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The Effect of Bromocriptine on Clinical and Laboratory Parameters in Patients With Peripartum Cardiomyopathy

Aim	To evaluate the effect of bromocriptine on clinical hemodynamic and functional indexes and to analyze life prognosis for patients with periportal cardiomyopathy divided into two groups: group 1, bromocriptine treatment (n=21) and group 2, standard treatment without bromocriptine (n=22). History was taken, examination and standard clinical evaluation were performed, the Clinical Condition Scale (CCS with V. Yu. Mareev, 2000, modification) was administered, and 6-min walk test (6MWT) was performed. Quality of life was determined with the Minnesota questionnaire. Standard 12-lead electrocardiography, echocardiography, and blood biochemistry with measuring C-reactive protein (CRP) and prolactin, were performed. Follow-up duration was one year.
Results	Heart rate was significantly decreased in group 1 (22.7%) compared to group 2 (18%); the 6-min distance was increased (61 and 50%, respectively), the total CCS score was decreased (66 and 55%, respectively, and the quality of life Minnesota questionnaire score was improved (from 68.4±12.4 to 26.4±12.4 and from 63.4±10.9 to 36.4±15.1, respectively). Also, left ventricular (LV) end-diastolic dimension was reduced from 66.82±7.07 to 60.67±3.79 mm (9.2%) in group 1 and from 61.92±4.41 to 58.91±4.68 mm (5%) in group 2, which was associated with increases in LV ejection fraction by 18.3 and 14.5%, respectively. In both groups, CRP concentration was decreased from 8.3±4.1 to 4.3±1.2 mg/l and from 8.5±3.5 to 6.3±1.5 mg/l, respectively. The bromocriptine treatment was associated with a significant decrease in prolactin level (62%). The LV function completely recovered in 66.6% of patients in group 1 and in 27% of patients in group 2.
Conclusion	The bromocriptine treatment of periportal cardiomyopathy in combination with an optimal drug therapy was associated with an additional beneficial effect on the clinical functional status, intracardiac hemodynamics, blood concentration of CRP, and a potentiality for complete recovery of the LV function.

Keywords	Periportal cardiomyopathy; heart failure; bromocriptine
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Currently, peripartum cardiomyopathy (PPCM) is of increasing interest for scientists and doctors, as demonstrated by numerous studies and the Guidelines for Diagnosis and Management of Peripartum Cardiomyopathy of the European Society of Cardiology [1, 2].

The worldwide epidemiological profile of PPCM is still unknown. However, the highest incidence of PPCM is reported in Haiti (1:299 live births), South Africa (1:1,000), and the United States (1:1,149–4,000). In Europe, Australia, and Asia, no centralized epidemiological studies have been conducted. Although incidence analysis of female ethnic groups in the United States identified that the prevalence of PPCM was 1 case per 1,421 in African American women, 1:2,675 in Asian American women, 1:4,075 in European American women, and 1:9,986 in Latino American women [3].

The exact cause of PPCM is unknown, though various theories have been proposed for the causes and mechanisms of its development [2].

A key role in the pathogenesis of PPCM is currently assigned to the formation of a cascade involving oxidative stress, prolactin-cleaving protease (cathepsin D), and prolactin. The 16 kDa prolactin subfragments impair cellular metabolism of cardiomyocytes and damages endothelial cells, which results in vasoconstriction and apoptosis [4].

Agents used in PPCM include the groups of drugs recommended for the treatment of heart failure (HF). Bromocriptine is a specific drug that reduces the secretion of prolactin and somatotropic hormone without affecting the levels of other pituitary hormones [5–7].

The objective of this study was to assess the effects of bromocriptine on clinical, hemodynamic, and functional

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parameters and analyze life expectancy in patients with PPCM.

Materials and methods

The study was approved by the ethics committee for scientific research of the Republican Cardiology Center of the Ministry of Health of the Republic of Uzbekistan. Data were studied for 43 patients with PPCM, who were included in the study from 2015 to 2019. The definition and criteria proposed by the European Society of Cardiology Working Group on PPCM in 2010 were used for diagnosis: «Peripartum cardiomyopathy is idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. The LV may not be dilated, but the LV ejection fraction (EF) is nearly always reduced below 45%" [1].

