International Heart and Vascular Disease Journal • Volume 7, № 23, September 2019
Journal of the Cardioprogress Foundation

The efficacy and cardiovascular safety of phosphodiesterase type 5 inhibitor in men with stable coronary artery disease and erectile dysfunction

A. K. Kerimov[1], B. U. Mardanov[2], A. P. Smirnov[3]

[1] Moscow City Outpatient Clinic No. 212 of Moscow Healthcare Department, Moscow, Russia
[2] National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Moscow, Russia
[3] Russian National Research Medical University named after N. I. Pirogov, Moscow, Russia

Authors

Anar K. Kerimov*, M.D., urologist of Moscow Cily Outpatient Clinic No. 212 of Moscow Healthcare Department, Moscow, Russia.
Bakhodir U. Mardanov, Ph.D., senior researcher of the Laboratory of Interdisciplinary Approach for Prevention of Chronic Non-infectious diseases of the Department of Comorbidities Prevention of National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Moscow, Russia.
Andrey P. Smirnov, Ph.D., M.D., neurologist, docent of the Department of Neurology, Neurosurgery and Medical Genetics of the Faculty of Medicine of Russian National Research Medical University named after N. I. Pirogov, Moscow, Russia.

Objective. *To study the efficacy and cardiovascular safety of sildenafil in men with stable coronary artery (CAD) disease and erectile dysfunction (ED).*

Materials and methods. *The prospective study included 50 men aged 40–69 years with stable CAD, low and medium cardiovascular risk of complications according to Princeton Consensus and ED. Men with CAD and ED were randomized into two comparable groups. The first group (n=27) received 25 mg of sildenafil 3 times a week additionally to standard therapy. In case of ineffectiveness, the dose reached 50 mg after 1 month of therapy. The control group (n=23) received only standard therapy. The duration of follow-up was 3 months. Before and after the therapy we assessed: the dynamics of erectile function, symptoms of urination, the severity of chronic stress, hemodynamic, anthropometric parameters and electrocardiographic (ECG) parameters.*

* Corresponding author. Tel. +7 (905) 547–78-58. E-mail: independent6000@mail.ru

Results. *The erectile function twice increased according to international index of ED by the end of the study that was statistically significant compared with the initial parameter and control group. The symptoms of urination decreased by 30 % according to international scale during sildenafil treatment compared with the control group without dynamics of total parameter according to MIEF-5 questionnaire. The level of chronic stress decreased by ⅓ according to questioning. The dynamics of stress severity did not differ significantly in control group. The analysis of ECG at rest did not reveal any negative dynamics in the frequency of heart rhythm disturbances and coronary circulation parameters during sildenafil treatment.*

Conclusion. *Course therapy with low doses of sildenafil as part of complex therapy can be used for ED treatment in patients with CAD with low and moderate risk according to Princeton Consensus.*

Key words: *Princeton Consensus, erectile dysfunction, sildenafil, coronary artery disease.*

Conflict of interests: none declared.

Received: 19.07.2019 **Accepted:** 18.08.2019

Introduction

Erectile dysfunction (ED) is male sexual dysfunction characterized by the inability to develop or maintain an erection during sexual activity that has always been one of the main issues of male health. Nowadays it remains complex and still significantly affects life quality of male population. Its prevalence among men from various age groups reaches 33 % and correlates with age and related diseases [1].

It is known that men of working age with coronary artery disease (CAD) have decreased exercise tolerance and life quality that also negatively affects men sexual activity. On the other hand, it is known that cardiovascular disease (CVD) risk factors are the main causes of ED development in men of working age. Many prospective studies noted that ED can serve as CAD and other CVDs predictor [2].

For a long time, there was an opinion that the risk of sudden cardiac death is higher in patients with CVD during sexual intercourse. However, further studies have shown that these ideas were exaggerated. New highly effective methods of ED treatment gave men the opportunity to resume their sex lives, including patients with CVDs. Princeton Consensus has been developed in order to standardize the problem of sexual activity and cardiovascular risk and divided patients with sexual dysfunction into three groups. Those at low risk could initiate or resume sexual activity and be treated for sexual dysfunction, at moderate risk — further investigations are needed. For those at high risk, sexual activity should deferred until stabilized cardiac condition [3].

