



ISSN (E): 2277- 7695
 ISSN (P): 2349-8242
 NAAS Rating: 5.03
 TPI 2020; 9(2): 46-51
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 www.thepharmajournal.com
 Received: 04-12-2019
 Accepted: 06-01-2020

Iryna Kupnovytska
 Ivano-Frankivsk National
 Medical University, Ukraine

Nelya Romanyshyn
 Ivano-Frankivsk National
 Medical University, Ukraine

Evaluation of sinus node if-channel inhibitor effect in patients with stable coronary artery disease after surgical myocardial revascularization

Iryna Kupnovytska and Nelya Romanyshyn

Abstract

The article studied clinical effectiveness of the sinus node If-channel inhibitor – ivabradine in combination with background therapy preparations in the patients with chronic single-vessel or multivessel coronary artery disease, heart failure with preserved left ventricular ejection fraction, who underwent myocardial revascularization surgery. The study included 120 patients randomized according to the number of the affected coronary arteries, the method of treatment and the duration of the postoperative period following carotid artery stenting. One month after myocardial revascularization for single-vessel or multivessel coronary artery disease, the dynamics of coronary artery disease manifestations in the patients receiving ivabradine and background therapy preparations (the main group) was almost similar to that in the patients undergoing background therapy only ($p>0.05$). On the 12th month of treatment, the patients with single-vessel and multivessel coronary artery disease, who received background therapy only, developed a greater need for additional use of nitroglycerine as compared to the patients who received background therapy in combination with ivabradine ($p<0.05$). At the end of the observation, the patients of the control group, who underwent single and multiple coronary artery stenting, walked 1.1, 1.2 times lower distance as compared to the patients of the main group ($p<0.05$). Twelve months after angioplasty with carotid artery stenting, the patients, who underwent multiple carotid artery stenting and received background therapy, required 62.2% more nitroglycerine tablets per week. After 1 month of treatment, according to the Seattle Angina Questionnaire and the Minnesota Living with Heart Failure Questionnaire, quality of life was almost similar in both groups. However, according to the Minnesota Living with Heart Failure Questionnaire and the Seattle Angina Questionnaire, on the 6th month of treatment, quality of life was 7.9% and 6.3% worse than that in the patients of the main group ($p<0.05$). After 12 months of treatment, the difference between the main and control groups, according to both questionnaires, was 10.9% and 29.3% (both $p<0.05$). During the observation, 10 (17.2%) patients of the main group sought medical attention for anginal pain during excessive exercises, while in the control group, there were 23 (37.1%) cardiac events (3 patients, including one with non-fatal MI, underwent angioplasty with re-stenting, 3 patients were hospitalized for angina pectoris exacerbation to functional class III and 16 individuals sought medical attention for stable angina signs). There were no cases of functional class IV angina pectoris according to the Canadian Cardiovascular Society Angina Grading Scale (2013), coronary artery bypass grafts, restenosis or fatal cardiovascular events.

Keywords: Stable angina, coronary arteries, stenting, ivabradine, clinical manifestations

1. Introduction

Cardiovascular diseases account for approximately 40% of all deaths in most developed countries nowadays. Over the past 10 years, cardiovascular mortality increased by 20%; among the working population, this indicator is 11.7%. Coronary artery disease (CAD) ranks first as a leading cause of cardiovascular mortality globally [1]. The most common form of CAD is stable angina. In different regions, its incidence varies from 1.8 to 6.5%. In CAD, gender-specific characteristics are observed. Myocardial infarction (MI) occurs much more frequently in men, while stable angina and painless CAD form are more common in women [1]. The age-specific analysis of CAD prevalence indicated its gradual increase with age. In people at the age of 30-39 years, CAD is represented by all its forms. One in twelve men at the age of 40-49 years presents with CAD signs. In 3-4 out of 10 men with CAD signs of the same age, typical stable angina is observed. Among men at the age of 50-59 years, the incidence of diagnosed MI and angina pectoris is 5.9% and 8.2%, respectively [3]. The statistical data mentioned above indicate the need for conservative treatment of CAD, as well as surgical correction of coronary arteries (CA) for long-term therapeutic outcomes.

