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Systemic inflammatory response in cardiac surgery: possibilities of using colchicine

Aim	To evaluate manifestations of systemic inflammatory response (SIR) and the effect of the colchicine therapy on SIR severity in patients with ischemic heart disease (IHD) after coronary artery bypass grafting (CABG) with extracorporeal circulation (EC).
Material and methods	This study included 100 patients aged 62+6.3 years with stable IHD and multivessel coronary atherosclerosis scheduled for CABG with EC. Patients of group 1 (n=50) were administered with a single dose of colchicine (Colchicum-Dispert) 500 μg 4 hours before surgery followed by 500 μg twice a day for 10 days after surgery. Patients of group 2 (n=50) received a standard treatment, including nonsteroid anti-inflammatory drugs after surgery. Severity of the inflammatory response was evaluated by measuring blood cytokines.
Results	In the postoperative period, patient of group 1 showed a tendency toward a lower incidence of pleurisy and heart rhythm disorders in the form of paroxysmal atrial fibrillation (AF) (p=0.18). Levels of the anti-inflammatory cytokines, interleukin-10 (IL-10) and interleukin-6 (IL-6), were significantly increased in both groups at 6 hours after surgery (p<0.05); at the same time, in group 1, IL-10 remained increased also at 10 days after surgery (p=0.0002). No significant time-related changes in the proinflammatory cytokines, tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β), were observed. At 3 days post-CABG, there were significant increases in tissue inhibitors of matrix metalloprotease 1 (TIMP-1) (p<0.0001) and matrix metalloproteinase 9 (MMP-9) (p<0.001); at the same time, patients of group 1 had lower MMP-9 concentrations than patients of group 2 (p<0.05). At 10 days of postoperative period, these values were comparable with the background values. Increases in neopterin compared to preoperative values were found in both groups on days 3 and 10 after surgery (p <0.0001).
Conclusion	CABG with EC is associated with the activation of SIR. The colchicine therapy at a dose of 500 μg 4 hours prior to surgery and 500 μg twice a day for 10 days after surgery reduces manifestations of SIR, which is clinically evident as a tendency to reduced incidence of pleurisy and arrhythmias, and does not result in the development of serious complications. The dynamics of matrix metalloproteinases indicates that the colchicine treatment is promising for decreasing the risk of CHF progression and myocardial remodeling in patients with IHD.

Keywords	Systemic inflammatory response; coronary artery bypass grafting; extracorporeal circulation; colchicine; cardiac surgery
For citation	Diakova M.L., Shipulin V.M., Svirko Yu.S., Gusakova A.M., Podoksenov Y.K., Kamenshchikov N.O. et al. Systemic inflammatory response in cardiac surgery: possibilities of using colchicine. Kardiologiia. 2023;63(7):39–46. [Russian: Дьякова М.Л., Шипулин В.М., Свирко Ю.С., Гусакова А.М., Подоксенов Ю.К., Каменщиков Н.О. и др. Системный воспалительный ответ в кардиохирургии: возможности применения колхицина. Кардиология. 2023;63(7):39–46].

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Introduction

Cardiopulmonary bypass (CPB) used in cardiac surgery leads, among other things, to the systemic activation of blood components and vascular endothelium, which causes an inflammatory response of the whole body. Systemic inflammatory response syndrome (SIRS) is based on the activation and release of various cellular, extracellular, and organ mediators. Such a reaction may be widespread or systemic depending on how severe the damaging effect is. Increased numbers of adhesion molecules and various cytokines, which to some extent may indirectly reflect changes in the immune response and its status, are thought to cause the inflammatory response.

The incidence of SIRS after so called on-pump surgeries is as high as 22.0–27.5%. However, due to lack of strict criteria of postperfusion SIRS, its incidence can vary considerably and affect to some degree nearly all cardiac surgical patients [1]. Atrial fibrillation (AF) in the early postoperative period and postcardiotomy

syndrome may be regarded as the clinical symptoms of SIRS [1, 2].

The incidence of AF after cardiac surgery is 30–50%. Postoperative AF significantly increases the risk of death and related complications [2].

