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NORETHISTERONE ACETATE ALONE VERSUS IN COMBINATION WITH LETROZOLE FOR TREATMENT OF CHRONIC PELVIC PAIN IN PATIENTS WITH ENDOMETRIOSIS

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ABSTRACT

Background: Endometriosis is a chronic inflammation which is estrogen-dependent and a major cause of chronic pelvic pain (CPP) and low quality of life among women of reproductive age. The treatment remains largely dependent on hormonal therapy although the optimal guidelines that should be applied in managing pain remain in research. **Objective:** To compare mean pain scores after six months of treatment with norethisterone alone versus in combination with letrozole in women with endometriosis. **Methodology:** It was a randomized controlled trial that was conducted at the Department of Obstetrics and Gynaecology, Services Hospital Lahore from April 2025 to October 2025. Sixty women who had endometriosis-related CPP were recruited and were randomly matched into two groups of equal size. Group A was given letrozole (2.5 mg/day) in combination with norethisterone acetate (2.5 mg/day), whereas Group B was given norethisterone acetate alone. The length of treatment was six months. The Visual Analog Scale (VAS) was used to assess the severity of pain at the baseline and subsequent to the therapy. The statistical analysis was done using SPSS version 25 and the mean difference between the groups was tested with an independent sample t-test with p 0.05 as significant.

Results: The combination therapy group had a much greater improvement in mean VAS pain scores at six months than the norethisterone-only group (1.8 ± 0.7 vs 4.3 ± 0.6; $p < 0.001$). The difference in the improvement of the base was in both groups but the level of pain reduction in the combination group was significantly higher.

Conclusion: Letrozole combined with norethisterone acetate is much more effective at treating endometriotic women. This combination therapy may be a potentially superior therapy in the treatment of chronic pelvic pain in this group.

KEYWORDS: Endometriosis, Chronic pelvic pain, Letrozole, Norethisterone acetate, Aromatase inhibitors, Randomized controlled trial.

INTRODUCTION

Chronic pelvic pain (CPP) is a widespread, multifaceted, and expensive problem that, disproportionately, affects women and has enormous consequences on their life quality. The diagnosis and the preliminary treatment of CPP are mainly in the field of obstetrics and gynecology specialists. It is important to consider management in a holistic manner which involves taking longer to consult, using proper clinical codes, and interdisciplinary teamwork where needed.[1,2] Endometriosis is characterized as the presence of endometrial glands and stroma extrauterine. It is an inflammatory disorder that is estrogen dependent and is marked by the growth of ectopic endometrial tissue. These implants are

ectopic and act like normal endometrium, with menstrual bleeding. Nevertheless, the abnormal location of the shed blood traps it, resulting in the development of endometriomas (especially in the ovaries), chronic inflammation, irritation of nearby structures like the peritoneum and urinary tract, and eventually fibrosis and adhesions.[2,3,5]

Endometriosis is a chronic cause of pelvic pain and infertility and is found in about 5%–50 per cent of infertile women and is a cause of CPP in over a third of cases. Clinically, it is associated with dysmenorrhea, deep dyspareunia, chronic, non-cyclic non-cyclic pelvic pain, heavy or irregular menstrual bleeding, and dysuria.[3,5]

Different medical treatments can be used to manage endometriosis-related pain, which includes combined oral contraceptive pills, progestins (e.g., norethisterone acetate), danazol, gestrinone and gonadotropin-releasing hormone agonists (GnRH agonists). Aromatase inhibitors (AIs), somewhat more recently, have become a promising treatment option because of their capacity to inhibit the production of estrogen.[5,6]

Letrozole is a third-generation non-steroidal aromatase inhibitor, which is selective due to its ability to inhibit aromatase enzyme, which causes a considerable decrease in estrogen level in the body. It is also common in the treatment of estrogen receptor-positive breast cancer and has demonstrated effectiveness in alleviating pain in endometriosis.[7]

There is some evidence that combination therapy can lead to better results than monotherapy. As an example, Ashraf et al. have found that the combination of norethisterone acetate with letrozole was much more effective than norethisterone alone in pain reduction at six months (1.72 ± 0.74 vs. 4.39 ± 0.64; $p < 0.001$).[4]

Although there has been an increasing evidence, there is little information comparing the efficacy of letrozole monotherapy and its combination with norethisterone acetate especially in local populations. Additionally, the literature on this comparison at the international level is rather sparse.[8,9,10]

Thus, the proposed research is expected to compare the efficacy of the use of letrozole versus a combination of letrozole with norethisterone acetate to alleviate endometriosis-related pain among our local population. The results of this research will be used to find a more efficient treatment plan and provide useful baseline data on the local and international clinical practice.

