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Opportunities for Non-Hormonal Treatment of Breast Benign Dysplasia

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Abstract--- *Benign breast dysplasia (BBD) is widespread in the female population and is one of the most important risk factors for breast cancer. The use of ultra-diluted natural products in the treatment of diseases and in the treatment of hyper proliferative processes and cancer causes great interest and controversies. The aim of the study was to investigate the effectiveness and safety of the non-hormonal drug Mastopol® in the treatment of various forms of BBD in women of reproductive age.*

Keywords--- *Estrogens Stimulate, Algological Analysis, Prospective, Double-Blind, Placebo-Controlled Study.*

I. INTRODUCTION

168 patients of reproductive age with a diagnosis of BBD were included in the Ist group and 30 conditionally somatically and gynecologically healthy women without mastalgia and BBD in the control group- C. Patients of the 1st group were stratified into two subgroups based on an algological analysis. Group A consisted of 68 patients with the presence of BBD and mastalgia, and group B included 70 women with BBD without mastalgia. Two subgroups were randomly allocated in groups A and B: patients of subgroups A1 (n = 34) and B1 (n = 35) received non-hormonal drug Mastopol® 1 tablet 3 times a day sublingually for 8 weeks; patients of subgroups A2 (n = 34) and B2 (n = 35) received placebo.

Clinical data collection, algological objectification, anxiety assessment on the Ch. D. Spilberger – Yu. L. Khanin scale, mammary sonography, determination of peripheral blood serum cytokines by flow cytometry were implemented.

II. STUDY DESIGN

Prospective, double-blind, placebo-controlled study.

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III. RESULTS

The application of Mastopol® was provided with a decrease in the number and intensity of clinical manifestations, an improvement in the sonostructure of the mammary gland, a decrease in the number of cases and severity of mastalgia, a decrease in personal anxiety, and a positive change in cytokine levels.

Benign breast dysplasia (BBD) (ICD-10 code N60) is widespread in the female population and is characterized by a variety of clinically significant abnormalities detected using instrumental methods, or in the form of palpable formations, which are determined by physical examination [1].

BBD as an independent nosological unit was noted at the end of the XIX century. Its synonyms: mastopathy, fibrocystic mastopathy, dishormonal breast hyperplasia, fibrocystic disease, benign breast disease, fibroadenomatosis [1]. For over 100 years, this disease was considered as a stage preceding the occurrence of breast cancer, which is detected in 30% of all new cancer cases diagnosed in women and makes up more than 50% of malignant neoplasms of the female reproductive system [12, 18].

Today, the views on BBD have undergone significant changes. Precancerous changes are found only in some women with BBD. However, in countries with a high incidence of breast cancer, prevalence of breast benign dysplasia is also high, while in countries with low levels of breast cancer, it is much less common for women to have breast benign dysplasia. A permanent increase in the incidence of breast cancer in the twentieth century was accompanied by a parallel increase in the prevalence of breast benign dysplasia [3]. BBD is the most common form of breast disease in women of reproductive age. This disease is diagnosed in 20-60% of women in the general population, and in the group of women with gynecological diseases, the frequency of BBDrises up to 95%. According to the literature, BBD is diagnosed in every fourth patient under the age of 30 and in 60% of patients after the age of 40 [3,23].

Despite the fact that BBD is not an obligate precancer, the incidence of breast cancer in this group of patients is 3-5 times higher than in general population. In a recent meta-analysis, M. Zendehdel et al. (2018) [33] emphasize the fact that BBD is one of the most important risk factors for breast cancer. With proliferative forms of BBD, the risk of developing breast cancer increases by 25-30 times [13]. Therefore, timely diagnosis and effective treatment of BBD are extremely important.

The morphological basis for the occurrence of BBD, as defined by WHO (1984), is a violation of the ratio of epithelial and connective tissue components in combination with a wide range of proliferative and regressive changes in breast tissue and changes in fibrous, cystic and proliferative nature. The polyetiological genesis of the formation of the diffuse fibrocystic form of BBD underlines the important role of genetic, endocrine, psychogenic and environmental triggers [1, 5, 13, 14, 23]. The proliferative activity of the epithelium of the breast varies depending on the degree of differentiation of the lobules. In cells composing type 1 lobules, the rate of cell proliferation is 3 times higher than in type 2 lobules and 10 times higher than in type 3 lobules [5]. Among the statistically significant factors, associated with an increased risk of BBD, are the low volume of adipose tissue mass in childhood and adolescence; tall at 10 years and rapid linear growth at 10-18 years; alcohol intake from menarche

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to the first birth; eating animal fat, meat more than 3 times per day in adolescence; the duration of menopausal hormone therapy is more than 8-15 years [5].

In a normal two-phase cycle, the reproductive system undergoes cyclic changes: in the first half of the cycle, estrogens stimulate the growth of the epithelium and connective tissue, and after ovulation, progesterone stops this process, while triggering mitosis in the glandular tissue. Insufficiency, absolute or relative deficiency of progesterone leads to the fact that the epithelial-stromal elements continue to proliferate into the second phase of the cycle, forming a mechanical obstacle to the outflow of glandular secretion [29]. Hormonal misbalance in the tissues of the breast is accompanied by edema and an increase in intralobular connective tissue, and the proliferation of ductal epithelium leads to the formation of cysts. Edema, engorgement and tenderness, a change in autonomic reactions can be caused by functional or pathological hyperprolactinemia [11].