Over the last years, many researched showed successful treatment of ED and other somatic diseases with low doses of phosphodiesterase type 5 (PDE5) inhibitors [4]. There are many studies on the effect of PDE 5 inhibitors on CVDs and its interaction with standard cardiac therapy. It is necessary to study the dynamics of main cardiovascular parameters during low doses of PDE5 inhibitors therapy in order to assess the possibilities of pharmacological treatment in patients with ED and CAD.

Objective

To study the efficacy and cardiovascular safety of sildenafil treatment in men with CAD and ED in patients with low and moderate risk according to Princeton Consensus.

Materials and methods

The study included 50 men aged 55.4±2.8 years with stable CAD and ED, who came to City Clinic No. 212 of the Moscow Health Department from September 2018 to February 2019.

Inclusion criteria: sexual dysfunction in men over 35 years in combination with one or more of the following diseases (chronic prostatitis, CAD, type 2 diabetes mellitus (T2DM), arterial hypertension (AH), International Index of Erectile Function (IIEF) below 21, controlled 1–2 grade of AH, stable CAD (I —II functional class of angina, postinfarction cardiosclerosis)), I —II FC of chronic heart failure (CHF).

Exclusion criteria: patients with high cardiovascular risk according to Princeton Consensus, grade 3 AH, uncontrolled AH, III –IV FC of CHF, unstable angina, myocardial infarction and acute cerebrovascular accident over the last 6 months, nitrate therapy, individual sildenafil intolerance, acute stage of chronic diseases, malignant neoplasms, T2DM, severe course or decompensation of the disease, participation in other studies.

Socio-demographic characteristics of men with CAD and ED included in the study are presented in table 1.

Table 1. **Socio-demographic characteristics of men with CAD and ED**

Parameters	Main group, n=27	Control group, n=23	p*
Age, years	55.9 ± 3.4	55.3 ± 1.8	insignificant
Education, n (%) Higher Secondary	8 (29.6 %) 19 (70.4 %)	8 (35 %) 16 (65 %)	insignificant insignificant
Family status, n (%) Married Single	24 (89 %) 3 (11 %)	19 (82 %) 4 (18 %)	insignificant insignificant
Employment, n (%) Employed Unemployed	17 (63 %) 10 (37 %)	15 (65 %) 8 (35 %)	insignificant insignificant
Alcohol consumption, n (%) Alcohol abuser Not an alcohol abuser	8 (29.6 %) 19 (70.4 %)	6 (26 %) 17 (74 %)	insignificant insignificant
Smoking, n (%) Smoker Non-smoker	19 (70 %) 8 (30 %)	16 (69.6 %) 7 (30.4 %)	insignificant insignificant

***** Insignificant — insignificant difference between groups.

Methods

The standard questioning was performed using specially developed for this study questionnaire (based on the ARIC, World Health Organization (WHO) and National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation questionnaires).

Chronic stress was assessed using the Reeder questionnaire that included 10 questions and five possible answers to each question. The questionnaire identifies three levels of stress: low (score 3.01–4), medium (score 2.01–3) and severe (score 1–2).

Studied anthropometric parameters included height, body mass, waist circumference (WC) and body mass index (BMI). According to WHO recommendations, WC was measured between the edge of the lower rib and ileum. BMI (Quetelet index) was calculated as the ratio of body mass in kilograms to the square of height in meters (BMI=/h2, where m — body mass of the patient (kg), h — height (m)).

Office blood pressure (BP) measurement was performed using tonometry on the patient's right hand while sitting after 5-minute rest. Systolic blood pressure (SBP) was recorded when 1 Korotkov sound appeared (phase I), diastolic blood pressure (DBP) — with the sounds disappeared (phase V). The level of BP was evaluated twice with 2–3 minutes interval, the average result was included into the study. The level of BP > 140/90 mm Hg was considered as AH and / or when the patient received antihypertensive therapy; awareness — the patient knows about the presence of AH; treatment — the patient receives antihypertensive therapy; treatment effectiveness — the patient receives antihypertensive therapy, and BP reaches target level. We also noted patient's heart rate (HR).

12-lead electrocardiogram (ECG) was registered at rest. ECG interpretation was performed according to scheme specially developed for this study (based on the Minnesota code standards, Rose G., Blackburn H., 1968).

