Chronic Diseases Journal

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

Farnaz Zandvakili[1], Fariba Seyedoshohadaie[1], Masoumeh Rezaiee[1], Nasrin Soofizade[1], Fariba Farhadifar[2], Ebrahim Ghaderi[3]

1 Assistant Professor, Department of Gynecology, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran
2 Associate Professor, Department of Gynecology, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran
3 Assistant Professor, Kurdistan Research Center for Social Determinants of Health, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran

Original Article

Abstract

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 sonographist. 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

Date of submission: 24 Oct 2013, ***Date of acceptance:*** 13 Nov 2013

Citation: Zandvakili F, Seyedoshohadaie F, Rezaiee M, Soofizade N, Farhadifar F, Ghaderi E. **Comparison of the effects of gonadotropin-releasing hormone and raloxifeneon the size of uterine leiomyoma.** Chron Dis J 2014; 2(1): 46-51.

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

Corresponding Author:
Fariba Farhadifar
Email: fariba.farhadifar@muk.ac.ir

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 drugs 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/m^2.

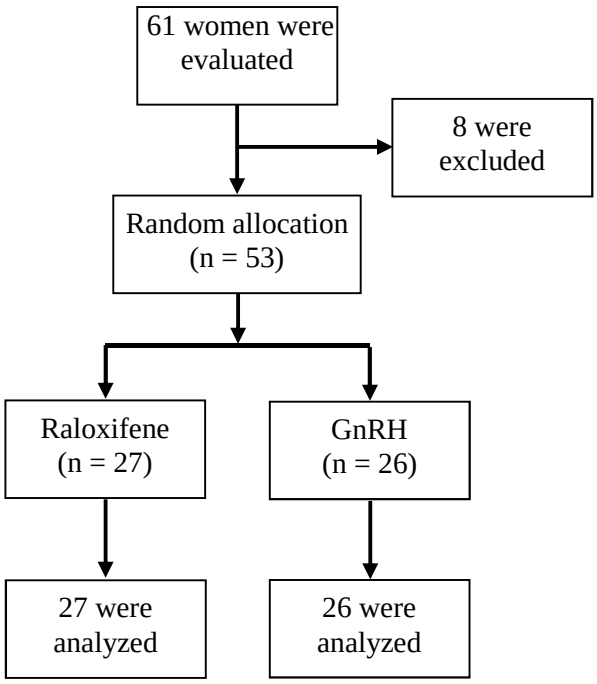

Figure 1. Participants profile in raloxifene and gonadotropin-releasing hormone (GnRH) groups during the study

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 sonographist determined the size of leiomyoma tumorbefore and three months after intervention. The size of leiomyoma was measured in 3

dimensions (D1 × D2 × D3 × 0.52). Thebiggest 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 sonographist 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-mentinsed 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 mm^3 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 toGnRH 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 (mm^3) 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	
	Month 1	5.3 ± 1.6	5.4 ± 2.2	0.026
	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

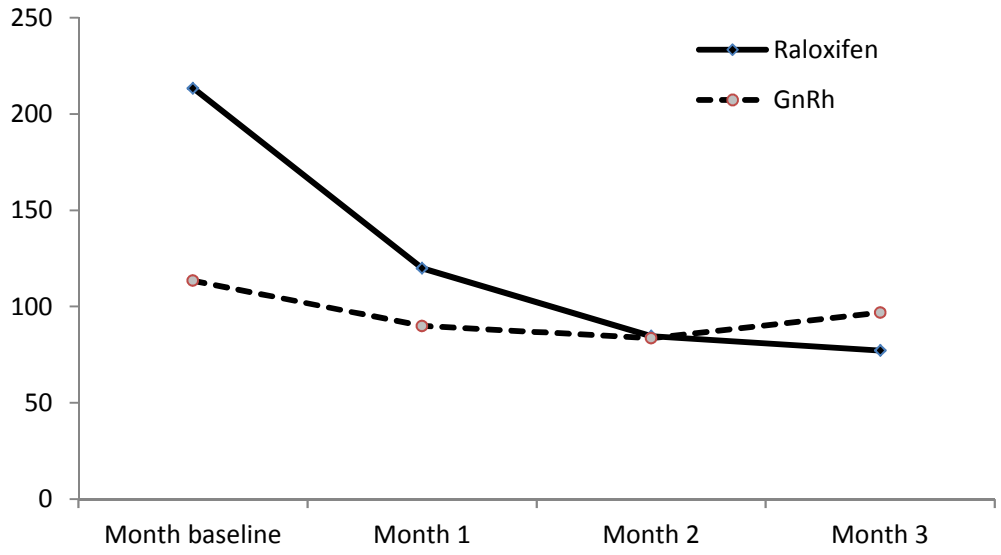

Figure 2. Trend of leiomyoma sizes (cm^3) in raloxifene and Gonadotropin-releasing hormone (GnRH) groups during the study

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, vriable 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

This study was financially supported by the Vice Chancellor for Research Affairs, Kurdistan University of Medical Sciences.