Corresponding Author:
 Iryna Kupnovytska
 Ivano-Frankivsk National
 Medical University, Ukraine

The use of stents to restore the main blood flow reduces the number of cardiovascular accidents [6, 7]. However, to prolong the therapeutic effect after stenting, it is necessary to potentiate CA reconstruction with antianginal and anti-ischemic agents [4, 8].

The aim of the study was to analyze clinical effectiveness, duration of antianginal and anti-ischemic effects of the sinus node If-channel inhibitor - ivabradine in patients after CA stenting; to study clinical effectiveness of ivabradine in patients after elective single or multiple CA stenting according to the exercise tolerance test (ETT); to evaluate the effect of ivabradine and myocardial revascularization on quality of life (QoL) in patients with stable CAD.

2. Materials and Methods

The study included 120 patients with chronic CAD, heart failure with preserved left ventricular (LV) ejection fraction (EF) who underwent CA stenting. All the patients were randomized according to the number of the affected CA, the method of treatment and the duration of the postoperative period following myocardial revascularization surgery.

The main group included 58 patients who, in accordance with the Unified Clinical Protocol of Primary, Secondary (Specialized) and Tertiary (Highly Specialized) Medical Care approved by the Order of Ministry of Health of Ukraine of March 02, 2016, No 152 "Chronic Coronary Artery Disease" (updated September 23, 2016, No 994), the recommendations of the European Society of Cardiology (ESC) "ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012" and the guidelines of the Ukrainian Heart Failure Association (2017), received ivabradine (Coraxan, Servier, France) at a dose of 12.55 ± 1.94 mg/day, in addition to background therapy (BT). During BT, the patients received acetylsalicylic acid at a dose of 75 mg/day, clopidogrel at a dose of 75 mg/day, bisoprolol at a dose of 2.5 mg/day, ramipril at a dose of 8.61 ± 2.85 mg/day or losartan at a dose of 84.62 ± 24.02 mg/day, atorvastatin at a dose of 36.55 ± 7.62 mg/day. Prior to stenting, the patients with single-vessel CAD additionally received nitroglycerin at a dose of 12.53 ± 0.69 tab/week, while in the patients with multivessel CAD, the dose of nitroglycerin increased to 14.01 ± 0.29 tab/week. Among the patients of the main group, there were 15 cases of single-vessel CAD and 43 cases of multivessel CAD.

The control group included 62 patients, who underwent percutaneous coronary intervention (PCI) with CA stenting and received BT preparations, namely acetylsalicylic acid at a dose of 75 mg/day, clopidogrel at a dose of 75 mg/day, bisoprolol at a dose of 7.56 ± 2.53 mg/day, ramipril at a dose of 5.90 ± 2.58 mg/day or losartan at a dose of 63.33 ± 22.89 mg/day, atorvastatin at a dose of 36.77 ± 7.42 mg/day. Sixteen patients of the control group presented with single-vessel CAD, while 46 patients were diagnosed with multivessel CAD. Prior to stenting, the patients with single-vessel CAD additionally received nitroglycerin at a dose of 11.81 ± 0.35 tab/week, while in the patients with multivessel CAD, the dose of nitroglycerin increased to 13.89 ± 0.24 tab/week.

The patients' condition and clinical effectiveness of treatment were evaluated and compared before stenting, 1 month, 6 months and 12 months after CA stenting. Among the examined patients, men prevailed – 101 (84.2%) individuals. The average age was 61.4 ± 0.5 years. The control group included 15 (3 females and 12 males) apparently healthy

individuals with the average age of 60 ± 0.8 years.

Prior to CA stenting, to better understand long-term therapeutic and cardiovascular outcomes of the treatment performed, the frequency of diseases that determined the number and significance of risk factors in the patients of both groups was analyzed. According to the patients' medical histories, prior MI was found in 27 patients of the main group and 28 patients of the control group; recurrent MI was observed in 4 and 3 patients, respectively (all the cases were recorded in the patients with multivessel CAD); second-degree arterial hypertension stage II-III was detected in 51 and 55 patients of the main and control groups, respectively; compensated type 2 diabetes mellitus (DM) was observed in the patients with multivessel CAD only – 12 patients of the main group and 7 patients of the control group; pre-obesity was diagnosed in 35 and 33 patients, respectively; grade 1 obesity was found in 14 and 15 patients of the main and control groups, respectively; dyslipidemia was detected in 51 and 49 patients, respectively; current smoking was reported by 43 patients of the main group and 49 patients of the control group; emotional stress was diagnosed with equal frequency in both observation groups.

