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PHARMACOECONOMIC ANALYSIS OF A MEDICINAL PRODUCT NEOTON (PHOSPHOCREATINE) IN PERIOPERATIVE MANAGEMENT OF CARDIAC SURGERY PATIENTS WITH EXTRACORPOREAL CIRCULATION, WITH ISCHEMIC HEART DISEASE OR WITH CHRONIC HEART INSUFFICIENCY

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Abstract: Cardiovascular disease (CVD) is the main mortality factor and the main reason of disability of the working-age population both in the Russian Federation and in the world. Due to the state statistical data, 1,878 persons per every 100,000 population died in Russia in 2014. 50.1 % of these deaths have been caused by CVD and more than half of them (52.3 %) have been caused by ischemic heart disease (IHD). The aim of this study was to determine the preferential scheme of medical therapy in perioperative management of cardiac surgery patients with extracorporeal circulation, with IHD or with chronic heart insufficiency (CHI) from the point of view of pharmacoeconomic analysis by comparing ratios between expenses and efficacy, safety and quality of life associated with the use of Neoton (phosphocreatine) in comparison with the control group.

Due to the efficacy analysis, the scheme "standard therapy + phosphocreatine" is more effective. Cost-effectiveness analysis has shown that the standard therapy + phosphocreatine is a preferable method of treatment in comparison with the standard therapy as it shows better clinical efficacy and lower "cost-effectiveness ratio. Results of the budget impact analysis have shown that the use of the standard therapy + phosphocreatine instead of the standard therapy itself in perioperative management of cardiac surgery patients with extracorporeal circulation, with IHD or with CHI has saved money.

Key words: efficacy analysis, cost analysis, cost-effectiveness analysis, budget impact analysis, sensitivity analysis, ischemic heart disease, chronic heart insufficiency, pharmacoeconomy, clinico-economic analysis.

Introduction

Rationale of the problem of CVD treatment is doubtless. Due to the data of the World Health Organization (WHO), about 40% of the total number of deaths in 2014 were caused by CVD. Herewith, the half of those deaths were caused by different kinds of IHD.

In Russia, indexes of morbidity and mortality caused by CVD, in particular by IHD, are one of the highest in Europe and in the world. Due to the Federal State Statistics Service, 1,878 persons per every 100,000 population died in Russia in 2014. 50.1 % of these deaths have been caused by CVD and more than half of them (52.3 %) have been caused by IHD [10].

These factors determine the rationale of early diagnostics and appropriate treatment of the pathology. WHO announced that 3/4 of all the deaths caused

by CVD, in particular by IHD, may be prevented by early preventive services and remedial actions. It contributes to preservation of more working-age population of the country and to reduction of a disability level.

Introduction of surgical methods of treatment of different heart and vascular diseases with the use of a bypass into clinical practice has significantly reduced the morbidity and mortality levels. The number of cardiac surgeries, including those with the use of the bypass, as well as clinics where they are performed increases each year. For instance, about 50,000 open-heart surgeries were performed in Russia in 2015, whereas the real need is 143,000 surgeries per year [8].

During the last years, development of new surgical technologies, improvement of anesthetic techniques, introduction of monitoring computer systems of estimation and control of vital functions of the body contributed to significant increase of surgeries performed in aged patients and in patients with initially low functional myocardial reserves. It should be mentioned that particular these categories of patients more likely are the subjects of perioperation myocardial ischemia with the development of low cardiac output syndrome. Acute myocardial dysfunction and, as a result, low cardiac output syndrome is one of the worst complications that may develop during cardiac surgeries and reduce to nothing the efficacy of the performed surgery.

One of the reasons of acute myocardial dysfunction is perioperative myocardial infarction (PMI) that is usually accompanied with acute heart insufficiency requiring the use of the expensive treatment.

Due to the literature, over the last years, frequency of PMI constitutes 0.9 - 6.2% depending on the category of operated patients and the experience of coronary artery bypass graft surgeries [1; 2; 5]. Most patients suffer from myocardial infarction during the surgery or within the first days after it. Mortality associated with PMI is approximately 20 - 24%, however, if it is accompanied with the clinics of cardiogenic shock, is constitutes 60-90%.

