



Comparison of the effects of gonadotropin-releasing hormone and raloxifene on the size of uterine leiomyoma

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Abstract

Original Article

BACKGROUND: Uterine leiomyoma is a prevalent benign tumor. Several studies have shown the positive effects of raloxifene in the treatment of leiomyomas. Since raloxifene has fewer side effects than the gonadotropin-releasing hormone (GnRH) agonist, if proven effective, it can be applied easily. This study aimed to compare the medical effects of raloxifene and GnRH on uterine leiomyoma size.

METHODS: This clinical trial included 53 women with uterine leiomyoma. Participants were randomly divided into 2 groups of raloxifene and GnRH. The GnRH group received 1 dose per month (intramuscular injection) and the raloxifene group received 60 mg raloxifene orally/day for 3 months. The size of the leiomyoma, prior and during the intervention, was determined by a sonographer. During the study, repeated measurement was used for comparing the trend of alterations in the tumor size.

RESULTS: Analysis of changes in leiomyoma tumor size (log of tumor size) by repeated measurement showed that decrease in tumor size in the raloxifene group was significantly higher than GnRH group ($P = 0.042$). The trends of changes in endometrial thickness were different in the 2 groups and the reduction of thickness was more significant in the GnRH group ($P = 0.026$).

CONCLUSION: This study showed that raloxifene is an appropriate medicine to reduce the size of uterine leiomyoma and is more effective than GnRH.

KEYWORDS: Uterus, Leiomyoma, Gonadotropin-Releasing Hormone, Raloxifene

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Introduction

Uterine leiomyoma, also called uterine fibroids, is a prevalent benign tumor that affects about 25% of women around their menopausal age. This is a tumor formed in uterine smooth muscles and

approximately one-third of patients have to undergo hysterectomy.¹ Uterine leiomyoma can cause complications such as miscarriage, premature labor, detachment of the placenta, and bleeding.^{2,3}

Several non-surgical treatments for the disease have been proposed.^{4,5} Gonadotropin-releasing hormone (GnRH) drugs, raloxifene, and letrozole are among medications proposed for the

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treatment of uterine leiomyomas and they are still under study.⁴⁻¹⁰ The hyperestrogenemia state induced by GnRH agonist is recognized as an effective treatment.^{1,11} This drug is also associated with some side effects including climacteric like symptoms, hot flashes, vaginal dryness, osteoporosis, and decreased libido.^{12,13}

Raloxifene is a non-steroidal drug that is derived from benzophenone. This drug is a selective estrogen receptor modulator (SERM) and acts as an estrogen agonist in the central nervous system, and skeletal and cardiovascular metabolism; however, it has a weak antagonistic effect on breast and uterine activity.¹⁴⁻¹⁶ This drug also prevents osteoporosis.¹⁷ Several studies have proved the positive effects of raloxifene in the treatment of leiomyomas.⁸⁻¹⁰ A study by Palomba *et al.*, administration of raloxifene had led to the reduction of leiomyoma size in menopausal women, though it had not been effective in premenopausal women.¹⁸ There is no other study showing the same effect, and the effect of this drug is still a controversial issue and more research is needed in this area.^{19,20}

Since raloxifene has fewer side effects than the GnRH agonist, if proven effective, it can be applied easily. This study aimed to compare the medical effects of raloxifene and GnRH on uterine leiomyoma size.

Materials and Methods

This study was a randomized controlled clinical trial (RCT registration code: IRCT2014032816490N2) on 53 women with uterine leiomyoma referring to the gynecologic clinic of Be'sat Hospital in Sanandaj, Iran. In the first step, 61 women were evaluated. 8 women did not meet our inclusion criteria and were excluded from the study (Figure 1). After approval of the ethics committee of Kurdistan University of Medical Sciences, signed consent forms were obtained from all the patients. Then, participants were randomly divided into 2 groups of raloxifene and GnRH using simple random sampling method.

This study included women at child bearing age with a history of leiomyomas having a

minimum size of 40 mm and a maximum of 60 mm in one dimension. Exclusion criteria included history of any metabolic, neoplastic, infectious diseases, blood disorders, venous thrombosis, liver disease, active rheumatoid arthritis, hormone therapy and surgery in the last 6 months, hypoechoic mass or calcified leiomyomas, endometrial abnormalities in sonography, lesions of the cervix and having body mass index (BMI) greater than 30 or less than 18 kg/m².