It should be noted that in the occurrence of breast pathology, the decisive role does not belong to the absolute value of hormone levels, but to the state and receptorsensitivity of breast tissue, which can be activated against the background of various genesis of stress and impaired adaptation reactions [9].

The trigger mechanisms of pathological proliferation are numerous and often not precisely established. Clinical and immunological aspects of the initiation of cancer proliferation are still being actively studied. A wide range of cytokines is known to initiate the proliferative potential of breast tissue cells [10].

Mastalgia is the initial sign or one of the main symptoms of BBD, as well as a potential risk factor for the development of proliferative processes, and sometimes breast cancer [29]. At different periods of life, up to 70% of women experience it, and in every third of them the symptom is severely expressed and significantly reduces the quality of life [22, 24]. In addition, cyclic mastalgia is one of the most common prognostic risk factors for breast cancer [27]. The etiology of mastalgia is not entirely clear. It is believed that cyclical fluctuations in the level of steroid hormones, a prolactin increase lead to increased synthesis of biologically active substances (prostaglandins, serotonin, histamine and histamine-like substances) in breast, an increase in the sensitivity of the glandular epithelium to hormones and bioactive substances, and an increase in vascular permeability with subsequent development of vascular permeability tissue and the appearance of pain. Even a slight increase in the concentration of prolactin helps to increase the sodium-retaining effect of aldosterone and antidiuretic vasopressin, leading to a change in electrolyte balance, fluid and electrolyte retention, which contributes to the edema of the breast microcytes, compression of the nerve endings, increased cell proliferation and, as a result, their soreness and tension [4].

A moderate correlation was established between mastalgia and the severity of depression in young women, a higher correlation was found between the level of anxiety disorders and mastalgia [20]. Psychogenic stress factors can be one of the key reasons for the implementation of mastalgia [32].

Modern approaches to the tactics of treating BBDare aimed at eliminating hormonal imbalances, treating concomitant diseases and reducing the influence of stress factors. Treatment should be multicomponent and have an

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etiopathogenetic rather than symptomatic focus. For the treatment of BBD, progesterone agonists, dopamine agonists, antigonadotropins, barley and indole-3-carbinol preparations, and homeopathic remedies are used [7].

Homeopathic doctors report successful treatment for hyperproliferative conditions and cancer prevention. Preclinical biological data are consistent with such claims. Controlled biological data on homeopathically prepared medicines indicate modulation of gene expression and biological signaling pathways that regulate cell cycles, immune responses, and central nervous system function based on studies in cells, animals, and humans. As a 200-year-old system of traditional medicine, used by millions of people around the world, homeopathy offers a low-dose pulse treatment strategy and a high level of safety [16]. The use of ultra-diluted natural products in the treatment of diseases and in the treatment of hyperproliferative processes and cancer, as before, is of great interest and debate [21].

Mastopol® is a homeopathic medicine registered in the Russian Federation for the treatment of BBD and mastodynia, the effectiveness of which, according to clinical recommendations for BBD, [1] is characterized by the level of evidence-based recommendations B and C, which requires further research.

This medicine is a combination of three plant and one mineral components (Conium maculatum (Conium) C6 0.075 g, Thujaoccidentalis (Thuja) C6 0.075 g, Hydrastiscanadensis (Hydrastis) C3 0.075 g, Calcium fluoratum C6 0.075 g) with proven therapeutic effectiveness due to anti-inflammatory, antiproliferative, antioxidant, decongestant, analgesic, immunomodulatory effects.

The aim of the study was to study the effectiveness and safety of the use of the non-hormonal drug Mastopol® in the treatment of various forms of BBD in women of reproductive age.

IV. Material and Methods

The total study included 527 women of reproductive age, 168 patients wereselected into group I based on the criteria for inclusion in a prospective, randomized, placebo-controlled study (category 2 according to BI-RADS system (Breast Imaging Reporting and Data System - a system for describing and processing data from radiation studies of the breast). 30 conditionally somatically and gynecologically healthy women without mastalgia and BBD were in group “C” control.They were examined on the basis of the oncology department of the Novorossiysk Clinical Center of the Federal Biomedical Agency and the State Budgetary Healthcare Institution “Oncology Dispensary No. 3” of the Ministry of Health of the Krasnodar Region, as well as the Department of Obstetrics and Gynecology No. 1 of Odessa National Medical University (Maternity Hospital No. 7 ”, Odessa).

All women signed informed consent to participate in the study. The criteria for inclusion in the study were: the age of women from 20 to 35 years old with BBDwith or without mastalgia; regular menstrual cycle; the absence of gynecological pathology, somatic diseases, thyroid dysfunction, diabetes mellitus. Patients with nodular forms of BBD requiring surgical treatment were excluded from the study. Pregnancy and lactation; the presence of benign and malignant tumors in the anamnesis, as well as with a failure to appear at the next medical examination were the reason to exclude.

