https://doi.org/10.30702/ujcvs/21.4203/g018047-052/155.16
УДК 616.126.42+616.126.5-089:616.155.16

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Preoperative Correction of Anemia of Chronic Diseases and Application of Bloodless Technology in Mitral and Aortic Valve Replacement

Abstract. The article is dedicated to the optimization of the treatment of postoperative anemia in patients with mitral and aortic valve replacement through blood saving technology (BST).

The aim. To investigate the preoperative combined effect of iron (III) hydroxide and erythropoietin on the level of postoperative anemia after mitral and aortic valve replacement (MAVR) through BST in the conditions of artificial circulation.

Material and methods. Preoperative levels of Hb, Ht, iron, and enzymes were studied in 53 patients with combined mitral and aortic heart defects. All the patients are divided into groups A, B, C. Patients with normal levels of Hb, Ht, RBC, iron were divided into groups A and B. Patients of group A were operated with the use of donor blood components, and in group B - no donor blood components were used. In group C where the patients had low iron values, preoperative iron correction and erythropoietin stimulation were performed. Operations in group C were performed using BST.

Results. According to the study results, the patients of group A needed sufficient volume components of donor blood (621.0 ± 103.0 ml of red cell mass and 713.0 ± 89.0 ml of fresh-frozen plasma) in the operative period. MAVR with BST in group B was possible without transfusion of donor blood preparations, however, Hb decrease by 17.1% dictated the need for preoperative preparation of donor blood components.

Correction of low levels of preoperative serum iron in group C resulted in its 8.9-fold rise compared to the preoperative level, as well as Hb increase by 5.8%. The use of BST during MAVR reduces postoperative anemia by 7.7% and helps to avoid transfusion of donor blood components.

Conclusions. Correction of low preoperative levels of iron and erythropoietin in patients with mitral and aortic heart defects reduces the level of postoperative anemia after operations with mitral and aortic valve replacement through BST.

Keywords: *anemia, iron (III) hydroxide, mitral and aortic heart defects, blood saving technology, artificial circulation.*

Replacement of two or more heart valves, especially in cases of coronary artery bypass, is accompanied by prolonged artificial blood circulation, trauma, heavy blood loss, hemolysis, and numerous complications in various organs and systems. During the operation, large volumes of donor blood components are transfused causing microcirculation disorders and multiple organ failure. It is sometimes dangerous to transfuse donor blood components because of possible transmission of bacterial, viral, and other pathogens [1, 2], as well as because of increased immunosuppressive effect of transfused blood products [3, 4]. Anemia of chronic diseases (ACD), iron deficiency anemia (IDA) or any combination of these conditions with other somatic diseases is found in a significant proportion of patients with cardiovascular diseases. In 2017, the Association of European Cardiac Surgeons and European Cardiac Anesthesiologists published a guideline on tactics and strategies for the treatment of surgical bleeding, correction of anemia and other pathologies with reduced blood clotting and iron levels [5, 6]. A positive strategy is to fill up the iron deficiency by intravenous iron-containing fluid administration [7]. The correction of iron deficiency increases exercise tolerance, improves the quality of life and decreases mortality [8]. Taking into account all these facts and the increased interest in blood-saving technologies (BST) [9, 10], we have conducted a study to determine the preoperative level of iron in patients with combined acquired mitral and aortic heart defects (MAHD). The aim of this study was to investigate the efficacy of preoperative correction of iron and erythropoietin levels in patients with MAHD accompanied by ACD, as well as the influence of such correction on postoperative anemia in cases of surgical interventions under artificial circulation (AC).

Material and methods. The study included 53 patients treated at the Department of Surgery for Acquired Heart Defects who were diagnosed with combined MAHD with stenosis domination, valve insufficiency or combination thereof (Table 1). The patients were diagnosed with mitral and aortic heart defects with circulatory disorders (CD) belonging to the HYHA FC III–IV. According to the history and coronary angiography data, 17 patients (32.0%) were diagnosed with coronary heart disease (CHD), 12 (70.5%) of them having undergone coronary artery bypass grafting (CABG). In all the cases biochemical control of serum iron (SI) and transferrin (TN) levels was carried out by a photometric method (Beckman Coulter AU 480 analyzer), ferritin (FN) was determined by chemiluminescence. Hb, Ht, and blood cells were calculated using SYSMEX XP-300 hematology analyzer.

