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Comparing the effect of aromatase inhibitor (letrozole) + cabergoline (Dostinex) and letrozole alone on uterine myoma regression, a randomized clinical trial

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ABSTRACT

Objective: To evaluate the effect of letrozole in combination with cabergoline and letrozole alone on regression of symptomatic uterine myomas in women of reproductive age.
Design: Randomized controlled clinical trial.
Setting: University hospital.
Patients: Ninety-one women of reproductive age were enrolled in the study and 88 women were eligible. Eight participants were excluded from the study.
Interventions: Eighty women of reproductive age with symptomatic myomas >4 cm were evaluated in two groups. Participants in Group 1 received 2.5 mg letrozole once daily and cabergoline 0.5 mg/week from the first day of the menstrual cycle for 12 weeks, and participants in Group 2 received letrozole alone.
Main outcome measures: Changes in uterine size and volume; myoma size, volume and number; and side effects of treatment.
Results: Overall, 76 patients completed the study. Compared with baseline values, mean uterine volume was reduced significantly in both groups ($p = 0.01$), and there was no significant difference between groups ($p = 0.99$). The mean number of dominant myomas was reduced significantly in both groups ($p = 0.03$), with no significant difference between groups ($p = 0.6$). The mean volume of myomas was reduced significantly in both groups ($p = 0.01$), with no significant difference between groups ($p = 0.45$). Although a significant decrease in number and volume of myomas was documented in each group ($p < 0.05$), the intergroup analyses did not reveal significant differences between the two groups in terms of the change in number ($p = 0.28$) and volume ($p = 0.96$) of myomas. Headache was significantly more common in the letrozole + cabergoline group (nine vs two cases, $p = 0.02$), but the two groups were comparable for the remaining minor side effects.
Conclusion: This study showed that 12 weeks of treatment with letrozole with and without cabergoline improved the size and volume of the uterus and myomas, led to symptom improvement, and could be used for short-term treatment prior to surgery or fertility programmes.
Condensation: Condensation letrozole in combination with cabergoline in the management of uterine fibroids.

Introduction

Uterine myomas are the most common benign gynecological tumours [1–3]. Although the exact aetiology is not well established, it appears to be due to the influence of several risk factors. There is evidence suggesting the role of oestrogen and progesterone [1]. The risk factors include increasing age, black ethnicity, early menarche, nulliparity, obesity, inactivity, alcohol consumption, caffeine use, stress, family history and environmental factors [2].

The strategy for treating uterine myomas usually relies on the severity of symptoms, size and location of the myoma, patient's age, proximity of menopause and patient's desire for pregnancy. Approximately 40% of patients need medical/surgical intervention [1–3]. Current treatments for uterine fibroids include a variety of surgical techniques. The therapeutic options include monitoring of patients, medical treatments, and less invasive surgical and radiological approaches [4,5]. Medical treatment is the only

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short-term option at present, and this could be developed to provide alternatives to surgical intervention [6].

Various medications have been tried in this regard, including gonadotropin-releasing hormone (GnRH) agonists and antagonists [7,8], dopamine agonists [9,10], aromatase inhibitors [11,12], antiprogestins [13,14], specific modulators of oestrogen and progesterone receptors [15–17], intrauterine progesterone releasing systems [18], danazol [19], gestrinone [20], vitamin D [21], progestins [22] and herbal agents [23].

Aromatase inhibitors prevent the production of ovarian and environmental oestrogens through a mechanism that involves inhibition of aromatase enzymes and prevention of the conversion of androgens to oestrogen [24]. In previous studies, letrozole was able to decrease the size of myomas, uterine bleeding and dysmenorrhoea with fewer common complications than the problems associated with GnRH agonists [11,24].

Cabergoline, a dopamine agonist, is also used for treating myomas [9]. Although the definitive treatment in patients with uterine myomas is surgical, this may be associated with complications and loss of fertility.

This study aimed to compare the effects of an aromatase inhibitor (letrozole) plus cabergoline with letrozole alone on the growth of uterine myomas.

Materials and methods

This randomized controlled clinical trial was conducted from April 2015 to March 2016 at Alzahra Teaching Hospital, Tabriz University of Medical Sciences, Iran. The study was registered at the Iranian Registry of Clinical Trials (www.irct.ir, No. IRCT201506205283N12), and written informed consent was obtained from patients. The Ethics Committee of Tabriz University of Medical Sciences approved this study (Ref. No. TBZMED. REC.1394.264). Ninety-one participants with one to five uterine submucosal or intramural myomas between 4 and 10 cm who were candidates for myomectomy due to fibroid-related problems [e.g. excessive and heavy menstrual bleeding (>80 cm^3 and/or menstrual bleeding that lasted for >7 days) or irregular menstrual bleeding (such as periods that occur <21 days apart or last for >7 days), pain or pressure in the pelvis, or problems with pregnancy or infertility] were enrolled, and 88 of them were eligible. Finally, 80 patients were randomized (Fig. 1).