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Group I patients were stratified into two subgroups based on an algological analysis. Group A consisted of 68 patients with the presence of BBD and mastalgia, and group B included 70 women with BBD without mastalgia. Two subgroups were randomly allocated in groups A and B: patients of subgroups A1 (n = 34) and B1 (n = 35) received the non-hormonal drug Mastopol® 1 tablet 3 times a day sublingually for 8 weeks; patients of subgroups A2 (n = 34) and B2 (n = 35) received placebo.

These groups were representative and homogeneous in age, clinical manifestations of the disease, and sonographic characteristics of the breast. The diagnosis of BBD was established on the basis of complaints, palpation and sonographic examination of the breast. In the presence of discharge from the nipples, a cytological study was carried out, which allowed excluding women with suspected malignancy of the process from the study.

For the purpose of algological objectification of the severity of mastalgia, a visual analogue scale (VAS) was used [2]. Marks of 1-3 points were regarded as weak intensity of mastalgia, 4-6 points - as moderate, 7-10 points - as expressed.

To assess the degree of anxiety, we used the C. D. Spilberger – Yu. L. Khanin reactive and personal anxiety scale [6]. When interpreting the indicators, the following grades of anxiety assessment were used: 30 points or less - low, 31-44 points - moderate; 45 and more - high.

All patients underwent ultrasound examination of the breast with a linear sensor of 7.10 MHz, color and energy Doppler mapping according to standard sonographic diagnostic criteria in accordance with the generally accepted methodology for various sensor inclinations. The state of the stroma, the ratio of the constituent elements of the breast, the distribution of fatty tissue, glandular structures, their thickness, the degree of degenerative processes, changes in the skin and subcutaneous fatty tissue, the presence of signs of mastopathy and other pathological changes or formations in the stroma of the breast and in the retro-mammary space were evaluated. To describe the elasticity of the glandular tissue, we used the method of dosed compression by the working surface of the sensor in a certain area, taking into account the fact that a large mass of glandular tissue is concentrated in the outer quadrants.

In all patients, before and after treatment, the levels of cytokines in the peripheral blood were determined on the 5-7th day of the menstrual cycle: interleukin-1β (IL-1β), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), IL-4, IL-6, IL-10 using flow cytometry using BD Cytometric Bead Array test systems (BD, USA) and FACStrack flow cytometer (BD, USA).

In the statistical processing of the research results, methods of analytical and variation statistics were used. Using the sampling method, the parameters of the population were estimated from the data of the sample (M - mean value, SE - standard deviation error); using statistical criteria, the validity of the hypotheses was determined: the t-test was used to compare the average values of independent samples and related (dependent) samples; $\chi 2$-criterion - for the analysis of conjugation of features, a comparison of the frequencies of events using the McNemar method (the Bonferroni correction was taken into account when making the decision). To determine the statistical

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significance of the relationship between the factor and outcomes, the odds ratio (OR) and the 95% confidence interval (CI) were calculated.

V. RESULTS AND DISCUSSION

The average age of women in group I was 27.50 ± 0.22 years, group A - 27.57 ± 0.26, subgroup A1 - 27.42 ± 0.33, subgroup A2 - 27.61 ± 0.35, group B - 27.31 ± 0.47, subgroups B1 - 27.56 ± 0.51, subgroups B2 - 27.22 ± 0.0.44, groups C - 27.99 ± 0.33 and did not have statistically significant differences between groups.

All women of group I with BBD and mastalgia discovered pain in breast, premenstrual syndrome, increased anxiety and the presence of palpable seals, increased sensitivity of the breast in 76.47% (52) individuals, engorgement in 76.47% (52), discharge from the nipple - in 32.35% (22).

When assessing the severity of mastalgia on the VAS scale, weak pain intensity was recorded in group A1 patients in 17.65% (6) cases, moderate in 47.06% (16), pronounced in 35.29% (12), in women of the group A2 - respectively in 20.59% (7), 52.94% (18) and 26.47% (9). No statistically significant differences in the severity of mastalgia between groups A1 and A2 were detected.

Patients with BBD and mastalgiawere characterized by increased personal anxiety, while differences in the severity of reactive anxiety were not observed. Personal anxiety in group A1 had a low degree of severity in 8.82% (3), average in 47.06% (16), high in 44.12% (15), and in group A2 - 14.71% (5), in 52.94% (18) and in 35.29% (12), respectively. In women with BBD without mastalgia in group B1 in 42.86% (15) and in group B2 in 48.57% (17) cases, personal anxiety was low, in 34.29% (12) and 40.00% (14) - on average, at 22.86% (8) and 11, 43% (4) - at high. If to concern the changes in the cytokine status in BBD, there was a statistically significant increase in the level of cytokines belonging to the Th1 type of immune response and having pluripotent local and systemic effects, both in the group with BBD andmastalgia and in the group with BBD without mastalgia (Fig. 1): the level of INF-γ in the peripheral blood in group A exceeded (10.50 ± 0.22 pg / ml) a similar indicator in patients of group C (6.42 ± 0.27 pg / ml) by 1.70 times (p <0 01) and in group B (9.44 ± 0.20 pg / ml) - at 1.52 (p <0.01), TNF-α - at 4.39 and 3.78 (43.28, respectively) ± 0.90 and 37.24 ± 1.10 vs 9.85 ± 0.47 pg / ml, p <0.01). An increase in the blood serum content of these cytokines in the pain and non-pain form of BBD indicates their important role in the mechanisms of autocrine and paracrine stimulation of proliferative and inflammatory processes in the breast and is one of the leading pathogenetic factors of intercellular interaction disorders in the development of BBD.