Objective

To compare mean pain scores after six months of treatment with norethisterone alone versus in combination with letrozole in women with endometriosis.

METHODOLOGY

It was a randomized controlled trial which was conducted in the Department of Obstetrics and Gynaecology, Services Hospital Lahore, during April 2025 and October 2025. A non-probability consecutive sampling was used to enroll 60 women with endometriosis-related chronic pelvic pain. The computer-generated random numbers were used to assign the participants to either of the two groups. Group A was given letrozole (2.5 mg/day) and norethisterone acetate (2.5 mg/day) and Group B was only given norethisterone acetate (2.5 mg/day). The therapy was the first day of menstruation and lasted six months. The severity of pain at the baseline and the end of the therapy was determined using Visual Analog Scale (VAS).

Inclusion Criteria

The women aged 18-60 years who were diagnosed with endometriosis due to clinical symptoms and sonographic appearance and who reported having chronic pelvic pain characterized by VAS score of more than 5 were included.

Exclusion Criteria

Women with over 3 cm long ovarian endometriomas with deep bowel or urinary tract involvement, those who have had hormonal therapy within the last three months, history of osteopenia or epilepsy, pregnancy or lack of informed consent were excluded.

Data Collection Procedure

The ethical approval was obtained and eligibility of the participants recruited in the outpatient department. The informed consent was obtained prior to enrolment in a written form. Demographic and clinical baseline data (age, BMI and disease duration) were obtained. Clinical examination and ultrasound were performed in all patients. The subjects were randomly chosen into two groups of treatment. Prescription was done as a group and follow up visits to supervise adherence. Pain was measured at the baseline and the 6 months of treatment with VAS. All the results were tabulated in a structured proforma in order to ensure uniformity and accuracy in the data gathering.

Data Analysis

The SPSS version 25 was used to analyze the data. The age, duration of disease and pain scores were taken as the means and standard deviation as quantitative variables. The qualitative variables were as frequencies and percentages. Mean VAS pain score at six months was the main outcome which was compared between the two groups using independent sample t-test. This stratification was aimed at balancing the modifying effects which could have been

present such as age, Body mass index and baseline pain marks. Post-stratification analysis was done using the same statistical test. The p-value of less than 0.05 was taken as a significant p-value.

RESULTS

Sixty women with chronic pelvic pain that was due to endometriosis were recruited and randomly assigned to two groups (n = 30 each). The mean age of the respondents was 28.6) 4.5 years. The two groups had similar baseline demographic and clinical characteristics with no statistically significant differences between the two groups ($p > 0.05$) implying that the two groups were sufficiently randomized.

Table 1: Demographic and Clinical Characteristics at baseline.

Parameter	Total (n = 60)	Group A (n = 30)	Group B (n = 30)	p-value
Age (years)	28.6 ± 4.5	28.4 ± 4.6	28.8 ± 4.3	0.78
BMI (kg/m²)	27.9 ± 3.6	28.1 ± 3.5	27.7 ± 3.7	0.69
Duration of disease (weeks)	18.2 ± 6.4	18.5 ± 6.2	17.9 ± 6.6	0.74
Baseline VAS score	7.5 ± 1.0	7.6 ± 1.1	7.4 ± 1.0	0.42

Baseline did not show any statistically significant group differences.

Table 2: Pre- and Post-treatment pain scores.

Group	Baseline VAS	6-Month VAS	Mean Reduction
Group A (Letrozole + Norethisterone)	7.6 ± 1.1	1.8 ± 0.7	5.8
Group B (Norethisterone Alone)	7.4 ± 1.0	4.3 ± 0.6	3.1

A greater reduction in pain scores was observed in Group A compared to Group B.

Table 3: Comparison of Mean Pain Scores 6 months.

Outcome	Group A (n = 30)	Group B (n = 30)	p-value
Mean VAS score (6 months)	1.8 ± 0.7	4.3 ± 0.6	< 0.001
Percentage pain reduction	76.3%	41.9%	< 0.001

There was a statistically significant difference in reduction of pain in the group of combination therapy.

Table 4: VAS Stratified Analysis 6 months.

Stratification Variable	Group A Mean VAS	Group B Mean VAS	p-value
Age ≤ 30 years	1.7 ± 0.6	4.2 ± 0.5	< 0.001
Age > 30 years	2.0 ± 0.8	4.5 ± 0.7	< 0.001
BMI ≤ 28 kg/m²	1.7 ± 0.7	4.1 ± 0.6	< 0.001
BMI > 28 kg/m²	2.0 ± 0.8	4.6 ± 0.7	< 0.001
High baseline pain (VAS ≥ 8)	2.1 ± 0.8	4.8 ± 0.6	< 0.001

The stratified analysis showed that combination therapy was equally high in all subgroups.