Parsanezhad et al. [11] found that letrozole decreased the size of myomas in 45.6% of their patients, and Sayyah-Melli et al. [9] reported that cabergoline led to a 46–53% reduction in the size of myomas. Thus, using Power and Sample Size Calculation software, based on a 45% reduction in the volume of myomas in the letrozole + cabergoline group and a further 12% reduction in the letrozole group, and comparing the letrozole + cabergoline group with 80% power, 38 cases were calculated for each group, resulting in a total of 76 cases. This figure was augmented to 80 cases to allow for possible dropouts. The patients were randomized using Rand Version 2.1 (DatInf GmbH, Tübingen, Germany) with sequentially numbered containers in two groups receiving either letrozole + cabergoline or letrozole alone.

The exclusion criteria were age >45 years, fibroids >10 cm, more than five fibroids, fibroids with subserosal location, a positive history of abnormal endometrial or cervical pathology, uterine infection, renal disease, hepatic disease, pregnancy-related toxaemia, cardiovascular disease, peptic ulcer, use of antipsychotic medications, receipt of oestrogen and progesterone in the last month, a hormone-based implant in the last 3 months, and previous history of medical/surgical treatment for uterine myomas.

After patients' demographic characteristics were recorded, Group 1 received letrozole 2.5 mg/day (Letrofem, Iran Hormone, Tehran, Iran) orally from the first day of the menstrual cycle and cabergoline 0.5 mg/week (Dostinex, Pharmacia, and Upjohn SPA, Milan, Italy) orally for 12 consecutive weeks. Group 2 received letrozole alone.

All patients were checked for changes/improvement in uterine bleeding in terms of amount, duration, frequency and blood tests to rule out anaemia. In addition, all patients were evaluated for headache, flushing, nausea, vomiting and musculoskeletal tenderness/pain.

Uterine size, and number and size of uterine myomas were determined before and at the end of interventions using

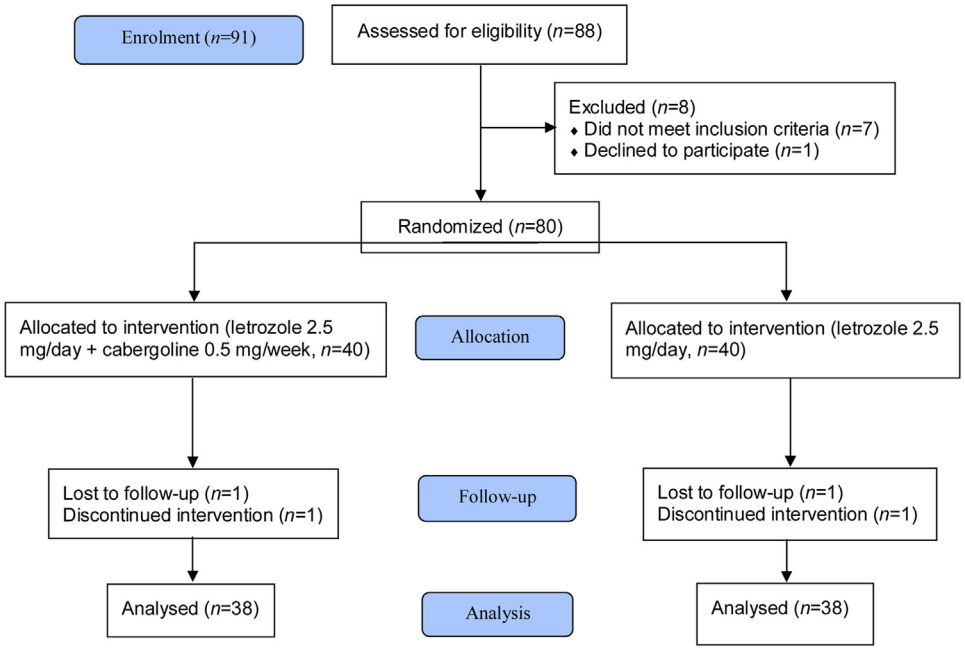

Fig. 1. Consort flowchart of study population.

transvaginal (6.5 MHZ) or transabdominal (3.5 MHZ) ultrasonography. The volume of myomas was calculated using the eclipse formula (R1.R2.R3/0.52), in which R1 is width, R2 is anteroposterior diameter and R3 is length of the tumour. The sonographer was blinded to patient group. In patients with more than one myoma, the largest one was included in the analysis. All patients received ferrous sulphate 60 mg/day. Haematocrit levels were checked before and 1 week after the interventions. Follow-up visits were performed 1 week after completion of treatment. Patient satisfaction was checked using a Likert checklist.