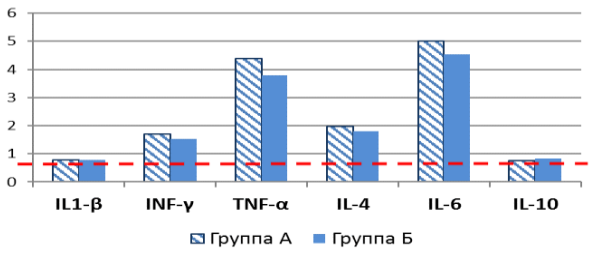

Fig. 1 The shift in the levels of the studied serum cytokines in patients with BBD with respect to the similar indicators of the control group, taken per unit (M ± SE, pg / ml).

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Analysis of cytokines of the Th2 type showed that the levels of IL-4 in groups A and B were increased 1.98 and 1.79 times (13.12 ± 0.77 and 11.82 ± 0.70 versus 6.61 ± 0.25 pg / ml, p <0.01), IL-6 - in 5.02 and 4.54 (23.76 ± 0.53 and 21.48 ± 0.65 against 4, 73 ± 0.32 pg / ml, p <0.01), and the content of IL-10 was reduced 1.32 and 1.21 times (6.03 ± 0.17 and 6.54 ± 0.16 versus 7, 94 ± 0.21 pg / ml, p <0.01). The content of IL-1β was reduced 1.28 and 1.29 times - 6.41 ± 0.10 and 6.33 ± 0.11 versus 8.17 ± 0.22 pg / ml, p <0.01. The levels of all studied cytokines did not have statistically significant differences between subgroups A1 and A2, as well as B1 and B2.

During thesonographic examination of women with BBD without mastalgia the glandular form prevailed - 81.43% (57/70), which was more common than in women with BBD with mastalgia (52.94% (36/68) 1.54 times (OS 3.90; 95% CI 1.81-8.40.) Sonographic study revealed a thickened glandular layer in the form of a continuous layer of glandular tissue of medium or reduced echogenicity in women with the glandular form of BBD. (Fig. 2).

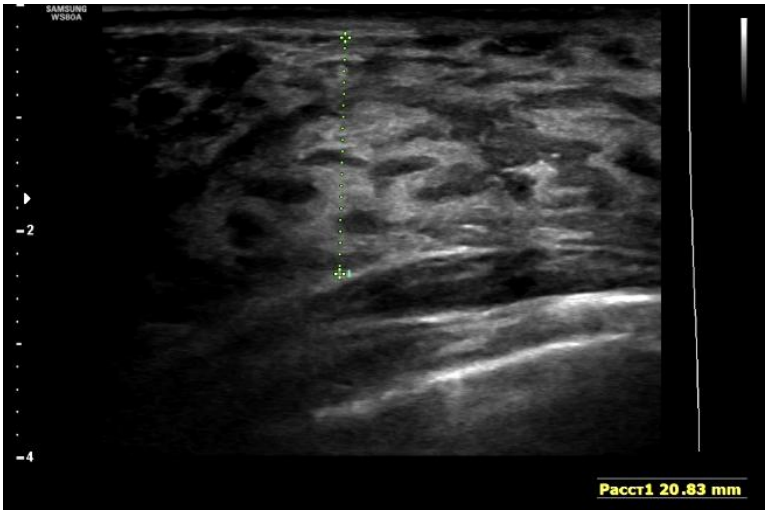

Fig. 2 A sonogram of the breast with the glandular form of BBD with a thickened glandular layer in the form of a continuous layer of glandular tissue of medium echogenicity.

By the proportion of cases of BBD with a predominance of the glandular component of the subgroup A1 (55.88% (19)) and A2 (50.00 5 (17)), B1 (80.00% (28) and B2 (82.86% (29)) did not have statistically significant differences.

With a prevailing fibrous component in 20.59% (14) patients of group A and 12.86% (9) of group B, a moderately thickened glandular layer was detected on sonograms with the phenomena of fibrosing of glandular tissue in the form of a diffuse increase in its echogenicity and linear fibrosis, which manifests itself compaction of the walls of the milky ducts, interlobular septa, and Cooper ligaments (Fig. 3). Fibrosis of breast tissue was often accompanied by the presence of small cystic inclusions and ductectasia. Subgroups A1 (17.65% (6)) and A2 (23.53% (8)), B1 (11.43% (4)) and B2 (14.29% (5)) were homogeneous in the number of cases of BBD with a predominance of the fibrous component.

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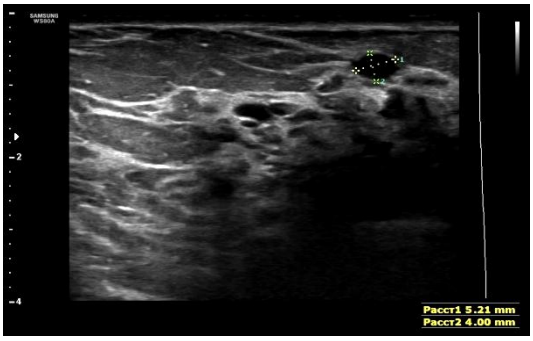

Fig. 3 Sonogram of the breast with BBD with the phenomena of fibrosing of glandular tissue and the presence of cystic inclusions.

