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Therapeutic Effect of Bromocriptine as a Dopamine Agonist on Endometrioma Size: A Double-Blind Randomized Controlled Trial

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Abstract

Objectives: This study aimed to assess the therapeutic effect of a dopamine agonist (bromocriptine) together with medroxyprogesterone for three months on ovarian endometrioma size.

Materials and Methods: In this double-blind randomized clinical trial, 60 women with clinical or ultrasonographic evidence of residual ovarian endometriomas were randomly assigned into two groups (n=30/each): the Bromo group received medroxyprogesterone (20 mg) and bromocriptine (1.25 mg) twice a day orally for three months and the placebo group received medroxyprogesterone (20 mg) and placebo twice a day orally for three months. Demographic characteristics, pre- and post-treatment endometrioma size, pelvic pain, dysmenorrhea, and dyspareunia were compared in both groups.

Results: Mean endometrioma size was significantly different in both groups compared with the pre-treatment stage ($P<0.0001$). Endometriosis symptoms of dysmenorrhea, dyspareunia, and pelvic pain improved after the treatment in Bromo group compared with placebo group ($P<0.01$).

Conclusions: We found that medroxyprogesterone with placebo is effective in reducing the ovarian endometrioma size and also improves dysmenorrhea, dyspareunia, and pelvic pain, but the combination of medroxyprogesterone and bromocriptine has a stronger effect than using medroxyprogesterone alone.

Keywords: Ovarian endometrioma, Dysmenorrhea, Dyspareunia, Pelvic pain, Bromocriptine

Introduction

Endometriosis is a gynecological disorder characterized by the presence of endometrial tissue, including glands and stroma in extra-uterine sites, most commonly in the ovaries and peritoneum (1,2). Ovarian endometriomas occur in 17%-44% of women with endometriosis (3) and affect their quality of life, work efficiency, and sexual life (4). The most common symptoms of endometrioma are severe pelvic pain, dysmenorrhea, dyspareunia, and infertility (5). Endometrioma has multifactorial causes, including genetic, environmental, and hormonal (especially estrogen) factors and alteration in the immune system (6,7). Histological examinations have shown the presence of blood vessels and the vascularized area around the endometriotic lesions, suggesting that angiogenesis plays an essential role in the development and continuation of endometriotic lesions (8). In animal models of endometriosis, several antiangiogenic agents target the angiogenesis pathway, and they have been used successfully to disrupt the endometrial vasculature (9).

Dopamine receptor agonists have recently been studied to disrupt the blood supply to endometriosis lesions (10,11). The development, maintenance and progression of endometriosis is due to various altered mechanisms including cell proliferation, immune function, apoptosis, and angiogenesis(12) The growing knowledge of the various molecular pathways involved in the development of endometriosis paves the way for the investigation of new drugs (13,14). So, the purpose of this study was to evaluate the effect of bromocriptine, as a dopamine agonist, on ovarian endometrioma size and its clinical symptoms.

Materials and Methods

Study Design and Participants

In this double-blind randomized clinical trial, 60 women with clinical or ultrasonographic evidence of residual ovarian endometriomas referred to the Ghadir Mother and Child Hospital, Shiraz, Iran from December 2020 to February 2021 were enrolled. The exclusion criteria were hyperprolactinemia, coagulation disorders, and having contraindications to medroxyprogesterone.

Interventions

The participants were randomly assigned into two groups: the Bromo group received 40 mg/day medroxyprogesterone (Abu Reihan Pharmacy, Iran) and

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Key Messages

- Combination therapy with medroxyprogesterone and bromocriptine reduces ovarian endometrioma size.
- Combination of medroxyprogesterone and bromocriptine relief pain in women with endometrioma.
- The combination of medroxyprogesterone and bromocriptine has a better effect on the endometriosis symptoms than medroxyprogesterone alone.

1.25 mg of bromocriptine twice a day (Minoo Co. Iran), orally for three months and the placebo group received medroxyprogesterone (40 mg/d, orally) and the placebo (prepared by Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran) twice a day for three months.