All the patients, 1, 6 and 12 months after CA stenting, underwent clinical examination including collection of the complaints, determination of the need for additional dose of nitroglycerine per week, evaluation of the distance walked according to the six-minute walk test (6 MWT), determination of QoL according to the Seattle Angina Questionnaire (SAQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ), physical examination with the ETT [2].

There were monitored the following cardiac complications: the frequency of hospitalizations for angina pectoris exacerbation; re-angioplasty with CA stenting including restenosis cases; the number of coronary artery bypass grafts (CABG); the number of non-fatal MI cases and fatal cardiovascular events; structural and functional cardiac changes to assess the progression or prevention of heart failure development.

In the absence of contraindications, coronary angiography (CAG) was performed after written consent was taken from all the patients. There were used the Infinix CC-i/FPD angiographs manufactured by Toshiba Medical Systems Corporation (Japan). CAG was performed via radial artery access. The following contrast agents were used - Ultravist 370 mg/ml, Omnipaque 350 mg/ml, or Visipaque 320 mg/ml. To dilate the CA, there were used drug-eluting stents (Medtronic Resolute Integrity).

The ETT was carried out using cycle ergometer Cardio+ (Ukraine) according to the method proposed by Zharinov O.Y. [5].

To assess New York Heart Association (NYHA) functional class FC of heart failure in cardiac patients, the 6 MWT was used.

To objectively assess the reliability of the research results, variational statistical analysis of the results obtained was conducted on a Pentium II PC using the Statistica 8.0 software package and Microsoft Excel statistical functions.

3. Results and Discussion

The dynamics of the clinical course of stable CAD in the patients, who underwent invasive intervention on a single CA on the background of additional ivabradine use was as follows (Table 1).

Table 1: Dynamics of the clinical course of stable CAD in the patients after single CA stenting on the background of BT in combination with ivabradine

Indicators	At the moment of hospitalization, main group (n = 15)	After treatment		
		1 month (n = 15)	6 months (n = 15)	12 months (n = 15)
	1	2	3	4
Need for nitroglycerine, tab/week; Δ%; p	12.53±0.69	1.67±0.58 86.7%; p ₁₋₂ <0.05	1.50±0.71 80.0%; p ₁₋₃ <0.05	1.50±0.71 80.0%; p ₁₋₄ <0.05
6 MWT, m; Δ%; p	245.97±16.42	245.97±16.42 33.9%; p ₁₋₂ <0.05	488.33±6.45 49.6%; p ₁₋₃ <0.05	523.33±8.59 53.0%; p ₁₋₄ <0.05
QoL according to the MLHFQ, points; Δ%; p	42.91±1.24	27.07±1.16 36.9%; p ₁₋₂ <0.05	13.27±0.70 69.1%; p ₁₋₃ <0.05	11.40±0.74 73.4%; p ₁₋₄ <0.05
QoL according to the SAQ, points; Δ%; p	51.34±1.41	78.20±1.01 34.3%; p ₁₋₂ <0.05	86.27±0.70 39.7% p ₁₋₃ <0.05	87.93±1.67 41.6% p ₁₋₄ <0.05
FC I (%)	0	11 (73.3)	12 (80.0)	14 (93.3)
FC II (%)	0	4 (26.7)	3 (20.0)	1 (6.7)
FC III (%)	15 (100.0%)	0	0	0

