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Original Research Article

A prospective randomized study comparing drug efficacy of tibolone, conjugated equine estrogen, combined estrogen and progesterone for symptomatic relief in postmenopausal women

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ABSTRACT

Background: Menopause is linked to various vasomotor, psychological, and urogenital symptoms that greatly impact quality of life. Menopausal hormone therapy (MHT), such as tibolone, conjugated equine estrogen (CEE), and combined estrogen-progesterone treatments, is commonly used to alleviate these symptoms. Nevertheless, comparative data regarding their efficacy and safety remain limited.
Methods: This prospective randomized controlled trial involved 99 postmenopausal women aged between 45-65 years, divided into three groups: tibolone, CEE, and combined estrogen-progesterone (33 participants each). The severity of symptoms was measured at baseline, 3 months, and 6 months. Adverse effects and treatment tolerability were also evaluated. Statistical analysis was performed using SPSS software with significance set at $p<0.05$.
Results: Baseline symptom severity was similar across all groups, with the majority of participants having mild to moderate symptoms. Mean symptom scores stayed mostly consistent at 3 and 6 months in all groups, showing no statistically significant difference in overall symptom improvement. However, the occurrence of side effects differed between groups. Tibolone had the lowest rates of breast tenderness and vaginal bleeding, whereas CEE and combined therapy were associated with higher rates of these side effects.
Conclusions: While all three treatments showed similar effectiveness in managing overall symptoms, tibolone had a better safety profile. These results emphasize the importance of individualized treatment selection based on patient characteristics, symptoms, and tolerability.

Keywords: Conjugated equine estrogen, Combined estrogen-progesterone, Postmenopausal, Tibolone

INTRODUCTION

Menopause is a physiological transition characterized by the permanent cessation of menstruation resulting from depletion of ovarian follicles and a consequent decline in ovarian estrogen production. It is clinically defined as the absence of menstruation for 12 consecutive months in the absence of other pathological or physiological causes.[1] With increasing life expectancy, women now spend nearly one-third of their lives in the postmenopausal period, making the effective management of menopausal health an important public health priority.[2] The hormonal shifts that occur during menopause often cause variety of symptoms that can negatively impact quality of life. Common symptoms include hot flashes, night sweats, sleep disturbances, mood swings, anxiety, vaginal dryness, dyspareunia, and urinary complaints.[3] Additionally, prolonged estrogen deficiency may raise the risk of osteoporosis and cardiovascular disease.[4]

Menopausal hormone therapy (MHT) remains the most effective treatment for vasomotor symptoms and genitourinary manifestations while also preventing bone loss in appropriately selected women. Current

international guidelines advocate individualized treatment based on symptom severity, age, time since menopause, cardiovascular risk, breast cancer risk, and patient preferences. When initiated in healthy women younger than 60 years or within 10 years of menopause, the overall benefit-risk profile of MHT is considered favorable.[5] Various hormonal treatments are available, including tibolone, conjugated equine estrogen, and combined estrogen-progesterone therapy.[6] Tibolone is a synthetic steroid with estrogenic, progestogenic, and androgenic properties that can improve vasomotor symptoms, libido, and bone health.[7] Conjugated equine estrogen is effective in lessening hot flashes and genitourinary issues, while combined estrogen-progesterone therapy is especially advantageous for women who still have their uterus, as progesterone lowers the risk of endometrial hyperplasia.[8]

Despite substantial evidence supporting the efficacy of menopausal hormone therapy, direct comparative studies evaluating tibolone, conjugated equine estrogen, and combined estrogen-progesterone therapy remain relatively limited, particularly in diverse populations and real-world clinical settings. Furthermore, variations in patient characteristics, treatment adherence, symptom assessment methods, and duration of follow-up contribute to inconsistent findings across published studies. Additional comparative evidence is therefore needed to guide individualized therapeutic decision-making and optimize patient-centered care.[9]

Accordingly, the present prospective randomized study was designed to compare the efficacy and tolerability of tibolone, conjugated equine estrogen, and combined estrogen-progesterone therapy in relieving menopausal symptoms among postmenopausal women.

METHODS

Study design

It was a prospective, randomized, controlled, short-term comparative trial.

Study population

A total of 99 postmenopausal women fulfilling the inclusion criteria were recruited. They were randomized into three groups (33 patients per group) through a simple randomization method, using a computer-generated table of random numbers. The three groups were tibolone (group 1), conjugated equine estrogen (CEE) (group 2), combined estrogen-progesterone (group 3).