The cystic form of BBD was characterized by a thickening of the glandular tissue and the presence of pathologicalcavities of more than 3 mm, consisting of a wall and a liquid or porridge content (Fig. 4).

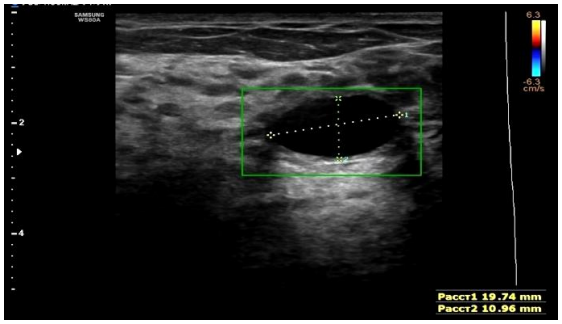

Fig. 4 Sonogram of the breast with cystic form of BBD.

The cystic form of BBD was observed in 19.12% (13) patients in group A and 3.35 times less often in group B - in 5.71% (4) (OR 3.90; 95% CI 1.20-12, 65). Subgroups A1 (20.59% (7)) and A2 (17.65% (6)), B1 (4.29% (3)) and B2 (2.86% (1)) were homogeneous in the frequency of the cystic for BBD.

Breast ductectasia, characterized by pathological expansion of the canals and ducts of the breast, was recorded only in 7.35% (5) of patients in group A, of which 5.88% (2) of women were subgroup A1 and 8.82% (3) of the subgroup A2 ($p > 0.05$) (Fig. 5).

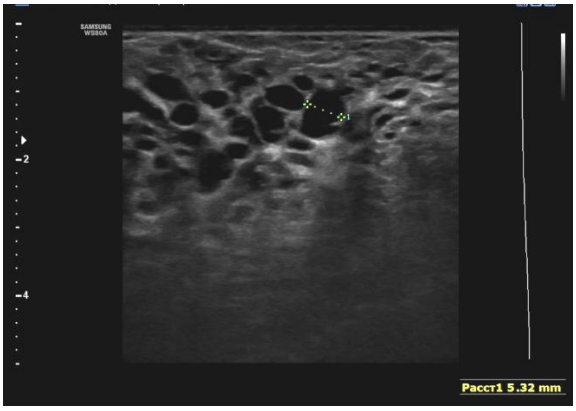

Fig. 5 Sonogramofthebreastwithductectasia.

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Signs of regression of the disease were determined by subjective and objective data after 3 months from the start of treatment for BBD. Analysis of the clinical efficacy of treatment with Mastopol® (Table 1) showed that, compared with placebo, patients of subgroup A1 after treatment, the proportion of patients with increased sensitivity of the breast became 7.67 timesless (8.82 versus 67.65%; OS 0.046; 95% CI 0.012-0.185), with painful sensations - at 8.25 (11.76 versus 97.06%; OR 0.004; 95% CI 0.000-0.038), with engorgement of the breast - at 7.34 (8 82 versus 64.71%; OR 0.053; 95% CI 0.013-0.209), with palpable seals - 3.40 (29.41 vs. 100%; p <0.01), with discharge from the nipple - 5 , 00 (5.88 vs 29.41%; OR 0.150; 95% CI 0.030-0.749), with premenstrual stress - 2.29 (41.18 versus 94.12%; OR 0.049; 95% CI 0.010-0.238).

Table 1. Dynamics of clinical complaints of women before and after treatment with Mastopol®, n (%)

Complaint	**Timeofinvestigation**	**Subgroups**			
		А1 (n=34)	А2 (n=34)	Б1 (n=35)	Б2 (n=35)
Hypersensitivityofthebreast	Before	27(79,41) b1	25(73,53) b2	0(0,00) a1	0(0,00) a2
	After	3(8,82) d,a2	23(67,65) a1,b2	0(0,00) a1	0(0,00) a2
Painful sensations	Before	34(100) b1	34(100) b2	0(0,00) a1	0(0,00) a2
	After	4(11,76)^{d,a2}	33(97,06) a1, b2	0(0,00) a1	0(0,00) a2
Engorgement	Before	28(82,35) b1	24(70,59) b2	5(14,29) a1	7(20,00) a2
	After	3(8,82) d,a2	22(64,71) a1,b2	0(0,00) a1	6(17,14) a2
The presence of palpable seals	Before	34(100) b1	34(100) b2	35(100)	35(100)
	After	10(29,41)^{d,a2}	34(100) a1	7(20,00)	35(100)
Nipple discharge	Before	12(35,29)	10(29,41)	8(22,86)	7(20,00)
	After	2(5,88)	10(29,41)	1(2,86)	7(20,00)
Premenstrual tension syndrome	Before	34(100) a2,b1	34(100) a1,b2	5(14,29) a1	7(20,00) a2
	After	14(41,18)^{d,a2,b1}	32(94,12) a1,b2	1(2,86) a1,b2	7(20,00) a2,b1

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Notes. 1. [a1, a2, b1, b2]– statistically significant differences with indicators of subgroups A1, A2, B1, B2 (p <0.05); 2. [d]– statistically significant differences with indicators before treatment; 3. Before, after – before treatment and three months from the start of treatment.