Modern complex therapy of patients suffering from IHD guarantees a significant clinical response of patients, however, in some cases, the positive effect of such treatment is insufficient.

The use of endovascular and surgical methods, in particular, coronary artery bypass graft surgery (CABG), mammary coronary bypass (MCB), transmyocardial laser revascularization (TMLR), and minimally invasive myocardial revascularization (MIMR) guarantees higher efficacy of the treatment

of patients with IHD. Recently, these methods are being improved and therefore the possibilities of successful treatment of patients with IHD is higher [8].

Due to the official recommendations, in case of multivessel coronary bed disease, including also patients with diabetes, CABG is the standard choice, efficacy of which is doubtless in spite of the increase of the follow-up period. Improvement of the surgical method and the concomitant treatment during intra- and post-surgical periods has a prognostic significance for minimization of the risk of complications and the increase of efficacy.

The main reason of high mortality among patients with IHD is heart insufficiency. Modern medicine searches for the means to minimize the myocardial injury in case of ischemia due to the injury of coronary arteries.

However, recovery of the blood flow in the stenosed coronary artery may result in myocardial reperfusion injury. Nowadays, the rationale for the use of high-energy compounds (adenosine tri-phosphate (ATP) and creatine phosphate (CP) in case of myocardial ischemia is doubtful due to their quick dephosphorylation and disintegration in blood flow and tissues. Phosphocreatine plays an essential role in muscle contraction. This is an energy reserve in myocardial cells and skeletal muscles and is used for ATP resynthesis, during the hydrolysis of which the energy for actomyosin contraction is released [6].

Creatine is a natural substance extracted by French chemist Chevreul in 1832. This substance takes part in energy metabolism in muscle and nerve cells. Creatine is synthesized mainly at bedtime in the quantity about 2-3 g daily. In the form of CP, creatine is a depot of energy rich bonds and is used for quick resynthesis of ATP during cell work. CP stock in muscle tissue is low, therefore is it used as the energy source only at the beginning of muscle work until the other more powerful sources are activated [4].

CP shortage leads to reduction of myocard contraction strength and its ability for functional recovery. There is a close correlation between the number of phosphorylated connections in cells reach for energy, cell viability and their ability to restore the contractivity.

The studies have shown that injection of CP into perfusate or its infusion into blood-vascular system stabilizes the sarcolemmal membrane of ischemic cardiomyocytes, slows down the reduce of cardiac muscle contractivity in case of ischemia, accelerates the recovery of contractile function of myocard after reperfusion, prevents the development of hypoxic myocardial contraction, reduces the infarct volume due to improvement of microcirculation in the zone of ischemia, prevents development of arrhythmia in case of ischemia and myocard reperfusion, inhibits thrombocyte aggregation and raises red-cell membrane plastisity [6].

The product Neoton is an exogenic CP widely used in myocard as a reservoir for quick ATP storage. CP is rapidly and efficiently converted into ATP with the participation of creatine kinase. As a result of such conversion, it reduces dysfunction of sarcolemma of ischemic cardiomyocytes and stimulates the energetic metabolism, so that the size of necrosis and ischemia are reduced. Such properties of Neoton have been proven in randomized studies when CP has protected myocard from ischemic and reperfusion injuries [3].

The aim of this study is a comparative pharmacoeconomic analysis of the use of the standard therapy + phosphocreatine in perioperative management of cardiac surgery patients with extracorporeal circulation, with IHD or with CHI.

To reach this aim the following tasks have been subsequently completed:

1. Search and choice of the correspondent clinical trials for conduction of a comparative pharmacoeconomic analysis of two therapy schemes (standard therapy and standard therapy + phosphocreatine).
2. Determination of the efficacy parameters of two therapy schemes on the basis of the published data of clinical trials.
3. Determination of the cost of treatment for patients due to the both therapy schemes.
4. Conduction of the cost-effectiveness analysis.
5. Determination of the parameters for budget impact analysis.
6. Conduction of sensitivity analysis.