History of all patients was collected, patients' condition was assessed using the Score of Clinical Condition (SHOKS as modified by V. Yu. Mareev, 2000), tolerance to exercises was estimated using the 6-minute walk distance (6MWD) test, and quality of life was assessed with Minnesota Living with Heart Failure Questionnaire (MLHFQ). Standard electrocardiography and transthoracic echocardiography were conducted using an ultrasound system SONOLINE Verso-Pro, fitted with electronic sector sensors 2.5 and 3.75 MHz, in standard M- and B-modes. Serum levels of C-reactive protein (CRP) and prolactin were determined using a turbidimetric method on a Daytona biochemical analyzer. Blood samples were collected to assess prolactin levels if there were clinical manifestations from the 34th week of pregnancy to the 4th month after delivery.

To assess the effect of bromocriptine on patient's findings, patients were divided into two groups: Group 1 patients were treated with bromocriptine (n=21) and Group 2 patients received standard therapy without bromocriptine (n=22). The decision whether to use bromocriptine was based on the guidelines of the Hanover Medical School, with several modifications. The following regimen was used: 2.5 mg twice per day for 2 weeks, followed by a decrease to 2.5 mg per day for another 2 weeks [8].

It should be noted that when PPCM was diagnosed, a recommendation was immediately made whether to interrupt pregnancy or deliver. In the case of the postpartum development of PPCM, breastfeeding was terminated, and the best possible drug therapy for chronic heart failure (CHF) was administered. The duration of the study was 1 year.

Statistical analysis of the data was performed using the Statistica 6.0 software package. The mean (M) and standard deviation (σ) were estimated. The significance of differences was estimated using the Student's t-test. The chi-squared test was used to analyze the significance of differences between qualitative attributes. The changes were significant at $p < 0.05$.

Results

The initial data are shown in Table 1.

The analysis of demographic characteristics showed that the mean age (29.72±5.38 years) of patients with PPCM did not differ significantly between groups. In our study, PPCM usually developed in the postpartum period (70%), 3 months or more postdelivery (4.26±2.38 months). Symptoms of CHF developed in the last trimester of pregnancy in 30% of cases.

During the 1-year follow-up, positive changes in the clinical and functional conditions were observed (Table 2). With the same central blood pressure (BP) effect, there

Table 1. Clinical characteristics of patients with PPCM

Parameter	Group with bromocriptine, n = 21	Group without bromocriptine, n = 22	p
Mean age, years	29.95±5.38	29.53±5.14	>0.05
Multipara, abs.	13	9	< 0.05
Multiple pregnancy, abs.	1	2	>0.05
Period from the onset of symptoms to admission, months	8.6±2.5	10.6±2.8	>0.05
Hypertension, abs.	5	3	>0.05
Preeclampsia/ eclampsia, abs.	2	2	>0.05
LVEF, %	34.02±8.56	36.65±7.98	>0.05
6MWD, m	193.3±9.8	186.6±11.7	>0.05
SBP, mmHg	105.3±12.5	108.7±12.7	>0.05
HR, bpm	86.3±12.1	88.2±15.4	>0.05
Hemoglobin, g/L	94.5±14.1	92.3±12.2	>0.05
Llow blood hemoglobin, abs.	16	16	
Creatinine, mmol/L	82.4±10.1	71.5±13.5	>0.05
CRP, mg/dL	8.3±4.1	8.5±3.5	>0.05
Prolactin, mU/L	584.49±189.40	521.68±116.20	>0.05
ACE inhibitor/ARB, abs.	18	19	>0.05
BB, abs.	20	22	>0.05
MCRA, abs.	18	18	>0.05
Diuretics, abs.	20	22	>0.05

PPCM, peripartum cardiomyopathy; LVEF, left ventricular ejection fraction; 6MWD, 6-minute walk distance; SBP, systolic blood pressure; HR, heart rate; CRP, C-reactive protein; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BB, beta-blocker; MCRA, mineralocorticoid receptor antagonist.