According to the 2020 Clinical Guidelines of the Ministry of Health of the Russian Federation, postcardiotomy syndrome is a condition of inflammatory and autoimmune nature that develops after open cardiac surgery and is accompanied by the following symptoms: fever of unknown origin; pericardial or pleural pain; pericardial and/or pleural friction rub; pericardial effusion and/or pleural effusion with elevated C-reactive protein (CRP). The diagnosis is established when at least two of the abovementioned symptoms are present. According to different authors, postcardiotomy syndrome occurs in 8.9–40% of patients who underwent open heart surgery [3].

Management of postcardiotomy syndrome is a pressing issue because there are now no drugs with a high level of evidence for the effective treatment of this pathology. The 2020 Clinical Guidelines of the Ministry of Health of the Russian Federation state that all drugs currently used for the treatment of postcardiotomy syndrome and pericarditis are off-label, i.e., they are not approved for the treatment of these conditions.

Thus, studying the possibility of using drugs with a significant anti-inflammatory effect is topical.

Colchicine is a potent anti-inflammatory agent, the effect of which is associated with a decrease in leukocyte migration to the site of inflammation. The drug has an antimitotic effect, inhibits (completely or partially) cell division in anaphase and metaphase, and prevents neutrophil degranulation [4].

It is still disputed whether it is reasonable to use colchicine in cardiologic and cardiac surgical patients. The findings of several international studies on the use of colchicine are contradictory.

Some studies showed a positive effect of colchicine in the postoperative period. Colchicine for Prevention of Post-pericardiotomy Syndrome (COPPS) trial showed that colchicine significantly reduced the 12-month incidence of pericarditis in cardiac surgical patients compared to placebo (12.2% vs. 25.6%, p=0.002) [5]. The COPPS subanalysis demonstrated a significantly lower likelihood of postoperative AF in colchicine-treated patients (p=0.02) [6].

Other trials obtained the opposite results when assessing colchicine's efficacy. The administration of colchicine in the COPPS-2 trial for 48 hours and 72 hours before surgery did not reduce the incidence of postoperative AF or pericarditis compared to placebo [4]. The POPE-2 trial showed that the administration of colchicine after cardiac surgery does not reduce the volume of pericardial effusion [7].

In light of the ambiguous results of using colchicine, we undertook a study to investigate the potential administration of colchicine in patients with coronary artery disease (CAD) who underwent direct myocardial revascularization in the perioperative period.

The study was carried out in the Cardiac Surgery Department No. 1 of Cardiology Research Institute, Tomsk National Research Medical Center.

Material and methods

The prospective open-label randomized study included 100 patients with stable CAD and multivessel coronary artery atherosclerosis confirmed by coronary angiography, for whom on-pump CABG was scheduled at the age of 61 [57; 66] years. Exclusion criteria were developed to exclude the possible influence of any other factors on the study results. They included reduced ejection fraction (≤ 35%) according to echocardiography, heart valve disease requiring surgical intervention, liver failure with hepatic transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] ≥1.5 times beyond the upper limit of normal, renal failure (elevated creatinine >130 μmol/L), permanent or persistent AF, history of hypersensitivity, neutropenia, alcoholism. Subjects were randomly divided into two groups based on chosen perioperative management strategies using sealed envelope method the day before surgery. In Group 1 (n=50), colchicine (Colchicum Dispert) was administered at a dose of 500 μg 4 hours before surgery followed by 500 μg twice a day for 10 days after surgery. In Group 2 (n=50), standard treatment including non-steroidal anti-inflammatory drugs (NSAIDs) was administered after surgery. Both groups were comparable in the main clinical and demographic characteristics at baseline (Table 1). The study was approved by the local ethics committee of Cardiology Research Institute, Tomsk National Research Medical Center (protocol No. 192 dated December 18, 2019). All patients signed the informed consent to participate in the study. The study was conducted following the Declaration of Helsinki.

