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

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Abstract

BACKGROUND: Uterine leiomyoma is a prevalent benign tumor. Several studies have proved 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 study was a clinical trial which involved 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 a daily dose of raloxifene 60 mg/orally 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 trend in the logarithm of 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: Overall, this study showed that raloxifene is an appropriate medicine to reduce the size of uterine leiomyoma and it is more effective than GnRH.

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

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

Raloxifene is a non-steroidal drug that is derived from benzophenone. This drug is a selective estrogen receptor modulator (SERM) and it functions 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.\textsuperscript{14-16} This drug also prevents osteoporosis.\textsuperscript{17} Several studies have proved the positive effects of raloxifene in the treatment of leiomyomas\textsuperscript{8-10}. In the study by Palomba et al., administration of raloxifene had led to the decrease in leiomyoma size in menopausal women, though it had not been effective in premenopausal women.\textsuperscript{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.\textsuperscript{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.

\textbf{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\textsuperscript{’}sat Hospital in Sanandaj, Iran. In the first step, 61 women were evaluated. Due to having the exclusion criteria, 8 women were excluded (Figure 1). After receiving permission from the ethics committee of Kurdistan Medical University, signed consent forms were obtained from all patients. Then, participants were randomly divided into 2 groups of raloxifene and GnRH using simple random sampling method by placing the names of intervention groups into envelops.

Inclusion criteria included not being menopausal, and having a history of leiomyomas with a minimum size of 40 mm and a maximum of 60 mm in one of the diameters of tumor. Exclusion criteria included having metabolic disease, neoplasia disease, infectious diseases, blood disorders, history of venous thrombosis, liver disease, active rheumatoid arthritis, body mass index (BMI) greater than 30 or less than 18 kg/m\textsuperscript{2}, hormone therapy in the last 6 months, surgery in the last 6 months, hypoechoic mass or calcified leiomyomas, endometrial abnormalities in sonography, and lesions of the cervix.

After assigning patients randomly, the GnRH group received 3.75 mg per month via intramuscular injection, and the raloxifene group received a daily dose of raloxifene 60 mg orally. Treatment duration was 3 months in both groups. Initial investigation and administration of drugs were performed by a gynecologist.

After selecting participants and performing random allocation, the size of the leiomyoma, prior to intervention, was determined by a sonographer using transvaginal sonography, and it was repeated again 3 months after initiation of intervention. The size of leiomyoma was measured.
for 3 diameters (D1, D2, and D3) and it was calculated using the equation D1 × D2 × D3 × 0.52. In cases where there was more than 1 leiomyoma, the biggest was studied. Furthermore, endometrial thickness was also measured for each case. Tumor size was measured by a sonographer without any knowledge of the type of intervention group. Simadzu SDU 2200 ultrasound machine (SIMADU, Japan) was used for performing sonography.

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

Results

There were 53 participants in our study, of whom 27 were in the raloxifene group and 26 in the GnRH group. Only 1 participant was a smoker. 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. Of all the patients, 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 difference was observed between the 2 groups in terms of mentioned variables (Table 1).

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

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

† Mann-Whitney test
†† Fisher’s exact test
Others were tested by chi-square test
GnRH: Gonadotropin-releasing hormone
BMI: Body mass index

Mean of leiomyoma size (mm³) was decreased from 213.4 ± 356.5 to 77.2 ± 136.8 mm³ in the raloxifene group. This measure was decreased from 113.4 ± 73.4 to 96.9 ± 74.6 mm³ in the GnRH group (Table 2). As shown in figure 2, 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 the 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 2. Mean and standard deviation of leiomyoma sizes (mm³) and endometrial thickness (millimeters) during the study

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Raloxifene (n = 27)</th>
<th>GnRH (n = 26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyoma sizes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month baseline</td>
<td>213.4 ± 356.5</td>
<td>113.4 ± 73.4</td>
<td>0.042</td>
</tr>
<tr>
<td>Month 1</td>
<td>119.9 ± 204</td>
<td>89.7 ± 71.9</td>
<td></td>
</tr>
<tr>
<td>Month 2</td>
<td>84.7 ± 131.8</td>
<td>83.6 ± 71.9</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>77.2 ± 136.8</td>
<td>96.9 ± 74.6</td>
<td></td>
</tr>
<tr>
<td>Endometrial thickness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month baseline</td>
<td>5.8 ± 1.8</td>
<td>6.2 ± 2.5</td>
<td>0.026</td>
</tr>
<tr>
<td>Month 1</td>
<td>5.3 ± 1.6</td>
<td>5.4 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>Month 2</td>
<td>6.4 ± 8.9</td>
<td>4.7 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>4.7 ± 1.1</td>
<td>4.5 ± 1.4</td>
<td></td>
</tr>
</tbody>
</table>

† Repeated measurement; GnRH: Gonadotropin-releasing hormone
Discussion

In this study, both groups were the same regarding basic variables; however, at the beginning of the study the average size of leiomyomas in the raloxifene group was bigger than in the GnRH group. The logarithm of tumor size was used to minimize its adverse effects on 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. Although, GnRH is recognized as an effective treatment for reducing the size of leiomyoma, its effects have been reported differently in different studies, from almost ineffective to positively effective. GnRH is more effective in women under 35 years; therefore, the differences in the results of different studies might be attributed to age. A wide range of ages was used in our study to increase the external validity. This drug, which induces a state of hypoestrogenism, can cause leiomyoma vascular vasoconstriction, 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 complications.

Raloxifene is a kind of selective estrogen receptor modulator (SERM), which can prevent osteoporosis in menopausal women. This drug can also prevent the synthesis of collagen in leiomyomas. Raloxifene decreases the proliferation of endometrial tissue and uses this mechanism to effect leiomyomas. Several studies have provided diverse results. In our study, raloxifene had a positive effect 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.

However, in a study, the simultaneous administration of raloxifene and GnRH for a long time (18 cycles) in premenopausal women prevented an increase in the levels of glucose,
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lipids, and osteoporosis and no special side effect was observed. In order for this drug to be effective 6 cycles is necessary. Raloxifene did not reduce the vasomotor symptoms associated with the GnRH.

In a study by Palomba et al., raloxifene had no effect on the size of leiomyomas and menstrual bleeding in premenopausal women. However, in this study there was no new case of tumor in the raloxifene group and no increase in the size of tumors. The administration of raloxifene was not as effective as GnRH in reducing the size of endometrial thickness. Hence, asymptomatic postmenopausal women are the ideal consumers of raloxifene because the drug does not have a great effect on the endometrial thickness and their vasomotor system. The study by Jirecek et al. showed that raloxifene had been able to prevent the growth and progress of the leiomyoma; however, there was no significant difference in the clinical symptoms in the 2 groups and the drug was well tolerated. Raloxifene can also reduce the risk of breast cancer and has a beneficial effect on skin elasticity. Unfortunately, a limitation of our study was that we did not assess the signs and symptoms of patients and only the size of leiomyomas was studied. Thus, it is suggested that further studies be performed to evaluate the effect of raloxifene on the patient's signs and symptoms.

Conclusion

Overall, 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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