ED was assessed using IIEF questionnaire (Rosen RC et al., 1997) that allows to estimate 5 components of sexual function: erection, orgasm, sexual attraction, sexual and general satisfaction. This study assessed erectile function [5]. 22–25 points was considered as normal erectile function, 17–21 points — mild impairment; 12–16 points moderate to mild impairment, 8–11 — moderate impairment, 5–7 points — severe impairment.

The severity of urination disorders was assessed using the IPSS questionnaire (The International Prostate Symptom Score, WHO, 1992). Patients answered each of 7 questions by noting the best answer. Interpretation of the results: from 0 to 7 points — mild; from 8 to 16 points — moderate; over 20 points — severe impairment.

Study protocol

Men with CAD and ED were randomized into 2 comparable groups:

The main group (27 patients) received standard CAD therapy and 25 mg of sildenafil 3 times a day. In case of ineffectiveness, the dose reached 50 mg after 1 month of therapy. The duration of follow-up was 3 months.

The control group (23 patients) received only standard CAD therapy. Characteristics of received medications is presented in table 2. The differences between groups by received therapy were insignificant.

Before and after the study we assessed risk factors (RF) dynamics, clinical condition and life quality in mild and moderate risk groups according to Princeton Consensus using instrumental cardiac and laboratory investigations and questionnaires [6].

During short control visit at the middle of the study (after 1 month) we performed short questioning, BP and HR measurement and ECG registration at rest.

Table 2. **Received therapy characteristics**

Medication	Main group, n (%)	Control group, n (%)	Significance of differences*
Sildenafil 25 мг	3 (11%)	-	-
Sildenafil 50 мг	24 (89%)	-	-
Calcium channel blockers	6 (22%)	5 (21.7%)	insignificant
Beta-blockers	8 (29.6%)	7 (30%)	insignificant
ACE inhibitors/ sartans	10 (37%)	9 (39%)	insignificant
Statinis	12 (44%)	10 (43%)	insignificant
Mineralocorticoid receptors antagonists	7 (30%)	5 (21.7%)	insignificant

***** Insignificant — insignificant difference between groups.

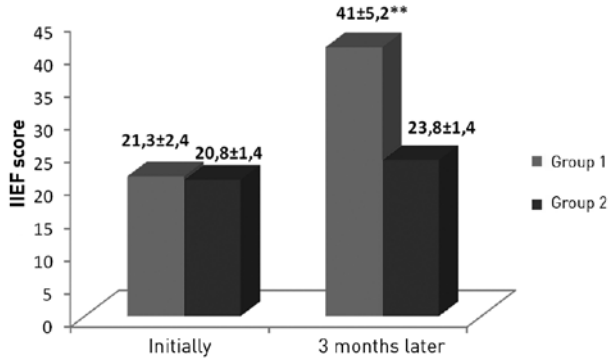

Figure 1. Erectile function dynamics in patients after the therapy

Statistical analysis of obtained data was performed using Statistica 6,0. Software. Quantitative variables are presented as mean (M) and standard error of mean (m). The significance of differences was assessed using Student and Wilcoxon paired t-test. A p value less than 0.05 was considered significant.

Results and discussion

Our study is dedicated to the investigation of the efficacy and cardiovascular safety of course therapy with PDE5 inhibitor sildenafil in patients with CAD. Previous studies have shown that course PDE5 inhibitor therapy was superior to its single use in patients with ED. But there are not so many studies on the course PDE5 inhibitor therapy in patients with CAD and ED. Before therapy it is necessary to asses its effectiveness, interaction with other medications, tolerance and safety.

The analysis of participants comorbidities was performed by assessing its frequency (Table 3).

Table 3. **Participant's comorbidities characteristics**

Clinical diagnosis	Main group, %	Control group, %
2nd stage AH	13 (48%)	10 (43%)
3rd stage AH	6 (22%)	5 (21.7%)
CAD	14 (52%)	13 (56%)
CHF	8 (29.6%)	7 (30%)
DM	6 (22%)	5 (21.7%)
Obesity	6 (22%)	6 (26%)
ED	27 (100%)	23 (100%)
Chronic prostatitis, remission	23 (85%)	20 (87%)

According to the protocol, patients were divided into two groups: the main group, which received sildenafil and the control group — without PDE type 5 inhibitors. Therapy received by patients before the investigation did not change. The dose of sildenafil reached 50 mg after 1 month of therapy in 89% of patients. By the end of the course erectile function improved twice that was statistically significant ($p<0,01$) compared with initial value and the control group (Figure 1).