Efficacy Analysis

Efficacy analysis is a first stage of the conducted clinical trial. This analysis implies data collection on efficacy of the medicinal product and selection of efficacy factor satisfying criteria of the conducted study [13; 17].

Efficacy analysis has been conducted on the basis of the results of meta-analysis of Landoni G. and co-authors, 2016 [3]. The use of standard therapy + fosfocreatine in perioperative management of cardiac surgery patients with extracorporeal circulation, with IHD or with CHI has shown such advantages

as: reduction of the frequency of perioperative cardiac infarction, reduction of the frequency of arrhythmia in postoperative period and inotropic agent-sparing effect (table 1). Patients receiving Neoton have been earlier transferred from the Department of Resuscitation and Intensive Care Unit (DRICU) [14].

In 2014-2015, FSBI A.N. Bakoulev Scientific Center . of the MOH of Russia conducted an open-label non-interventional comparative study, phase VI, Efficacy of the Use of Phosphocreatine during the Coronary Artery Bypass Graft Surgery. A total of 129 patients have been included into the study. Patients have been randomized into two groups: Group 1 - the group of treatment, and Group 2 - the control group. 65 patients in treatment group have received phosphocreatine in the dose of 8-12 g prior to the scheduled surgery and in the dose of 4 g intraoperationally following the clamping of coronary arteries. 64 patients of the control group have not received phosphocreatine, the standard pre- and post-operative treatment has been used.

Final points of the study are estimation of the efficacy and safety of the product. The received data confirms that the use of phosphocreatine during CABG is safe. Introduction of the product prior to surgery and immediately prior to the bypass reduces myocard injury, volume of the used inotropic support, and the low cardiac output syndrome during the post-operation period.

Besides, the influence of phosphocreatine use on hospitalization period has been estimated. It was determined, that the average number of inpatient days following surgery constituted 8.3 days for the control group and 7.3 days for the group of treatment.

Table 1. Clinical efficacy estimation of the use of phosphocreatine

Parameter	Standard therapy + phosphocreatine	Standard therapy
Severe arrhythmia	11.88%	21.60%
The need of inotropic therapy	16.75%	34.62%
Perioperative myocardial infarction	1.4%	4.7%
The need to be nursed in the ICU (on the next day)	17%	40%
The number of days spent in in-patient cardiac surgery clinic	7.3	8.3

Estimation of expenses and efficacy in our analysis has been based on such parameter as life years gained (LYG).

Use of the scheme standard therapy + phosphocreatine in perioperative management of cardiac surgery patients with extracorporeal circulation, with IHD or with CHI has led to the biggest values of life years gained in comparison with the use of the scheme of standard therapy, in particular 0.96 and 0.88 years for a patient respectively.

Cost Analysis

Cost analysis was the the following stage of the conducted pharmacoeconomic study. During the study, expenses for the use of the standard therapy + phosphocreatine in comparison with the use of the standard therapy have been determined. Expenses for perioperative and operative management of cardiac surgery patients with extracorporeal circulation, with IHD or with CHI reflected in standards of rendering technology intensive care constitute 317,850 rubles¹ and are the same in both comparison groups, so that those expenses have been accepted as constant and have not been taken into consideration in the study. Final value of the expenses analysis consisted from the direct expenses associated with complications due to the surgery, namely:

1. Cost of medical services and medicinal products for:
 - a. therapy of perioperative myocardial infarction;
 - b. therapy of arrhythmia in post-operative period;
 - c. inotropic therapy;
2. cost of an inpatient day
 - a. in cardio surgical department
 - b. in the resuscitation and intensive care unit.

Time horizon for the study constituted 1 year.

To estimate expenses for medical care, data has been taken from the rate agreement for payment for medical care provided due to compulsory health

¹RF Government Regulation as of December 19, 2016 No. 1403 «On State Guarantee Program on Free Universal Health Care for 2017 and for the Planned Period of 2018 and 2019»



insurance in Moscow city for 2017, and for medical therapy - data on cost of the MP in accordance with the State register of extreme sale prices [9; 11; 12].