Two out of 40 patients were excluded in the letrozole + cabergoline group: one case was excluded due to musculoskeletal pain, headache, severe haemorrhage and oedema of the lower extremity 1 month after starting treatment, and another case was excluded because of failure to follow-up. Two patients in the letrozole group were excluded due to complications: severe haemorrhage in one case and failure to follow-up in the other case. Finally, the study was analysed with 38 patients in each group (Fig. 1).

Statistical analysis

Data are presented as mean [standard deviation (SD)] and frequency (%). Statistical Package for the Social Sciences Version 18 (IBM Corp., Armonk, NY, USA) was implemented for analysis. A normal distribution of the quantitative data was assured using the Kolmogorov-Smirnov test. Numerical data were compared using the independent samples *t*-test or Mann–Whitney *U* test. Categorical data were compared using the Chi-squared or Fisher's exact test, as appropriate. Repeated measures analysis was used to compare inter- and intragroup changes at different times. Considering the pretreatment values as the baseline, $p < 0.05$ was considered to indicate significance.

Results

Thirty-eight patients in the letrozole + cabergoline group and 38 patients in the letrozole group were studied. The characteristics of the patients are summarized in Table 1. The two groups were comparable in terms of age, age at menarche, gravidity, parity, previous abortion and menstruation status.

Blood tests showed that the post-treatment serum hematocrit levels in both groups were improved significantly, and haematocrit level increased by 12.1% and 11.8% at the end of the treatment for Groups 1 and 2, respectively (32.4% and 33.2%, respectively, $p < 0.001$). There was no significant difference between the groups.

Percentage of overall complications and types of complications are depicted in Fig. 2. Accordingly, overall complications were significantly more common in the letrozole + cabergoline group than in the letrozole group (31 cases vs 22 cases, $p = 0.03$). Flushing was seen in eight patients in each group. Musculoskeletal pain was reported in seven patients in the letrozole + cabergoline group and in nine patients in the letrozole group. There was no significant difference between the two groups ($p = 0.57$).

Insomnia was reported by one patient in each group. Headache was significantly more common in the letrozole + cabergoline group than in the letrozole group (nine patients vs two patients, $p = 0.02$).

Nausea was reported by 11 patients in the letrozole + cabergoline group and by six patients in the letrozole group, with no significant difference between the two groups ($p = 0.17$). Vomiting occurred in two cases in the letrozole + cabergoline group and in one patient in the letrozole group. There was no significant difference between the two groups ($p = 0.50$)

The median pretreatment uterine volume was 274 ml (88.6–1425) in the letrozole + cabergoline group and 278.75 ml (97.4–1274) in the letrozole group. There was no significant difference between the two groups ($p = 0.98$).

The median post-treatment uterine volume was 236.5 ml (83.3–1333) in the letrozole + cabergoline group and 281.35 ml (96–1164) in the letrozole group. Changes in uterine volume before and after treatment are shown in Fig. 3. In both groups, the uterine volume decreased significantly after treatment ($p = 0.01$). Despite this finding, there was no significant difference between the two groups ($p = 0.99$). The mean percentage decrease in uterine volume after treatment compared with before treatment was 10.14 (SD 5.16) in the letrozole + cabergoline group and 6.23 (SD 4.69) in the letrozole group. There was no significant difference between the two groups ($p = 0.58$).

The mean pretreatment number of uterine myomas was 1.63 (SD 0.79) (range 1–3) in the letrozole + cabergoline group and 1.50 (SD 0.80) (range 1–4) in the letrozole group. There was no significant difference between the two groups ($p = 0.47$).

The mean post-treatment number of uterine myomas was 1.50 (SD 0.73) (range 1–3) in the letrozole + cabergoline group and 1.45 (SD 0.80) (range 1–4) in the letrozole group. Changes in the number of uterine myomas before and after treatment are shown in Fig. 4. In both groups, the number of uterine myomas decreased significantly after treatment ($p = 0.03$). Despite these findings, there was no significant difference between the two groups ($p = 0.60$). The mean percentage decrease in the number of uterine myomas after treatment compared with before treatment was 5.70 (SD 2.46) in the letrozole + cabergoline group and 4.12 (SD 4.61) in the letrozole group. There was no significant difference between the two groups ($p = 0.28$).

