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Bromocriptine value in the treatment of patients with peripartum cardiomyopathy

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Abstract
A peripartum cardiomyopathy is a relatively rare heart disease that affects women in the third trimester of pregnancy and/or after giving birth, characterized by high variability of the course and prognosis with the potential for full restoration of left ventricular function. The pathophysiological mechanism in this disease is associated with prolactin degradation disorder, and therefore, the medications that suppress lactation have promising clinical significance.

Keywords: peripartum cardiomyopathy, heart failure, bromocriptine

Introduction

Peripartum cardiomyopathy (PCMP) is increasingly attracting the attention of scientists and doctors at the beginning of the XXI century, as evidenced by numerous studies and the development of recommendations for the diagnosis and treatment of PCMP by the European Association of Cardiology [1, 2].

The epidemiological situation of PCMP is currently unknown worldwide, although the largest number of PCMP has been reported in Haiti (1 per 299 live births), 1 per 1000 in South Africa and 1 per 1149-4000 in the USA. The centralized epidemiological studies have not been conducted in Europe, Australia and Asia, although an analysis of the incidence of ethnic groups of women in the USA found that the prevalence of PCMP was 1 per 1421 in African American women, 1 per 2675 in Asian women, 1 per 4075 in Caucasian women and 1 per 9986 in Spanish women [3].

The exact reason for the development of PCMP is unknown, although various theories are expressed to explain the causes and mechanisms of the development of this disease [2].

Currently, the main role in the pathogenesis of PCMP is given to the formation of the so-called cascade "oxidative stress — prolactin protease (cathepsin D) — prolactin". The appearance of prolactin subfragments with a molecular weight of 16 kDa worsens the cellular metabolism of cardiomyocytes and damages endothelial cells leading to vasoconstriction and apoptosis [4].

The therapeutic measures for PCMP are represented by groups of medication recommended for the treatment of heart failure (HF). A specific remedy is bromocriptine, which reduces the secretion of prolactin, somatotropin without affecting the level of other pituitary hormones [5, 6, 7].

The purpose of the study

To examine the effectiveness of bromocriptine in patients with peripartum cardiomyopathy.

Material and Methods

The approval of the local ethics committee for research was obtained before the start of the study. A prospective data analysis was performed in 43 patients with PCMP. The definition and criteria of the Study Group for the Research of Peripartum Cardiomyopathy of the European Society of Cardiology were used to make the diagnosis [1].

All patients underwent a medical history, an objective status assessment, a generally accepted clinical examination, a 6-minute walk test (6 MWT), a Minnesota Quality of Life Questionnaire (MQQL). The transthoracic echocardiography (Echo) was performed using a SONOLINE Verso-Pro ultrasound device (Siemens, Germany), which has electronic sector sensors with a frequency of 2.5 and 3.75 MHz, according to the standard methodology of generally accepted recommendations in M- and B-modes.

The patients were divided into 2 groups to assess the effect of bromocriptine on the studied parameters: the 1st group received basic treatment with bromocriptine (n=21); the 2nd group also received basic treatment but without bromocriptine (n=22). We adhered to the recommendations of the Hanover School with some changes, as a basis for the appointment of bromocriptine, according to the following scheme: for 2 weeks 2.5 mg 2 times a day, followed by a dose reduction to 2.5 mg per day for 2 weeks [8]. The duration of the study was 1 year.

Statistical processing of the obtained data was carried out using the software package Statistica 6.0. Indicators such as arithmetic mean (M) and standard deviation (σ) were calculated. The significance of differences was determined using Student's criterion (t). The chi-square test was used to analyze the significance of differences between qualitative traits. The changes corresponding to $p < 0.05$ were considered significant.

The results of the study

The source data are presented in table 1.

Table 1: Clinical characteristics of patients with PCMP

Parameters	the 1st group, n=21	the 2nd group, n=22	p
Average age, years old	29,95±5,38	29,53±5,14	>0,05
Multiparous, absolute number	13	9	<0,05
Multiple pregnancy, absolute number	1	2	>0,05
Dates from the onset of manifestation of symptoms of the disease to admission to the clinic, months	8,6±2,5	10,6±2,8	>0,05
AH, absolute number	5	3	>0,05
Preeclampsia, eclampsia, absolute number	2	2	>0,05
LVEF, %	34,02±8,56	36,65±7,98	>0,05
6 MWT, m	193,3±9,8	186,6±11,7	>0,05
SBP, mmHg	105,3±12,5	108,7±12,7	>0,05
HR, beats/min	86,3±12,1	88,2±15,4	>0,05
ACE inhibitors/ARA, absolute number	18	19	>0,05
Beta blockers, absolute number	20	22	>0,05
MRAs, absolute number	18	18	>0,05
Diuretics, абс. Число	20	22	>0,05
PCMP — peripartum cardiomyopathy; AH — arterial hypertension; LVEF — left ventricular ejection fraction; 6 MWT — 6-minute walk test; SBP — systolic blood pressure; HR — heart rate; ACE — angiotensin converting enzyme; ARA — angiotensin-II-receptor antagonists; MRAs — mineralocorticoid receptor antagonists.			

It was noted in the analysis of demographic characteristics that the average age of patients with PCMP did not significantly differ between groups, averaging 29.72±5.38 years old. In our study, it was characteristic that PCMP developed mainly in the postpartum period (70%): after 3 months or more (4.26±2.38 months). The symptoms of HF developed in the last trimester of pregnancy in 30% of cases.