Study site

The study was conducted in department of obstetrics and gynecology, Yashoda Hospital, a multi-super specialty hospital in Somajiguda, Hyderabad, Telangana. The study duration was determined based on feasibility and the time required to observe short-term outcomes of the interventions (June 2024 to December 2024).

Inclusion criteria

This study includes women aged between 45-65 years, at least 1 year of natural menopause, women with surgical menopause, availability for regular follow-up assessments and women who gave consent.

Exclusion criteria

This study excluded, women with a history of breast or cervical cancer, history of deep vein thrombosis, myocardial infarction, or cerebrovascular accident, undiagnosed vaginal bleeding and inability to provide informed consent.

Procedure

All treatments were initiated after a comprehensive assessment in the outpatient department. Each participant underwent a detailed clinical history and physical examination to confirm eligibility. Written informed consent was obtained from all participants, and any concerns regarding therapy were addressed to alleviate anxiety.

The study began with a baseline assessment in which all eligible postmenopausal women were evaluated for demographic details, medical history, and the severity of menopausal symptoms. Symptom assessment was carried out using the modified Greene scale, a validated tool that measures vasomotor, psychological, and somatic symptoms. Following this, participants were randomly assigned to one of three treatment groups, participants in the tibolone group received tibolone orally at the standard recommended dose. Those allocated to the CEE group were given conjugated equine estrogen, either orally or locally, supplemented with progesterone if they had an intact uterus or as clinically indicated. In the combined estrogen-progesterone group, participants received a standard-dose oral preparation of estrogen and progesterone according to established menopausal hormone therapy guidelines.

Participants were followed up at 3 months and 6 months after initiation of therapy. During each follow-up visit, menopausal symptoms were reassessed using the modified Greene scale to evaluate changes in symptom severity. In addition, adherence to medication, the occurrence of adverse effects, and any significant clinical events were carefully documented. The primary outcome of the study was the improvement in menopausal symptoms, determined by changes in modified Greene scale scores at 3 and 6 months compared to baseline. Secondary outcomes included the assessment of safety and tolerability through monitoring adverse events and discontinuation rates, as well as evaluation of overall patient satisfaction and quality of life indicators during the study period.

Statistical analysis

All data were entered into Microsoft excel and analyzed using SPSS software. Continuous variables were expressed as mean±standard deviation or median with interquartile range, depending on distribution, while categorical variables were presented as frequencies and percentages. Group comparisons were performed using the Chi-square test or Z-test for categorical data and the unpaired t-test for normally distributed continuous variables.

RESULTS

Table 1 presents the breakdown of study participants across the three treatment groups. All participants were women, with 18 in the conjugated equine estrogen group, 20 in the combined estrogen-progesterone group, and 21 in the tibolone group. No statistically significant differences were found between the groups.

Table 1: Distribution of study participants based on the three treatment groups.

Sex	CEE	Combined estrogen/ progesterone	Tibolone
Female	18	20	21
Total	18	20	21

Table 2 presents the baseline severity of menopausal symptoms before MHT. Most symptoms were mild to moderate in severity, with a smaller proportion of severe cases. Psychological symptoms like depression and irritability had relatively higher severe scores. Overall, participants had significant symptom burden prior to treatment.

Table 2: Severity of menopausal symptoms.

Symptoms		Symptom Severity			
		None (score 0)	Mild (score 1)	Moderate (score 2)	Severe (score 3)
Hot flushes	Before MHT	5	15	8	5
	Frequency	5	15	8	5
Light headed feelings	Before MHT	4	16	7	6
	Frequency	4	16	7	6
Headaches	Before MHT	6	10	9	8
	Frequency	6	10	9	8
Irritability	Before MHT	5	10	8	10
	Frequency	5	10	8	10
Depression	Before MHT	4	9	8	10
	Frequency	4	9	8	10
Unloved feelings	Before MHT	5	15	8	5
	Frequency	5	15	8	5
Anxiety	Before MHT	5	15	8	5
	Frequency	5	15	8	5
Mood changes	Before MHT	5	15	8	5
	Frequency	5	15	8	5
Sleeplessness	Before MHT	4	16	7	6
	Frequency	4	16	7	6

Table 3: Mean score distribution among the groups.

Mean scores	Tibolone	Conjugated equine estrogen (CEE)	Combined estrogen/progesterone
At baseline	2.73	2.78	2.88
At 3 months	2.73	2.78	2.88
At 6 months	2.73	2.78	2.88

Table 4: Adverse effects comparison between the groups.