Postoperative course, accumulation of pleural and pericardial fluid, the development of arrhythmias (AF), and infectious complications were analyzed, and the levels of hepatic transaminases (ALT, AST) and creatinine were monitored. Biochemical markers of inflammation were estimated. Serum interleukins (IL-6, IL-10, IL-1β), tumor necrosis factor alpha (TNF-α) (before surgery, 6 hours after surgery, and on postoperative day 10), matrix metalloproteinase-9 (MMP-9), and tissue inhibitor of

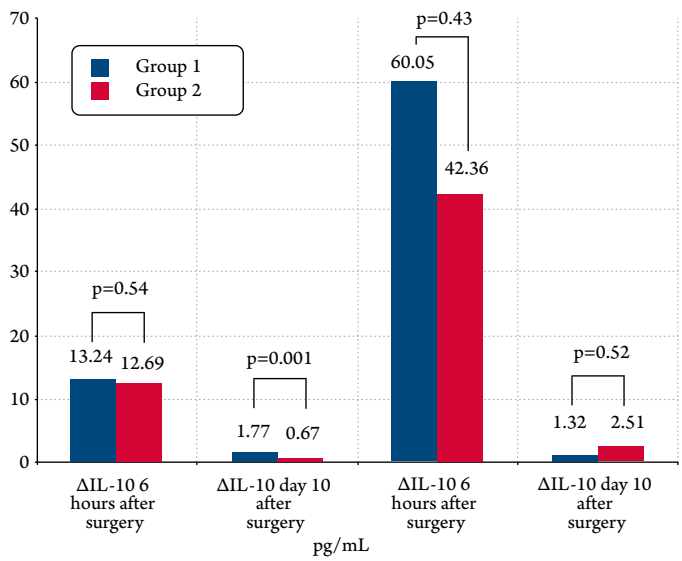
ISSN 0022-9040. Kardiologiia. 2023;63(7). DOI: 10.18087/cardio.2023.7.n2229

Table 1. Patient demographic information and clinical characteristics

Variable	Group 1 (n=50)	Group 2 (n=50)	p
Age, years	59.9 [56.5; 64.5]	60.7 [55; 67]	p=0.4
Male Female	38 (76) 12 (24)	42 (84) 8 (16)	p=0.3
CCS grading of angina pectoris II III	 7 (14) 43 (86)	 13 (26) 37 (74)	 p=0.1 p=0.1
History of MI	28 (56)	30 (60)	p=0.7
Hypertension	48 (96)	49 (98)	p=0.6
DM type 2	14 (28)	11 (22)	p=0.5
Overweight Obesity Grade 1 Grade 2, Grade 3	12 (24) 10 (20) 8 (19) –	19 (38) 11 (22) 4 (8) 1 (2)	p=0.1 p=0.8 p=0.2 p=0.3
LVEF, %	59.6 [56.5; 64.5]	60.9 [57; 70]	p=0.97
Time of CPB, min	87.7 [67; 96.5]	88.4 [67; 102]	p=0.7

Data are presented as the medians and interquartile ranges (Me [25; 75]), numbers and percentages of patients (n (%)); CCS, Canadian Cardiovascular Society; MI, myocardial infarction; diabetes mellitus; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass.

Figure 1. Changes in the levels of IL-10 and IL-6 6 hours and 10 days after surgery compared to the baseline (presented by Δ means versus baseline values)



matrix metalloproteinases-1 (TIMP-1) (before surgery, on postoperative days 3 and 10) were determined by multiplex immunoassay using MILLIPLEX® MAP KIT Human Cytokine/Chemokine Panel (Merck KGaA, Darmstadt), Human MMP Panel 2, Human TIMP Panel 1, and FLEXMAP 3D System (Luminex® Corporation). Neopterin was determined (before surgery, on postoperative days 3 and 10) by enzyme immunoassay using the Neopterin diagnostic test system (IBL International, GmbH).

The data were analyzed using STATISTICA 10 (StatSoft, Inc., 1984–2011, USA). Quantitative values were expressed as the medians and quartiles (Me [Q25; Q75]). Quantitative characteristics were compared using the Mann-Whitney U-test (independent samples) and Wilcoxon W-test (dependent samples). Qualitative characteristics were compared using Fisher's exact test. Hazard ratios (HR), odds ratios (OR), and 95% confidence intervals (CI) were calculated online in StatTech (https://medstatistic.ru/calculators/calcrisk.html). Deltas (Δ) were calculated at the observation points by calculating the difference between the means and the baseline values. The differences were considered to be statistically significant with $p<0.05$.