Table 2: Dynamics of clinical and functional indicators in the groups

Parameters	the 1st group, n=21		the 2nd group, n=22	
	initially	after 1 year	initially	after 1 year
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, beats/min	86,3±12,1	70,3±12,1*	88,2±15,4	74,3±11,2*
6 MWT, m	193,3±9,8	312,3±29,8**	186,6±11,7	280,3±33,4*
MQQL, scores	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; 6 MWT — 6-minute walk test; MQQL — Minnesota Quality of Life Questionnaire; * — p<0,05; ** — p<0,01.				

According to the results of a year-long observation, a positive dynamic of the clinical and functional state was observed in both groups. A more pronounced decrease in heart rate (HR) was noted in the group of bromocriptine use (by 18.6%) compared with the 2nd group (by 15.7%) taking into account the same effect on the parameters of central blood pressure (BP). The improving of the physical condition was expressed by a significant increase in the distance traveled during the 6 MWT (by 38.1 and 33.4%, respectively). At the same time, patients noted an improvement in the quality of life according to the MQQL with a decrease in in estimates from 68.4±12.4 to 26.4±12.4 scores in the 1st group and from 63.4±10.9 to 36.4±15,1 scores in the 2nd group (by 61.4% and 43%, respectively).

Analysis of the parameters of intracardiac hemodynamics according to the results of Echo revealed an improvement in linear heart sizes in both groups. Thus, the LV end-diastolic dimension (LVEDd) decreased from 66.82±7.07 to 60.67±3.79 mm in the 1st group (by 9.2%) and from 61.92±4.41 to 58.91±4.68 mm in the 2nd group (by 5.0%; p> 0.05). At the same time, an improvement in myocardial contractility was noted as the form of an increase in the LV ejection fraction (LVEF) from 34.02±8.56 to 52.33±6.21% (18.3% increase) in the 1st group and from 36.65±7,98 to 51.18±6.28% (by 14.5%) in the 2nd group. In addition, there was a positive effect on the parameters of the right heart with a decrease in the size of the right ventricle (RV) by 10 and 6% with an expected decrease in mean pressure in the pulmonary artery (mPPA) by 52 and 46%, respectively, in the 1st and 2nd groups (see table 3).

Table 3: Dynamics of intracardiac hemodynamics in groups

Parameters	the 1st group, n=21		the 2nd group, n=22	
	initially	after 1 year	initially	after 1 year
LVEDd, mm	66,82±7,07	60,67±3,79*	61,92±4,41	58,91±4,68*
LVEDs, mm	55,69±7,93	34,67±3,79*	50,63±5,50	43,55±6,96*
LVEF, %	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
mPPA, mmHg	52,5±10,4*	25,1±6,6	45,2±12,2	25,2±4,2*
LVEDd — left ventricular end-diastolic dimension; LVEDs — left ventricular end-systolic dimension; LVEF — left ventricular ejection fraction; LA — left atrium; RV — right ventricle; IVS and LVPW — interventricular septum and left ventricle posterior wall; mPPA — mean pressure in the pulmonary artery; * p<0,05, ** p<0,001 — significance of differences between the initial data and after 1 year of observation.				

Discussion

The last two decades have been marked by the development of diagnostic criteria, a pathogenetic model and treatment methods for PCMP. The leading role in understanding the pathogenesis of PCMP belongs to oxidative stress. An increasing of the oxidative stress in an advanced state of pregnancy and in the early postpartum period leads to a high content of prolactin in the blood, which is broken down by the action of an activated specific protein, cathepsin D, to angiospastic and proapoptotic sub-fragments [4]. It has been shown in experimental studies that such sub-fragments have a damaging effect on the heart and blood vessels, worsen the cellular metabolism of cardiomyocytes and damage endothelial cells, leading to vasoconstriction, apoptosis, inflammation and dissociation of capillary structures [9].

Treatment of patients with PCMP is based on the treatment of clinical manifestations of HF and specific therapy based on the pathogenetic link of the disease. The studies using bromocriptine, a synthetic ergot derivative with the properties of D_2-dopamine agonists, have shown an inhibition of both physiological and pathological hypersecretion of prolactin [10]. The possibility of using bromocriptine to inhibit prolactin was first demonstrated in a study by K. Sliwa *et al*. in women suffering from PCMP in South Africa [11]. The researchers from Germany who used bromocriptine in women with PCMP found an increase in LVEF by 10% or more compared with the control group [12].

A good positive response to bromocriptine therapy in women with initially high prolactin levels was demonstrated in our study. The increase in LVEF during 6 months amounted to more than 50% of the initial level in this group. We used low doses of bromocriptine in patients with PCMP with low LVEF (34.02±8.56%), high HR (86.3±12.1 beats/min), low BP and high prolactin in the blood.

An inhibition of prolactin as a treatment method obviously has practical benefits. However, questions remain regarding the initiation and duration of such therapy. According to M. Tremblay-Gravel *et al*., the use of bromocriptine in the initial period of the disease can limit the degree of damage, if the need to inhibit prolactin is put at the forefront [13]. Concerns about the potential risk to the brain and possible complications such as thromboembolism and cardiac arrhythmias when taking high doses of bromocriptine were previously expressed [14, 15]. In our study, the tolerability of bromocriptine when prescribed against the background of optimal medical therapy for HF was assessed as satisfactory and did not affect the duration of its use.

The use of bromocriptine is widespread in clinical practice. This drug is successfully prescribed for a wide range of diseases, such as prolactinoma, galactorrhea, diabetes mellitus, acromegaly and Parkinson's disease [7, 16, 17, 18, 19]. Its use as a pathogenetically substantiated drug in patients with PCMP is a new solution to the issue of treatment and rehabilitation of such a heavy contingent of patients.

Conclusion

The appointment of bromocriptine in combination with optimal medical therapy for HF is accompanied by a positive effect on the indicators of clinical and functional status and intracardiac hemodynamics in patients with PCMP.

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