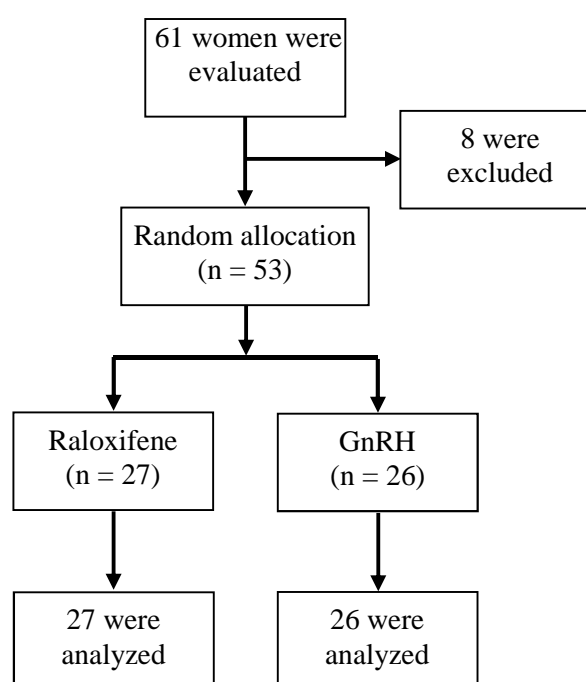


Figure 1. Participants profile in raloxifene and gonadotropin-releasing hormone (GnRH) groups during the study

After random assignment of the patients, the GnRH group received 3.75 mg of GnRH/month via intramuscular injection, and the raloxifene group received a daily dose of 60 mg oral raloxifene. Treatment duration was 3 months for both groups. Initial investigation and administration of drugs were performed by the same gynecologist.

Using transvaginal sonography, our sonographer determined the size of leiomyoma tumor before and three months after intervention. The size of leiomyoma was measured in 3

dimensions (D1 × D2 × D3 × 0.52). The biggest leiomyoma was studied when there were more than 1 tumor. Furthermore, endometrial thickness was measured for each case. Tumor size was measured by the same sonographer with no knowledge of the type of intervention. We used Simadzu SDU 2200 ultrasound machine (SIMADU, Japan) for performing sonography.

Data were entered in SPSS for Windows (version 11.5; SPSS Inc., Chicago, IL, USA). We used chi-square and Fisher's exact tests to compare qualitative variables and Student's independent t-test and Mann-Whitney test to compare quantitative variables between the 2 groups. During the study, repeated measurement was used to detect the changes in the tumor size. The sphericity assumption was assessed via Mauchly's sphericity test.

Results

This study included 53 participants, 27 in the raloxifene group and 26 in the GnRH group. Only 1 participant had history of smoking. Mean age of the participants was 42.1 ± 7.9 years, and their age ranged from 21 to 51 years; the mean of parity was 2.1 ± 1.8 . 43 (81.1%) were married and the rest were single (virgin, divorced, or widowed). In addition, 5 patients (9.4%) had hypertension. Menorrhagia was observed in 50 patients (94.3%), pelvic pain in 31 patients (58.5%), and flushing in 7 patients (13.2%). No statistically significant differences were observed between the 2 groups regarding the above-mentioned variables (Table 1).

Mean of leiomyoma size (mm³) decreased from 213.4 ± 356.5 to 77.2 ± 136.8 mm³ in the raloxifene

group and from 113.4 ± 73.4 to 96.9 ± 74.6 mm³ in the GnRH group (Table 2). Figure 2 indicates analysis of changes in leiomyoma tumor size (log of tumour size) by repeated measurement. Tumour size was significantly higher in the raloxifene group compared to GnRH group ($P = 0.042$). The trends of changes in endometrial thickness were different in the 2 groups and the reduction of thickness was more significant in the GnRH group ($P = 0.026$).

Table 1. Comparison of individual characteristics between raloxifene and Gonadotropin-releasing hormone (GnRH) groups

Variables	Raloxifene (n = 27)	GnRH (n = 26)	P
Age	42.4 ± 4.8	39.6 ± 8.2	0.143 [†]
Parity	1.88 ± 1.39	2.36 ± 2.1	0.68 [†]
BMI	28.8 ± 5.3	27.7 ± 3.9	0.559 [†]
Smoking	0 (0%)	1 (3.8%)	0.491 ^{††}
Hypertension	2 (7.4%)	3 (11.5%)	0.669 ^{††}
Married	22 (81.5%)	21 (80.8%)	0.947 ^{††}
Menorrhagia	25 (92.6%)	25 (96.2%)	1 ^{††}
Tension sense	16 (61.5%)	21 (80.8%)	0.126
Pelvic Pain	15 (57.7%)	15 (57.7%)	1
Hot flash	5 (19.2%)	2 (7.7%)	0.419 ^{††}

[†] Mann-Whitney test

^{††} Fisher's exact test

Others were tested by chi-square test

GnRH: Gonadotropin-releasing hormone

BMI: Body mass index

Discussion

In this study, both groups were similar regarding basic variables; however, at the beginning of the study the average size of leiomyomas in the raloxifene group was bigger than what was found

Table 2. Mean and standard deviation of leiomyoma sizes (mm³) and endometrial thickness (millimeters) during the study

Indicator		Raloxifene (n = 27)	GnRH (n = 26)	P [†]
Leiomyoma sizes	Month baseline	213.4 ± 356.5	113.4 ± 73.4	0.042
	Month 1	119.9 ± 204	89.9 ± 71.9	
	Month 2	84.7 ± 131.8	83.6 ± 71.9	
	Month 3	77.2 ± 136.8	96.9 ± 74.6	
Endometrial thickness	Month baseline	5.8 ± 1.8	6.2 ± 2.5	0.026
	Month 1	5.3 ± 1.6	5.4 ± 2.2	
	Month 2	6.4 ± 8.9	4.7 ± 1.4	
	Month 3	4.7 ± 1.1	4.5 ± 1.4	