Results

The analysis of the postoperative period showed a trend to a lower incidence of pleuritis in Group 1. The frequency of thoracentesis was 28% (n=14) in Group 1 and 42% (n=21) in Group 2 (OR 0.537; 95% CI: 0.233–1.237; HR 0.667; 95% CI: 0.384–1.157; p=0.14) There was also a trend to a lower incidence of paroxysmal AF – 6% (n=3) in Group 1 and 14% (n=7) in Group 2 (OR 0.392; 95% CI: 0.095–1.613; HR 0.429; 95% CI: 0.117–1.564; p=0.18)

The cytokine levels were determined: IL-10, IL-1β, IL-6, TNF-α (Table 2). The levels of anti-inflammatory cytokines – IL-10 and IL-6— were significantly elevated 6 hours after surgery in both groups. In Group 1, IL-10 and IL-6 increased almost 9-fold ($p<0.0001$) and 100-fold ($p<0.0001$), respectively (Table 2, Figure 1, Figure 2). In Group 2, IL-10 and IL-6 were elevated 13-fold ($p<0.0001$) and more than 100-fold ($p<0.0001$), respectively (Figure 1, Figure 2). In Group 1, the levels of IL-10 remained 2-fold on day 10 compared to the preoperative values (p=0.0002) and also about 2 times higher than in Group 2 ($p<0.001$) (Table 2, Figure 1, Figure 2). There were no significant changes in the levels of pro-inflammatory cytokines TNF-α and IL-1β.

The levels of matrix metalloproteinase-9 (MMP- 9) and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) were determined, and their ratio

Table 2. Changes in interleukin levels in the postoperative period

Variables	Group 1 (n=50)	p (point 1 versus point 2, point 1 versus point 3 in Group 1)	Group 2 (n=50)	p (point 1 versus point 2, point 1 versus point 3 in Group 2)	p (Group 1 versus Group 2)
IL-10 (pg/mL): before surgery, 6 hours after surgery, on day 10 after surgery	1.66 [1.02; 2.7] 14.9 [7.6; 41.2] 3.43 [2.2; 8.13]	p_{1-2}< 0.0001 p_{1-3}=0.0002	1.01 [0.59; 2.36] 13.7 [5.8; 29.46] 1.68 [0.75; 3.51]	p_{1-2}< 0.0001 p_{1-3}=0.11	0.10 0.54 0.001
IL-1β (pg/mL): before surgery, 6 hours after surgery day 10 after surgery	0.39 [0.15; 0.6] 0.45 [0.35; 0.7] 0.43 [0.2; 0.59]	p_{1-2}= 0.13 p_{1-3}= 0.95	0.43 [0.3; 0.83] 0.48 [0.39; 0.72] 0.45 [0.31; 0.72]	p_{1-2}= 0.95 p_{1-3}= 0.41	0.05 0.43 0.52
IL-6 (pg/mL): before surgery, 6 hours after surgery day 10 after surgery	0.45 [0.1; 1.53] 60.5 [39.1; 79.5] 1.77 [0.93; 5.7]	p_{1-2}< 0.0001 p_{1-3}= 0.0005	0.44 [0.13; 2.94] 42.8 [32.4; 69.72] 2.95 [0.75; 6.56]	p_{1-2}< 0.0001 p_{1-3}= 0.0039	0.3 0.1 0.5
TNFα (pg/mL): before surgery, 6 hours after surgery day 10 after surgery	13.6 [6.4; 19.5] 12.3 [5.2; 20.8] 16.2 [7.6; 23.2]	p_{1-2}= 0.42 p_{1-3}= 0.07	12.7 [7.6; 15.97] 10.55 [4.2; 14.6] 11.68 [7.8; 19.7]	p_{1-2}=0.4 p_{1-3}=0.24	0.6 0.3 0.1

The data are presented as the medians and interquartile ranges (Me [25; 75]);
point 1 – before surgery, point 2 – 6 hours after surgery, point 3 – day 10 following surgery.

