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S.R. Maruniak [1, 2], **O.A. Loskutov** [1, 2], **I.R. Malysh** [1]

[1] Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine
[2] Heart Institute of the Ministry of Health of Ukraine, Kyiv, Ukraine

ОРИГІНАЛЬНІ ДОСЛІДЖЕННЯ

Analysis of early cardiac complications after coronary artery bypass grafting under two different regimens of anesthesia

The aim – to analyze the effect of two different schemes of anesthesia on early cardiac complications in patients with coronary artery bypass grafting (CABG) with cardiopulmonary bypass.

Materials and methods. The study included 120 patients who underwent CABG with cardiopulmonary bypass (CPB). The median surgery risk according to EuroSCORE II was 3.45 % (2.15 %; 4.05 %). According to the scheme of anesthesia, all patients were divided into two groups: the first group (60 patients) – low-opioid scheme of anesthesia; the second group (60 patients) – a standard scheme of anesthesia.

Results. Patients in the first group were more than twice as likely to develop postoperative atrial fibrillation compared to the second group (9 (15.0 %) vs. 19 (31.7 %), p = 0.031). In addition, patients in the first group were 2.3 times significantly less likely to have low cardiac output syndrome (LCOS) compared to the second group (11.7 % vs. 26.7 %, p = 0.037). The duration of CPB (p = 0.032) and the level of interleukin-6 after CPB (p = 0.004) were reliable indicators for predicting LCOS. The final statistical model [F (4, N = 120) = 12.52, p < 0.001, R2 = 0.304] covers almost a third of all factors in the development of LCOS. Only the level of interleukin-6 after CPB (the final statistical model (F (4, N = 120) = 11.54, p < 0.001, R2 = 0.286) was a reliable indicator for predicting postoperative atrial fibrillation.

Conclusions. The obtained results confirm the safety of clinical use of anesthesia schemes with low doses of opioids in cardiac surgery patients and emphasize the possibility of a more conservative use of opioids in cardiac surgery.

Key words: coronary artery bypass grafting, low-opioid anesthesia, low cardiac output syndrome, postoperative atrial fibrillation.

Coronary artery disease (CAD) is one of the most common pathologies of the cardiovascular system characterized by a high mortality rate [14]. To date, the main method of treatment of this disease is surgery; in patients who have undergone coronary artery bypass grafting (CABG) five-year mortality is 1.5 times lower compared to only drug therapy [12]. At the same time, despite improvements in surgical and anesthetic care over the past 15 years, which has contributed to a sharp reduction in the incidence of complications and mortality during this type of surgery, their frequency still remains higher than for other types of surgery [9]. One of the studies showed that the mortality rate during CABG using cardiopulmonary bypass (CPB) was 2–3 %, and the level of postoperative complications reached 20–30 % [2]. Moreover, the mechanisms of development of postoperative complications in patients who underwent CABG with CPB are multifactorial and currently not fully established.

Despite the significant number of publications on the influence of components of anesthesia schemes on the development of postoperative complications, the question of choosing the optimal scheme of anesthesia during coronary artery bypass grafting in patients with coronary heart disease remains unsolved. The anesthesia regimens with high doses of opioids during cardiac surgery remained a basis

Маруняк Степан Романович, аспірант кафедри анестезіології та інтенсивної терапії
E-mail: maruniak.stepan@gmail.com

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of cardiac anaesthesia for many decades due to their ability to maintain hemodynamic stability and reduce hormonal and metabolic responses to surgical stress [4]. In particular, after a number of publications by E. Lowenstein on the safety of anesthesia with high doses of morphine (3 mg/kg), the use of high doses of opioids has become a characteristic feature of cardiac anesthesia [11]. However, high doses of opioids required prolonged ventilation of patients for 12–24 h during the early postoperative period. At the same time, prolonged mechanical ventilation and prolonged stay in the intensive care unit significantly increased the cost of treatment, which required the search for qualitatively new solutions [5]. The economic efficiency and efficient use of medical resources after cardiac surgery has been one of the factors that stimulated the use of anesthesia regimens with low doses of opioids [3, 8].

The aim – to compare the effect of low-opioid and high-opioid anesthesia regimens on early clinical outcomes in patients undergoing CABG with CPB.

Materials and methods

The study included 120 patients with CAD, which on the basis of the State Institution «Heart Institute of the Ministry of Health of Ukraine» underwent CABG with CPB. The age of patients was 59.0 (55.0; 62.0) years (48 to 65 years). The average body weight was 90.5 ± 13.8 kg (from 73 to 125 kg). The number of men was 86 (71.6 %), women – 34 (28.9 %). The median surgery risk by EuroSCORE II was 3.85 % (2.15 %; 4.25 %).