Patients with SI and normal enzyme values were randomly divided into A and B groups. The patients of group A underwent mitral and aortic valve replacement (MAVR) with the use of donor blood fractions during surgery. In patients of groups B and C, autologous blood was transfused during the MAVR.

The patients of group C had low baseline Hb, Ht, erythropoietin, and SI levels. They had a history of chronic infectious diseases and were classified as those having ACD. Given the initially increased preoperative C-reactive protein and decreased erythropoietin levels, erythropoiesis was stimulated with erythropoietin. One week before the operation, 30,000 units of erythropoietin were administered. In the patients' history there were no data concerning iron deficiency anemia. Taking these data into consideration, a week before surgery the preoperative correction of low SI levels was provided with iron (III) hydroxide. During the first week, 1000 mg of the drug was administered intravenously, but not more than 600 mg per day. In accordance with the Recommendations of the European Associations (EACTS, EACTA 2017) for patients with anemia, we adjusted the level of iron and erythropoietin, and then performed MAVR in the conditions of artificial circulation through BST without the use of donor blood. For the groups B and C, donor red cell mass and fresh-frozen plasma (FFP) were prepared taking into account the patients' blood type and Rh status; the platelet mass was also prepared for surgery and could be transfused as needed.

The study was conducted in 3 stages:

Stage 1 of the study was performed one week before surgery in all 3 groups.

Stage 2 of the study was performed only for the group C patients with initial anemia, 7 days after correction of low SI levels with iron (III) hydroxide and erythropoietin. This stage coincided with the beginning of the operation. In patients of this group, no blood transfusion was performed, and the intervention was carried out through BST.

At the stage 3, all the research works were performed with the patients of the groups A, B, and C after the surgery.

For the groups A and B, the following general criteria for MAHD surgical correction in AC conditions were developed and implemented:

a) no history of anemia and discontinuation of drugs with effect on blood clotting 7 days before surgery;
b) anesthesia: central venous pressure (CVP) ≥ 5 mm Hg). Arterial and mean arterial pressure (MAP) ≥ 110 mm Hg (BVC) ≥ 4.5 ± 0.3 L.

At the first stage of the study, the initial laboratory parameters in A and B groups were not lower than the following ones: Hb: 141.0 ± 3.2 g/L, Ht: 0.40 ± 0.03%, platelets: 274 ± 42 × 10^9/L, RBC: 4.3 ± 0.23 × 10^{12}/L, protein: 69 ± 4.2 g/L.

The A group included 17 patients with preoperative baseline levels of Hb, Ht, and RBC within the physiological norm. Among this group patients there were 11 (64.7%) men and 6 (35.3%) women aged from 32 to 67 years (mean age: 45.7 ± 6.4 years).

The B group (22 patients) was characterized by normal levels of Hb, Ht, and RBC. This group included 13 (59.0%) men and 9 (41.0%) women aged from 38 to 59.3 years (mean age 47.9 ± 4.6 years).

On the stage 1 of the study the C group included patients with initially low values of Hb (131 ± 3.7 g/L), erythropoietin (4.7±1.9 mU/mL) and SI (7.48 μmol/L ± 4.9 μmol/L), their state was interpreted as moderate anemia.

The C group included 14 patients, 8 (57.1%) men and 6 (42.9%) women, their mean age being 43.8 ± 5.7 years.

Anesthesiological support was performed by one anesthesiologist according to a unified method for all groups. After the central venous line placement, autologous blood was collected and deposited with normovolemic hemodilution (NVG) using 6% hydroxyethyl starch solution up to 8-10 ml/kg. The reinfusion of autologous blood was performed after complete cessation of the surgery, warming the patient to 37°C, and stabilization of hemodynamics.

Results. Combined acquired heart defects in different variations were presented for all patient groups studied (Table 1).