Table 3. Changes in matrix metalloproteinase levels in the postoperative period

Variables	Group 1 (n=50)	p (point 1 versus point 2, point 1 versus point 3 in Group 1)	Group 2 (n=50)	p (point 1 versus point 2, point 1 versus point 3 in Group 2)	p (Group 1 versus Group 2)
TIMP-1 (ng/mL): before surgery, day 3 after surgery day 10 after surgery	70,7 [57,7; 94] 104,8 [83,7; 122,6] 126,8 [113,1; 147]	p_{1-2}<0,0001 p_{1-3}<0,0001	78,9 [66; 93,15] 104,9 [89,9; 116,6] 144,6 [113,6; 168]	p_{1-2}< 0,0001 p_{1-3}< 0,0001	0,11 0,68 0,07
MMP-9 (ng/mL): before surgery, day 3 after surgery day 10 after surgery	102,3 [39,3; 187,8] 172,7 [90,7; 251,6] 124,6 [45,5; 188,6]	p_{1-2}<0,001 p_{1-3}= 0,32	112,6 [82,4; 186,5] 226,5 [150,4; 330,1] 135,1 [84; 211]	p_{1-2}< 0,0001 p_{1-3}= 0,32	0,18 0,02 0,09
MMP-9/TIMP-1: before surgery, day 3 after surgery day 10 after surgery	1,7 [0,6; 2,25] 1,5 [0,87; 2,8] 0,86 [0,43; 1,5]	p_{1-2}= 0,2 p_{1-3}= 0,001	1,54 [1,08; 2,2] 2,17 [1,4; 3,3] 0,87 [0,57; 1,5]	p_{1-2}=0,01 p_{1-3}= 0,03	0,58 0,06 0,41

The data are presented as the medians and interquartile ranges (Me [25; 75]);
point 1 – before surgery, point 2 – 6 hours after surgery, point 3 – day 10 following surgery.

Table 4. Changes in neopterin levels in the postoperative period

Variables	Group 1 (n=50)	p (point 1 versus point 2, point 1 versus point 3 in Group 1)	Group 2 (n=50)	p (point 1 versus point 2, point 1 versus point 3 in Group 2)	p (Group 1 versus Group 2)
Neopterin (nmol/L): before surgery, day 3 after surgery day 10 after surgery	6.8 [5.1; 8.99] 8.83 [7.16; 12] 10.2 [7.6; 14.1]	p_{1-2}<0.0001 p_{1-3}<0.0001	7.9 [5.66; 9.4] 8.8 [7.2; 11.2] 10.02 [8.8; 13.95]	p_{1-2}< 0.0001 p_{1-3}< 0.0001	0.31 0.95 0.97

The data are presented as the medians and interquartile ranges (Me [25; 75]);
point 1 – before surgery, point 2 – 6 hours after surgery, point 3 – day 10 following surgery

ISSN 0022-9040. Kardiologiia. 2023;63(7). DOI: 10.18087/cardio.2023.7.n2229

Table 5. Postoperative complications

Complications	Group 1 (n=50)	Group 2 (n=50)	p
Pneumonia	8 (16)	6 (12)	0,56
COPD exacerbation	2 (4)	3 (6)	0,64
Infectious complications of sternal wound	3 (6)	2 (4)	0,64
Bleeding in the early postoperative period	0	3 (6)	0,07
Acute MI	1 (2)	0	0,07
Nausea, vomiting	0	1 (2)	0,3
ARVI	3 (6)	0	0,07
Acute cholecystitis	0	1 (2)	0,3
Elevated AST and ALT (>3 times beyond the upper limit of normal)	1 (2)	0	0,3

The data are presented as the numbers and percentages of patients (n (%));
COPD, chronic obstructive pulmonary disease, MI, myocardial infarction; ARVI, acute respiratory viral infection; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Figure 3. Changes in the levels of TIMP-1 and MMP-9 3 and 10 days after surgery compared to the baseline (presented by Δ means versus baseline values)