According to the scheme of anesthesia, using computer software for randomization, all patients were divided into two groups. The first group using low-opioid anesthesia included 60 patients. Induction consisted of intravenous administration of propofol at a dose of 1.5 mg/kg of 40 mg at intervals of 15–20 seconds. After the administration of hypnotics, all patients were administered intravenous fentanyl at a dose of 1–1.5 μg/kg. After achieving an adequate level of anesthesia, muscle relaxation was achieved by intravenous administration of pipecuronium bromide at a dose of 0.1 mg/kg, followed by tracheal intubation. To maintain anesthesia, sevoflurane was inhaled along a semi-closed circuit with the target maintenance of its concentration according to the age indicator of the minimum alveolar concentration (MAC). The target concentration of sevoflurane was calculated by the formula: MACawake = 0.34×MACtable×2, where MACawake is the minimum alveolar concentration in the patient's exhaled air, and MACtable – tabular value of the MAC according to age. Before starting surgery, a subnarcotic dose of ketamine (0.5 mg/kg) and lidocaine 1 mg/kg bolus were added intravenously, with simultaneous adjustment of a continuous infusion of the latter at a dose of 1.5–2 mg/kg/h and dexmedetomidine of 0.7 μg/kg/h. Lidocaine infusion was continued throughout the operation until the patient was admitted to the intensive care unit. Analgesia was maintained during surgery by the administration of fentanyl. The average dose of fentanyl that was used for the entire duration of anesthesia was 1.0 μg/kg/hour.

The second group with a standard anesthesia scheme included 60 patients. Induction into anesthesia in patients of this group consisted of intravenous administration of propofol at a dose of 1.5 mg/kg of 40 mg at intervals of 15–20 seconds. After the administration of a hypnotic agent, all patients were administered intravenous fentanyl at a dose of 1–1.5 μg/kg. After achieving an adequate level of anesthesia, muscle relaxation was achieved by intravenous administration of pipecuronium bromide at a dose of 0.1 mg/kg, followed by tracheal intubation. Maintenance of anesthesia – sevoflurane 1.5–2 MAC, analgesia was provided with fentanyl (8–10 μg/kg/hour), relaxation – pipecuronium bromide at a dose of 0.1 mg/kg.

Detailed initial characteristics of the compared groups are given in *Table 1*.

As can be seen from *table 1*, there were no significant baseline differences of patients in the study groups.

Mechanical ventilation of the lungs in the examined patients of both groups was performed with an air-oxygen mixture with FiO_2 50 % in the normoventilation mode under the control of blood gas composition (mean value of arterial blood pCO_2 was 35–40 mm Hg).

CPB was performed on a SYSTEM 1 (Terumo, USA) using AFFINITY disposable membrane oxygenators (Medtronic, USA) under conditions of moderate hypothermia (32 °C). CPB blood flow was maintained at the level of 2.4–2.5 l/min/m^2. Normovolemic hemodilution was used during CPB with an average hematocrit level of 25–30 % and hemoglobin of 80–90 g/l. Blood clotting was evaluated by activated clotting time (ACT), maintaining it in the range of 500–600 seconds.

The clinical endpoints analyzed in this study included low cardiac output syndrome (LCOS) and postoperative atrial fibrillation (POAF). LCOS include a decrease in cardiac index (CI) to < 2.0 l/min/m^2 and systolic blood pressure < 90 mm Hg in combination with signs of tissue hypoperfusion (cold periphery, sticky, moist skin, confusion,

Table 1
Characteristics of the initial parameters of the studied groups

Parameters	First group (n = 60)	Second group (n = 60)	The value of p at a = 0.05
Age, years	60 (56; 63)	59 (54; 62)	0.419
Gender, n (%) men women	 44 (73.33) 16 (26.67)	 42 (70.00) 18 (30.00)	0.408
Body weight, kg	95.7 ± 16.1	98.6 ± 17.3	0.345
FC, n (%) > 2 > 3	 27 (45.00) 33 (55.00)	 24 (40.00) 36 (60.00)	0.428
EF, %	46.52 ± 8.06	47.18 ± 9.61	0.681
EDV, ml	147.48 ± 20.14	145.15 ± 21.17	0.537
MI, n (%)	13 (21.67)	11 (18.33)	0.741
PCI, n (%)	9 (15.00)	8 (13.33%)	0.886
AH, n (%)	40 (66.67)	42 (70.00)	0.723
Initial Hb, g/l	119.86 ± 13.11	124.63 ± 12.49	0.064

FC – functional class NYHA; EF – ejection fraction; EDV – end-diastolic volume; MI – myocardial infarction; PCI – percutaneous coronary interventions; AH – arterial hypertension.

oliguria, elevated lactate) in the absence of hypovolemia.