For the therapy, phosphocreatine has been introduced into composition of cardioplegic solution immediately prior to bypass 4 g, then for rhythm recovery 4-16 g i.v. by stream infusion depending on the severity of myocard injury and the intensity of postpericardiotomic violations.

Financial expenses for treatment of perioperative myocardial infarction of cardiac surgery patients comprise of many components including medicinal products, first of all, cardiotoxic agents (for instance, MP Levosimendan) and treatment procedures (for instance intra-aortic counterpulsation, stenting of coronary arteries, etc.) and the use of different methods of diagnosing (for instance, echo-cardiography, coronography, catheterization of pulmonary artery, transpulmonary and thermodilution method of determination of cardiac output, etc.). Yet, this is not a complete list of the used medicines or procedures which should be applied in case of the developed myocardial infarction during surgeries on heart or during the post-operative period. It should be noted that those expenses may increase by several times in case of cardiogenic shock development.

The optimal choice for use of the products with a positive inotropic effect is a representative of calcium sensitization subgroup - Levosimendan (Simdax), with the frequency of administration for improvement of myocardial contractile function - 1 vial as a single dose.

Expenses for a 12-month standard therapy and for a standard therapy + phosphocreatine constituted 83,566 rubles and 75,337 rubles correspondingly (table 2).

Cost-effectiveness

Cost-effectiveness has been conducted at the next stage of the study. Analysis results have been presented as expenses for LYG with the consequent comparison of the received results.

Evaluation of cost-effectiveness ratio (CER) in two groups of patients are specified in the Table 3.

Table 3. Cost-effectiveness analysis in two groups (standard therapy + phosphocreatine vs standard therapy), rubles

Parameter	Standard therapy + phosphocreatine	Standard therapy
Expenses	75,337	83,566
LYG	0.96	0.88
Coefficient expenses - efficacy (CER)	78,444	95,176

Due to the results of the conducted cost-effectiveness analysis, in perioperative management of cardiac surgery patients with extracorporeal circulation, with IHD or with CHI in comparison with the use of the standard therapy, it has been determined that due to a positive influence of phosphocreatine on the increase of duration of life, cost-effectiveness ratio for the standard therapy + phosphocreatine has been less and constituted 78,444.

Due to the results of pharmacoeconomic analysis of treatment in perioperative management of cardiac surgery patients of the two groups, it is possible to conclude that the standard therapy + phosphocreatine is a dominant method of treatment in comparison with the standard therapy itself as it demonstrates better clinical efficacy and is characterized by lower cost-effectiveness ratio.

Budget impact analysis

This kind of analysis is an estimation of all the expenses associated with introduction of a new treatment technology or a MP into a real practice taking into consideration its efficacy. Final result is expressed as a sum of money to be saved or spent on the use of estimated medical technology. From the point of view of the budget impact analysis, the dominant position has the technology with lower total expenses.

The results of the budget impact analysis have revealed that the use of the standard therapy + phosphocreatine is preferable as it results in saving 8,229 rubles for a patient in comparison with the standard therapy which corresponds to reduction of expenses by 9.8%.

Sensitivity analysis

Analysis of sensitivity is a compulsory procedure for conduction of pharmacoeconomic study and is used for estimation of stability and efficacy of the conclusions received within the study. A single-factor sensitivity analysis due to the parameter of the cost of the MP Neoton (phosphocreatine) has been used for this study with the aim to determine the stability level of the received pharmacoeconomic conclusions on preference of the MP. Study of the influence of the price change for phosphocreatine in the range of ±50% on pharmacoeconomic study results - cost-effectiveness ratio and the results of the budget impact analysis has been conducted.

The sensitivity results have demonstrated that the change of price for Neoton in the range from -50% to +50%, it is still characterized by lower cost-effectiveness ratio saving money in comparison with the standard therapy (table 4).

