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Effectiveness of Cabergoline in Comparison with Control in Women with Fibroids Uterus: A Randomized Clinical trial

Marzieh Vahid Dastjerdi, Afsaneh Tehranian, Sare Hatamian, Lida Tozande jani and Akram Ghahghaei-Nezamabadi*

Department of Obstetrics and Gynecology, Arash Women's Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

*** Corresponding author**

Akram Ghahghaei-Nezamabadi, MD
Department of Obstetrics and Gynecology, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 777 10090
Email: agna57@yahoo.com

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Abstract

Background: Uterine fibroids are one of the most common benign tumors that cause abnormal bleeding and pain in women of reproductive age. One of the objectives of this study is to evaluate the effect of cabergoline drug on the size and volume of uterine bleeding as well as menopausal symptoms in women with uterine myomas.

Methods: This double-blind clinical trial was conducted among 80 women with fibroid myomas and Abnormal Uterine Bleeding (AUB). The participants were allocated to two groups after random allocation. Group I received Cabergoline, 1 tablet (0.5 *mg*/w) orally once a week for 3 months. Group II obtained a placebo tablet (0.5 *mg*/w), taken at the same time.

Results: 80 patients were included in the study (40 patients in the control group and 40 patients in the cabergoline treatment group). No statistically significant difference was observed between the two groups in terms of age, number of pregnancies, number of births, body mass index, uterine myoma characteristics, myoma type, myoma volume, and myoma number. A 37% decrease in myoma size was observed in the cabergoline recipients, as well as a 25% decrease in the placebo group, which is not statistically significant (p-value >0.05).

Conclusion: Cabergoline drug reduces the volume of bleeding and the number of uterine myomas, but this reduction is not statistically significant and requires more studies in this field.

Keywords: Cabergoline, Leiomyoma, Menopause, Myoma, Pain, Uterine hemorrhage

Introduction

Uterine fibroids (leiomyomas or myomas) are the most common benign tumors affecting women during their reproductive years, which can cause significant health issues (1). The etiology of uterine myomas is still unknown; however, hormones such as estrogen and progesterone affect this disease (2,3).

Since uterine fibroids usually do not occur before menstruation and their size significantly decreases after menopause, it is assumed that the growth of uterine fibroids is dependent on estrogen (1). Several clinical studies have shown that progesterone stimulates the growth of uterine fibroids, while anti-progestin has the opposite effect. The exact mechanism of how these drugs affect uterine fibroids has not yet been determined, but it is believed that sex hormones regulate the growth of uterine fibroids by influencing apoptosis and cell proliferation in the fibroid tissue (4,5).

Several factors influence the choice of treatment for uterine fibroids, such as the severity of symptoms, the patient's age, and their desire for pregnancy. Treatment options for fibroids include surgical, radiological, and medical interventions, as well as monitoring. Considering that fibroids are the most common type of tumor in women of reproductive age, with a prevalence of 70-80% during the reproductive years and symptomatic in 20-40% of women over 35, patients with fibroids may present abnormal uterine bleeding, anemia, pelvic pain or pressure, urinary symptoms, and rarely, some adverse reproductive outcomes, such as recurrent pregnancy loss, preterm delivery, placental abruption, mal presentation, and growth restriction (2,6-8). Therefore, fibroids can have significant physical, emotional, social, and financial implications for an individual, and they can also impact their overall quality of life (9,10). The definitive treatment for patients with uterine fibroids is surgery. However, due to advanced age or being in their first pregnancy, hysterectomy may not be a suitable option for everyone with fibroids. Therefore, the discussion regarding interventions to preserve the uterus has increased in the past 20 years.

Various drugs have been tested in this regard, including agonists and antagonists of gonadotropin-releasing hormone. Dopamine agonists, on the other hand, do not have the ability to treat fibroids but may help control their symptoms (11).

One of the other drugs that has been suggested for symptom control of fibroids is cabergoline. Cabergoline is a dopamine receptor agonist and can reduce prolactin secretion. Prolactin is one of the hormones that affects fibroid growth and is secreted by pituitary cells and uterine cells. It can act as a growth hormone in an autocrine and paracrine manner on the myometrium. Therefore, prolactin-lowering agents such as dopamine agonists can inhibit fibroid growth and be accompanied by a reduction in fibroid symptoms (2,6). However, studies in this regard are limited. Therefore, this study was designed with the aim of determining the effect of cabergoline on fibroid size and uterine bleeding in individuals with uterine fibroids.