Table 1

Characteristics of groups with combined heart disorders (combined MAHD)

Index	Group A (n = 17)	Group B (n = 22)	Group C (n = 14)
Mitral stenosis + aortic stenosis	2	1	2
Mitral stenosis +aortic insufficiency	3	4	1
Aortic stenosis + mitral regurgitation	5	9	7
Aortic insufficiency + mitral regurgitation	7	8	4

Table 2

Disease etiology in patients with combined MAHD

Etiology of mitral and aortic heart defects	Group A (n=17)	Group B (n=22)	Group C (n=14)
Rheumatic diseases	(n=14)	(n=18)	(n=11)
%	82.3%	81.8%	78.5%
up to 5 years	(n=3)	(n=4)	(n=3)
%	21.4%	22.2%	30.0%
up to 10 years	(n=11)	(n=14)	(n=7)
%	78.6%	77.8%	70.0%
Non-rheumatic diseases	(n=3)	(n=4)	(n=3)
%	17.7%	18.2%	21.5%
Total	100%	100%	100%

In all patients with combined MAHD, the etiology of disease detected for the last 5 and 10 years of life was traced (Table 2).

According to the data shown above, there was predominance of patients with rheumatic MAHD etiology. The largest was the group of patients who were ill over the last 5-10 years. The initial levels of Hb, Ht, SI, enzymes, blood cells on the first stage of the study in patients of A and B groups were in the normal range. The patients of group C had baseline decrease in Hb and Ht values. There were also a SI decrease and an increase of C-reactive protein activity which is an indicator of preoperative anemia caused by chronic diseases (Table 3).

The leading role in this process was played not only by iron deficiency [11], but also by activation of autoimmune processes inhibiting germ erythropoietic cells. Some authors explain the mechanism of anemia accompanied by chronic heart failure (CHF) by the worsening of this disease as well as by increase in the NYHA functional class (FC) [12], heart failure (HF), increase in the left ventricle myocardial mass, and the frequency of complications [13]. The TN level in all three groups was normal.

In patients of group C, the stage 2 of the study was performed on the day of surgery. After correction of low SI levels, the levels of Hb and WBC increased to 5.8% and 14.3%, respectively (*p <0.05) – an improvement which may be due not only to the increase in young RBC forms, but also to the immune response following the iron (III) hydroxide infusion.

Preoperative correction of iron and erythropoietin levels in patients of group C resulted in SI 8.9-fold rise compared to the initial level (*p <0.05), but the TF activity decreased by 14.2% (*p <0.05). After the correction the iron transferrin saturation coefficient (ITSC) increased by 25.8% (*p <0.05), and the level of FN increased by 6.7 times (*p <0.05). At the same time, the serum iron-binding capacity (SIBC) value became higher by 31.1% (*p <0.05).

Discussion. The collection of autologous blood was carried out from the beginning of the operation until artificial blood circulation fully takes over. In the A group, donor blood preparations (621.0 ± 103.0 mL of red cell mass and 713.0 ± 89.0 mL of FFP were used during MAVR to correct operative anemia. BPT were used during the MAVR in patients of the groups B and C. Blood reinfusion was performed in the reverse order from the collection of autologous blood after warming the patient to 36.6 °C (Table 4). In the groups B and C , the autologous blood intake was 874.0 ± 52.0 mL and 806.0 ± 47.0 mL, respectively.

After surgery in group A patients, the HB level decreased by 5.0% (*p <0.05), and HT by 14.7% (*p <0.05). Levels of RBCs and platelets decreased and amounted to 16.3% (*p <0.05) and 17.8% (* p <0.05) accordingly. The average Hb concentration per RBC, as well as the average Hb contents per RBC, slightly decreased. In patients of the group A, the Hb and Ht stabilization during the operation was maintained by massive transfusions of donor blood components.

During the MAVR surgery in patients of the group B, we used the BPT including intraoperative acute NVG with pre-perfusion collection of autologous blood and its subsequent reinfusion. In patients of the group B, after blood-sparing operations, Hb and Ht contents decreased by 17.1% (*p <0.05) and by 15.0% (*p <0.05), respectively. The number of platelets and RBCs dropped in this case by 32.2% (*p <0.05) and by 18.7% (*p <0.05), respectively. The average Hb concentration and its average contents per RBC decreased only slightly after the surgery (Table 5).

