

ORIGINAL ARTICLE

Effectiveness of tibolone in the management of postmenopausal symptoms

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Abstract

Background: Tibolone is a synthetic hormone replacement therapy preparation with estrogenic, progestogenic and androgenic tissue selective mechanism of action. It has advantages over traditional preparations of estrogen and progesterone considering the risks and adverse effects.

Objective: To evaluate the extent of effectiveness and adverse effects of Tibolone.

Method: This clinical trial was done in Khulna Medical College Hospital between January to December 2019. Postmenopausal women were selected by inclusion and exclusion criteria. Alternate participant was included in two different group. Participants of group A was treated with Tibolone for 6 months and participants of group B was treated with placebo for 6 months. Each participant was followed up after 3 and 6 months. Four categories of postmenopausal symptoms (hot flushes, night sweats, sleep disturbance and mood swinging) were evaluated. Participants were monitored for any adverse effects. Severity of postmenopausal symptoms was measured by using menopausal visual analogue scale.

Results: Total 90 participants, were enrolled in this study, half of them were included in each group. Baseline assessment in group A participants revealed mild, moderate and severe symptoms in 05 (12%), 29 (64%) and 11 (24%) women respectively. After 6 months of treatment with tibolone, 35 (78%) participants became asymptomatic. This improvement is statistically significant ($p < 0.001$). In group B, participant's baseline assessment revealed mild, moderate and severe symptoms in 07 (16%), 28 (62%) and 10 (22%) cases respectively. After 6 months of treatment with placebo, 02 (05%) women were asymptomatic. This improvement is not statistically significant. No adverse event was observed during treatment with tibolone. Comparison between the tibolone and placebo treatment group showed, tibolone treatment is better.

Conclusion: Tibolone effectively relieves the postmenopausal symptoms and improves the quality of women's health at menopause.

Key words: Tibolone, Hormone replacement therapy, Postmenopausal women

Introduction

Hormone replacement therapy (HRT) is the most efficient treatment for prevention of long term estrogen deficiency due to depletion of ovarian follicle in women at menopause. The extensive postmenopausal symptoms can be categorized into somatic, organic and metabolic symptoms.¹ Symptoms begin several years before the last menstrual period when hormone levels are fluctuating. It may last for about 7 to 10 years. Vasomotor symptoms, manifests with chronic

insomnia, concentration disorder, decreased libido and increased cardiovascular risks.² There may be parkinsonism, dementia and eye problems.³ Evaluation of Bangladeshi women at menopause reveals feeling of tiredness in 83%, hot flushes in 64%, night sweats in 63%, depression in 82% and osteoporosis in 72%.⁴

Traditional HRT with estrogen and progestogen bring certain risks and undesirable adverse effects. Long term use of estrogen more than 10

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years, though does not induce breast cancer and endometrial carcinoma, can promote its growth. Undesirable adverse effects are mastodynia, fluid retention, nausea, lower extremities cramp, headache and venous thromboembolism.⁵

These concern of risks and adverse effects led to the search for alternative HRT. Tibolone is a synthetic preparation with estrogenic, progestogenic and androgenic properties that relieves climacteric symptoms and prevents osteoporosis. Tibolone possesses a tissue selective mechanism of action that differs from that of estrogen and progestogen. Its 3 hydroxymetabolites bind and activate estrogen receptors in vagina, bone and other sites which is responsible for relieving postmenopausal symptoms.

Adverse effects of Tibolone are few that include leucorrhoea, abdominal pain and weight gain. Vaginal bleeding and breast pain are less common with tibolone than with traditional estrogen-progesterone therapy.⁷ Tibolone does not cause atherosclerosis and coronary artery disease.⁸

So far known, tibolone trial has not been done in Bangladesh. Therefore this study was performed to evaluate the extent of effectiveness and the adverse effects of tibolone.

Methods and materials

Ninety women with postmenopausal symptoms were enrolled in this open level placebo-controlled clinical trial. The menopausal state was defined according to the criteria of World Health Organization (WHO) as permanent cessation of natural menstruation resulting from depletion of ovarian follicular activity and amenorrhoea for at least 12 consecutive months. The study period was one year from January 2019 to December 2019. The postmenopausal women attending the medicine out-patient department, admitted in the medicine ward of Khulna medical college hospital and in the private chamber of medicine specialists of Khulna city, Bangladesh were included. Ethical clearance was taken from the Ethical committee of Khulna medical college.

Inclusion criteria was a gynaecological history with normal finding in physical examination- a normal mammography, a vaginal ultrasonography reporting an endometrial thickness of <5 mm and good general health based on medical history, physical examination and laboratory reports. The exclusion criteria was history of exogenous sex hormone intake within last six months, presence of breast lump, breast cancer, endometrial cancer, vaginal bleeding, hypertension, diabetes mellitus,

active or history of venous thromboembolism, liver disease, kidney disease, body mass index of >35 kg/m² and smoking habit.

Total participants were alternately allocated into two groups. Informed written consent was taken from each participant. The use of Menopausal visual analogue scale (MVAS) was described to each participant. Forty five participants of group-A was treated with one tablet of Tibolone 2.5 mg once daily orally for 6 months and 45 participants of group B was treated with one tablet of placebo once daily orally for the same period of 6 months. Combined preparation of calcium and vitamin D was used as placebo.