References

1. Stewart EA. Uterine fibroids. Lancet 2001; 357(9252): 293-8.
2. Cox S, Werner C, Hoffman B. Williams Obstetrics. 22nd ed. New York, NY: McGraw-Hill Companies, Incorporated; 2005.
3. Sheiner E, Bashiri A, Levy A, Hershkovitz R, Katz M, Mazor M. Obstetric characteristics and perinatal outcome of pregnancies with uterine leiomyomas. J Reprod Med 2004; 49(3): 182-6.
4. Sabry M, Al-Hendy A. Innovative oral treatments of uterine leiomyoma. Obstet Gynecol Int 2012; 2012: 943635.
5. Palomba S, Falbo A, Russo T, Zullo F. GnRH analogs for the treatment of symptomatic uterine leiomyomas. Gynecological Surgery 2005; 2(1): 7-13.
6. Requena A, Herrero J, Landeras J, Navarro E, Neyro JL, Salvador C, et al. Use of letrozole in assisted reproduction: a systematic review and meta-analysis. Hum Reprod Update 2008; 14(6): 571-82.
7. Gurates B, Parmaksiz C, Kilic G, Celik H, Kumru S, Simsek M. Treatment of symptomatic uterine leiomyoma with letrozole. Reprod Biomed Online 2008; 17(4): 569-74.
8. Fuchs-Young R, Glasebrook AL, Short LL, Draper MW, Rippy MK, Cole HW, et al. Raloxifene is a tissue-selective agonist/antagonist that functions through the estrogen receptor. Ann N Y Acad Sci 1995; 761: 355-60.
9. Porter KB, Tsibris JC, Porter GW, Fuchs-Young R, Nicosia SV, O'Brien WF, et al. Effects of raloxifene in a guinea pig model for leiomyomas. Am J Obstet Gynecol 1998; 179(5): 1283-7.
10. Lethaby AE, Vollenhoven BJ. An evidence-based approach to hormonal therapies for premenopausal women with fibroids. Best Pract Res Clin Obstet Gynaecol 2008; 22(2): 307-31.
11. Sankaran S, Manyonda IT. Medical management of fibroids. Best Pract Res Clin Obstet Gynaecol 2008; 22(4): 655-76.
12. Pickersgill A. GnRH agonists and add-back therapy: is there a perfect combination? Br J Obstet Gynaecol 1998; 105(5): 475-85.
13. Adashi EY. Long-term gonadotrophin-releasing hormone agonist therapy: the evolving issue of steroidal 'add-back' paradigms. Hum Reprod 1994; 9(7): 1380-97.
14. Mosca L. Rationale and overview of the Raloxifene Use for the Heart (RUTH) trial. Ann N Y Acad Sci 2001; 949: 181-5.
15. Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hoszowski K, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. JAMA 2002; 287(7): 847-57.
16. Goldstein SR, Scheele WH, Rajagopalan SK, Wilkie JL, Walsh BW, Parsons AK. A 12-month comparative study of raloxifene, estrogen, and placebo on the postmenopausal endometrium. Obstet Gynecol 2000; 95(1): 95-103.
17. Clemett D, Spencer CM. Raloxifene: a review of its use in postmenopausal osteoporosis. Drugs 2000; 60(2): 379-411.
18. Palomba S, Orio F, Morelli M, Russo T, Pellicano M, Zupi E, et al. Raloxifene administration in premenopausal women with uterine leiomyomas: a pilot study. J Clin Endocrinol Metab 2002; 87(8):

3603-8.
19. Palomba S, Orio F, Jr., Morelli M, Russo T, Pellicano M, Nappi C, et al. Raloxifene administration in women treated with gonadotropin-releasing hormone agonist for uterine leiomyomas: effects on bone metabolism. J Clin Endocrinol Metab 2002; 87(10): 4476-81.
20. Deng L, Wu T, Chen XY, Xie L, Yang J. Selective estrogen receptor modulators (SERMs) for uterine leiomyomas. Cochrane Database Syst Rev 2012; 10: CD005287.
21. Olive DL, Lindheim SR, Pritts EA. Non-surgical management of leiomyoma: impact on fertility. Curr Opin Obstet Gynecol 2004; 16(3): 239-43.
22. Shozu M, Sumitani H, Segawa T, Yang HJ, Murakami K, Inoue M. Inhibition of in situ expression of aromatase P450 in leiomyoma of the uterus by leuprorelin acetate. J Clin Endocrinol Metab 2001; 86(11): 5405-11.
23. Palomba S, Russo T, Orio F, Sammartino A, Sbano FM, Nappi C, et al. Lipid, glucose and homocysteine metabolism in women treated with a GnRH agonist with or without raloxifene. Hum Reprod 2004; 19(2): 415-21.
24. Boss SM, Huster WJ, Neild JA, Glant MD, Eisenhut CC, Draper MW. Effects of raloxifene hydrochloride on the endometrium of postmenopausal women. Am J Obstet Gynecol 1997; 177(6): 1458-64.
25. Premkumar A, Venzon DJ, Avila N, Johnson DV, Remaley AT, Forman MR, et al. Gynecologic and hormonal effects of raloxifene in premenopausal women. Fertil Steril 2007; 88(6): 1637-44.
26. Palomba S, Orio F, Russo T, Falbo A, Cascella T, Doldo P, et al. Long-term effectiveness and safety of GnRH agonist plus raloxifene administration in women with uterine leiomyomas. Hum Reprod 2004; 19(6): 1308-14.
27. Palomba S, Sammartino A, Di CC, Affinito P, Zullo F, Nappi C. Effects of raloxifene treatment on uterine leiomyomas in postmenopausal women. Fertil Steril 2001; 76(1): 38-43.
28. Jirecek S, Lee A, Pavo I, Crans G, Eppel W, Wenzl R. Raloxifene prevents the growth of uterine leiomyomas in premenopausal women. Fertil Steril 2004; 81(1): 132-6.
29. Hansdottir H. Raloxifene for older women: a review of the literature. Clin Interv Aging 2008; 3(1): 45-50.
30. Sumino H, Ichikawa S, Kasama S, Takahashi T, Kumakura H, Takayama Y, et al. Effects of raloxifene and hormone replacement therapy on forearm skin elasticity in postmenopausal women. Maturitas 2009; 62(1): 53-7.