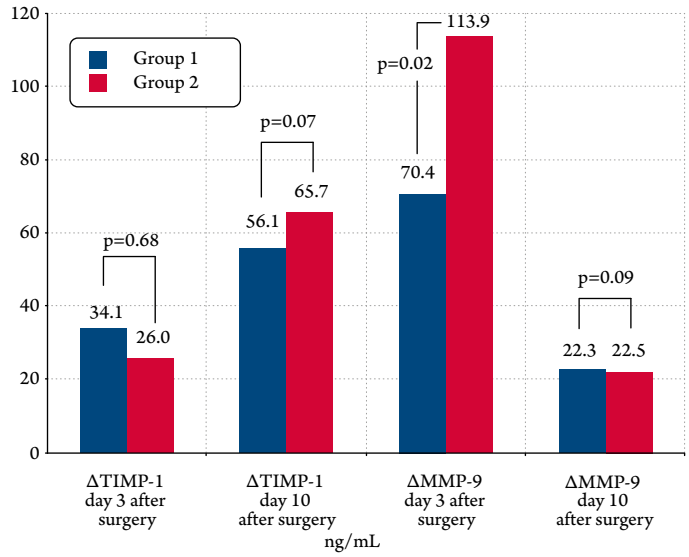


Figure 2. Changes in the levels of IL-1β and TNF-α 6 hours and 10 days after surgery compared to the baseline (presented by Δ means versus baseline values)

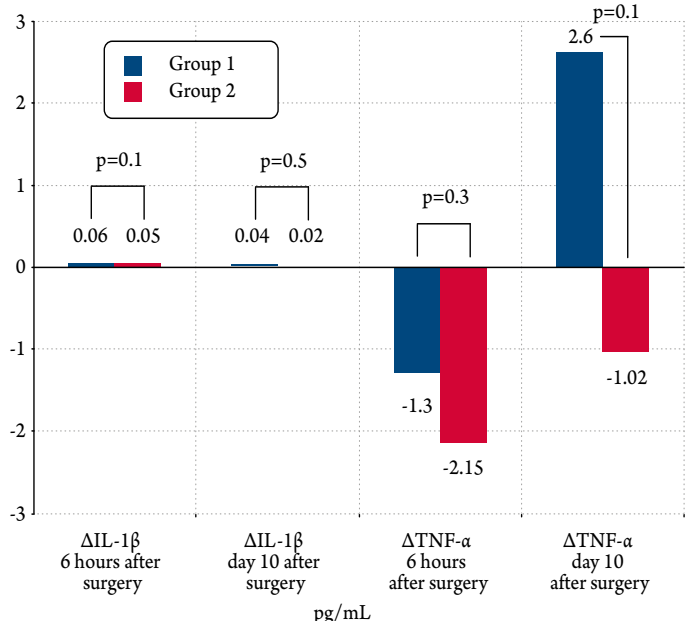
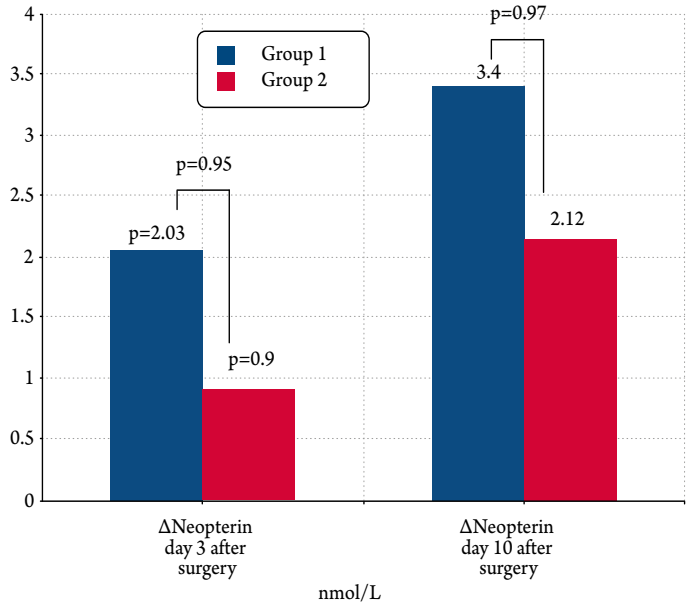


Figure 4. Changes in the neopterin levels 3 and 10 days after surgery (presented by Δ means versus baseline values)



