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Research Article

COMPARISON OF LETROZOLE, NORETHISTERONE ACETATE, AND TRIPTORELIN FOR PAIN RELIEF IN PREMENOPAUSAL WOMEN WITH ENDOMETRIOSIS: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

In premenopausal women with endometriosis, the use of aromatase inhibitors necessitates additional medications to suppress gonadal estrogen biosynthesis. This study compared the efficacy and tolerability of Letrozole versus Norethisterone Acetate or Triptorelin in providing pain relief. Patients with rectovaginal endometriosis were administered Letrozole (2.5 mg/day) or Norethisterone Acetate for a duration of six months. Symptom assessment utilized both a visual analog scale and a multidimensional categorical rating scale, while virtual organ computer-aided analysis estimated endometriotic nodules. Adverse effects of treatment were also monitored. A total of 70 women were randomized into two treatment groups. In the Norethisterone Acetate group, 64.7% of patients reported satisfactory or very satisfactory treatment outcomes, compared to 22.2% in the Triptorelin group. Both treatment groups demonstrated significant reductions in pain intensity throughout the study duration, with no statistically significant difference between them. However, the Triptorelin group exhibited a more significant reduction in the number of endometriotic nodules compared to the Letrozole group. Adverse effects leading to treatment interruption were more common in the Triptorelin group, with eight women discontinuing treatment compared to one participant in the Norethisterone Acetate group. Additionally, six women in the Norethisterone Acetate group experienced adverse effects. Furthermore, a significant decrease in mineral bone density was observed in the Triptorelin group but not in the Norethisterone Acetate group. In conclusion, aromatase inhibitors effectively reduce endometriosis-related pain. Combining Letrozole with oral Norethisterone Acetate resulted in fewer side effects and a lower discontinuation rate compared to Triptorelin alone.

Keywords:- Endometriosis, Aromatase Inhibitors, Letrozole, Norethisterone Acetate, Triptorelin.

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INTRODUCTION

There is significant evidence that aromatase inhibitors reduce endometriosis pain [1]. Aromatase inhibitors increase FSH secretion, which stimulates ovarian follicle growth in premenopausal women. Functional ovarian cysts were caused by women with rectovaginal endometriosis taking letrozole and desogestrel daily. Letrozole monotherapy for symptomatic uterine leiomyomas developed functional ovarian cysts in more than 50% of women [4, 5], and after laparoscopic treatment for endometriosis, after two months of receiving letrozole for endometriosis, 24% of women developed functional ovarian cysts.

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If premenopausal women are administered aromatase inhibitors at the same time as they are taking them, ovaries and gonadal estrogen biosynthesis should be effectively reduced [6]. Aromatase inhibitors (letrozole or anastrozole) have been combined with oral contraceptives [7], norethister-one acetate [8-12] or gonadotropin-releasing hormone analogues [13, 14] in previous studies of women with endometriosis. Currently, no studies have been published on pain symptoms and adverse effects associated with progestins. This study examined the efficacy and tolerability of progesterone along with gonadotropin-releasing hormone analogues in rectovaginal endometriosis.

METHODOLOGY

The objective of this prospective, randomized, open-label study was to compare letrozole versus norethisterone acetate or triptorelin for treating rectovaginal endometriosis symptoms of pain. A center for endometriosis diagnosis and treatment conducted this study. Pain symptoms were compared between the two study protocols after 6 months. Additionally, as a secondary objective of the study, participants evaluated adverse effects. A tertiary objective was to determine the volume of rectovaginal nodules.

STUDY POPULATION

Participating women underwent laparoscopy or laparotomy for symptoms of endometriosis, however deep lesions were not removed. Despite this, endometriosis was found to be present. Pain symptoms recurred or persisted after surgery in these patients. Study participants had pain symptoms lasting over a year and wanted to avoid additional surgery. The study included only premenopausal women. Rectal water contrast ultrasonography confirmed rectovaginal endometriosis [15-17]. An enteroclysis using multidetector computerized tomography was performed on patients with gastrointestinal complaints suggesting bowel endometriosis [18-20]. The following criteria were included: signs of bowel stenosis, such as uropathy or endometriotic nodules; nonsteroidal anti-inflammatory drug treatment within three months of inclusion; undiagnosed vaginal bleeding; osteopenia; and pulmonary, cardiac, hepatic, or renal diseases; pregnancy; psychiatric disturbances; or a history of substance abuse.