According to previous studies PDE5 inhibitors therapy positively affects urinary function that is commonly associated with hyperplasia or other prostate disorders [8]. According to IPSS questionnaire (The International Prostate Symptom Score, WHO, 1992) most patients had ED and moderate urinary function impairment [9]. During sildenafil treatment, symptoms of urinary dysfunction decreased by 30% compared with the control group where there were no dynamics of IPSS score. The differences between groups were statistically significant (Figure 2).

It is known that ED is associated with life quality and psychosomatic status of men of reproductive age [1,5]. We assessed chronic stress level in patients before and after the study. The chronic stress indicator improved by 1/3 (from 2.8± 0.2 points to 4.1±0.2 points, $p<0.01$) in patients from the main group according to the questioning. The dynamics of chronic stress was insignificant in patients from the control group (2.9±0.1 versus 3.4±0.2 points, $p>0.05$). The differences between groups were statistically significant ($p<0.05$).

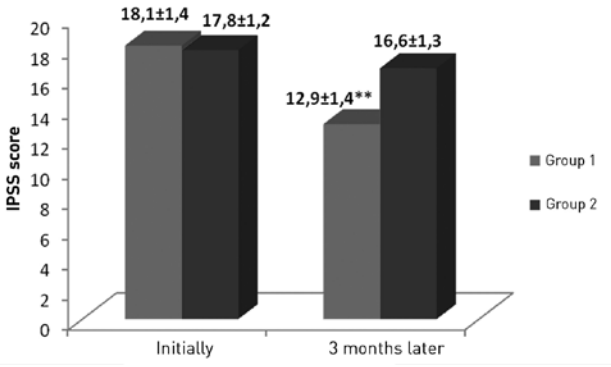

Figure 2. The dynamics of International Prostate Symptom Score

Table 4. **Hemodynamics and anthropometric parameters during sildenafil course therapy**

Parameter	Main group		Control group	
	Before therapy, n=27	After therapy, n=27	Before therapy, n=23	After therapy, n=23
SBP	141.1 ± 9.45	134.9 ± 6.2	138.6 ± 3.8	132.7 ± 2.6
DBP	83.2±6.4	78.7 ± 3.6	79.6±2.5	75.1 ± 1.7
HR	74 ± 4.8	77 ± 4.3	74.8 ± 3.2	72.4 ± 2.8
WC, cm	96.8 ± 1.5	93 ± 1.4*	95.9 ± 1.8	94.8 ± 1.2
Body mass, kg	84.4 ± 1.7	79.4 ± 1.6*	83.6 ± 1.4	82.4 ± 1.7
BMI	28.6±1.27	25.2±1.3*	28.9±0.9	27.8 ±1.3

* $p < 0,05$.

One of the main objectives of our research was the assessment of the dynamics of the main RF in study participants (table 4).

There are two features that we need to consider while prescribing PDE5 inhibitors in patients with cardiovascular pathology. Firstly, these medications reduce BP by 8 mmHg on average. But PDE type 5 inhibitors are not contraindicated in patients with AH. Secondly, PDE type 5 inhibitors interact with nitrates [10].

Thus, patients from both groups received antihypertensive therapy from four groups, and this therapy did not change during the investigation. Hemodynamic parameters (SBP and DBP) slightly decreased in both groups and did not differ between groups. HR was normal during the study.

We also assessed the dynamics of anthropometric parameters. Initially, about 60 % of men with CAD and ED had abdominal obesity. During the course of sildenafil therapy waist circumflex significantly decreased in the main group that may be associated with increased sexual and physical activity. But these changes were not statistically significant compared with the control group. The dynamics of body mass and BMI had similar pattern.

We assessed not only the effectiveness, but also the safety of sildenafil course therapy in patients with CAD. Our study included patients with low and moderate cardiovascular risk of sexual activity according to Princeton Consensus. Thus, the results of our study show that FC of CAD and the frequency of its episodes did not change in patients with angina pectoris. Thadani et al. also showed that during the therapy with 10 mg of vardenafil per day, symptoms of angina pectoris and myocardial circulation did not change in patients with CAD and ED [11]. According to ECG analysis, there were no negative dynamics of vascularization and conduction during 50 mg of sildenafil treatment (Table 5). The main group data were comparable with the control group.