At the end of the first month of treatment, in the main group, there were 3 patients with a single CA stent who required the additional use of 1.67±0.58 nitroglycerine tablets per week ($p<0.05$). The remaining patients did not require any additional use of short-acting nitrates. When carrying out the ETT, 11 patients of the main group developed typical electrocardiogram (ECG) signs of myocardial ischemia and chest pain after reaching an exercise load of 125 W, while 4 patients of this group developed similar signs after reaching an exercise load of 75 - 100 W, that indicated FC I stable angina and FC II stable angina, respectively. On the 6th and 12th months of the observation, 2 patients reported the additional use of 1.5±0.71 nitroglycerine tablets per week. Within a 6-month and 12-month periods, the ETT revealed FC I stable angina in 12 and 14 patients, while FC II stable angina was detected in 3 and 1 patients, respectively. During the observation, the patients, who required the additional use of short-acting nitrates, were subjected to excessive physical and psycho-emotional stress.

According to the 6 MWT, 1 month after myocardial revascularization, the distance walked by the patients with single-vessel CAD, who belonged to the main group, increased by 33.9% ($p<0.05$). Thereafter, the distance walked by the patients tended to increase, and in the final observation period, it was 523.33±10.39 m being 53.0% greater than before treatment ($p<0.05$).

According to MLHFQ, QoL tended to increase immediately after cardiac surgery started and therapy was administered, during all the observation periods, namely in 1, 6 and 12 months – by 36.9%, 69.1 and 73.4%, respectively. According to the SAQ, the improvement of physical and psychosocial health in all the patients of this subgroup was noted during all the observation periods. On the 12th month of treatment, QoL improved by 41.5% as compared to the moment of hospitalization. One month after therapy, seven patients with multivessel CAD, co-existent DM, obesity and dyslipidemia, who underwent surgery and were treated with ivabradine, required the additional use of 1.86±0.38 nitroglycerine tablets per week ($p<0.05$). This was due to excessive exercising and smoking 8-10 cig/day (Table 2). On the 6th month of the observation, 5 patients needed extra 1.80±0.45 nitroglycerine tablets per week, while at the end of the observation, there were 4 patients, who required extra 1.75±0.50 nitroglycerine tablets per week. One month after starting treatment, by means of the ETT, FC I stable angina was detected in 31 patients, and FC II stable angina was found in 12 patients. Thereafter, the ETT results indicated the increase in the number of patients with FC I stable angina and the reduction in the number of patients with FC II stable angina. Thus, on the 6th and 12th months of the observation, there were 33 and 38 patients with FC I stable angina, while FC II stable angina was diagnosed in 10 and 5 patients, respectively.

Table 2: Dynamics of the clinical course of stable CAD in the patients after multiple CA stenting on the background of BT in combination with ivabradine

Indicators	At the moment of hospitalization, main group (n = 43)	After treatment		
		1 month (n = 43)	6 months (n = 43)	12 months (n = 43)
	1	2	3	4
Need for nitroglycerine, tab/week; Δ%; p	14.01±0.29	1.86±0.38 86.7%; p ₁₋₂ <0.05	1.80±0.45 87.2%; p ₁₋₃ <0.05	1.75±0.50 87.5%; p ₁₋₄ <0.05
6 MWT, m; Δ%; p	211.35±15.29	317.33±7.66 33.4%; p ₁₋₂ <0.05	410.23±6.81 48.5%; p ₁₋₃ <0.05	447.67±14.77 52.8%; p ₁₋₄ <0.05
QoL according to the MLHFQ, points; Δ%; p	65.21±1.81	42.79±1.21 34.4%; p ₁₋₂ <0.05	24.14±1.41 63.0%; p ₁₋₃ <0.05	18.26±2.46 72.0%; p ₁₋₄ <0.05
QoL according to the SAQ, points; Δ%; p	47.12±1.36	67.60±1.41 30.3%; p ₁₋₂ <0.05	74.20±1.40 36.5%; p ₁₋₃ <0.05	79.25±2.19 40.5%; p ₁₋₄ <0.05
FC I (%)	0	31 (72.1)	33 (76.7)	38 (88.4%)
FC II (%)	0	12 (27.9)	10 (23.3)	5 (11.6%)
FC III (%)	43 (100.0%)	0	0	0

One month after starting treatment, the patients of the main group with multiple CA stents walked the distance that significantly increased by 33.4% (from 211.35±15.29 m to

317.33±7.66 m, $p<0.05$). After six months of treatment with ivabradine, the distance walked by the patients increased to 410.23±6.81 m being 48.5% greater as compared to the

moment of hospitalization ($p<0.05$); after 12 months of treatment with ivabradine, the distance walked by the patients was 447.67 ± 14.77 m, that was 52.8% greater as compared to the moment of hospitalization ($p<0.05$).
QoL, according to both questionnaires, tended to improve

during all the observation periods (Table 2).