Data are presented as arithmetic mean (M) according to the results of each study ± standard deviation (SD). In case of abnormal distribution of results, they were presented as Median (Me) and 1st (Q1) and 3rd (Q3) quartiles – Me (Q1; Q3). Differences at $p < 0.05$ (95.5 %) were considered significant. Regression analysis of the obtained results was performed with the help of the computer program Statistica 10.

The study was conducted in compliance with the basic provisions of the «Rules of ethical principles of scientific medical research with human participation», approved by the Declaration of Helsinki (1964–2013). Each patient signed an informed consent to participate in the study. The study was approved by the Ethics Commission of the Shupyk National Healthcare University of Ukraine.

Results

We found a significantly shorter duration of mechanical ventilation in patients of the first group compared with the second group (2.0 (2.0; 3.0) h versus 4.0 (3.0; 5.0), $p < 0.001$) in the early postoperative period. It is also worth noting that in the early postoperative period, patients in the first group were 1.75 times ($p = 0.088$) less likely to need reintubation compared with the second group, but without a significant difference (6.7 % vs. 11.7 %, $p = 0.088$).

The patients of the first group developed POAF more than twice less often ($p = 0.031$) compared to the second group *(Table 2)*.

Ventricular tachycardia or fibrillation were also 2.0 times less likely to occur in the first group, although the results were insignificant (3.3 % vs. 6.6 %, $p = 0.402$). When analyzing the frequency of conduction disturbances between study groups, it was found that in the first group the development of atrioventricular block was observed 1.5 times more often (10.0 % vs. 6.7 %, $p = 0.509$), but all episodes were associated with AV Grade I and II blockades that were not life-threatening and did not require the use of a pacemaker.

One of the most common cardiac complications, which were found in both groups of the study, was LCOS *(Table 3)*.

In particular, the patients of the first group were 2.3 times less likely to develop LCOS compared to the second group (11.7 % vs. 26.7 %, $p = 0.037$). Accordingly, the inotropic agents in this group were used less often during 24 hours compared to the second group (16.7 % vs. 31.7 %, $p = 0.055$).

In general, the length of stay in the ICU of patients of the first group was significantly less compared to the second group (2.0 (2.0; 3.0) days versus 3.5 (3.0; 4.0) days, $p < 0.001$). However, the total duration of hospitalization didn't significantly differ between the study groups (11.0 (9.25; 12.75) days versus 12.0 (11.0; 13.0) days, $p = 0.056$).

The results of the regression model [$F(8, N = 120) = 6.748$, $p < 0.001$, $R2 = 0.327$] showed that only LVEF before surgery ($p = 0.036$),

Table 2
Frequency of postoperative atrial fibrillation

Research groups	Atrial fibrillation		Total number of patients	Chi-square	P-value
	So	No			
First group (n = 60)	9 (15.0 %)	51 (85.0 %)	60	4.658	0.031
Second group (n = 60)	19 (31.7 %)	41 (68.3 %)	60		

Table 3
Frequency of LCOS in the early postoperative period

Research groups	Low cardiac output syndrome		Total number of patients	Chi-square	P-value
	So	No			
First group (n = 60)	7 (11.7 %)	52 (88.3 %)	60	4. 357	0.037
Second group (n = 60)	16 (26.7 %)	44 (73.3 %)	60		

Table 4
Regression analysis of LCOS predictors

Indexes	Step 1 Beta (SE)	Step 2 Beta (SE)
Age, years	–0.012 (0.07)	
AH, degree	0.098 (0.074)	–
LV EF before surgery, %	–0.102 (0.004) *	0.097 (0.004)
Duration of CPB, min	0.203 (0.03) *	0.176 (0.003) *
Duration of operation, min	0.042 (0.002)	
Aortic cross-clamping, min	–0.078 (0.007) *	0.089 (0.007)
IL-6, pg/ml	0.565 (0.003) *	0.529 (0.002) *
Need for RBCM, doses	–0.109 (0.052)	

* $p < 0.05$; LV EF – left ventricular ejection fraction; RBCM – red blood cell mass.