Protocol and randomization of the study

Each patient received letrozole, vitamin D3, and calcium. Additionally, they received triptorelin depot injections or oral norethisterone acetate. Treatment was scheduled to last six months. A computer-generated randomization list was prepared by an independent statistician not involved in the rest of the study. A sequentially numbered sealed opaque envelope containing cards with group assignments was prepared based on the list. At the endometriosis clinic, patients' sequential numbers were written on sealed envelopes. As needed, subjects received nonsteroidal anti-inflammatory drugs. Each month, they had to record how many tablets they used. Before starting treatment, during treatment, and at the end of treatment, blood counts, serum electrolytes, kidney and liver function tests, as well as lipid tests were performed. A DEXA scan was performed one month prior to the study and one month afterward.

Symptom evaluation

Each patient completed a questionnaire on symptoms associated with dysmenorrhea, nonmenstrual pelvic pain as well as deep dyspareunia during their visit. As previously described [10], pain symptoms were assessed using a 10-cm visual analogue scale (VAS). Moderate pain is defined as 5.1 to 8.0, and severe pain as 8.1 to 10.0. All participants reported moderate or severe pain. The questionnaire assessed dysmenorrhea, deep dyspareunia, and nonmenstrual pelvic pain using multidimensional categorical rating scales. Dysmenorrhea was defined in the scale as bedrest and discomfort, nonmenstrual pelvic pain as pain and analgesics, and deep dyspareunia as sexual limitations. Three and six months after starting the treatment, symptoms were evaluated for severity. When treatment was completed or interrupted, the women responded to the following question about how satisfied they were with their treatment overall: "Considering your level of satisfaction with quality of life, pain symptoms, overall well-being, and adverse effects, if any?", according to the previous article [10]. The responses were rated using a 5-point Likert scale. During monthly consultations, negative effects were noted.

Volume assessment of rectovaginal nodules

Ultrasonography was used to estimate endometriotic nodule volume before and after hormonal therapy for six months. Virtual organ computer-aided analysis was used to estimate rectovaginal endometriotic nodule volume. A sequence of 20 sections around a fixed axis of each endometriotic nodule, rotated 9° from the previous section, was obtained using the VOCALTM technique, which achieved reliability, validity, and speed. Using the 3D ultrasound machine's roller ball cursor, each nodule's volume was manually drawn. Measurements were taken off-line by a trained operator who didn't know the hormone therapy type. It took 10 to 15 minutes to perform these measurements.

STATISTICS

As appropriate, student t tests, C tests, and Fisher's exact tests were conducted in order to compare

the baseline characteristics of the participants. In order to assess the intensity of pain symptoms, student t tests were conducted between groups on the VAS scale to measure intensity of pain symptoms. Pain symptoms were compared using Mann-Whitney rank sum tests between study groups. In order to examine whether the intensity of pain symptoms was different prior to and following treatment, Wilcoxon signed rank tests were used. It was considered statistically significant when P 0.05 was used. Software versions 3.5 and 13.0 of Sigma Stat were used for data analysis.