Table 3 presents the dynamics of the clinical course of stable CAD in the patients of the control group who underwent single CA stenting.

Table 3: Dynamics of the clinical course of stable CAD in the patients after single CA stenting on the background of BT

Indicators	At the moment of hospitalization, main group (n = 16)	After treatment		
		1 month (n = 16)	6 months (n = 16)	12 months (n = 16)
	1	2	3	4
Need for nitroglycerine, tab/week; $\Delta\%$; p	11.81 \pm 0.35	1.80 \pm 0.45 84.8%; $p_{1-2}<0.05$	1.75 \pm 0.50 85.2%; $p_{1-3}<0.05$	2.0 \pm 0.82 83.1%; $p_{1-4}<0.05$
6 MWT, m; $\Delta\%$; p	251.46 \pm 8.41	370.31 \pm 7.85 32.1%; $p_{1-2}<0.05$	428.44 \pm 9.08 41.9%; $p_{1-3}<0.05$	455.63 \pm 12.50 44.8%; $p_{1-4}<0.05$
QoL according to the MLHFQ, points; $\Delta\%$; p	40.31 \pm 0.94	27.44 \pm 1.37 31.9%; $p_{1-2}<0.05$	14.69 \pm 0.91 63.6%; $p_{1-3}<0.05$	13.25 \pm 1.06 67.1%; $p_{1-4}<0.05$
QoL according to the SAQ, points; $\Delta\%$; p	52.12 \pm 1.45	77.50 \pm 1.15 32.7%; $p_{1-2}<0.05$	81.06 \pm 2.11 35.7%; $p_{1-3}<0.05$	81.50 \pm 3.29 36.0%; $p_{1-4}<0.05$
FC I (%)	0	9 (56.3)	10 (62.5)	11 (68.8)
FC II (%)	0	7 (43.7)	6 (37.5)	5 (31.2)
FC III (%)	16 (100.0%)	0	0	0

One month after single CA stenting, 5 patients of the control group required the additional use of 1.80 ± 0.45 nitroglycerine tablets per week. In 6 and 12 months, 4 patients needed extra 1.75 ± 0.50 and 2.0 ± 0.82 nitroglycerine tablets per week.

After 1 month of treatment, the ETT revealed FC I stable angina in 9 patients and FC II stable angina in 7 patients of this subgroup (anginal pain behind the sternum with radiation to the left arm developed after reaching an exercise load of 125 and 100 - 75 W, respectively; ECG recorded descending ST segment depression ≥ 1 mm). During the next observation periods, there was a tendency towards a slight increase in the number of patients with FC I stable angina and reduction in the number of patients with FC II stable angina.

The distance walked by the patients, who underwent single CA dilation, increased significantly during the observation periods; up to the 12th month, it increased by 44.8% ($p<0.05$). QoL, according to the MLHFQ, improved significantly after one month of treatment already ($p<0.05$). According to the results of assessing physical and social aspects of life, the total MLHFQ score was 31.9% lower as compared to that at the moment of hospitalization. Until the 6th month of treatment, QoL in this subgroup increased by 63.6% that corresponded to score reduction to 14.69 ± 0.91 ($p<0.05$). Up to the 12th month of treatment, QoL increased slightly; however, there was no statistically significant difference as compared to the 6-month observation period (to 13.25 ± 1.06 points) ($p>0.05$).

According to the SAQ, QoL in the patients with angina pectoris improved by 32.7% (from 52.12 ± 1.45 to 77.50 ± 1.15 points) after 1 month of treatment after PCI on the background of BT ($p<0.05$). Thereafter, various dynamics in QoL improvement was observed: until the 6th month of treatment, the total SAQ score was 35.7% higher than that before treatment, while during the 12-month observation period, there was observed no statistically significant difference as compared to the 6-month observation period (81.06 ± 2.11 vs. 81.50 ± 3.29 , $p>0.05$).