Treatment with Mastopol® contributed to a greater decrease in the severity of mastalgia on the VAS scaleinthe A1 subgroup compared with the A2 placebo subgroup: the proportion of patients without pain was 9.00 times more (52.94 versus 5.88%; OS 18.00; 95% CI 3.170-87.333); with moderate pain was 3.40 timesless (14.71 versus 50.00%; OR 0.172; 95% CI 0.054-0.552). Noneofthe 35.39% ofpatientsinsubgroup A1 with severe pain before treatment registert his after the end of taking Mastopol®. In the A2 subgroup receiving a placebo, there were no statistically significant changes in the number of women with severe mastalgia (Table 2).

Table 2 The dynamics of the severity of mastalgia on the VAS scale after treatment with Mastopol® in patients with BBD and with mastalgia, n (%)

Pain intensity	**Time of investigation**	**Subgroups**	
		A1 (n=34)	A2 (n=34)
No pain (0 points)	before	0(0,00)	0(0,00)
	after	18(52,94)[d,a2]	2(5,88)[a1]
Weak pain (1-3 points)	before	6(17,65)	8(23,53)
	after	11(32,35)	9(26,47)
Moderate pain (4-6 points)	before	16(47,06)	18(52,94)
	after	5 (14,71) [d,a2]	17(50,00) [a1]
Expressed pain (7-9 points)	before	12(35,29)	8(23,53)
	after	0(0,00) [d,a2]	6(17,65) [a1]

Notes. 1. [a1, a2, b1, b2]– statistically significant differences with indicators of subgroups A1, A2, B1, B2 (p <0.05); 2. [d]– statistically significant differences with indicators before treatment; 3. Before, after – before treatment and three months from the start of treatment.

It should be noted that weal so found a positive effect of Mastopol® on the echo structure of the breast (Table 3). Thus, the number of individuals with glandular form of BBD in the subgroup A1 decreased after treatment 3.80 times (from 55.88 to 14.71%; OR 7.35; 95% CI 2.290-23.572), inthesubgroup B1 - at 7.00 (from 80.00 to 11.43%; OR 31.00; 95% CI 8.194-117.275). During the treatment with Mastopol® there has been a tendency to decrease breast fibrosis in the A1 subgroupby 1.50 times (from 17.65 to 11.76%) and in the B1 subgroupby 2.00 (from 11.43 to 5.71%), a decrease in the cystic component, respectively, by 3.50 times (from 20.59 to 5.88%) andby 4.29%. Treatment with Mastopol® led to the disappearence of previously existing ductect as is in 5.88% of women with BBD and mastalgia (Table 3).

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Table 3 The dynamics of the data of sonographyof breast in patients with BBD after treatment with Mastopol®, n (%)

Sonographic form of BBD	**Time of investigation**	**Subgroups**			
		А1 (n=34)	А2 (n=34)	Б1 (n=35)	Б2 (n=35)
Glandular	Before	19 (55,88) б1	17 (50,00) б2	28 (80,00) а1	29(82,86) а2
	after	5(14,71) а2,д	17(50,00) б2	4(11,43) б2,д	29(82,86) а2,б1
Fibro-cystic	Before	6(17,65)	8(23,53)	4(11,43)	5(14,29)
	after	4(11,76)	8(23,53)	2(5,71)	5(14,29)
With cysts	Before	7(20,59)	6(17,65)	3(4,29)	1(2,86)
	after	2(5,88)	6(17,65)	0(0,00)	1(2,86)
Ductectasis	Before	2(5,88)	3(8,82)	0(0,00)	0(0,00)
	after	0(0,00)	3(8,82)	0(0,00)	0(0,00)

Notes. 1. $^{a1, a2, b1, b2}$ – statistically significant differences with indicators of subgroups A1, A2, B1, B2 ($p < 0.05$); 2. ^{d} – statistically significant differences with indicators before treatment; 3. Before, after – before treatment and three months from the start of treatment.

An important clinical effect of Mastopol® was an improvement in personal anxiety indicators due to the neutralization of the effects of psychogenic stress factors (Table 4). After treatment, patients of subgroups A1 and B1 did not exhibit high personal anxiety; its average severity was found in group A1 in 14.71% (5) cases; not one woman was registered in subgroup B1. The number of women with low personal anxiety in subgroup A1 exceeded that in subgroup A2 by 4.83 times (85.29 versus 17.65%; OS 27.07; 95% CI 7.41-98.87), in subgroup B1 the same in subgroup B2 - 1.84 times (100 versus 54.29%; $p < 0.01$).