Table 2. Changes in clinical and functional parameters by groups

Parameter	Group 1 (n=21)		Group 2 (n=22)	
	Baseline	After 12 months	Baseline	After 12 months
SBP, mmHg	105.3±12.5	108.3±10.4	108.7±12.7	110.3±9.4
DBP, mmHg	75.3±8.5	76.3±7.5	72.4±18.5	73.3±7.5
HR, bpm	86.3±12.1	70.3±12.1*	88.2±15.4	74.3±11.2*
6MWD, m	193.3±9.8	312.3±29.8**	186.6±11.7	280.3±33.4*
SHOKS score	10.6±0.3	3.6±0.3**	10.2±0.2	4.5±1.1**
MLHFQ score	68.4±12.4	26.4±12.4**	63.4±10.9	36.4±15.1**

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; 6MWD, 6-minute walk distance;
SHOKS, clinical status scale; MLHFQ, the Minnesota Living with Heart Failure Questionnaire. *, p <0.05; **, p <0.01.

Table 3. Changes intracardiac hemodynamic by groups

Parameter	Group 1 (n=21)		Group 2 (n=22)	
	Baseline	After 12 months	Baseline	After 12 months
EDD, mm	66.82±7.07	60.67±3.79*	61.92±4.41	58.91±4.68*
ESD, mm	55.69±7.93	34.67±3.79*	50.63±5.50	43.55±6.96*
EF, %	34.02±8.56	52.33±6.21**	36.65±7.98	51.18±6.28*
LA, mm	38.79±6.81	34.64±5.48*	40.35±5.80	35.00±3.46*
RV, mm	33.71±6.14	30.45±5.45*	33.13±6.97	31.13±6.88*
IVS, mm	8.45±0.80	8.55±0.69	8.15±1.32	8.21±0.75
LVPW, mm	8.54±0.75	8.55±0.69	8.40±1.08	8.8±0.7
mPAP, mmHg	52.5±10.4*	25.1±6.6	45.2±12.2	25.2±4.2*

EDD, end-diastolic dimension; ESD, end-systolic dimension; EF, ejection fraction; LA, left atrium; RV, right ventricle;
IVS, interventricular septal thickness; LVPW, thickness of the left ventricular posterior wall; mPAP, mean pulmonary artery pressure.
*, p <0.05, **, p <0.001 significance of the difference between the baseline data and after 1 year of follow-up.

was a more pronounced decrease in heart rate (HR) in Group 1 (18.6%) versus Group 2 (15.7%). Improved clinical status accounted for a significant increase in 6MWD (38.1% and 33.4%, respectively) and a reduction of the total SHOKS score (66% and 55%, respectively). At the same time, patients noted improvements in quality of life, according to the Minnesota questionnaire. The score decreased from 68.4±12.4 to 26.4±12.4 in Group 1 and from 63.4±10.9 to 36.4±15.1 in Group 2 (61.4% and 43%, respectively).

Analysis of the echocardiographic measurements of intracardiac hemodynamics showed improvements in linear dimensions of the heart in both groups. For example, LV end-diastolic dimension (EDD) decreased from 66.82±7.07 to 60.67±3.79 mm (9.2%) in Group 1 and from 61.92±4.41 to 58.91±4.68 mm in Group 2 (5%; p>0.05). At the same time, myocardial contractility improved: EF increased from 34.02%±8.56% to 52.33%±6.21% (18.3%) in Group 1 and from 36.65%±7.98% to 51.18%±6.28% (14.5%) in Group 2. Moreover, there were positive effects on the right heart parameters, with a 10% and 6% reduction in RV dimensions and an expected 52% and 46% decrease in mean pulmonary artery pressure (mPAP) in Groups 1 and 2, respectively (Table 3).

As for the laboratory measurements, low baseline hemoglobin levels should be noted. Hemoglobin levels increased from 94.5±14.1 to 100.4±10.1 mg/L in Group 1 and from 92.3±12.2 to 105.5±12.1 mg/L in Group 2. CRP levels decreased from 8.3±4.1 to 4.3±1.2 mg/dL (48%) in Group 1 and from 8.5±3.5 to 6.3±1.5 mg/dL (26%) in Group 2. The use of bromocriptine was associated with a statistically significant decrease in prolactin levels, from 584.49±189.40 to 221.68±46.20 mU/L (62%). By contrast, the prolactin level in Group 2 was 421.68±86.20 mU/L (19%; Table 4).