[†] Repeated measurement; GnRH: Gonadotropin-releasing hormone

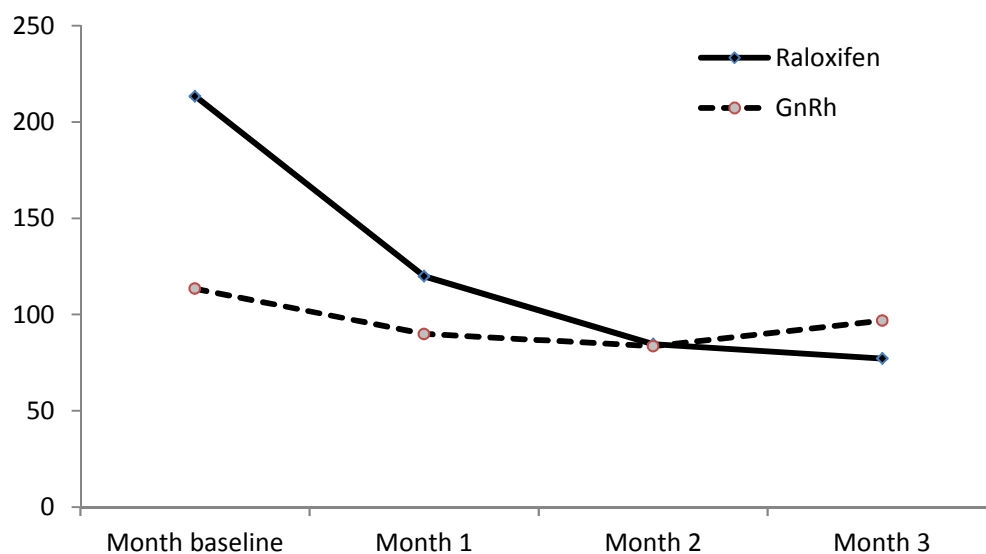


Figure 2. Trend of leiomyoma sizes (cm³) in raloxifene and Gonadotropin-releasing hormone (GnRH) groups during the study

in the GnRH group. The logarithm of tumor size was used for improving the precision of the statistical tests. Based on the results, prescribing raloxifene for 3 months was more effective than GnRH in reducing the size of uterine leiomyomas. The endometrial thickness had a greater reduction in the GnRH group compared to the raloxifene group.

Leiomyomas are estrogen-dependent tumors. GnRH is one of the most common drugs used for leiomyomas and its effects usually begin within 3 months.²¹ Although, GnRH is recognized as an effective treatment for reducing the size of leiomyoma, variable results have been reported in different studies.^{5,10,22} GnRH is more effective in women under 35 years; therefore, the variations in the results of different studies might be attributed to age.⁵ The wide age range in our study increased the external validity. This drug, which induces hypoestrogenism can cause vascular vasoconstriction in leiomyoma, but it may also have some other side effects such as insulin resistance, hyperlipidemia, and osteoporosis. Thus, the long-term administration of the drug can lead to several complications.^{12,13,23} Raloxifene is a kind of

selective estrogen receptor modulator (SERM), which can prevent osteoporosis in menopausal women.¹⁷ This drug can also prevent collagen synthesis in leiomyomas.²⁰ Raloxifene decreases the proliferation of endometrial tissue and this mechanism can affect leiomyomas.²⁴ In our study, raloxifene was effective in reducing the size of leiomyomas. In some studies, administration of an appropriate dose of raloxifene in premenopausal women failed to significantly reduce the size of leiomyomas.^{18,25}

However, in a study, the simultaneous administration of raloxifene and GnRH for a long time (18 cycles) in premenopausal women prevented osteoporosis and any increase in the levels of glucose and lipids with no special side effects. For a better therapeutic effect 6 cycles of treatment are necessary. However in our study, Raloxifene did not reduce the vasomotor symptoms associated with the GnRH.²⁶ In a study by Palomba *et al.*, raloxifene had no effect on the size of leiomyomas and menstrual bleeding in premenopausal women.¹⁸

However, in the raloxifene group we found no new case of tumor and no increase in the size of tumors. Administration of raloxifene was not as

effective as GnRH in reducing the size of endometrial thickness. Hence, raloxifene is a suitable medication for asymptomatic postmenopausal women as the drug does not have a great effect on the endometrial thickness and the vasomotor system.²⁷

Jirecek et al. showed that raloxifene prevented the growth and progress of the leiomyoma; however, there was no significant difference in the clinical symptoms between the 2 groups and the drug was well tolerated.²⁸ Raloxifene can also reduce the risk of breast cancer and has a beneficial effect on skin elasticity.^{29,30}

One limitation of our study was that we did not assess the signs and symptoms of the patients and only the size of leiomyomas was studied. Thus, we recommend further studies for evaluation of the effect of raloxifene on the patient's signs and symptoms.

Conclusion

This study showed that raloxifene is an appropriate medicine to reduce the size of uterine leiomyoma and it is more effective than GnRH.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

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