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ORIGINAL ARTICLE

Hormone Replacement Therapy for Surgical Menopause: Is there an Ideal Drug? A Comparative Study of Conjugated Equine Estrogens and Tibolone

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ABSTRACT

Objective: To compare the effects of continuous combined conjugated equine estrogens (CEE) with those of tibolone on symptom control, lipid profile, and tolerability in women with surgical menopause.

Materials and methods: This was a randomized controlled trial study conducted in the Department of Obstetrics and Gynaecology of Global Rainbow Hospital Pvt. Ltd., Agra (2014–2016) comprising 150 women. Generally, healthy postmenopausal women having undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy irrespective of age and indication of surgery and no absolute contraindications to hormone replacement therapy (HRT) or tibolone were enrolled. Fifty subjects did not receive any HRT, 50 were treated with CEE 0.625 mg, and 50 were given tibolone 2.5 mg for 13 treatment cycles, each of 28 days. Results were statistically analyzed regarding drug efficacy in amelioration of menopausal symptoms and side effects at follow-up periods of 1, 6, and 12 months.

Results: A total of 150 subjects were enrolled and received at least one dose of the study medication, of which 134 (89.4%) subjects completed the study (n = 40 in CEE and n = 44 in tibolone). The incidence of postmenopausal symptoms decreased significantly over time in the treatment groups, compared with baseline, including significant decreases in the incidence of urogenital and sexual health symptoms, with p-values 0.001 and 0.004 in cases that received CEE and tibolone respectively.

Significant differences in symptom control (other than hot flashes) were observed between treatment groups in a few different cycles for different symptoms, but no consistent or clinically significant trends were observed.

Significant decreases in total cholesterol (5.6%) and low-density lipoprotein cholesterol (7.5%) were observed at cycle 13, compared with baseline, in the CEE group, and significant decreases in high-density lipoprotein cholesterol (8.5%) and triglycerides (13.7%) were observed at cycle 13, compared with baseline, in the tibolone group.

Significant weight gain was observed at cycle 13 in the tibolone group (3.05 kg), compared with the CEE group (0.96 kg). The incidences of adverse events were similar in both treatment groups.

Conclusion: Women treated with CEE and tibolone showed significant improvement of climacteric symptoms, including urogenital and sexual health symptoms. Treatment with either preparation significantly improved subjective wellbeing, vasomotor symptoms, and vaginal dryness.

The CEE and tibolone each induced a different mix of beneficial changes in the lipid profile.

It is seen that tibolone seems to be effective on estrogen withdrawal symptoms and with its acceptable androgenic side effects can be an appropriate selection for HRT in postmenopausal women with decreased sexual desire.

Keywords: Conjugated equine estrogens, Menopausal hormone therapy, Tibolone.

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INTRODUCTION

Menopause transition is that critical phase of a woman's life characterized by physiological and psychic changes where she combats the disturbing array of symptoms, ranging from hot flashes, night sweats, and difficulties in sleeping to loss of sexual desire, depression, vaginal dryness, and urinary and bleeding complaints. For some, the resulting discomfort greatly diminishes their quality of life (QoL). With proper understanding of the problem and an individualized approach in patient care, this turbulent time can be given a positive turn which women cease to dread.

Natural menopause, which is defined by the World Health Organization as the "permanent cessation of menstruation resulting from the loss of ovarian follicular activity," corresponds to a single point in time—the final menstrual period. It is the culmination, however, of some 50 years of reproductive aging – a process which unfolds as a continuum from birth through the menopause transition and ovarian senescence. The menopause transition represents a period of dynamic changes in reproductive

and nonreproductive tissues and, hence, is believed to play a pivotal role in the biology and health status of the aging woman. The average age of menopause in Indian women is about 48 years, as opposed to about 51 years in Western countries.[1]

Surgical menopause is being commonly performed at the time of hysterectomy for benign diseases, with potential benefits ranging from reduction of the risk of ovarian cancer in high-risk women (BRCA carriers) or to reduce pelvic pain for women with endometriosis or dense adhesions around the ovary. Similar to natural menopause, this causes a derangement in the normal hormonal homeostatic milieu with characteristically elevated levels of follicle-stimulating hormone, luteinizing hormone, and androgens with decrease in levels of estrogen, progesterone, dehydroepiandrosterone (DHEA), and inhibin.

This hormonal turbulence leads to various menopausal symptoms like vasomotor symptoms, urogenital symptoms, breast and osteoporotic changes, and cardiovascular-related problems.

Research has identified a number of hormonal and nonhormonal approaches that show promise for managing menopause-related symptoms. A careful examination of these strategies for symptom management is urgently needed to provide women and their health care providers with options that will best control their symptoms and restore their QoL.