(MMP-9/TIMP-1) was calculated (Table 3, Figure 3). There was a significant increase in the TIMP-1 and MMP-9 level on day 3 after surgery. The levels of these indicators were comparable on day 10 after surgery to the baseline values. In Group 1, lower levels of MMP-9 were observed on day 3 after surgery – by 31% ($p<0.05$) compared to patients who received standard therapy. Postoperative neopterin levels were analyzed (Table 4, Figure 4). There was an increase on days 3 and 10 after surgery compared to preoperative values in both groups. The analysis of the postoperative course showed a significant increase in the levels of AST to 320 U/l and ALT to 467 U/l was detected in 1 patient in Group 1 on day 5 after surgery, which required discontinuing colchicine. There were no events of intestinal disorder, diarrhea, nausea, and a significant increase in creatinine levels in the patient groups. There was no significant difference in other postoperative complications between the groups (Table 5, Figure 5).

Discussion

On-pump surgeries lead to the development of SIRS, which is manifested clinically as pleuritis, cardiac arrhythmia, such as AF. These complications require additional treatment costs and increase length of stay in hospital. In our study, the incidence of pleuritis requiring thoracentesis in the postoperative period during conventional therapy, including the administration of NSAIDs, was 41%, the incidence of AF was 14%.

Colchicine (Colchicum Dispert) was used in our study to reduce the severity of SIRS. The drug was administered at a dose of 500 μg 4 hours before surgery, and at a dose of 500 μg twice a day for 10 days after surgery. There was trend during therapy to a 28% decrease in the incidence of pleuritis requiring thoracentesis and a 6% decrease in the incidence of paroxysmal AF. However, the small number of observations may have contributed to the lack of statistical significance in the development of these complications compared to patients receiving standard treatment in the postoperative period.

Our findings confirm the development of a powerful inflammatory response after the intervention (changes in the levels of cytokines, MMP-9, TIMP-1, neopterin).

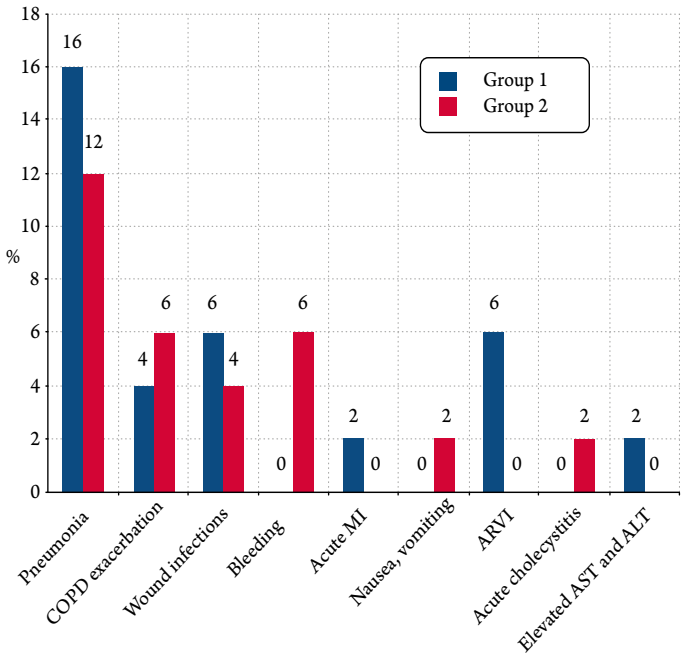
Our study revealed a feature in changes of the cytokine levels after systemic exposure to CPB, specifically a significant increase in the levels of anti-inflammatory cytokines IL-10 and IL-6 as soon as 6 hours after surgery, which persists for up to 10 days after the intervention (mostly refers to IL-6). At the same time, the levels of pro-inflammatory cytokines (IL-1β and TNF-α) remain almost unchanged. Similar data have been obtained earlier by other authors studying SIRS after on-pump surgeries [8].

Colchicine therapy resulted in a more significant production of anti-inflammatory cytokines, notably by day 10 following surgery. During standard therapy, IL-10 levels did not change from baseline in these times.