Material and Methods

This randomized controlled clinical trial was conducted from April to March 2020 at Arash Teaching Hospital , at Tehran University of Medical Sciences, Iran. The study was registered at the Iranian Registry of Clinical Trials (www.irct.ir, IRCT20170917036227N4, Registered 2019-04-02, prospectively registered 2020-03-19) and approved by the Ethics committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1397.279). Written informed consent was obtained from the patients.

In this clinical trial, a randomized, double-blind study was conducted to investigate the efficacy of a treatment for uterine fibroids in women experiencing abnormal uterine bleeding and pelvic pain, who sought care at the women's clinic of Arash Hospital. In this study, the patients aged between 20-50 years old who had a myoma with a size of 3 to 8 *cm* confirmed through ultrasound, abnormal uterine bleeding and pelvic pain were included in the study. Also, the participants who were post-menopausal, had a pedunculated myoma, recieved hormonal treatments during the past 6 months, or suffering from any underlying serious diseases such as diabetes and liver disorders were not recruited. Also, people who had a desire for myomectomy were not included. First, the demographic and fertility information was recorded. Then, all the participants underwent abdominal ultrasound performed by a single sonographer.

Myoma data including type of myoma (intramural, subserosal, submucosal), number, and maximum diameter and volume of the myoma (depth in *cm* multiplied by width in *cm* multiplied by 0.25) were documented. Additionally, the volume of bleeding was estimated based on the number of sanitary pads used and the number of days of bleeding. Afterwards, the patients were randomly assigned using simple randomization list to either the intervention or placebo group. In the intervention group, Cabergoline tablets 0.5 *mg* (Dostinex, manufactured in Italy with the generic code 00562) were prescribed once a week for a duration of 3 months.

The placebo group received a weekly oral dosage of one tablet consisting of starch and cellulose, which appeared similar to Cabergoline. After 3 months, the study participants underwent abdominal sonography to measure the volume, diameter, and number of myomas. The amount of bleeding was recorded based on the number of pads used and the number of bleeding days. Menopausal symptoms such as facial flushing, night sweats, and general sweating, as well as potential drug side effects, were also documented. Then, the rate of reduction in the size of uterine fibroids was compared between the two comparison groups.

T-test (or its non-parametric alternative Mann-Whitney when the assumption of normality was not met) was utilized to compare the results between the two groups. SPSS version 19 was used to analyze the data and considered p-values less than 0.05 as a significant difference.

Results

In this study, 40 individuals were enrolled in the cabergoline group and 40 individuals were enrolled in the placebo group. The mean age in the cabergoline group was 2.1±43.6, and in the control group, it was 2.2±43.8. The mean BMI in the cabergoline group was 2.5±28.6, and in the placebo group, it was 2.2±28.9. There were no significant differences between the two groups in terms of other variables (all p>0.05) (Table 1).

Intramural Myomas had the highest frequency in two groups (Cabergoline 47.5%, placebo 62.5%). The average volume of myomas in the cabergoline 38.5±1.01 and placebo groups 38.8±1.04 was in order.

Table 1. Characteristics of the two groups

	Cabergoline/case group (N=40)	Placebo (40)	p-value
Age (year) (M±SD)	43.6±2.1	43.8±2.2	0.609
BMI (kg/m^2) (M±SD)	28.6±2.5	28.9±2.2	0.860
Gravity (M±SD)	2.42±0.8	2.45±0.6	0.734
Parity (M±SD)	1.8±0.6	2.1±0.6	0.160

BMI: Body Mass Index

Additionally, the number of myomas was also present in cabergoline group 2.27±0.7 and placebo 2.57±0.9. Two groups demonstrated no significant differences in terms of myoma characteristics (Table 2).

After 3 months, a reduction in myoma size was observed in 37% of the cabergoline recipients, while it was observed in 25% of the placebo group. Duration of bleeding after treatment, number of myomas and menopausal signs had no significant differences (p>0.05).