All the patients before the study were supplied with self-control diary of adverse effects. The most common adverse effect was transient flushing that was registered almost in every forth patient (table 6). Every fifth patient had dizziness. These results were comparable with previous data and did not lead to therapy interruption or canceling [8].

Table 6. **Adverse effects of course sildenafil treatment**

Adverse affect	N (%)
Flushing	7 (26 %)
Priapism	2 (7 %)
AP increase	4 (15 %)
Dizziness	5 (18 %)
Chest discomfort, abdominal pain	3 (11 %)

Conclusion

This study shows that ED is common in patients with CAD risk factors. Performed course of sildenafil therapy significantly improved erectile function, decreased urinary dysfunction symptoms and the severity of chronic stress. Course therapy with low doses of sildenafil affected hemodynamic and anthropometric parameters as well as ECG pattern. Thus, PDE type 5 inhibitors as part of complex therapy can be used for ED treatment in patients with CAD with low and moderate risk according to Princeton Consensus.

Conflicts of interest: None declared.

Table 5. **ECG features during sildenafil treatment**

Parameter	Main group		Control group	
	Before therapy, n=27	After therapy, n=27	Before therapy, n=23	After therapy, n=23
Atrial fibrillation (AF), n (%)	2 (7 %)	2 (7 %)	1 (4 %)	1 (4 %)
QRS ⩾ 120 ms, n (%)	3 (11 %)	3 (11 %)	2 (9 %)	2 (9 %)
Left ventricular hypertrophy (LVH) signs, n (%)	17 (63 %)	17 (63 %)	15 (65 %)	15 (65 %)
Negative T wave in chest leads, n (%)	10 (37 %)	8 (29 %)	7 (30 %)	6 (26 %)
Pathologic Q wave, n (%)	2 (7 %)	2 (7 %)	2 (9 %)	2 (9 %)
Vesicular extrasystole, n (%)	6 (22 %)	5 (18 %)	5 (21,7 %)	4 (17 %)
Supraventricular extrasystole	7 (26 %)	8 (29 %)	6 (26 %)	5 (21,7 %)
AV block, 1st stage	3 (11 %)	3 (11 %)	1 (4,3 %)	1 (4,3 %)

References

1. Glina S., Sharlip I.D., Hellstrom W.J. Modifying risk factors to prevent and treat erectile dysfunction. J Sex Med. 2013;10:115–119.
2. Pushkar D.Yu., Kamalov A.A., Al-Shukri S.H. et al. Epidemiological study of the prevalence of erectile dysfunction in the Russian Federation. The Urals Medical Journal. 2012;3:75–79. Russian.
3. Mamedov M.N. Men's health problems in cardiology practice. — M.: Cardioprogress, 2016. — 130 p. Russian.
4. Chrysant S.G. Effectiveness and safety of phosphodiesterase 5 inhibitors in patients with cardiovascular disease and hypertension.Curr Hypertens Rep. 2013;15 (5): 475–83.
5. Rosen R.C., Riley A., Wagner G. et al. The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49:822–830
6. Nehra A.L., Jackson G., Miner M., Billups K.L. et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87 (8): 766–78.
7. Kim E., Seftel A., Goldfischer E., Baygani S., Burns P. Comparative efficacy of tadalafil once daily in men with erectile dysfunction who demonstrated previous partial responses to as-needed sildenafil, tadalafil, or vardenafil. Curr Med Res Opin. 2015;31 (2): 379–89.
8. Akhvlediani N.D., Matyukhov I.P. Modern place of sildenafil in the treatment of erectile dysfunction. Urology. 2018; 2: 142–146. Russian.
9. Hwang E.C., Kim S.O., Nam D.H. et al. Men with Hypertension are More Likely to Have Severe Lower Urinary Tract Symptoms and Large Prostate Volume. Low Urin Tract Symptoms. 2015;7 (1): 32–6.
10. Diosdado-Figueiredo M., Balboa-Barreiro V., Pértega-Diaz S. et al. Erectile dysfunction in patients with arterial hypertension. Cardiovascular risk and impact on their quality of life. Med Clin (Barc). 2019;152 (6): 209–215.
11. Thadani U., Smith W., Nash S. et al. The effect of vardenafil, a potent and highly selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease. J Am Coll Cardiol. 2002;40 (11): 2006-