Interpretation

The results of the study showed that both of the treatment regimens led to the substantial reduction in chronic pelvic pain in endometriosis women. However, when letrozole was added to norethisterone acetate, there was a much greater reduction of the severity of pain compared to that of norethisterone alone.

The VAS mean score at six months was much lower in the combination group (1.8 ± 0.7 vs 4.3 ± 0.6; $p < 0.001$) with almost twice the percentage pain decrease. Stratified analysis was also used to make sure that this benefit was consistent across all age groups, BMI groups and baselines of pain severity.

These results indicate that dual hormonal suppression that is directed at the systemic and local estrogen synthesis is more beneficial in the treatment of chronic pelvic pain related to endometriosis.

DISCUSSION

The current research shows that combination therapy with norethisterone acetate and letrozole is much better in alleviating chronic pain in the pelvis than the use of norethisterone. This coincides with Ashraf et al.[4] that reported superior pain relief in combination therapy in patients with endometriosis related pain.

The primary causes of endometriosis-related pain, resulting in continued production of estrogen, continued inflammation and sensitization of pain pathways are the inflammatory processes caused by estrogen and the local expression of aromatase in the ectopic endometrial tissue. Letrozole and aromatase inhibitors, like aromatase, inhibit extra-ovarian production of estrogen, which decreases lesion activity and has better pain outcomes.[5,6]

These results of the present study are also consistent with the results given by Zhao et al.[7], who demonstrated that regimens of letrozole are superior to the conventional hormonal therapy in the management of symptoms in isolation. These findings prove that aromatase inhibition is a useful complementary treatment of pain in endometriosis.

Further evidence by Ferrero et al.[8] has shown that combination regimen involving letrozole and progestins are far more effective in the treatment of pain due to endometriosis compared to the use of progestins. It is explained by the synergistic effect, when norethisterone induces the suppression of the endometrial ectopic tissue, its decision and atrophy, and letrozol inhibits the peripheral and local synthesis of estrogen, resulting in the more complete control of the disease.[8, 17]

Biological plausibility of the clinical benefit identified in the present study can also be explained by the fact that Almassinokiani et al.[9] also found an improvement in the symptoms of pelvic pain with aromatase inhibitor treatment. All these have shown that interference with the estrogen biosynthesis is a dominant part in reduction of the intensity of the symptoms in endometriosis.[9, 18]

Even the effectiveness of combination hormonal therapy that involves the use of regimens that included letrozole has been supported by randomized clinical evidence whereby the regimens that included letrozole yielded better pain outcomes in comparison to the traditional treatment regimens.[10]

The concept of endometriosis being an estrogen-dependent, long-term, and chronic inflammatory disease requiring multi-targeted hormonal suppression may be the reason behind the biological relevance of the dual suppression approach.[11,13]

Recent systematic reviews also confirm that neuroangiogenesis, central sensitization, and local estrogen production in lesion are associated with long-term pain in endometriosis, which confirms the need to use multi-pathway hormonal suppression.[14,18]

In addition, recent pharmacological reviews indicate that aromatase inhibitors, used in combination with progestins, are far more effective than mono therapy, in terms of enhancing pain scores in refractory cases, although special caution is needed to avoid hypoestrogenic adverse effects.[15,16]

Together, the available data are very compelling to support the biological, clinical rationale of the combination of letrozole and norethisterone acetate to achieve improved symptom control of chronic pain in the pelvis related to endometriosis.

The shortcomings of the current study would be a rather limited sample size and duration of follow up. There was no evaluation of long-term safety outcomes especially in terms of hypoestrogenic effects of aromatase inhibitors. It is recommended that a large scale randomized controlled trial with a long follow-up period should be carried out in the future to further prove the efficacy and safety of such a combination therapy.

CONCLUSION

The current research paper concludes that the combination of letrozole and norethisterone acetate is very effective as opposed to norethisterone in treatment of chronic pelvic pains caused by endometriosis. Dual hormonal suppression can be attributed to the fact that this is an improvement in the effectiveness of combination therapy as it suppresses both systemic and local estrogen production. The results support the use of aromatase inhibitors in the treatment plan of the patients with moderate to severe pains who are not responding well to the conventional treatment.

Given the recurrence and chronicity of endometriosis, there is need to improve the quality of life and functioning outcomes through optimization of pain management measures. The results are promising but larger multicenter trials with a longer follow-up are needed to establish long-term safety, recurrence, and cost-effectiveness of combination therapy. The research provides a good background of information to be applied in other future research and clinical practice in the management of chronic pelvic pain associated with endometriosis.

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