After one month of the proposed treatment, 11 patients of the control group, who underwent minimally invasive surgery on several CAs on the background of BT, required the additional dose of nitroglycerine, namely 2.27 ± 0.47 tab/week ($p<0.05$). Six months after starting treatment, 7 patients needed extra 1.86 ± 0.69 nitroglycerine tablets per week. In the final observation period, 8 patients required the additional dose of nitroglycerine, namely 4.63 ± 2.83 tab/week.

After 1 month of treatment, the ETT results confirmed FC I stable angina in 26 patients and FC II stable angina in 20 patients; after 6 months of treatment, FC I stable angina was found in 29 patients and FC II stable angina was detected in 17 patients. After 12 months of treatment, according to the ETT results, FC I stable angina was found in 30 patients, FC II stable angina was detected in 13 patients, FC III stable angina was seen in 3 patients.

Table 4: Dynamics of the clinical course of stable CAD in the patients after multiple CA stenting on the background of BT

Indicators	At the moment of hospitalization, main group (n = 46)	After treatment		
		1 month (n = 46)	6 months (n = 46)	12 months (n = 46)
	1	2	3	4
Need for nitroglycerine, tab/week; $\Delta\%$; p	13.89 \pm 0.24	2.27 \pm 0.47 83.66%; $p_{1-2}<0.05$	1.86 \pm 0.69 86.6%; $p_{1-3}<0.05$	4.63 \pm 2.83 68.1%; $p_{1-4}<0.05$
6 MWT, m; $\Delta\%$; p	219.21 \pm 10.58	315.33 \pm 7.77 30.5%; $p_{1-2}<0.05$	378.80 \pm 17.52 42.1%; $p_{1-3}<0.05$	386.20 \pm 25.21 43.2%; $p_{1-4}<0.05$
QoL according to the MLHFQ, points; $\Delta\%$; p	62.11 \pm 1.37	43.11 \pm 1.22 30.6%; $p_{1-2}<0.05$	26.22 \pm 2.36 57.8%; $p_{1-3}<0.05$	25.83 \pm 6.40 58.4%; $p_{1-4}<0.05$
QoL according to the SAQ, points; $\Delta\%$; p	47.13 \pm 1.81	66.98 \pm 0.91 29.6%; $p_{1-2}<0.05$	69.53 \pm 2.34 32.2%; $p_{1-3}<0.05$	70.60 \pm 4.44 33.3%; $p_{1-4}<0.05$
FC I (%)	0	26 (56.5)	29 (63.0%)	30 (65.2%)
FC II (%)	0	20 (43.5)	17 (37.0)	13 (28.3%)
FC III (%)	46 (100.0%)	0	0	3 (6.5%)

The patients of the control group walked 30.5% greater distance (from 219.21±10.58 m to 315.33±7.77 m, $p<0.05$) one month after multiple CA stenting. Six months after multiple CA stenting, the distance was 42.1% greater than that at the moment of hospitalization ($p<0.05$); 12 months after multiple CA stenting, the distance did not differ significantly from that walked within the 6-month observation period (386.20±25.21 m, $p>0.05$).

According to the MLHFQ, QoL improved significantly after one month of treatment already ($p<0.05$). According to the results of assessing physical and social aspects of life, the total MLHFQ score was 30.6% lower than that at the moment of hospitalization. Until the final observation period, the total score reduced by 58.4% that significantly differed from the data obtained prior to PCI. It should be noted, that after 6

months of treatment, QoL did not differ from the indicators obtained during the first 6-month observation period (26.22±2.36 vs. 25.83±6.40 points, $p>0.05$).

According to the SAQ, similar data were obtained, namely the improvement of physical and psychological aspects of life after 1 and 6 months of treatment and no changes up to the 12th month of treatment.

The comparison of clinical data in the patients, who underwent single CA stenting, for a certain observation period showed that the patients of the main group, to relieve pain, received 25% of extra nitroglycerine tab/week less than the patients of the control group (Table 5). After 12 months of the observation, 4 patients of the control group and only 2 patients of the main group required additional nitroglycerine dose.