The median pretreatment volume of uterine myomas was 93 ml (0.4–985.9) in the letrozole + cabergoline group and 84.80 ml (3.6–1053) in the letrozole group. There was no significant difference between the two groups (Mann–Whitney *U* test, $p = 0.46$).

The median post-treatment volume of uterine myomas was 54.75 ml (1.4–1049) in the letrozole + cabergoline group and 72 ml (2–970.6) in the letrozole group. Changes in the volume of uterine myomas before and after treatment are shown in Fig. 5. In both groups, the mean volume of the uterine myomas decreased

Table 1
Characteristics of the patients in the letrozole + cabergoline and letrozole groups.

Variable		Letrozole + cabergoline group (n = 38)[a]	Letrozole (n = 38)[a]	*p*-value*
Age (years)		37.76 (3.94) [31–45]	39.29 (3.88) [31–44]	0.09
Age at menarche (years)		11.30 (1.24) [9–13]	11.56 (1.40) [9–14]	0.41
Gravidity		1.63 (0.25) [0–7]	2.24 (0.28) [0–7]	0.11
Parity		1.24 (0.19) [0–5]	1.68 (0.22) [0–5]	0.13
Previous abortion		0.45 (0.11) [0–3]	0.53 (0.14) [0–3]	0.65
Menstrual cycles, n (%)	Regular	17 (44.7)	21 (55.3)	0.40
	Irregular	21 (55.3)	17 (44.7)	

[a] Data are presented as mean (standard deviation) [range] unless otherwise indicated.
* $p < 0.05$ was considered to indicate significance.

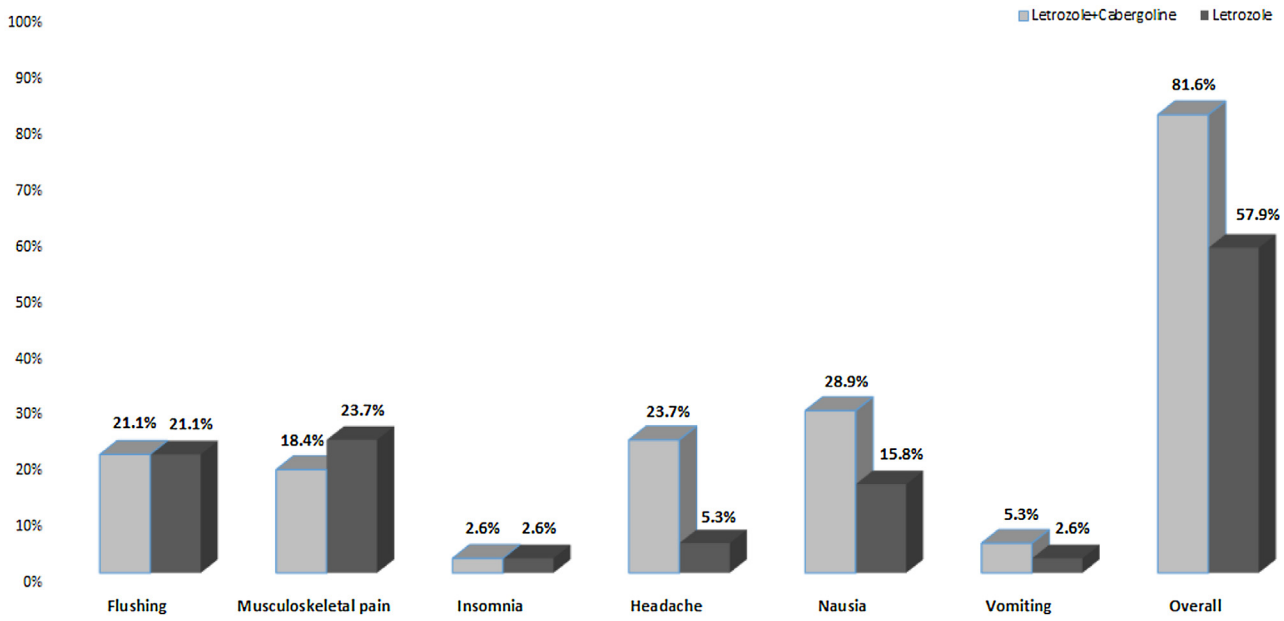

Fig. 2. Percentage of treatment-associated side effects in the letrozole + cabergoline and letrozole groups.