For many decades, menopausal hormone therapy (MHT) using estrogen (or, in a woman with a uterus, a combination of estrogen and progestin) has been the therapy of choice for relieving menopause-related symptoms. But recently, several large clinical trials have found mixed results – a greater chance of serious health problems, such as blood clots, stroke, heart disease, or breast cancer, and benefits like fewer hip fractures in certain groups of women using MHT. Nevertheless, many women and their doctors are concerned about the use of MHT for their menopausal symptoms and interested in learning about alternatives.

This study was conducted to compare the efficacy and safety of conjugated equine estrogen (CEE) and tibolone, aiming to find a near-ideal drug for prevention of menopausal symptoms and study their effects on lipid profile and their tolerability in hysterectomized patients experiencing surgical menopause.

MATERIALS AND METHODS

This was a randomized controlled clinical trial conducted in the Department of Obstetrics and Gynaecology of Global Rainbow Hospital Pvt. Ltd., Agra, Uttar Pradesh, India (2014–2016), comprising 150 women.

Generally, healthy postmenopausal women having undergone *total abdominal hysterectomy* with bilateral salpingo-oophorectomy irrespective of age and indication of surgery and no absolute contraindications to hormone replacement therapy (HRT) or tibolone were enrolled.

Patients having carcinoma of the endometrium, liver, breast or ovary, endocrine diseases (thyroid, diabetes), cardiovascular, cerebrovascular and peripheral vascular disease, hypertension, severe renal disease, liver disease or gallbladder disease, bone metabolic diseases, obesity [body mass index (BMI) > 30], smokers, alcoholics, and with history of thrombophlebitis or on immunosuppressive drugs were excluded from the study. Also excluded were patients who were treated with medication known to affect coagulation, fibrinolysis, or lipid or bone metabolism.

Fifty subjects did not receive any HRT; these served as control group. Fifty patients were treated with CEE 0.625 mg orally once-daily (OD) and 50 subjects were given tibolone 2.5 mg OD orally daily for 13 treatment cycles, each of 28 days.

Some of the cases did not turn up for the follow-up visit. These cases were reported as loss of follow-up. After excluding the cases which were lost to follow-up, the rest of the cases were available for analysis.

A thorough clinical history was elicited and detailed physical examination of each patient was conducted to ensure that the subjects fulfilled the aforementioned parameters. The basic investigations required for patient fitness for surgery were obtained from patient records – complete blood count, liver function test (LFT), renal function test (RFT), Papanicolaou (PAP) smear, ultrasound whole abdomen and pelvis, electrocardiography, chest X-ray posteroanterior view, and urine routine microscopy.

Additionally, to facilitate the variables under study, few more investigations namely lipid profile including serum cholesterol, serum triglyceride, serum high-density lipoprotein (HDL), and serum low-density lipoprotein (LDL) were carried out.

Subjects were randomized into cases and controls. Fifty subjects did not receive any HRT and served as controls. A total of 50 were treated with CEE 0.625 mg OD orally and 50 were given tibolone 2.5 mg OD orally daily for 13 treatment cycles, each of 28 days totaling up to a net span of 1 year.

Results were statistically analyzed regarding drug efficacy in amelioration of menopausal symptoms and side effects at follow-up periods of 1, 6, and 12 months.

FOLLOW-UPS

Each case was followed up for 1 year, periodically at 1, 6, and 12 months.

First Follow-up Visit

Patients were subjected to a thorough physical examination and were enquired about the emergence of any menopausal symptom, namely hot flashes, night sweats, sleep disruption, dysphoric mood, vaginal dryness, cognitive change, depression, nervous tension, palpitations, irritability, headaches, insomnia, lack of energy, difficulty concentrating, and dizzy spells, somatic/pain, bone and joint pains, urinary, and sexual symptoms like dyspareunia, loss of libido, vaginal discharge, pruritus vulvae, and urinary symptoms.

Appearance of any side effects like nausea, vomiting, breast tenderness, weight gain, acne, hirsutism, hair loss, and deepening of voice was noted.

Second Follow-up Visit

In addition to the protocol followed in the first visit, a PAP smear was done.

Third Follow-up Visit

Along with the above-mentioned history and examination, a PAP smear, LFTs, RFTs, and lipid profile were also performed.

RESULTS

Table 1 depicts the basic parameters of women who had undergone surgical menopause as regards their mean age, mean parity, and mean BMI.