RESULTS

The study included 80 women, of whom 70 consented and were randomized to one of two treatments. During the interim analysis, 18 women were assigned to group T and 17 to group N. A similar average age was observed in group T (35.0 years + 3.6 years) and in group N (35.2 years + 4.0 years; p = 0.857). One woman in group N and eight women in group T discontinued treatment because of adverse effects (5.9%) (p = 0.018). A total of 8 patients in group T stopped the treatment after 3.9 months, while a patient in group N stopped after four months. At the time of interruption, there were 4 women (11.1%) who were very dissatisfied, 20 women (55.6%) who were dissatisfied, 4 women (11.1%) who were uncertain, and 3 women (16.7%) were satisfied. Group N included 1 very dissatisfied woman (5.9%), 8 dissatisfied women (23.5%), 2 uncertain woman (5.9%), 16 satisfied women (47.1%), and 6 very satisfied women (17.6%). Four of the women in group T were satisfied or very satisfied, while 22 of the women in group N were satisfied or very satisfied. A comparison of the intensity of pain symptoms at baseline and during treatment is shown in Table 1. On both the VAS and multidimensional categorical rating scales, symptoms were similar at baseline. The intensity of nonmenstrual pelvic pain and deep dyspareunia was significantly lower in both study groups. In both groups T and N, pain symptoms were similar after three and six months of treatment. According to a VAS scale comparison of pain intensity after 6 months and 3 months, group T and group N showed Significant reductions in non-menstrual pelvic pain were observed in groups T and N. At 6-month, group N experienced a significant decrease in deep dyspareunia intensity; at 3-month, deep dyspareunia intensity decreased, but the difference was not statistically significant, perhaps because there were fewer patients in this group finished the treatment. At 3- and 6-months, multidimensional categorical rating scale scores did not differ significantly between study groups.

Rectovaginal endometriotic nodule volume in groups T and N was similar at baseline. Both study groups showed significant reductions in endometriotic nodules six months after treatment. The mean percent reduction in group T's nodule volume was significantly greater than in group N.

Each month, patients in group T took an average of 6.7 Naproxen sodium tablets, while patients in group N took an average of 6.5 Naproxen sodium tablets. In both groups T and N, naproxen sodium tablets were significantly less used each month after 3 months of treatment compared to the control group. In group N, naproxen sodium tablets were used less after 6 months of treatment. After 6 months, patients used naproxen sodium tablets less frequently in group T, but the difference was not statistically significant. 14 women and 6 women experienced adverse effects in group T. There were five women who interrupted treatment due to arthralgia, two women with flushes as well as hair loss, two women with decreased libido, one woman with arthralgia and flushing, one woman with myalgia and hot flushes, and one woman with myalgia and depression. Two patients in group N discontinued treatment due to weight gain, one woman due to arthralgia, 1 woman due to breakthrough bleeding, 1 woman due to depression, and 1 woman due to decreased libido. There was no effect on the count of red blood cells, the function of the liver, the function of the kidney, or the profile of lipids. During the treatment period of six months, DEXA scans revealed significant loss of mineral bone density. DEXA scans of group N revealed no significant changes in mineral bone density at the lumbar spine or hip. At the end of the treatment, no woman had osteopenia.

Table 1: Pain symptoms at baseline and during treatment.

	VAS scale			Multidimensional categorical rating scale		
	Group T (n = 36)	Group N (n = 34)	p	Group T (n = 36)	Group N (n = 34)	p
Dysmenorrhea baseline	9.7 ± 2.1	9.6 ± 2.3	0.981	4 (2-3)	4 (0-3)	0.990
Nonmenstrual pelvic pain baseline	7.1 ± 2.4	7.0 ± 2.4	0.88	3 (0-3)	23(0-3)	0.1057
3 months of treatment	4.2 ± 2.3	4.3 ± 2.5	0.882	2(0-2)	12(0-2)	0.918
6 months of treatment	1.2 ± 1.3	2.0 ± 1.8	0.286	0 (0-2)	1 (0-2)	0.171
P value for 3 months of treatment versus baseline	< 0.001	< 0.001		< 0.001	< 0.001	
p-value for 6 months of treatment compared to baseline	< 0.001	< 0.001		0.004	< 0.001	
6 month vs 3 month treatment P value	0.001	< 0.001		0.063	0.156	

Deep dyspareunia baseline	7.4 ± 2.9	7.6 ± 3.1	0.901	3(0-3)	3(0-3)	0.601
3 months of treatment	4.4 ± 2.2	4.6 ± 2.5	0.735	2 (0-2)	2(0-2)	0.953
6 months of treatment	3.0 ± 0.10	3.2 ± 2.4	0.827	2(0-1)	2(0-2)	0.506
Treatment 3 months vs. baseline p value	< 0.001	< 0.001		0.031	< 0.001	
6 month treatment vs baseline p value	0.022	< 0.001		0.042	< 0.001	
p 0.05: 6 vs 3 months of treatment	0.088	< 0.001		0.076	0.125	

Table 2: Patients' adverse reactions to treatment.