Table 5
Regression analysis of POAF predictors

Indexes	Step 1 Beta (SE)	Step 2 Beta (SE)
Age, years	0.535 (0.003)	
AH, degree	0.153 (0.084) *	0.144 (0.083)
LV EF before surgery, %	0.023 (0.004)	
Duration of CPB, min	–0.003 (0.003) *	–0.059 (0.003)
Duration of operation, min	0.027 (0.002)	
Aortic cross-clamping, min	–0.108 (0.008)	
IL-6, pg/ml	0.535 (0.003) *	0.524 (0.003) *
Need for RBCM, doses	–0.46 (0.06) *	–0.063 (0.058)

* $p < 0.05$.

the duration of CPB (p = 0.028), the duration of aortic cross-clamping = 0.044) and the level of interleukin(IL)-6 after CPB (p = 0.001) were significant predictors of LCOS *(Table 4)*.

At the same time, when removing insignificant factors from the regression model, reliable indicators for the prediction of LCOS were the duration of CPB (p = 0.032) and the level of IL-6 after CPB (p = 0.004) *(Table 4)*. The final statistical model [F (4, N = 120) = 12.52, p < 0.001, R2 = 0.304] covers almost a third of all factors in the development of LCOS. Thus, patients with longer CPB and higher IL-6 levels were characterized by a higher incidence of LCOS.

When constructing the regression model [F (8, N = 120) = 6.11, p < 0.001, R2 = 0.335] according to the predictors of POAF, we found that only the degree of hypertension, duration of CPB, level of IL-6 after CPB and the need in the RBCM were significant predictors of POAF *(Table 5)*.

Further, after removing insignificant factors from the regression model, only the level of IL-6 after CPB was a reliable indicator for prediction of POAF (the final statistical model [F (4, N = 120) = 11.54, p < 0.001, R2 = 0.286]). *(Table 5)*. Thus, patients with higher levels of IL-6 were characterized by a higher incidence of POAF.

Discussion

To date, multimodal low-opioid anesthesia for pain control has become an important component of perioperative management of the cardiac surgery patients. It involves the use of additive or synergistic combinations of analgesics to achieve clinically necessary analgesia while minimizing significant side effects associated with higher opioid doses [7]. As we can see from the results, our study demonstrated the relative safety of low-opioid anesthesia in coronary artery bypass grafting in patients with coronary artery disease.

The safety of a low-opioid anesthesia has also been reported in a number of other publications. In particular, Wong WT and colleagues, in the latest Cochrane meta-analysis, collected data from 28 studies (4438 patients) and did not note significant differences in complications between high- and low-dose opioid anesthesia regimens, namely heart attack (BP 0.98, 95 % CI 0.48–1.99; eight studies, 1683 participants, low level of evidence), stroke (BP 1.17, 95 % CI 0.36–3.78; five studies, 562 participants, low level of evidence) and reintubation of the trachea (BP 1.77, 95 % CI 0.38–8.27; five studies, 594 participants, low level of evidence) [15]. However, this analysis did not focus on high- and low-dose opioid anesthesia regimens.

In addition, M. Greco et al., comparing the results of patients given short-acting remifentanil and traditional opioids (fentanyl and sufentanil), found that remifentanil reduced troponin levels, duration of mechanical ventilation, and overall hospital stay [8]. However, as in the study by W.T. Wong et al., this study did not specifically analyze the doses of opioids used.

L.Q. Rong et al. in a large meta-analysis of 1,400 patients showed that low-opioid anesthesia is safe and effective for use in cardiac surgery in adult patients, and its effectiveness does not depend on clinical characteristics of patients, type of opioid used and opioid dose in groups with low-opioid anesthesia [13]. Thus, in the meta-regression analysis, the authors did not observe the effect of age, sex, or type of opioids on the difference between groups, although the length of stay in the intensive care unit was shorter when comparing short- and long-term opioids. In addition, the study did not show a difference in secondary clinical outcomes: perioperative hypotension, vasopressor requirements, perioperative MI, and perioperative stroke.

As for our study, low-opioid anesthesia was characterized by a significantly lower incidence of LCOS and POAF. Also, according to our data, LVEF before surgery (p = 0.036), duration of CPB (p = 0.028), duration of aortic cross-clamping (p = 0.044) and the level of IL-6 after CPB (p = 0.001) were significant predictors of LCOS. Similar results were also demonstrated in a study by W. Ding et al., who attributed the LV EF below 35 %, age less than 65 years, CABG with CPB, emergency surgery and ineffective revascularization [6]. In turn, according to our data, the degree of hypertension, the duration of CPB, the level of IL-6 after CPB and the need for RBCM were significant predictors of POAF.