Table 4 The dynamics of indicators of personal anxiety in patients with BBD after treatment with Mastopol®, n (%)

Personal anxiety	**Time of investigation**	**Subgroups**			
		A1 (n=34)	A2 (n=34)	B1 (n=35)	B2 (n=35)
Low	before	3(8,82) b1	5(14,71) b2	15(42,86) a1	17(48,57) a2
	after	29(85,29) b1,d	6(17,65) b2	35(100) a1,d	19(54,29) a2
Medium	before	16(47,06)	18(52,94)	12(34,29)	14(40,00)

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	after	5(14,71) d	19(55,88)	0(0,00) d	12(34,29)
High	before	15(44,12)	12(35,29)	8(22,86)	4(11,43)
	after	0(0,00) d	9(26,47)	0(0,00) d	4(11,43)

Notes. 1. a1, a2, b1, b2 – statistically significant differences with indicators of subgroups A1, A2, B1, B2 ($p < 0.05$); 2. d – statistically significant differences with indicators before treatment; 3. Before, after – before treatment and three months from the start of treatment.

To assess the effectiveness of Mastopol® as a means to reduce the activity of the processes of regulation of cell proliferation and inflammation, we studied the dynamics of serum levels of cytokines (Table 5).

Table 5 The dynamics of the level of serum cytokines in women with BBD after treatment with Mastopol®, M ± SE, pg / ml.

Cytokines	**Time of investigation**	**Subgroups**				**Control group (n=30)**
		A1 (n=34)	A2 (n=34)	B1 (n=35)	B2 (n=35)	
IL1-β	before	6,30±0,12 c	6,51±0,17 c	6,36±0,17 c	6,29±0,14 c	8,17± 0,22
	after	7,18±0,10 c,a2,d	6,47±0,19 c,a1	7,12±0,13 c,b2,d	6,24±0,11 c,b1	
INF-γ	Before	10,47±0,38 c,b1	10,54±0,22 c,b2	9,20±0,35 c,a1	9,68±0,19 c,a2	6,20± 0,19
	After	7,08±0,34 c,a2,d	10,69±0,42 c,a1	6,86±0,36 b2,d	9,91±0,70 c,b1	
TNF-α	Before	43,97±0,80 c,b1	42,59±1,62 c,b2	37,44±1,30 c,a1	37,04±1,80 c,b2	9,85± 0,47
	After	25,54±0,41 c,a2,d	43,44±2,25 c,a1	24,07±1,33 c,b2,d	39,30±2,40 c,b1	
IL-4	Before	13,40±1,28 c,b1	12,83±0,89 c,b2	12,49±1,15 c,a1	11,16±0,80 c,a2	6,61± 0,25
	After	7,36±0,85 a2,d	13,02±0,98 c,a1	6,58±0,54 b2,d	11,48±0,92 c,b1	
IL-6	Before	23,90±0,60 c,b1	23,63±0,89 c,b2	21,31±0,86 c,a1	21,65±0,99 c,a2	4,73± 0,32

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	After	13,20±0,70 c,a2,d	24,01±1,42 c,a1	11,53±0,77 c,b2,d	22,38±0,70 c,b1	
IL-10	Before	5,67±0,25 c,b1	6,39±0,20 c,b2	6,51±0,24 c,a1	6,58±0,21 c,a2	7,94± 0,21
	After	7,05±0,26 c,a2,d	6,19±0,31 c,a1	7,65±0,27 c,b2,d	6,40±0,21 c,b1	

Notes. 1. $^{a1, a2, b1, b2}$ – statistically significant differences with indicators of subgroups A1, A2, B1, B2 ($p < 0.05$); 2. ^{d} – statistically significant differences with indicators before treatment; 3. Before, after – before treatment and three months from the start of treatment.

According to the table. 4, after the end of treatment with Mastopol® in women with BBD with mastalgia and without mastalgia, positive shifts in the cytokine status occurred, serum INF-γ levels decreased significantly 1.48 and 1.34 times, respectively, TNF-α - 1.72 and 1.56, IL-4 - at 1.82 and 1.90, IL-6 - at 1.81 and 1.85 against increased concentrations of IL1-β by 1.14 and 1.12 times and IL-10 - at 1.24 and 1.18. In women with BBD and mastalgia who received Mastopol®, compared with patients taking placebo, statistically significantly lower levels of INF-γ were recorded 1.51 times 3 months after the start of treatment, and in women with BBD without mastalgia - 1.44 times, TNF-α - respectively 1.70 and 1.63, IL-4 - 1.77 and 1.74, IL-6 - 1.82 and 1.94 and large levels of IL1-β in 1, 11 and 1.14 times and IL-10 1.14 and 1.20.

Homeopathy is known to be an alternative medical system used worldwide [31]. Possible low-dose exposure mechanisms for which there is evidence for nanoparticles and / or homeopathically manufactured drugs include hormesis, time-dependent sensitization, and stochastic resonance. All the proposed mechanisms depend on the endogenous nonlinear amplification processes in the recipient's organism in interaction with the essential, albeit weak signaling properties of the drug. The effects of homeopathically prepared nanophytomedicine preparations include bidirectional changes in body function, depending on the state of the host [16].

The multicomponent homeopathic medicine Mastopol® used in the study is characterized by a wide range of biological effects. The components of plant origin that make up its composition, have a common chemical structure with gonan (the basis of steroids) and, accordingly, affinity for receptors.