Outcomes and Data Collection

Pre- and post-treatment assessments of endometrioma size were performed by ultrasonography. The impact of this treatment on pelvic pain, dysmenorrhea, and dyspareunia was assessed by using a visual analog scale (VAS), which was a 10 cm ruler with 11 grades as follows: 0 (no pain), 1-3 (mild pain), 4-7 (moderate pain), and 8-10 (severe) pain. This scale has adequate validity and reliability (12).

Sample Size

Due to the lack of the similar research, the sample size was estimated to be minimum of 60 (30 in each group) by considering $\alpha = 0.05$, power 80%, and acceptable difference, based on our pilot study

Randomization

To conceal the random allocation process, 60 treatment cards were written in sequential order, then the cards were placed in sealed envelopes. On each envelope, a random code was written with no sequences that only the methodologist was aware of the code. When the physician announced a participants' eligibility, the methodologist provided the envelope. The person who evaluated the final outcomes was unaware of the random allocation process and the type of treatment performed. Data were analysed by a statistical expert who was separated from the study process and unaware of all the processes performed.

Data Analysis

All data were evaluated using descriptive statistics (i.e., mean, standard deviation, frequency, and percentage). The Student *t* test was used to compare the quantitative data. The normal distribution of data was assessed by the Kolmogorov-Smirnov and chi-square tests. Data were analyzed by the Statistical Package for the Social Sciences software (SPSS, version 20.0 for Windows; SPSS Inc., Chicago, IL). A *P* value of < 0.05 was considered statistically significant.

Results

Initially, 80 women were eligible to enter the study. Out of them, 20 women were excluded due to having coagulation disorders (n = 6) and hyperprolactinemia (n = 6), also declined to continue participating in the study (n = 8). Finally, a total of 60 women aged 18 to 45 years (median age 31 years) were assigned to two groups (n=30/each), and their data were analyzed (Figure 1).

There were no statistically significant differences between the two groups in demographic characteristics, such as age, body mass index (BMI), gravidity, live birth rates, and endometrioma size (Table 1). The endometrioma size in the placebo and Bromo groups

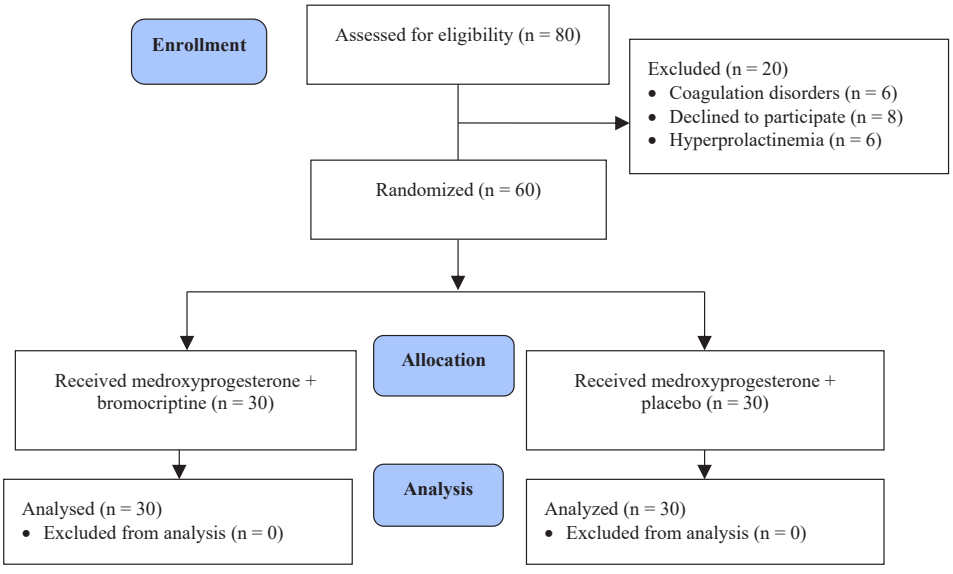

Figure 1. The Consort Flow Chart of the Study.

was 54.4 ± 14.79 mm and 51.67 ± 13.75 mm, respectively. After the 3-month treatment, mean endometrioma size significantly decreased in the both group ($P<0.0001$). Also, pelvic pain, dysmenorrhea, and dyspareunia significantly decreased compared with pre-treatment in two groups and in any of the participants, the score of 8-10 was not observed (Table 2). As well as, we did not find any significant differences between the two groups after treatment in the Endometrioma size and pain symptoms (Table 3).