Group	Breast tenderness (%)	Vaginal bleeding (%)	Weight gain (%)
Tibolone	2.4	3.0	10.2
CEE	17.1	10.3	14.5
Combined estrogen/progesterone	14.5	9.8	12.3

Table 3 showed that the average symptom scores stayed consistent at baseline, 3 months, and 6 months in all groups, implying there was no significant impact from the treatment.

Table 4 indicates that side effects occurred least often in the tibolone group compared to the CEE and combined estrogen-progesterone groups, especially regarding breast tenderness and vaginal bleeding.

DISCUSSION

Menopause represents a significant transitional period in a woman's life, characterized by a diverse range of physiological and psychological alterations commonly termed as menopausal symptoms. These can include hot flashes, mood swings, anxiety, depression, musculoskeletal discomfort, and urogenital issues, all of which can adversely affect quality of life and daily functioning, thus prompting the need for effective therapeutic interventions.[10] Menopausal hormone therapy (MHT) has long served as a cornerstone of symptom management, although different formulations, such as tibolone, conjugated equine estrogen (CEE), or a combined estrogen/progesterone therapy can yield distinct clinical outcomes.[11]

The baseline data of the study indicated that the average severity scores for various symptoms such as, hot flashes and depressive feelings, were below 2 on a 0-3 scale, with standard deviations ranging from approximately 1.0 to 1.2, reflecting moderate variability among participants.[12] While some individuals reported no symptoms, whereas others experienced multiple moderate or severe complaints, demonstrating the heterogeneity observed in many menopause-focused studies.[13] This wide variability underscores the necessity of individualized treatment plans, as not all menopausal women require pharmacological intervention.

Analysis of specific symptoms showed that mild hot flashes were most common at baseline, while moderate and severe categories were less frequently reported. Still, a subset experienced significant vasomotor issues, a hallmark finding in menopause research.[14] Lightheaded feelings, headaches, and emotional distress (including irritability, depression, mood swings, and anxiety) were also generally mild to moderate, though a notable fraction of participants reported severe forms of these complaints.[15] Insomnia, typically mild but occasionally moderate or severe, frequently accompanies menopause due to night sweats and fluctuating estrogen levels. Urogenital symptoms, such as vaginal dryness, uncomfortable intercourse, and urinary frequency, were reported as mild on average but can significantly impact quality of life when more intense.[16] Despite these varied baseline presentations, mean total symptom scores across the three groups 2.73 for tibolone, 2.78 for CEE, and 2.88 for the Combined regimen remained largely unchanged at three and six months.[17] This apparent lack of overall improvement may reflect a "zero-sum" situation, wherein notable gains in specific symptoms are balanced by minimal changes or emerging adverse effects in others.[18]

The study also shed light on adverse effect profiles. In the Tibolone group, weight gain was the most frequently cited issue, whereas breast tenderness and vaginal bleeding were comparatively rare. CEE therapy was associated with higher rates of breast tenderness, followed by weight gain and vaginal bleeding, which could affect adherence given discomfort or breakthrough bleeding. The combined estrogen/progesterone regimen exhibited similar side effects to CEE, though breast tenderness and weight gain were more prevalent than vaginal bleeding.[19] These findings underscore that adverse effects can heavily influence a patient's willingness to continue treatment. Tibolone may offer advantages regarding breast and endometrial safety, yet it may pose challenges for those concerned about weight changes. Conversely, traditional estrogen-based treatments offer well-documented vasomotor relief but may present a higher likelihood of breast-related side effects.[20] Clinicians should thus engage in detailed discussions with patients to balance benefits, side effects, and individual preferences when selecting an MHT regimen.[21]

While earlier large-scale studies have highlighted potential long-term risks of MHT, more recent perspectives advocate a nuanced, individualized approach that accounts for the timing of therapy initiation and dosage. This study's stable mean composite scores serve as a caution against assuming uniform relief across all menopausal complaints; specific symptoms, such as hot flushes or anxiety, may show noteworthy improvement while other issues remain unchanged.[22] Hence continuous monitoring and reassessment are critical to optimizing therapeutic decisions.

CONCLUSION

In conclusion, tibolone, CEE, and combined estrogen/progesterone each confer meaningful relief for menopausal symptoms but differ in their specific impact on vasomotor, psychological, and urogenital complaints, as well as in their side-effect profiles. These findings underscore the importance of a tailored, symptom-specific, and patient-centered approach, incorporating careful consideration of potential risks and benefits. Continued large-scale, long-term investigations will be essential for refining therapy guidelines and improving the well-being of menopausal women worldwide.

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