Matrix metalloproteinases (MMPs) and their inhibitors MMP-9 and TIMP-1 are considered as independent predictors of cardiovascular diseases and cardiovascular death in patients with CAD, and as biomarkers of CHF progression and LV remodeling [9, 10]. Elevated MMP-9 and CRP, is a risk factor for rapid progression of coronary artery atherosclerosis and functional class deterioration of stable angina pectoris [11]. It is interesting to analyze the MMP levels in CAD patients after on-pump CABG from the point of view of their involvement in inflammatory processes and the role of biomarkers of CHF progression.

On-pump surgeries had a significant effect on the levels of MMP in our study. TIMP-1 and MMP-9 increased significantly on day 3 after surgery. We

Figure 5. Incidence of postoperative complications (%)



COPD, chronic obstructive pulmonary disease, MI, myocardial infarction; ARVI, acute respiratory viral infection; AST, aspartate aminotransferase; ALT, alanine aminotransferase

observed a progressive increase in TIMP-1 by day 10 following surgery. MMP-9 decreased by day 10 after surgery compared to day 3 of the postoperative period, yet there was a trend to higher levels compared to the baseline values. As for the MMP-9/TIMP-1 ratio, it increased significantly by day 3 following the surgery and decreased by day 10. The observed changes in the MMP levels confirm the negative effect of on-pump surgeries on the body as a whole and are indicative of high patient's vulnerability in the early postoperative period after on-pump intervention, a high risk of adverse cardiovascular complications caused by SIRS.

Colchicine therapy leads to a more rapid decrease in MMP-9 and a trend to lower levels of TIMP-1 on day 3 following surgery. The revealed changes in the MMP-9 levels in patients with CAD during colchicine therapy in the postoperative period open up new prospects for its use given the positive effect of reducing the severity of SIRS and a possible positive effect on the course of CHF.

Neopterin is produced by activated macrophages and is considered a pro-inflammatory and pro-atherosclerotic agent. However, neopterin was shown to inhibit vascular inflammation and atherosclerosis in vitro and in vivo [12].

We showed a dynamic increase in the levels of neopterin on day 3 and day 10 of the postoperative period, which indicates the complex impact of on-pump surgeries on the body and inflammatory processes continuing for

ISSN 0022-9040. Kardiologiia. 2023;63(7). DOI: 10.18087/cardio.2023.7.n2229

more than 10 days after intervention. Changes in the postoperative neopterin levels during colchicine therapy did not differ significantly.

A decrease in the severity of the inflammatory processas a link in the pathogenesis and progression of CAD during colchicine therapywas also indirectly confirmed in the COLCOT study. The risk of cardiovascular mortality, stroke, and the need for coronary revascularization decreased for patients with a history of myocardial infarction (within 30 days) who received colchicine [13]. In the LoDoCo² trial, colchicine therapy was associated in patients with stable CAD with lower incidence of ischemic complications and the need for revascularization [4].

The administration of colchicine was not associated in our study with the development of gastrointestinal complications. The levels of hepatic transaminases increased significantly in 1 (2%) patient on day 5, which required discontinuation of colchicine. There was no difference in the incidence of postoperative complications in patients taking colchicine and those receiving standard therapy. Thus, the postoperative use of colchicine did not lead to the development of serious complications, which proves its safety in the proposed regimen.

Limitations

The study was limited by a small number of subjects.

Conclusion

On-pump coronary artery bypass grafting is associated with the development of systemic inflammatory response syndrome. Colchicine at a dose of 500 μg 4 hours before surgery and 500 μg twice a day for 10 days following surgery has an anti-inflammatory effect, reduces the manifestations of systemic inflammatory response syndrome, which is clinically expressed in a trend to lower incidence of pleuritis and cardiac arrhythmias and does not cause serious complications.

In addition to the pronounced anti-inflammatory effect, colchicine is promising in terms of reducing the risk of chronic heart failure progression and myocardial remodeling in patients with coronary artery disease, as indicated by detected changes in the levels of matrix metalloproteinases. The lack of statistically significant results during the study may have been caused by the small number of clinical observations and requires further research in this direction.

Funding

No funding was received for this study.

No conflict of interest is reported.

The article was received on 01/07/2022

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