In patients of the group B, post-operative TF and iron transferrin saturation coefficient (ITSC) were lower by 11.8% and by 10.4% (* p<0.05), respectively, proving not

Table 3

Reactive C-protein and erythropoietin activity in the groups studied

	Group A (n=17)		Group B (n=22)		Group C (n=14)		
Index	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After correction	After surgery
C-reactive protein, mg/L	22.7±8.2	26.1±9.7	25.3±11.7	28±8.3	34±7.8*	51.3±10.5*	66.8±9.6*
Erythropoietin, mU/mL	0.5±0.3	0.8±0.3	0.6±0.4	0.9±0.5	0.5±0.4*	1.3±0.5*	1.5±0.3

* p<0.05, the difference is statistically significant.

Table 4

Characteristics of transfusions of donor blood and autologous blood during MAVR operations

	Group A (n=17)	Group B (n=22)	Group C (n=14)
Donor RBCs, mL	621.0±103.0	–	–
Fresh-frozen plasma, mL	713.0±89.0	–	–
Autologous blood, mL	–	874.0±52.0	806.0±47.0
Total, mL	1334.0±76.0	874.0±52.0	806.0±47.0

only a decrease in the activity of the TF transport function, but also a decrease in its iron saturation. With BST, post-MAVR SI and serum iron-binding capacity (SIBC), values decreased by 15.8% (* p<0.05) and 10.7% (* p<0.05), respectively.

In patients of the group C after MAVR operations, there was a trend towards Hb drop by 9.4%. The numbers of RBCs and platelets at the end of the operation decreased by 10.6% (* p<0.05) and by 24.2% (* p<0.05), respectively. The Ht level decreased by 5.6% with a relatively slight decrease of the Hb content per RBC (Table 6).

At the end of the operation in patients of the group C, the levels of SI and TF decreased by 7.1% and by 16.7%, respectively, compared with the level post correction. The TF increase by 35.4% (* p<0.05) activates the iron transport to the target organs stimulating the iron intake in the maturation process of new young RBC forms.

Conclusions. In 26.4% of patients with acquired mitral and aortic heart defect and ACD, the levels of the SI and erythropoietin become reduced by 2.0 times and by 2.5 times, respectively.

The correction of low SI content in group C with ACD in the preoperative period increases its level by 8.9 times (*p <0.05), and Hb by 5.8% (* p<0.05), while the activity of FN becomes 6.7 times (*p <0,05) higher than the initial value.

Stabilization of Hb levels in MAVR patients belonging to the group A was achieved by volumetric transfusions of

Table 5

Changes in Hb, Ht and blood cells before and after MAVR surgery

Index		Hb, g/L	RBCs, (× 10^{12}/L)	Ht, %	Platelets, (× 10^9/L)	WBC, (× 10^9/L)	Average Hb concentration per RBC, g/dL	Average Hb contents per RBC, pg
Group A (n=17)	Before surgery	141±3.2*	4.2±0.23[1*]	0.41±0.03[1*]	288±34	7.2±1.8	32.5±1.4	33.4±1.6
	After surgery	134±3.0[1*]	3.6±0.28[1*]	0.35±0.02[1*]	237±49	8.8±1.5	30.7±1.3	31.0±1.8
Group B (n=22)	Before surgery	141±3.7*	4.3±0.25[1*]	0.40±0.03[1*]	274±42[1*]	8.1±2.3	31.5±1.8	32. 8±1.2
	After surgery	117±3.7*	3.5±0.16[1*]	0.34±0.02[1*]	186±33[1*]	9.4±2.5	30.2±1.5	29.4±1.7
Group C (n=14)	Before surgery	131±3.7*	3.7±0.26	0.36±0.02	284±36	7.8±1.4[2*]	28.7±1.4[2*]	30.7±1.9
	After correction	139±3.8*	3.8±0.16[2*]	0.36±0.03	298±31[2*]	9.1±1.1[2*]	33.1±1.5[2*]	32.6±1.4
	After surgery	126±4.4*	3.4±0.19[2*]	0.34±0.02	226±37[2*]	9.9±1.7[2*]	32.5±1.3	31.3±1.5

* p<0.05, the difference is statistically significant.