Table 5: Comparative characteristics of dynamics in the clinical course of stable CAD in the patients of the main and control groups who underwent single CA stenting

Indicator	After treatment					
	1 month		6 months		12 months	
	MG (n=15)	CG (n=16)	MG (n=15)	CG (n=16)	MG (n=15)	CG (n=16)
Need for nitroglycerine, tab/week; Δ%; p	1.67±0.58	1.80±0.45	1.5±0.71	1.75±0.50	1.50±0.71	2.0±0.82
	7.2%; $p>0.05$		14.3%; $p>0.05$		25%; $p<0.05$	
6 MWT, m; Δ%; p	372.33±7.04	370.31±7.85	488.33±6.45	428.44±9.08	523.33±8.59	455.63±12.50
	0.5%; $p>0.05$		12.3%; $p<0.05$		12.9%; $p<0.05$	
QoL according to the MLHFQ, points; Δ%; p	27.07±1.16	27.44±1.37	13.27±0.70	14.69±0.91	11.40±0.74	13.25±1.06
	1.3%; $p>0.05$		9.7%; $p<0.05$		14.0%; $p<0.05$	
QoL according to the SAQ, points; Δ%; p	78.20±1.01	77.50±1.15	86.27±0.70	81.06±2.11	87.93±1.67	81.50±3.29
	0.9%; $p>0.05$		6.0%; $p<0.05$		7.3%; $p<0.05$	
FC I (%)	11	9	12	10	14	11
FC II (%)	4	7	3	6	1	5

One month after angioplasty with single CA stenting, the patients of both groups walked the distance that did not differ significantly ($p<0.05$). On the 6th and 12th months of treatment, the distance tended to increase in both groups; however, the patients of the main group walked significantly higher distance.

According to the MLHFQ and the SAQ, QoL of all the patients included in the study improved significantly as compared to the data obtained before treatment; however, after 6 months of treatment, the total scores increased significantly in the patients receiving ivabradine.

Up to the 12th month of treatment, the disease manifested itself as FC I anginal attacks; the number of FC II cases in the patients of the main group, who underwent single CA dilation, reduced. Among the similar patients of the control

group, there was observed the increase in the number of patients with FC I stable angina; however, this number did not significantly differ from the indicator obtained on the 6th month of treatment.

In the patients, who underwent multiple CA stenting, during the first month of treatment, the need for additional use of nitrates was 18.1% higher. In 6 months, this need slightly decreased in both subgroups and was 3.2% higher in the patients of the control group. This was obviously due to the effectiveness of CA stenting and the compliance of pharmacotherapy for stable CAD. After 12 months of therapy, this need increased to 4.63±2.83 tab/week in the patients of the control group and reduced to 1.75±0.50 tab/week in the patients of the main group.

Table 6: Comparative characteristics of dynamics in the clinical course of stable CAD in the patients of the main and control groups who underwent multiple CA stenting

Indicator	After treatment					
	1 month		6 months		12 months	
	MG (n=43)	CG (n=46)	MG (n=43)	CG (n=46)	MG (n=43)	CG (n=46)
Need for nitroglycerine, tab/week; Δ%; p	1.86±0.38	2.27±0.47	1.80±0.45	1.86±0.69	1.75±0.50	4.63±2.83
	18.1%; $p<0.05$		3.2%; $p>0.05$		62.2%; $p<0.05$	
6 MWT, m; Δ%; p	317.33±7.66	315.33±7.77	410.23±6.81	378.80±17.52	447.67±14.77	386.20±25.21
	0.6%; $p>0.05$		7.7%; $p<0.05$		13.7%; $p<0.05$	
QoL according to the MLHFQ, points; Δ%; p	42.79±1.21	43.11±1.22	24.14±1.41	26.22±2.36	18.26±2.46	25.83±6.40
	0.7%; $p>0.05$		7.9%; $p<0.05$		29.3%; $p<0.05$	
QoL according to the SAQ, points; Δ%; p	67.60±1.41	66.98.91	74.20±1.40	69.53±2.34	79.25±2.19	70.60±4.44
	0.9%; $p>0.05$		6.3%; $p<0.05$		10.9%; $p<0.05$	
FC I (%)	31	26	33	29	38	30
FC II (%)	12	20	10	17	5	13
FC III (%)	0	0	0	0	0	3