Four category of postmenopausal symptoms: hot flushes, night sweats, sleep disturbance and mood swinging were evaluated. The severity of each category of symptom was scored as none = 0, mild =1, moderate = 2 and severe = 3. Baseline assessment and response to the treatment was measured by using the MVAS. Pre-formed data sheet was used for each participant. Particulars of the participants was recorded in the data sheet. Each participant was visited at three occasions. 1st visit for the baseline assessment, 2nd Visit after 3 months of treatment and last visit after 6 months of treatment to evaluate the response and adverse effects of treatment. The data collected in pre-formed proforma was analysed by using the software Statistical Package for the Social Science (SPSS) version 21. P value was calculated by chi square test.

Results

Total 90 participants were enrolled in this study, half of them were included in each group. The age of the participants was between 50 to 55 years. Mean age was 52 (± 0.6) years. All of 45 participants of group A completed the study but 5 participants of group B were dropped out.

Table I
Response after treatment with Tibolone

Severity of symptoms	Baseline No (%)	After 3 month No (%)	After 6 month No (%)	P value
Severe	11 (24)	00 (00)	00 (00)	<0.001
Moderate	29 (64)	20 (44)	04 (09)	
Mild	05 (12)	12 (27)	06 (13)	
None	00 (00)	13 (29)	35 (78)	
Total	45	45	45	

Baseline assessment of 45 participants of group A revealed that 05 (12%), 29 (64%) and 11(24%)

women were with mild, moderate and severe symptoms respectively. After 6 months of treatment with tibolone, 35 (78%) participants became asymptomatic, 04 (09%) had moderate symptoms and 06 (13%) had mild symptoms. The response to tibolone treatment is statistically significant ($p < 0.001$) (Table I).

Table II

Response after treatment with Placebo

Severity of symptoms	Baseline	After 3 month	After 6 month	P value
	No (%)	No (%)	No (%)	
Severe	10 (22)	06 (14)	06 (15)	> 0.05
Moderate	28 (62)	27 (63)	22 (35)	
Mild	07 (16)	10 (23)	10 (25)	
None	00 (00)	00 (00)	02 (05)	
Total	45	43	40	

Baseline assessment of 45 participants of group B revealed that 07 (16%), 28(62%) and 10(22%) cases were with mild, moderate and severe symptoms respectively. After 6 months of treatment with placebo only 2 (05%) participants became asymptomatic, 22(55%) had moderate symptoms and 10 (25%) had mild symptoms. This response to treatment with placebo is not statistically significant (p value >0.05) (Table-II).

Table III

Comparison of outcome between two groups

Treatment	Cured No %	Not cured No %	Total	p value
Tibolone	35 (78)	10 (22)	45	< 0.001
Placebo	02 (05)	38 (95)	40	
Total	37	48	85	

Chi square test ($X^2=45.44$; $df = 1$)

35 (78%) patients were cured and 10 (22%) cases were not cured in tibolone treatment group. Two (05%) participants were cured and 38 (95%) cases were not cured in placebo treatment group. Comparison between the response to tibolone and placebo treatment group by chi square test shows p -value <0.001 . So the tibolone treatment is better (Table III).

Discussion

Postmenopausal symptoms adversely affect the quality of women's health. Burger HG et al described in their study that hot flushes and night

sweats may affect 70% of postmenopausal women and 20% of them may have severe symptoms. Median duration of symptoms may be 5.2 years, but symptoms may continue for many years in 10% of women.⁹ HRT is effective treatment for endocrine postmenopausal symptoms and urogenital atrophy.¹⁰

Tibolone is better than estrogen as HRT considering the risks and adverse effects. In our study we evaluated the extent of effectiveness and adverse events of tibolone. This study revealed significant improvement of postmenopausal symptoms and the adverse events were insignificant. Study conducted by Tasmin S et al in Bangladesh described that at menopause 50% women suffer from hot flushes, 33% from night sweats, 51.8% from insomnia, 44.3% from body ache and 31.3% suffer from feeling sad. Hormone replacement therapy in these postmenopausal women efficiently relieve these distressing symptoms.¹¹ Menopausal visual analogue scale (MVAS) has reliability and validity for assessing severity of postmenopausal symptoms in women.¹²

Tibolone is a steroid hormone derived from the Mexican yam.¹³ Tibolone has estrogenic effect which is responsible for relieving hot flushes, vaginal dryness and soreness. Its androgenic effect play role in improving mood disturbance and libido, although response is variable.¹⁴ Cummings et al described in their study that tibolone prevents estrogen dependant bone loss at menopause and reduces spinal fracture. They also described that breast cancer rate in healthy women is not increased by tibolone. Slight vaginal bleeding may occur initially but tends to subside after a few months.¹⁵ Lieu JH revealed the beneficial effect of tibolone, on menopausal women for the treatment of vasomotor symptoms, decreased libido, mood swinging and bone loss. 35% to 45% menopausal women taking tibolone experience vasomotor symptoms and 67% taking placebo experience vasomotor symptom.¹⁶

There are a number of limitations in this study. This is a short term study with limited participants. Blinding of the trial and comparison with other HRT could have yielded better result.

Conclusion

Tibolone significantly alleviate postmenopausal symptoms without the risk or adverse events. Large scale longitudinal study will be justified to quantify the long term risk and benefit of tibolone.

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