Table 6

Dynamics of changes in iron and enzyme levels in the groups studied

Index		Transferrin (TF), g/L	Serum iron-binding capacity (SIBC), μmol/L	Ferritin (FN), ng/mL	Serum iron (SI) content, μmol/L	Iron transferrin saturation coefficient (ITSC) ratio, %
Group A (n=17)	Before surgery	2.91±0.22	59.72±3.8	88.34±9.7	23.29±5.0	30.43±3.6
	After surgery	3.14±0.27	67.94±4.5	92.52±8.3	22.35±4.1	31.24±3.8
Group B (n=22)	Before surgery	2.72±0.24	61.26±3.5*	86.63±7.1	24.82±4.6	30.07±3.4
	After surgery	2.40±0.31	54.73±4.4*	73.59±9.0	20.93±3.8	26.97±4.1
Group C (n=14)	Before surgery	2.62±0.34	52.47±4.6*	59.26±13.4*	7.24±4.5*	26.35±3.2*
	After correction	2.25±0.20*	76.06±5.8*	398.17±40.8*	64.72±6.3*	35.51±4.0*
	After surgery	3.48±0.33*	69.27±4.3	331.82±36.1	60.18±5.2*	36.13±4.7

* p<0.05, the difference is statistically significant.

blood components [621.0 ± 103.0 mL of red cell mass and 713.0 ± 89.0 mL of fresh-frozen plasma, which is about 1/3 of the BVC.

During MAVR operations using BST in B group patients, the decrease in Hb by 17.1%, RBCs by 18.7%, platelets by 32.2%, indicates the need for preoperative procurement of the necessary components of donor blood.

Preoperative correction of ACD with iron (III) hydroxide with stimulation of erythropoietin in patients of the group C, in combination with BST during MAVR surgery with AC decreases the level of postoperative anemia by 7.7% (*p <0.05) and reduce the probability of donor blood components transfusion.

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Передопераційна корекція анемії хронічних захворювань та застосування безкровних технологій при протезуванні мітрально-аортальних клапанів серця

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Резюме. Стаття присвячена оптимізації лікування післяопераційної анемії у пацієнтів із протезуванням мітрально-аортальних клапанів серця за безкровною технологією.

Мета. Дослідити передопераційний комбінований ефект заліза (III) гідроксиду та еритропоетину на рівень післяопераційної анемії після протезування мітрального та аортального клапанів (ПМАК) за безкровною технологією в умовах штучного кровообігу.

Матеріали та методи. Доопераційні рівні Hb, Ht, заліза та ферментів досліджували у 53 пацієнтів із поєднаними мітрально-аортальними вадами серця. Всі пацієнти розділені на групи А, В, С. Пацієнти з нормальним рівнем Hb, Ht, еритроцитів, заліза, розділені на групи А та В. Пацієнти групи А оперовані із застосуванням донорських компонентів крові, групи В – без донорських компонентів крові. У групі С, з низькими значеннями заліза, проводили передопераційну корекцію заліза та стимуляцію еритропоетином. Операції в групі С проводили з використанням кровозберігаючих технологій (КЗТ).

Результати. Представлені результати дослідження показують, що пацієнти групи А в операційному періоді потребують достатньо об'ємних компонентів донорської крові (621,0 ± 103,0 мл маси еритроцитів і 713,0 ± 89,0 мл свіжозамороженої плазми). Проведення операцій ПМАК із КЗТ у групі В можливо без переливання препаратів донорської крові, проте зниження рівня Hb на 17,1 % створює необхідність у передопераційній заготівлі компонентів донорської крові.

Корекція низького рівня передопераційного сироваткового заліза в групі С збільшує його передопераційні параметри в 8,9 раза, а Hb – на 5,8 %. Застосування КЗТ під час ПМАК зменшує післяопераційну анемію на 7,7 % та сприяє уникненню переливання компонентів донорської крові.

Висновки. Корекція низьких передопераційних рівнів заліза та еритропоетину у хворих із мітральними та аортальними хворобами серця знижує рівень післяопераційної анемії після операцій з протезуванням мітрального та аортального клапанів методом КЗТ.

***Ключові слова**: анемія, залізо (III) гідроксид, мітрально-аортальна вада серця, технологія кровозбереження, штучний кровообіг.*

Стаття надійшла в редакцію 25.01.2021 р.