Discussion

Ovarian endometriomas occur in 17%-44% of women with endometriosis. Studies have shown estrogen stimulates the growth of endometriosis and increases the risk of disease (15,16). On the other hand, studies have reported that patients with endometriosis have high levels of angiogenic and proteolytic factors (17). Therefore, the pathogenesis and treatment of endometriosis is controversial and a challenge for the health care system (13,14). Some studies on endometriosis have examined the effect of medroxyprogesterone to partially or fully suppress estrogen (15,16) and dopamine agonists to inhibit angiogenesis (19-17). In this study, the effects of both medroxyprogesterone and bromocriptine on size and clinical symptoms of ovarian endometrioma were investigated. We found that medroxyprogesterone is effective for ovarian endometrioma, and the combination of medroxyprogesterone and bromocriptine has a stronger effect than the single medication. The results of this study showed that the mean endometrioma size was significantly different in both groups compared with

Table 1. Comparison of Demographic Characteristics between Two Study Groups (n=30/each)

Variables	Bromo Group	Placebo Group	*P* Value
Age (y), mean ± SD	31.6 ± 4.7	31.9 ± 4.5	0.82[a]
BMI (kg/m^2), mean ± SD	25.1 ± 3.4	25.1 ± 2.5	0.98[a]
Endometrioma size, mean ± SD	54.40±14.7	51.76±13.7	0.47[a]
Gravidity, No. (%)			
0	9 (30.0)	6 (20.0)	0.78[b]
1	10 (33.3)	10 (33.3)	
2	7 (23.3)	8 (26.7)	
≥ 3	4 (13.3)	6 (20.0)	
Live birth, No. (%)			
0	9 (30.0)	6 (20.0)	0.61[b]
1	10 (33.3)	10 (33.3)	
> 2	11 (36.7)	14 (46.7)	

[a] Independent t test; [b] Chi-squared test.

Table 2. Comparison of the Endometrioma Size, Pelvic Pain, Dysmenorrhea, and Dyspareunia in Two Study Groups Before and After Treatment

Outcomes	Placebo Group (Before Treatment)	Placebo Group (After Treatment)	Bromo Group (Before Treatment)	Bromo Group (After Treatment)
Endometrioma size (mm), mean ± SD	54.40±14.7	36.16 ±10.0	51.76±13.7	32.40±9.0
P value[a]	<0.001		<0.001	
Pelvic Pain, No. (%)				
Absent	5 (16.7)	8 (26.7)	3 (10.0)	11 (36.7)
Mild (1-3)	5 (16.7)	15 (50.0)	5 (16.7)	16 (53.3)
Moderate (4-7)	13 (43.3)	7 (23.3)	18 (60.0)	3 (10.0)
Severe (8-10)	7 (23.3)	0 (0.0)	4 (13.3)	0 (0.0)
P value[b]	0.013		0.003	
Dysmenorrhea, No. (%)				
Absent	0 (0.0)	3 (10.0)	0 (0.0)	4 (13.3)
Mild (1-3)	0 (0.0)	18 (60.0)	0 (0.0)	14 (46.7)
Moderate (4-7)	14 (46.7)	9 (30.0)	11 (36.7)	12 (40.0)
Severe (8-10)	16 (53.3)	0 (0.0)	19 (63.3)	0 (0.0)
P value[b]	0.014		0.01	
Dyspareunia, No. (%)				
Absent	6 (20.0)	8 (26.7)	6 (20.0)	7 (23.3)
Mild (1-3)	3 (10.0)	14 (40.7)	1 (3.3)	13 (43.3)
Moderate (4-7)	11 (36.7)	8 (26.7)	10 (33.3)	10 (33.3)
Severe (8-10)	10 (33.3)	0 (0.0)	13 (43.3)	0 (0.0)
P value[b]	0.002		0.001	

[a] Paired *t* test; [b] Kappa test.