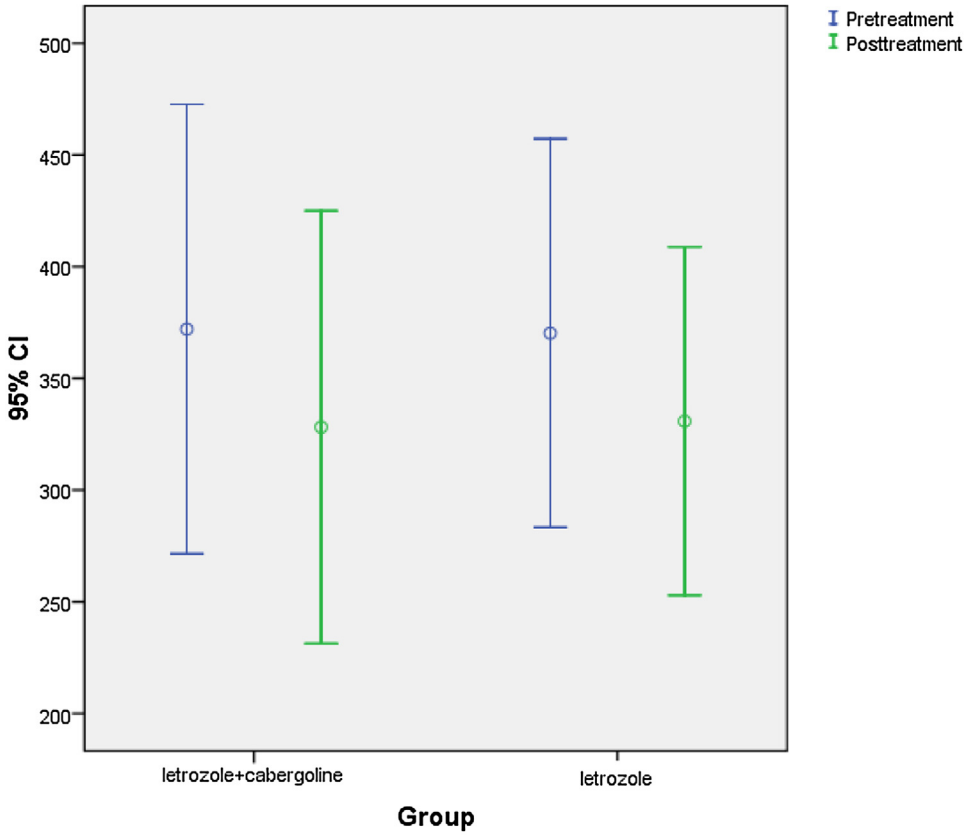

Fig. 3. Changes in uterine volume before and after treatment in the letrozole + cabergoline and letrozole groups. CI, confidence interval.

significantly after treatment ($p = 0.01$). Despite this finding, there was no significant difference between the two groups ($p = 0.45$). The mean percentage decrease in the volume of uterine myomas after treatment compared with before treatment was 22.06 (SD 9.16) in the letrozole + cabergoline group and 21.52 (SD 6.29) in the letrozole group. There was no significant difference between the two groups ($p = 0.96$).

The frequency and percentage of cases with decreased volume, no change in volume or increased volume of uterine myomas after treatment in the two groups are set out in Table 2. There was no significant difference between the two groups ($p = 0.18$).

The changes in patient satisfaction are shown in Table 3. A five-point Likert scale was used for rating satisfaction with treatment (excellent, good, poor, very poor, no answer) to evaluate symptoms