Due to the importance of IL-6 levels in the development of early cardiac complications, a possible mechanism for reducing their frequency in low-opioid anesthesia is a reduction of the inflammatory response, which could be achieved by direct opioid dose reduction and the addition of lidocaine, ketamine or dexmedetomidine. This hypothesis is confirmed by our previous study, in which low-opioid anesthesia was characterized by significantly lower levels of IL-6 after CPB compared to standard doses of opioids [10].

Taken together, the results confirm the safety of clinical use of low-dose opioid anesthesia regimens in cardiac surgery patients and emphasize the possibility of a more conservative use of opioids in cardiac surgery.

Conclusions

Patients in the first group had a significantly shorter duration of mechanical ventilation compared to the second group (2.0 (2.0; 3.0) h vs. 4.0 (3.0; 5.0), $p < 0.001$).

Patients in the first group were more than twice ($p = 0.031$) less likely to develop postoperative atrial fibrillation; 2.3 times less frequently observed low cardiac output syndrome (11.7 % vs. 26.7 %, $p = 0.037$) compared to the second group; the length of stay of patients in ICU in the first group was significantly lower compared to the second group (2.0 (2.0; 3.0) days versus 3.5 (3.0; 4.0) days, $p < 0.001$).

Significant predictors of low cardiac output syndrome were the duration of cardiopulmonary bypass ($p = 0.032$) and the level of interleukin-6 after cardiopulmonary bypass ($p = 0.004$), the final statistical model [$F (4, N = 120) = 12.52$, $p < 0.001$, $R2 = 0.304$], while only the level of interleukin-6 after cardiopulmonary bypass was a reliable predictors of low cardiac output syndrome, the final statistical model [$F (4, N = 120) = 11.54$, $p < 0.001$, $R2 = 0.286$].

The authors declare no a conflict of interest.

Participation of authors: project of work – S.M., O.L., I.M.; article writing – S.M., O.L., I.M.; critical review of the material – O.L., I.M.

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С.Р. Маруняк [1, 2], **О.А. Лоскутов** [1, 2], **І.Р. Малиш** [1]

[1] Національний університет охорони здоров'я України імені П.Л. Шупика, Київ
[2] ДУ «Інститут серця МОЗ України», Київ

Аналіз ранніх кардіальних ускладнень після аортокоронарного шунтування при використанні двох різних схем анестезіологічного забезпечення

ОРИГІНАЛЬНІ ДОСЛІДЖЕННЯ

Мета роботи – аналіз впливу двох різних схем анестезіологічного забезпечення на виникнення ранніх кардіальних ускладнень у пацієнтів під час аортокоронарного шунтування зі штучним кровообігом.

Матеріали і методи. У дослідження залучено 120 пацієнтів, яким виконували аортокоронарне шунтування в умовах штучного кровообігу. Медіана операційного ризику за EuroSCORE II – 3,45 % (2,15 %; 4,05 %). Відповідно до схеми анестезіологічного забезпечення пацієнтів розділили на дві групи: перша група (n = 60) – малоопіоїдна схема анестезіологічного забезпечення; друга група (n = 60) – стандартна схема анестезіологічного забезпечення.

Результати. У пацієнтів першої групи більше ніж удвічі рідше спостерігався розвиток післяопераційної фібриляції передсердь порівняно з другою групою (15,0 % проти 31,7 %, p = 0,031). Крім того, в пацієнтів першої групи у 2,3 разу рідше спостерігався синдром низького серцевого викиду (СНСВ) порівняно з другою групою (11,7 % проти 26,7 %, p = 0,037). Достовірними показниками для передбачення СНСВ виявилися тривалість штучного кровообігу (p = 0,032) та рівень інтерлейкіну-6 після припинення штучного кровообігу (p = 0,004). Остаточна статистична модель [F (4; N = 120) = 12,52, p < 0,001, R2 = 0,304] охоплює майже третину всіх факторів розвитку СНСВ. Достовірним показником для передбачення післяопераційної фібриляції передсердь був рівень інтерлейкіну-6 після припинення штучного кровообігу, остаточна статистична модель [F (4; N = 120) = 11,54; p < 0,001; R2 = 0,286].

Висновки. Отримані результати підтверджують безпеку клінічного використання схем анестезіологічного забезпечення з низькими дозами опіоїдів у кардіохірургічних хворих та підкреслюють можливість більш консервативного використання опіоїдів у кардіохірургії.

Ключові слова: аортокоронарне шунтування, малоопіоїдна анестезія, синдром малого серцевого викиду, післяопераційна фібриляція передсердь.