Table 3. Comparison of the Endometrioma Size and Pain Symptoms in Two Study Groups Before and After Treatment

	P Value[a]			
	Placebo Group (Before Treatment)	Bromo Group (Before Treatment)	Placebo Group (After Treatment)	Bromo group (After Treatment)
Endometrioma size	0.47		0.13	
Pelvic pain	0.54		0.34	
Dysmenorrhea	0.43		0.58	
Dyspareunia	0.69		0.85	

[a] Chi-squre test.

pre-treatment ($P<0.001$) (Table 1). Also, we did not find any significant differences between the two groups after treatment in the Endometrioma size and pain symptoms (Table 3). Ercan and co-workers indicated that dopamine agonists are effective in the regression of endometriotic implants in rats, and after treatment, the endometriotic surface areas are significantly reduced. They also suggested that dopamine agonists are useful therapeutics, most likely by acting through a mechanism that reduces angiogenesis (9). Gómez and colleagues described a reduction in the size of human peritoneal endometriotic lesion by repeated laparoscopy of same patients after dopamine agonist administration (18). Other studies in a murine model, demonstrated that treatment with a dopamine agonist reduces the number of immature blood vessels and endometriosis-related nerve fiber and the size of the endometriotic (11,19,20). These findings are in line with our results. A study was carried out on the effect of cabergoline as a dopamine agonist on endometrioma size. They observed a significant decrease in 64.7% of subjects treated with cabergoline. The impact of cabergoline was attributed to an antiangiogenic effect through the inactivation of vascular endothelial growth factor receptor-2 (21). More than 60% of the women in both groups before treatment had experienced pelvic pain. Women who reported an increase in pain pelvic were also more likely to report dysmenorrhea, dyspareunia. In the present study, pelvic pain, dysmenorrhea, and dyspareunia significantly decreased compared with pre-treatment, and severe pelvic pain, dysmenorrhea, and dyspareunia disappeared after treatment in all patients. Also, in the present study, after three months of treatment, pelvic pain, dysmenorrhea, and dyspareunia showed a decrease in the Bromo than the placebo groups; however, this difference was not significant (Table 3). Erkayıran et al showed a reduction in the visual analog scale score for pelvic pain, dysmenorrhea, and dyspareunia after using medroxyprogesterone in women with myoma (22). Some studies have suggested that dopamine agonists such as bromocriptine, cabergoline, and quinagolide may reduce lesion size and can be used to relieve pain in women with endometriosis (9,23). Finally, our suggestions were presented for future studies on the effect of dopamine agonists in the treatment of endometriosis in a different part of the pelvis.

Limitations of the Study

Limitations of the study include a small sample size and a retrospective study design, the low accuracy in estimating endometrioma size and the relatively short follow-up, which did not allow us to draw definitive conclusions.

Conclusions

We found that medroxyprogesterone with placebo is effective in reducing the ovarian endometrioma size and also improves dysmenorrhea, dyspareunia, and pelvic pain, but the combination of medroxyprogesterone and bromocriptine has a stronger effect than using medroxyprogesterone alone.

Authors' Contribution

TP conceived and designed the evaluation and drafted the manuscript. MP participated in designing the evaluation, performed parts of the statistical analysis and helped to draft the manuscript. EH re-evaluated the clinical data, revised the manuscript and performed the statistical analysis and revised the manuscript. EA collected the clinical data, interpreted them and revised the manuscript. AKH re-analyzed the clinical and statistical data and revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interests

Authors have no conflict of interest.

Ethical Issues

The study proposal was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (Code: IR.SUMS.REC.1399.979) and registered in the Iranian Registry of Clinical Trials (identifier: IRCT20140802018655N6). All participants signed a written informed consent form before entering the study.

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