Spotted hemlock (Conium maculatum) contains alkaloids - koniin, methylkoniin, conhydrin, pseudocongydrin, konicein; lipids containing glycerides of petrozelinic and petrozelidic acids; essential oil; caffeic acid; flavonoids - campferol and quercetin. The multicomponent combination of biologically active plant substances determines the powerful antiproliferative, antioxidant properties of Conium maculatum. Even in the manuscripts of Ancient Russia, dating from the reign of Yaroslav the Wise, the healing properties of the hemlock were known. It has been famous as a painkiller and for its sedative effect.

Thujaoccidentalis (Thujaoccidentalis) includes active anti-cancer ingredients of the tropolon class, which have a cytostatic effect, that provides the promising application in oncology. The leaves and fruits of the thuja western are sources of phenolic compounds and terpenoids - α-pinene, α-cedrol, Δ^3-karen, which exhibit anti-inflammatory, bacteriostatic, bactericidal, antiseptic, and disinfectant effects.

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Canadian yellow root (Hydrastis canadensis) contains isoquinoline alkaloids - berberine (causing yellow color), hydrastin and canadines - as well as trace elements, vitamins C, B, A and E, bitterness, essential oils, etc. Due to the high concentration of alkaloids and essential Hydrastis canadensis oils has a pronounced anti-inflammatory effect, affects the classes of T-lymphocytes. Canadian yellow root is a classic means of resorption and is traditionally used in homeopathy for breast sealing.

Calcium fluoratum (calcium fluorate, raw materials - fluorspar, calcium fluoride) is actively used in homeopathic medicines for hypothyroidism, obesity, metabolic disorders, nervous and mental disorders, as well as to reduce the risk of cancer, supports and increases the elasticity of connective tissues and ligaments, strengthens the walls of the vessels of the breast [6, 8, 10, 17, 19, 26, 28, 30].

The antiproliferative and antitumor effect of the drug components has been confirmed in a number of works recently. Thujaoccidentalis has been published to have the antitumor effect, as well as the anticancer and antimetastatic effects of Conium maculatum and Hydrastis canadensis [10, 17, 19, 26, 28, 30, 33].

M. Frenkel et al. (2010) [21] studied four ultra-diluted plants (Conium, Thuja, Carcinosin, Phytolacca) against two human adenocarcinoma cell lines (MCF-7 and MDA-MB-231) and cell lines obtained from immortalized normal breast epithelial cells (HMLE). The drugs exerted predominantlya cytotoxic effect against cancer cell lines, caused a delay / stop of the cell cycle and apoptosis. These effects were accompanied by altered expression of cell cycle regulatory proteins, including the suppression of phosphorylated Rb and activation of the CDK p27 inhibitor, which were probably responsible for the delay / stop of the cell cycle, as well as for the induction of the apoptotic cascade, which was manifested in caspase-7 activation and PARP cleavage (poly (ADP-ribose) polymerase), an enzyme that catalyzes the post-translational modification of proteins in treated cells. The data obtained demonstrate the biological activity of these natural products in ultra-low doses [21].

Hydrastis canadensis contains berberine, well known for its anti-inflammatory, lipid-modifying, antitumor, antidiabetic, antibacterial, antiparasitic and fungicidal activities. The multiple pharmacological effects of berberine stem from various molecular targets of this phytochemical compound. S.H. Ayati et al. (2017) [15] proved that berberine regulates miRNA expression in several oncological and non-oncological diseases. It is known that microRNAs are important regulatory elements in almost all biological processes, such as cell proliferation, apoptosis, differentiation and organogenesis, and numerous human diseases, such as cancer and diabetes.

The proven fact is that the use of berberine with the chemotherapeutic drug cisplatin sensitizes MCF-7 breast cancer cells to cisplatin by inducing DNA breaks and caspase-3-dependent apoptosis, restricts the expression of cellular PCNA and increases the DNA damage caused by cisplatin [34].

J. A. McCubrey et al. (2017) [25] indicate that a key target of exposure to natural products may be the regulation of the PI3K / PTEN / Akt / mTORC1 / GSK-3 pathway. Using berberine can improve their use as an antiproliferative agent, which can be beneficial for many health problems.

According to the results, in the groups of patients receiving placebo, after the given observation period (3 months), there were no significant changes in the clinical signs of BBD, neuropsychological status, sonographic

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characteristics of the disease, and cytokine levels. Regression of the disease or individual symptoms did not occur in any of the patients; in 2 patients with mastalgia, increased sensitivity of the breast after 3 months turned into painful sensations.

Summarizing the results obtained during this study, it should be emphasized the positive effect when using Mastopol® for the treatment of pain and painless forms of BBD in women of reproductive age. This is manifested by a decrease in the intensity of the clinical signs of BBD, which coincides with the results of sonographic monitoring and changes in cytokine levels. Thus, the use of Mastopol® is aimed both at the pathogenetic treatment of BBD and the prevention of breast cancer. No side effects were observed during the treatment. There were no refusals from taking the drug.

VI. CONCLUSION

The use of the multi-component non-hormonal drug Mastopol® in the treatment of BBD in women of reproductive age significantly improves the clinical condition of patients and restores the sonostructure of the breast, reduces the subjective and objective symptoms of the disease, improves the cytokine status of patients. Mastopol® may be the medicine of choice for conservative monotherapy in women of reproductive age with BBD, with or without mastalgia. High drug compliance is due not only to proven clinical efficacy, but also to exceptional safety, good tolerance and ease of use.

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