The adverse effect	Group T (N = 36)	Group N (N = 34)	p
Arthralgia	14	2	0.051
Symptoms of myalgia	6	2	0.703
Bleeding from a persistent breakthrough	0	4	0.329
Depression	8	2	0.438
Insomnia	6	0	0.329
Libido decreases	8	4	0.758
Vaginal dryness	6	0	0.329
Having hot flushes	8	0	0.204
Loss of hair	4	0	0.586
Having a headache	4	0	0.586
Gaining weight	2	4	0.703
Adverse effects are at least one	28	12	0.028

DISCUSSION

The use of hormonal therapies does not cure endometriosis, so it is recommended that women with endometriosis take them chronically. Adverse effects can affect compliance with therapy from this perspective. This randomized prospective study demonstrated progestin co-treatment is more acceptable to patients than gonadotropin-releasing hormone analogue co-treatment. Letrozole combined with triptorelin has a significantly higher risk of adverse effects than letrozole combined with nor-ethisterone acetate. At least one adverse effect was experienced by 77.8% of the women who were in group T and 35.3% of the women who were in group N. More patients interrupted treatment in group T (44.4% versus 5.9%). As a result, the study was terminated before 80 subjects had been enrolled. Aromatase inhibitors can cause adverse effects. A total of two women (5.7%) discontinued treatment before the fourth month due to adverse effects associated with the prolonged treatment with aromatase inhibitors for a short period of time. Similarly, letrozole was reported to have no significant side effects associated with the endometriosis laparoscopic procedure. Aromatase inhibitors can cause several adverse effects when administered for longer periods of time (six months) [3, 7-12]. For 6 months, a prospective randomized trial comparing goserelin with anastrozole did not report adverse effects associated with aromatase inhibitors. Our study patients may have been more active postoperatively and demonstrated lower tolerance for adverse events than those receiving aromatase inhibitors. For six months, a group of 90 women with relapsing pain symptoms following medical and surgical treatment received either anastrozole combined with goserelin, or just goserelin alone, for a duration of six months. It was important to note that those receiving the double-drug regimen had no adverse effects or higher discontinuation rates related to aromatase inhibitors, but it was important to note that those receiving the double-drug regimen reported fewer pain relapses. There is no clear explanation for these differences in adverse effects and discontinuation rates. The current study's monthly consultations may have increased adverse effects reporting. Combining aromatase inhibitors with gonadotropin-releasing hormone analogs reduces bone mineral density [13]. Women included in group N, however, showed no significant change in mineral bone density following treatment, which we had previously observed [9, 11] and other authors [8]. The use of norethisterone acetate may promote bone metabolism. It has been found that norethisterone acetate converts into ethinyl estradiol to a degree of 0.20 to 0.33, depending on the study.

The difference between triptorelin and norethisterone acetate in pain symptoms was not significant. Due to a small number of patients, definitive conclusions cannot be drawn regarding treatment effectiveness on pain symptoms. Several studies have investigated how hormonal therapy affects rectovaginal endometriotic nodules. Rectovaginal endometriotic nodules are reduced by progesterone, oral contraceptives, vaginal danazol, gonadotropin-releasing hormone analogs, and levonorgestrel intrauterine devices.

Letrozole combined with progestin or gonadotropin-releasing hormone analogues significantly reduced rectovaginal endometriotic nodules. Triptorelin significantly reduced nodule volume compared to norethisterone acetate.

CONCLUSION

Aromatase inhibitors were effective in treating endometriosis pain. Since the study only consists of a small number of patients, definitive conclusions cannot be drawn about which treatment is more effective. This study shows progestin co-treatment is more acceptable to patients for the first time. Combining aromatase inhibitors with analogues of gonadotropin-releasing hormones may result in more adverse effects and higher discontinuation rates. Accordingly, progestins should be the first line of treatment for premenopausal women receiving aromatase inhibitors. In combination with aromatase inhibitors, combined oral contraceptives may be as effective and tolerable as progestins in suppressing ovarian activity.

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