The distribution of cases according to menopausal symptom regression is depicted in Table 2. Most notably, the reporting of hot flashes or night sweats is dramatically higher among the control group women as compared with cases, closely followed by psychological symptoms and urogenital symptoms. Patients reported a significant reduction in the occurrence of vasomotor, psychological, sexual, and genitourinary symptoms in case groups in comparison with controls.

Table 1: Patient characteristics in all the groups

Parameter	*Control group*	*CEE group*	*Tibolone group*
Mean age	39.8 years	39.9 years	39.2 years
Mean parity	3.6	3.4	3.1
Mean BMI	27.8	28.2	27.9

Table 2: Menopausal symptom regression in control and study groups

Symptoms	*Control (%)*	*CEE (%)*	*Tibolone (%)*	*DHEA (%)*
Hot flashes and palpitations	35	12	11	16
Tiredness	62	21	20	22
Night sweats	40	11	16	12
Insomnia	21	–	–	–
Depression	16	4	–	–
Loss of libido	40	3	–	–
Vaginal dryness	16	4	–	4
Pruritus vulvae	18	4	–	4
Urethral syndrome	22	7	3	3

All the two drugs under study were found to be equally effective in amelioration of vasomotor symptoms. Tibolone was found to be equally efficacious as CEE in treating psychological symptoms.

Tibolone had promising results on decreased libido and other sexual symptoms, much more effective than CEE. Both CEE and tibolone showed significant effects on lipid profile, with tibolone causing a net reduction in total cholesterol, HDL and triglycerides, while CEE caused a net beneficial effect on lipid profile by reducing total cholesterol and increasing HDL and triglycerides (Table 3).

Side effects reported were much more frequent with CEE, mainly headache and nausea. Side effects were rarely reported with tibolone group.

Patient satisfaction was high in both the groups, with only 1% cases choosing to discontinue HRT at the end of 1st month and 3% cases discontinuing treatment at the end of 2nd month. In CEE group, 25% cases were highly satisfied, and 75% cases were satisfied, but concerned

Table 3: Effects of hormone replacement therapy on lipid profile

Variable	*Control*	*p-value*	*Conjugated equine estrogens*	*p-value*	*Tibolone*	*p-value*
Total cholesterol						
Pretreatment	231 ± 1.4	0	224 ± 2.5	0	208 ± 5.1	0
Posttreatment	235 ± 11		211 ± 7.4		174 ± 4.0	
LDL cholesterol						
Pretreatment	156 ± 4.8	0.034	148 ± 3.8	0	134 ± 2.1	1.00
Posttreatment	159 ± 4.9		130 ± 4.3		134 ± 2.2	
HDL cholesterol						
Pretreatment	47 ± 1.9	0.044	47 ± 1.7	0	51 ± 1.8	0
Posttreatment	48 ± 1.5		51 ± 2.4		36 ± 2.4	
Triglycerides						
Pretreatment	139 ± 6.1	0.54	145 ± 3.3	0	118 ± 2.0	0
Posttreatment	140 ± 5.4		162 ± 4.8		91 ± 1.4	

Table 4: Distribution of cases according to side effects in the study group

Side effect	*CEE group (%)*	*Tibolone group (%)*
Nausea	28	8
Leg cramps	–	–
Headache	40	8
Breast tenderness	20	4
Bloating	16	18
Weight gain	16	8
Acne	–	–
Hair loss	–	–

about side effects, with only one case with no relief. In tibolone group, 56% cases reported high satisfaction and 22% cases were satisfied, but expressed concern about side effects (Table 4).

DISCUSSION

This study aimed to compare the effects of continuous combined CEE with those of tibolone on symptom control, lipid profile, and tolerability in women with surgical menopause.

The percentage of women reporting hot flashes, night sweats, and psychological symptoms declined noticeably in cases receiving any type of HRT compared with controls.

In studies done by Genazzani et al,[2-4] it was concluded that tibolone seems to be effective on estrogen withdrawal symptoms, such as hot flashes, sweating, insomnia, headache, and vaginal dryness, with results generally comparable with the effects exerted by estrogen-based treatments, and the additional property of a progestogenic activity on the endometrium. As well as relieving vasomotor symptoms, tibolone has positive effects on sexual well-being and mood, and improves dyspareunia and libido.

In a similar study, Kokcu et al[5] found that treatment with either CEE or tibolone significantly improved subjective well-being, vasomotor symptoms, and vaginal dryness. It was observed that tibolone is as effective as CEE in reducing psychological symptoms.

Several other clinical studies[6] have examined the impact of tibolone administration on mood scales and QoL-measuring questionnaires. In a placebo-controlled, cross-over study of 256 postmenopausal women, total weekly mood score improved, measured using a 16-item visual analog scale.