Table 2. Results of the conducted analysis of expenses in the use of standard therapy + phosphocreatine in perioperative management of cardiac surgery patients with extracorporeal circulation, with IHD or with CHI in comparison with the use of standard therapy, rubles

Parameter	Rate	Standard therapy + phosphocreatine		Standard therapy	
		Frequency	Expenses	Frequency	Expenses
Therapy of perioperative myocardial infarction ²	288,255	1.40%	4,036	4.70%	13,548
Therapy of arrhythmia in post-operative period	36,742	11.88%	4,363	21.60%	7,936
The need of inotropic therapy	24,708	16.75%	4,138	34.62%	8,553
The need to be nursed in the ICU (on the next day) ³	8,000	17.00%	9,360	40.00%	11,200
Inpatient days in the cardiac surgery clinic ²	5,100	7.3 days	37,230	8.3 days	42,330
Expenses for the product	16,210	100.00%	16,210	0.00%	0
Direct expenses, total			75,337		83,566

¹ RF Government Regulation as of December 19, 2016 No. 1403 «On State Guarantee Program on Free Universal Health Care for 2017 and for the Planned Period of 2018 and 2019»
² Presented pharmacological aspects of intensive therapy of perioperative myocardial infarction of cardiac surgery patients are based on the experience of treatment of such patients in cardiac surgery clinics of two highly authoritative medical institution of Russia - clinics of cardio-vascular surgery I.M. Sechenov and RSSC named after B.V. Petrovskiy
³ Data of FSBI A.N. Bakoulev Scientific Center of the MOH of Russia

Table 4. Results of sensitivity analysis at simultaneous change of price for medicinal products, rubles

Change of price for phosphocreatine	Results of the cost-effectiveness analysis		Results of the budget impact analysis	
	Standard therapy + phosphocreatine	Standard therapy	Standard therapy + phosphocreatine	Standard therapy
+50%	86,84	95,176	83,442	83,566
0	78,444	95,176	75,337	83,566
-50%	70,005	95,176	67,232	83,566

Results

1. Analysis of treatment efficacy in patients has demonstrated the preference of the treatment scheme. In case of the standard therapy + phosphocreatine, the values of life years gained constituted 0.96 years, and in case of the standard therapy – 0.88 years.

2. Due to the results of the conducted analysis of expenses, the cost of a 12-months treatment with standard therapy and with standard therapy + phosphocreatine constituted 83,566 rubles and 75,337 rubles respectively.

3. Cost-effectiveness analysis has shown that the Cost-effectiveness ratio in the group of standard therapy + phosphocreatine constituted 78,444 rubles, whereas in the group of standard therapy - 95,176 rubles. So, standard therapy + phosphocreatine is a dominant method of treatment in comparison with the standard therapy.

4. Due to the results of the budget impact analysis, it has been determined that the use of scheme standard therapy + phosphocreatine resulted in saving of 8,229 rubles per each patient.

5. A single-factor sensitivity analysis due to the parameter of the cost of the MP Neoton has shown the stability of the received results at the change of factor in the range of [-50%; +50%].

Conclusions

Use of phosphocreatine in perioperative management of cardiac surgery patients with extracorporeal circulation, with IHD or with CHI has led to the biggest values of life years gained in comparison with the use of the scheme of standard therapy and is more efficient as a result of improvement such parameters as: frequency of myocardial infarction cases, frequency of arrhythmia cases, the need in inotropic therapy, the need to stay in DRICU and the number of inpatient days.

Based on the results of pharmacoeconomic analysis of treatment it is possible to conclude: standard therapy + phosphocreatine is a dominant treatment method in comparison with the standard therapy and results in cost saving.

The results of conducted pharmacoeconomic estimation have determined the preference of the standard therapy + phosphocreatine in comparison with the standard therapy in perioperative management of cardiac surgery patients with extracorporeal circulation, with IHD or with CHI from the point of view of the cost-effectiveness analysis parameter: standard therapy - phosphocreatine is characterized by lower cost-effectiveness ratio. From the point of view of budget impact analysis, the standard therapy + phosphocreatine also represents a dominant alternative requiring less expenses and guaranteeing cost saving in the healthcare system in comparison with the standard therapy.

So, insignificant increase of the standard therapy cost by adding Neoton makes it possible to prevent perioperative complications and mortality of cardiac surgery patients, is cost saving and make expenses efficient.

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