The analysis of changes in the course of the disease and life expectancy in patients with PPCM showed that the concomitant use of bromocriptine and standard treatments of CHF is initially associated with full recovery of LV function (LVEF > 55%) and significant regression of CHF symptoms in 14 (66.6%) cases; and only 4 (27%) cases of recovery in the control group.

We observed the highest benefits of bromocriptine use in the group with high baseline levels of prolactin, while the use of bromocriptine in patients with normal baseline prolactin levels was not associated with any additional advantages over Group 2.

Discussion

Over the past 2 decades, diagnostic criteria, the pathogenetic model, and different treatments for PPCM were developed. Oxidative stress has a key role in the pathogenesis of PPCM. Increased oxidative stress in

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Table 4. Changes in laboratory findings by study group

Parameter	Group 1 (n=21)		Group 2 (n=22)	
	Baseline	After 12 months	Baseline	After 12 months
Hemoglobin, g/L	94.5±14.1	100.4±10.1	92.3±12.2	105.5±12.1
Creatinine, μmol/L	82.4±10.1	72.4±12.1	71.5±13.5	72.4±10.1
CRP, mg/L	8.3±4.1	4.3±1.2*	8.5±3.5	6.3±1.5**
Prolactin, mU/L	584.49±189.40	221.68±46.20*	521.68±116.20	421.68±86.20

CRP, C-reactive protein; *, p <0.05, **, p <0.001 significance of the difference between the baseline data and after 1 year of follow-up.

late pregnancy and early postpartum results in elevated levels of prolactin that degrade due to activated specific protein cathepsin D into angiospastic and proapoptotic subfragments [4].

Experimental studies showed that such subfragments damaged the heart and vessels, impaired cellular metabolism of cardiomyocytes, and damaged endothelial cells, which resulted in vasoconstriction, apoptosis, inflammation, and disintegration of capillary continuous medium [9].

The treatment of patients with PPCM involves the management of clinical manifestations of HF and specific treatments based on the pathogenesis of the disease. Studies using bromocriptine, a synthetic ergot derivative with properties of D2 dopamine agonists, demonstrated that both physiological and pathological hypersecretion of prolactin was inhibited [10].

The possibility of using prolactin-inhibiting bromocriptine was demonstrated for the first time by Sliwa et al. in South-African female patients with PPCM [6].

Researchers from Germany who administered bromocriptine in female patients with PPCM established an increase in LVEF by 10% or more versus the control group [11].

We demonstrated a good positive response to bromocriptine in women with high baseline levels of prolactin. A 6-month increase in LVEF was more than 50% of the baseline level in this group.

We used low doses of bromocriptine in patients with PPCM and low LVEF (34.02±8.56%), high HR (86.3±12.1 bpm), low BP, and elevated blood prolactin. The inhibition of prolactin as a treatment method is obviously of practical use. However, it is still unclear when to start such therapy and for how long to use it.

Tremblay-Gravel et al. suggested that the use of bromocriptine in the initial period of the disease can limit the degree of damage if prolactin inhibition is the top priority [12].

Concerns have been raised previously about the potential risk for the brain and possible complications, such as thromboembolism and rhythm disorders, if high doses of bromocriptine are used [13, 14].

In our study, the tolerability of bromocriptine, when used with the best possible drug therapy for HF, was satisfactory and did not affect the duration of its use.

Bromocriptine is commonly used in clinical practice. This drug is successfully administered for various diseases, such as prolactinoma, galactorrhea, diabetes mellitus, acromegalia, and Parkinson's disease [7, 15–18].

Its pathogenetically reasonable use in PPCM is a new treatment and rehabilitation solution for this very severe patient population.

Conclusions

The use of bromocriptine in patients with peripartum cardiomyopathy in combination with the best possible drug therapy for heart failure has additional positive effects on patients' clinical and functional status, intracardiac hemodynamics, levels of serum C-reactive protein, and the possibility of full recovery of left ventricle function.

No conflict of interest is reported.

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