	14 (47 %)	12 (40 %)	0.794
Systematic inflammatory response**	6 (20 %)	14 (47 %)	0.048
Respiratory disorders and SIRS#	4 (13 %)	8 (27 %)	0.333

*One or more signs — pneumonia, atelectasis, effusion in the pleural cavity more than 500 ml. **Combination of two or more characteristics — need for vasoconstrictors > 24 hours, fever > 38 °C, leukocytosis > 20 × 10^9/l. # Combination of (*) and (**).

Table 4. Comparative analysis of the early postoperative period in patient groups

Parameters	Group 1 (*n* = 30) with ascorbic acid	Group 2 (*n* = 30) without ascorbic acid	*p*
LV, hours	5 (3; 8)	6 (4; 12)	0.133
Inotropic therapy, hours	0 (0; 5.5)	8 (0; 26)	0.2
Vasopressor therapy, hours	0 (0; 0)	0 (0; 6)	1
Duration of stay in ICU, days	2 (1; 3)	2 (1; 4)	0.252
Cases of rehospitalization in ICU	1 (7 %)	1 (7 %)	1
Duration of hospitalization, days	9 (8; 10)	11 (10; 16)	0.013
Frequency of long-term fever* after transfer from ICU, *n* (%)	2 (7 %)	9 (30 %)	0.041
Lethality, *n* (%)	1 (3 %)	1 (3 %)	1

Data is presented as Me (Q1; Q3).
LV — lung ventilation.
* Fever > 38 °C lasting more than 3 days.

Thus, the initial expectancy of ascorbic acid evident benefit in sepsis and septic shock was not fully justified [14]. At the same time, the possible mechanism and potential rationale for the effectiveness of ascorbic acid in high-risk cardiac surgery are fundamentally different. Unlike sepsis therapy, ascorbic acid infusion performed even in emergency coronary bypass grafting has prophylactic effect (conducted before surgery, prior to CPB onset). This allows us to hope for a pathogenetic effect already at the earliest stages of perioperative SIRS development.

The benefits and even the need for perioperative infusion of ascorbic acid when conducting surgery under CPB are reported by Hill et al. [11]. The authors point at optimization of almost all organs and systems functioning, including modulation of postperfusion immune response. In a series of observations of postperfusion vasoplegia resistant to high dosages of catecholamines, vasopressor sparing effect after high-dose ascorbic acid therapy was shown [15]. However, in a pilot double-blind randomized study, the tendency to shorten the duration (from 34.7 ± 41.1 to 27 ± 16.5 hours) of postperfusion vasoplegia when infusing high doses of ascorbic acid fell just short of statistical significance ($p = 0.4$), which may occur due to a small number of observations (with 25 patients in placebo and ascorbic acid therapy groups) [10].

Thus, the effect of ascorbic acid in cardiac surgery has been studied in a limited number of small single-center studies [10, 15]. Although, all of them point out a positive effect of the studied therapeutic measure, the statistical analysis design and volume do not allow us to draw a final conclusion. The obtained data on shortening the duration of hospitalization time after transfer from ICU in the studied group is statistically reliable and require further major studies.

Conclusion

Although, the preventive infusion of ascorbic acid had not reduced the severity of early post-surgery period directly, however, it had a beneficial effect on a more distant period of hospital rehabilitation. This data requires further research.

Disclosure. The authors declare no competing interests.

Author contribution. All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

Ethics approval. This study was approved by the local Ethical Committee of Pirogov Russian National Research Medical University (reference number: 181-28.01.2019).

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