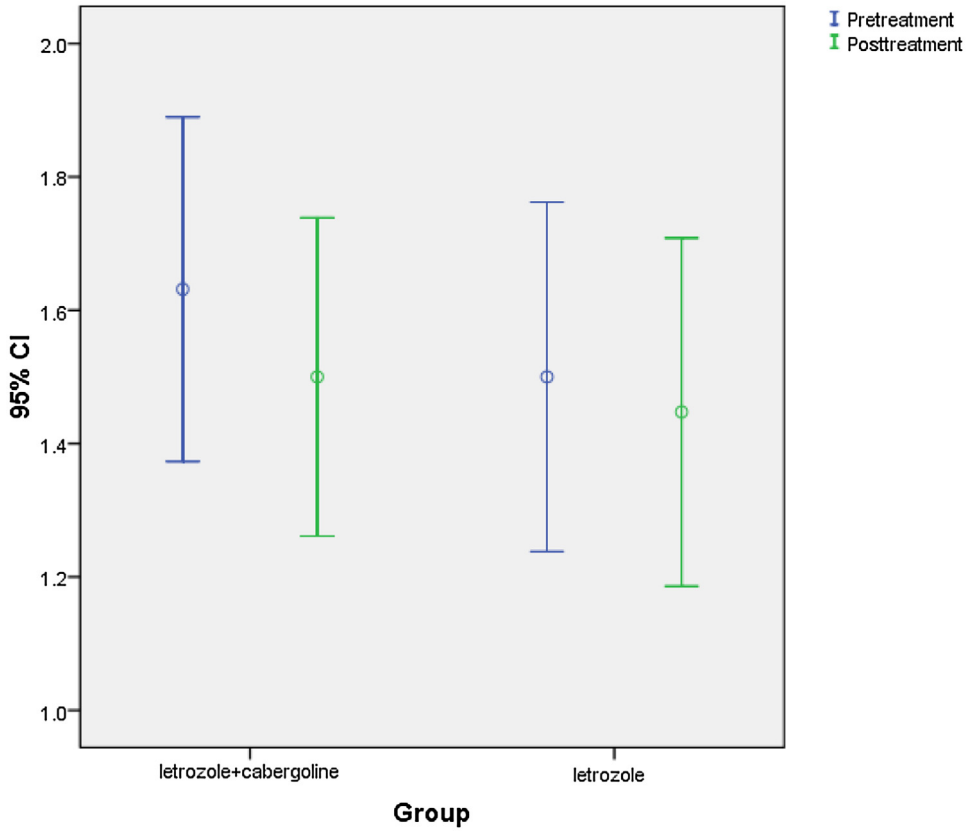

Fig. 4. Changes in the number of uterine myomas before and after treatment in the letrozole + cabergoline and letrozole groups. CI, confidence interval.

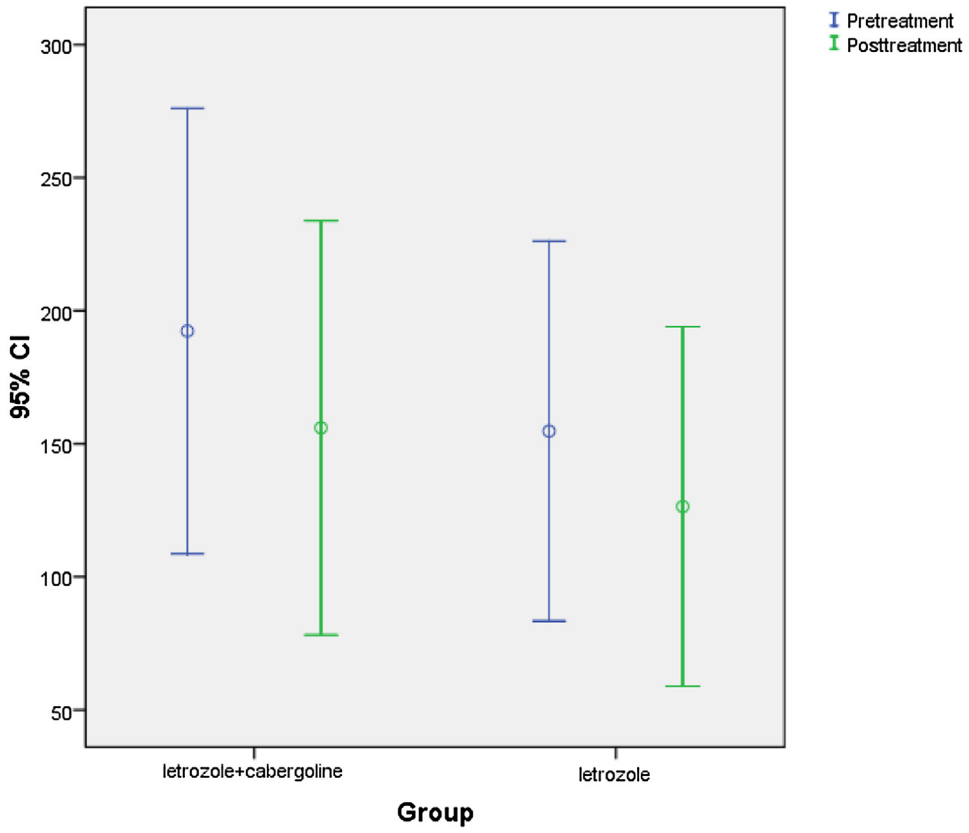

Fig. 5. Changes in the volume of uterine myomas before and after treatment in the letrozole + cabergoline and letrozole groups. CI, confidence interval.