According to the 6 MWT, the distance walked was greater in the patients receiving ivabradine. One month after minimally invasive surgery, the patients of the main and control groups walked 33.4% and 30.5% greater distance, respectively. There was no significant difference in the numeric value indicating the effectiveness of minimally invasive CA surgery. Thereafter, the distance walked by the patients tended to increase with a significantly increasing tendency in the patients of the main group ($p < 0.05$).

According to the MLHFQ and the SAQ, QoL was similar in the patients of both groups 1 month after starting treatment; however, after 6 months of treatment, in the patients of the control group, QoL was 7.9% and 6.3% worse than that in the patients of the main group ($p < 0.05$). After 12 months of treatment, the difference between the main and control groups was 29.3% and 10.9% ($p < 0.05$). This was clinically manifested as an improved clinical course of angina pectoris and reduced number of the patients with FC II.

In the group of patients with multivessel CAD receiving ivabradine, during the final observation period, there were 38 patients with FC I stable angina and 5 patients with FC II stable angina; in the control group, there were 30 cases of FC I stable angina, 13 cases of FC II stable angina, and 3 cases of FC III stable angina.

The number and structure of cardiac complications in the patients of both groups differed. In the main group, there were recorded 10 (17.2%) cardiac events (all the patients sought medical attention for angina pectoris exacerbation), while in the control group, there were 23 (37.1%) cardiac events (3 patients, including one with non-fatal MI, underwent angioplasty with re-stenting, 3 patients were hospitalized and 16 individuals sought medical attention for angina pectoris exacerbation). It should be noted that cardiac complications leading to re-angioplasty with CA stenting and non-fatal MI occurred in the patients with multivessel CAD, co-existent DM, obesity and dyslipidemia. During the observation, there were no cases of FC IV angina pectoris according to the Canadian Cardiovascular Society Angina Grading Scale (2013), CABG, restenosis or fatal cardiovascular events.

The variety and frequency of cardiac complications increased after the 8th month of treatment that was, probably, caused by the progression of atherosclerosis.

Thus, the maximum number of complications was recorded for the period of 6 to 12 months after CA stenting. An important factor is the absence of fatal cases among the patients of both groups and no cases of in-stent restenosis that confirmed the advantage of using drug-eluting stents.

4. Conclusions

In the patients with single-vessel CAD, who underwent myocardial revascularization surgery, the dynamics of clinical manifestations of CAD, one month after surgery, slightly differed. The need for additional nitroglycerine doses was detected in 20.0% of the patients receiving ivabradine versus 31.3% of the patients of the control group.

On the 6th month after surgery, the need for additional use of short-acting nitrates reduced in the patients of both groups; however, it was greater in the patients of the control group as they received 14.3% more nitroglycerine tab/week. During the final observation period, in the patients undergoing BT, the need for nitroglycerine tablets increased by 25% as compared to the patients receiving ivabradine; additional nitroglycerine use was reported by 4 (25.0%) versus 2 (13.3%) patients, respectively.

After one month of treatment, the patients of the control group, who underwent single and multiple CA stenting, walked 1.1, 1.2 times lower distance as compared to the patients, who received ivabradine. According to the MLHFQ and the SAQ, QoL was almost similar in the patients of both groups; however, during the period of 6 to 12 months, there was observed a significant improvement of QoL by social and medical aspects in the patients who underwent single and multiple CA stenting and received BT preparations in combination with ivabradine.

Surgical myocardial revascularization improves QoL, reduces the number of severe cardiac complications, contributes to the increase in the patients' work capacity in the immediate and remote postoperative periods.

Myocardial revascularization surgery alongside with the treatment including ivabradine improve exercise tolerance, reduce FC of angina pectoris and the need for short-acting nitroglycerine that results in QoL improvement and returning of patients to work.

5. References

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