Discussion

In the present study, myomas volume, number of myomas, and menopausal sign had no significant differences between women who used cabergoline and control groups. This finding was in contrast with the study conducted by Vahdat (2). Definite treatment for patients with Uterine Fibroids is usually conducted through surgery. In some cases, surgery to remove the fibroids (myomectomy) is performed, while in other cases, uterine surgery (hysterectomy) may be proposed by the way women are eager to preserve their potential fertility and therefore prefer to use medical treatments instead of surgery. Although the initiative myomas growth mechanism is unknown (2), many factors affected this process. Estrogen and progesterone in this cycle are very well known contributors (12). In different myometrium tissues, prolactin receptors had been identified. In some tissues, prolactin can act as a growth hormone. A contradiction has been observed between the findings regarding the effect of prolactin on myoma

Table 2. Comparison between two groups

		Cabergoline	Placebo	p-value
Type of myomas	Intra molar	19(47.5)	25(62.5)	0.322
	Submucosal	13(32.5)	10(25)	
	Sub serosa	8(20)	8(20)	
Myomas volume		38.5±1.01	38.8±1.04	0.344
Number of myomas		2.27±0.7	2.57±0.9	0.112
Fibroma size reduction		15(37.5%)	10(25%)	0.337
No difference		25(62.5%)	30(75%)	
Menopausal signs (before)				0.401
Flushing		10(25%)	2(5%)	
Insomnia		3(7.5%)	2(5%)	
Headache		2(5%)	6(15%)	
Nausea		11(27.5%)	3(7.5%)	
Vomiting		4(10%)	10(25%)	
Overall		10(25%)	17(42.5%)	
Menopausal signs (after)				0.368
Flushing		0	2(5%)	
Insomnia		3(7.5%)	0	
Headache		2(5%)	6(15%)	
Nausea		5(12.5%)	1(2.5%)	
Vomiting		9(22.5%)	16(40%)	
Overall		21(52.5%)	15(37.5%)	

tissue. By the way, cabergoline was identified as dopamine agonist and lysergic acid derivative was used for hyper prolactinemia treatment and improved the symptoms of myomas by inhabitation of GnRH releasing. Reports on the effectiveness of cabergoline for the treatment of uterine myomas are limited in the medical literature.

The results of the study conducted in 2017 among 76 women treated with cabergoline and letrozole for the treatment of uterine myoma regression, showed that the volume of myoma decreased significantly in both groups, but this difference was not statistically significant (6). Considering the present study's data and the results of other studies, it is concluded that the use of cabergoline had no significant effect on the side effects. In addition, headache was more common in the present study (35%), whereas the rate of flushing and insomnia were lower. It noteworthy that in the present study, cabergoline and placebo were used to determine whether or not they were effective. As in the authors previous study, two medication of cabergoline and differeline, letrozole were compared in terms of their effect on the growth of uterine myomas. Accordingly, cabergoline was effective similar to other GnRH agonist for reducing the size of uterine myomas. The effectiveness of cabergoline in inducing regression of uterine myomas was confirmed by both studies (13).

In addition, in Elbareg *et al'*s study (14), it was found that cabergoline 0.5 *mg/week* and goserelin reduced large uterine myomas significantly in both groups, with no significant difference between them. Side effects, however, were less common in the cabergoline group. The decrease in myoma size was 39–58% in the cabergoline group. It was concluded that due to a lower rate of complications with cabergoline

and comparable therapeutic outcomes of the two medications, cabergoline could be used as a surrogate for GnRH agonists. To the authors' knowledge, this is the first study to compare the therapeutic effect of cabergoline and placebo in patients with uterine myomas. Further studies are required to reach a definite conclusion on the role of hormonal therapies for women with fibroids, particularly add-back options. Limitations of this study were the long course of treatment to control bleeding, being single centre, and small sample size.

Conclusion

This study found that 6 weeks of treatment with cabergoline was no significant difference between two groups in terms of volume of uterine myomas , the number of uterine myomas and changes in uterine volume. The side effects were negligible, although headache was more common with cabergoline.

Conflict of Interest

Authors declare no coflict of interest.

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