Table 2
Percentage of volume changes in uterine myomas after treatment in the two studied groups.

Variable	Letrozole + cabergoline ($n = 38$)	Letrozole ($n = 38$)	p-value*
Increased volume	12 (19%)	9 (15.3%)	0.18
No change in volume	2 (3.2%)	7 (11.9%)	–
Decreased volume	49 (77.8%)	43 (72.9%)	–

* $p < 0.05$ was considered to indicate significance.

Table 3
Percentage of overall satisfaction after completion of treatment in the letrozole + cabergoline and letrozole groups.

Item	Excellent	Good	Poor	Very poor	Answered
Relief of acute bleeding	76	20	1	0.0	3.0
Letrozole + cabergoline group	75	20	1	1.0	3.0
Letrozole group					
Amount of bleeding	60	35	1	0.0	4.0
Letrozole + cabergoline group	57	35	2	0.0	6.0
Letrozole group					
Lethargy/Fatigue	60	33	1.0	0.0	6.0
Letrozole + cabergoline group	54	36	1.0	0.0	9.9
Letrozole group					
Paleness	40	57	1.0	0.0	2.0
Letrozole + cabergoline group	42	54	1.0	0.0	3.0
Letrozole group					
Daily activities	45	53	2.0	0.0	0.0
Letrozole + cabergoline group	44	54	1.0	0.0	1.0
Letrozole group					
Pain	37	53	4.0	0.0	6.0
Letrozole + cabergoline group	42	54	1.0	0.0	3.0
Letrozole group					
Pelvic pressure	60	37	1.0	0.0	2.0
Letrozole + cabergoline group	52	44	1.0	0.0	3.0
Letrozole group					
Health	30	67	1.0	0.0	2.0
Letrozole + cabergoline group	42	57	1.0	0.0	2.0
Letrozole group					
Illness	50	47	1.0	0.0	2.0
Letrozole + cabergoline group	50	45	1.0	0.0	4.0
Letrozole group					

and patient-based outcome measures. The items checked by questionnaire were the relief of acute bleeding, amount of bleeding, bleeding-related symptoms (lethargy, fatigue, paleness, daily activities), pain, pelvic pressure and menstrual-bleeding-specific quality of life (health and illness from the patient's perspective). The percentages of overall satisfaction after completion of treatment are shown in Table 3.

Comments

Medical treatment helps to control symptoms in order to replace or delay surgery. This study compared the therapeutic effects and probable side effects of administration of letrozole in combination with cabergoline vs letrozole alone in women of reproductive age with symptomatic uterine myomas >4 cm. Twelve weeks of treatment with letrozole with or without cabergoline was associated with a reduction in uterine volume and a significant decrease in the number and size of uterine myomas; however, no significant difference was observed between the two groups. Besides headache, which was significantly higher in the letrozole + cabergoline group, the two groups were comparable in terms of other complications.

Letrozole is a reversible, competitive, selective non-steroidal inhibitor of aromatase that has been shown to reduce the volume of uterine myomas and relevant symptoms by inhibiting oestrogen synthesis [11,12,25–33].

Among the different drug groups available for medical treatment of uterine myomas, the GnRH agonists are used most frequently and are able to reduce the volume of both the uterus and uterine myomas [34,35]. Nevertheless, aromatase inhibitors are superior to GnRH agonists for this purpose as the former inhibits oestrogen synthesis in uterine myomas directly without affecting ovarian oestrogen, and thus avoids the consequences of oestrogen deprivation. Another benefit of aromatase inhibitors over GnRH agonists is the lack of initial flare-ups with this group [36,37]. The third benefit in this regard is the abrupt action of aromatase inhibitors in decreasing oestrogen [11,38].

Since the first report of treating symptomatic myomas with fadrozole [29], four other studies have increased the information available in this regard. Studies by Hilario et al. and Varelas et al. showed that anastrozole significantly decreased the volume of uterine myomas, the uterine volume itself and associated symptoms [28,30]. In a study by Gurates et al., letrozole led to a decrease in the volume of uterine myomas (46.7%) and uterine size (21.7%) [25].