Ross et al[7] investigated the psychological effects of tibolone *vs* CEE 0.625 mg/day with cyclical norgestrel 150 µg using the Women's Health Questionnaire and the Irritability, Depression, and Anxiety Scale. Both treatments improved psychological symptoms to a similar extent.

TIBOLONE

Tibolone is a synthetic steroid with estrogenic, progestagenic, and androgenic properties, which has been used in Europe for almost two decades, primarily for the prevention of postmenopausal osteoporosis and treatment of climacteric symptoms. Tibolone itself has no biological activity; its effects are the results of the activity of its metabolites on various tissues. After administration, tibolone is quickly metabolized into 3α-hydroxytibolone and 3β-OH-tibolone compounds, which are also present in an inactive, sulfated form. A third compound, the Δ4-isomer, is formed from tibolone directly or from the 3β-OH-metabolites.

The concentrations of tibolone metabolites and the metabolic regulation of hormonal activities vary depending on tissue type. Tibolone has estrogenic effects on bone and vaginal tissue. In endometrial tissue, the Δ4-isomer functions as a progestagen, whereas in the brain and liver, it has androgenic effects. In breast tissue, the main actions of tibolone are strong inhibition of sulfatase activity and weak inhibition of 17β-hydroxysteroid dehydrogenase activity, which result in blocking the conversion of estrone sulfate to E2.

Tibolone given orally is rapidly absorbed, metabolized mainly in the liver, and excreted in the urine and feces. The elimination half-life is approximately 45 hours.

The increased risk of stroke with tibolone has also been reported with estrogen therapy, but the biologic mechanism is not certain. A randomized, placebo-controlled trial showed that 2.5 mg of tibolone and CEE plus medroxyprogesterone slightly increased the intima–media thickness by 0.004 mm per year. In randomized trials,[8,9] tibolone decreased HDL cholesterol levels, but improved lipoprotein(a) levels, did not significantly change homocysteine levels, and increased plasminogen levels. Treatment with tibolone had no effect on blood pressure or fasting blood glucose levels.

Tibolone has been used by women between the ages of 50 and 60 years for menopausal symptoms and the prevention of osteoporosis when the risk of stroke was low, but it should be avoided in women who have strong risk factors for stroke, such as hypertension, smoking, diabetes, and atrial fibrillation. Although the overall number of adverse events was small, there was no increased risk of venous thromboembolism, as has been seen with hormone therapy and selective estrogen receptor modulators, or an increased risk of coronary events, as has been seen with conjugated estrogen combined with medroxyprogesterone.

CONCLUSION

Menopause-associated symptoms impair QoL for many women. More than 75% of postmenopausal women

experience hot flashes and sweating. Other symptoms, such as insomnia, headache, or fatigue, as well as changes in mood and libido may result directly from menopause or indirectly, such as effects of hot flashes on sleep. The HRT effectively alleviates menopausal symptoms and causes reduction in osteoporotic fractures and coronary artery disease, greatly improving the QoL in menopausal women.

The CEE is an effective low-cost drug, which has beneficial effects on lipid profile and bone density. It is very effective in relieving climacteric symptoms, although frequently its use is associated with side effects.

Although estrogen–progestin replacement therapy is considered the most effective approach to manage menopausal symptoms, several studies have focused on androgen replacement therapy, especially for patients suffering from sexual disorders, loss of pubic and axillary hair, loss of well-being and energy, mood disorders, and metabolic and bone mass effects despite apparently adequate estrogen replacement. All these symptoms are part of the androgen deficiency syndrome.

New synthetic steroid with a unique tissue specific action has been highlighted in newer studies. It has positive effects on controlling climacteric symptoms, prevents bone loss as evident on serial bone densitometry, and exerts a beneficial androgenic effect on mood and libido.[10-12] Additionally, it has the advantage of zero stimulation of endometrium and breast tissue. Moreover, studies suggest that tibolone potentially confers benefits on cognitive performance too. However, its use is fraught with side effects in a few women, and its high cost is a major deterrent for its use as a near-ideal HRT drug.

Sexuality improved significantly with all treatments, but the combined regimen of androgens and ERT increased sexual activity in postmenopausal women equal to that of tibolone and to a greater extent than ERT alone.

Facing ground realities, we must understand the need to individualize HRT for every patient and provide her with a realistic picture of what to expect from HRT, degree of symptom control along with the possible side effects of the same. Individual counseling, both before and after treatment, is essential for ensuring compliance of treatment. Alternative therapies and lifestyle modifications must also be offered along with HRT as an additional boost to menopausal women.

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