Letrozole alone also led to decreases in the volume of uterine myomas and the uterus by 21.5% and 6.2%, respectively, which were less than the values reported by the aforementioned study. In a multicentric randomized study by Parsanezhad et al., the effect of triptorelin (a GnRH agonist) and letrozole (2.5 mg/day) for 12 weeks was examined for the treatment of uterine myomas in 70 patients. Both letrozole and triptorelin were found to be similarly effective in reducing the volume of uterine myomas (45.6% vs 33.2%) [8]. Although the decrease in volume of uterine myomas in the present study was almost half the value reported by Parsanezhad et al., the changes induced by letrozole were significant.

Badawy et al. studied 32 patients with uterine myomas treated by letrozole (2.5 mg/day) or a GnRH agonist (goserelin) for 12 weeks. They found that letrozole did not decrease the uterine volume, but it led to a greater decrease in the volume of uterine myomas than the present study (49.1% in letrozole group) [39].

Song et al. found that letrozole was not associated with major side effects [27]. The present study found minor side effects in 57.9% of patients who received letrozole; many of these side effects were self-limited and negligible (Fig. 1).

Duhan et al. found a significant decrease in myoma volume after 12 weeks of treatment with letrozole 2.5 mg/day (52.5% on average). The reduction in myoma volume was higher compared with the present study, but fewer side effects were observed [12].

Leone Roberti Maggiore et al. found that administration of presurgical letrozole 2.5 mg/day plus norethindrone for 3 months improved the quality of surgical intervention in patients with large myomas (≥8 cm) [26].

On the basis of this study, both treatments could be expected to have a favourable effect on surgical interventions. However, larger studies should be performed in order to reach an appropriate conclusion.

Bizzarri et al. used letrozole 2.5 mg/day before surgical treatment for uterine myomas and observed a significant decrease (34.5%) in the volume of uterine myomas after treatment [40]. In comparison, the degree of myoma regression was slightly higher in the present study.

As seen in the aforementioned studies, the volume of uterine myomas was reduced successfully by use of an aromatase inhibitor, and the results were in line with findings regarding the effectiveness of letrozole in reducing the volume of uterine myomas, its safety and the lack of major side effects. Nonetheless, as emphasized earlier, there are differences between reports in terms of the degree of effectiveness; this may be due to between-study differences in patients' individual physical characteristics, genetic factors and the severity of disease at admission.

In contrast to letrozole, reports on the effectiveness of cabergoline (a dopamine receptor stimulator) for the treatment of uterine myomas are limited in the medical literature. In a previous study, the present authors compared the effectiveness of cabergoline with diphereline (a GnRH agonist) in patients with uterine myomas. In the cabergoline group, the degree of myoma regression ranged between 46% and 53%, the side effects were less frequent, and the drug was better tolerated than diphereline [9].

In the present study, the degree of myoma regression in the letrozole + caberoline group was 22.1%, which was lower than that reported previously [9]. In addition, headache was more common in the present study (23.7%), whereas the rates of nausea and vomiting were comparable (28.9% and 5.3%, respectively). Of note, the present study used a combination of cabergoline and letrozole to determine whether or not the combination of two drugs was effective. As in the authors' previous study, the same two medications were compared in terms of their effect on the growth of uterine myomas and histological, ultrasonographic and intra-operative changes. Accordingly, cabergoline was as effective as diphereline for reducing the size of uterine myomas, and enhancing ultrasonographic, clinical and intra-operative outcomes with no significant side effects [10]. Although the variables differ between the abovementioned work and the present study, the effectiveness of cabergoline in inducing regression of uterine myomas was confirmed by both studies. In addition, Elbareg et al. 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 [41]. However, the therapeutic effect of cabergoline in combination with letrozole in inducing myoma regression was less in the present study than in the aforementioned report, and its effectiveness has been confirmed.

Long-term use of aromatase inhibitors (≥24 weeks) with the consequent hypo-estrogenaemia could result in bone turnover, loss of bone mineralization, increased fracture risk and the need for add-back therapy [42–44]. However, the treatment course was not long in the present study.

Brufsky et al. showed that letrozole had no significant impact on fractures [45].

To the authors' knowledge, this is the first study to compare the therapeutic effect of a combination of letrozole and cabergoline in patients with uterine myomas. Further studies are needed 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 a single centre, being unblinded, lack of a placebo arm and small sample size.

Conclusion

This study found that 12 weeks of treatment with letrozole with or without cabergoline induced regression of uterine myomas, led to symptomatic improvement, and could be used for short-term treatment prior to surgery or fertility programmes. There was no significant difference between the two groups in terms of the degree of reduction in the 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.

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