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ORIGINAL ARTICLE

A Comparative Study of CEE, Tibolone, and DHEA as Hormone Replacement Therapy for Surgical Menopause

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Abstract

Objective(s) The objective of this study was to compare the efficacy and safety of CEE, tibolone, and DHEA for prevention of menopausal symptoms.

Method(s) One hundred patients with surgical menopause were included in this study: 25 of whom were not treated with any HRT, 25 were treated with 0.625 mg of CEE, 25 were treated with 2.5 mg of tibolone, and 25 were treated with 25 mg of DHEA for 1 year, and the results were statistically analyzed regarding drug efficacy and side effects at follow-up periods of 1, 6 and 12 months.

Result(s) Frequency of menopausal symptoms was significantly less in cases received with CEE, tibolone, DHEA with p values 0.001, 0.004 and 0.004, respectively. Percentage gain in BMD was 2.8 % with CEE at lumbar spine, which was greater than that caused by DHEA and tibolone, but this difference was not statistically significant. CEE caused side effects like headache (40 %) and nausea (28 %).

Conclusion(s) CEE, Tibolone, and DHEA are very effective in alleviating climacteric symptoms. CEE has beneficial effects on lipid and bone and is a low-cost drug but frequently causes side effects. Tibolone offers beneficial androgenic effects on mood and libido with fewer side effects but is a costly drug. DHEA shows positive effects on psychological symptoms. However, its cost and androgenic side effects limit its use as long-term HRT.

Keywords Menopause · Climacteric · HRT

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Introduction

Menopause can be a time of positive changes for women provided they understand and individualize their care. Two hundred years ago, only 30 % of women lived long enough to reach the menopause, whereas 90 % of today's women will experience the climacteric. Menopause (meno—menses, pause—stoppage) is defined as permanent cessation of menses that occurs after the termination of ovarian function and reflects a state of hypoestrogenenemia with serum FSH levels >40 IU/L. Most Indian studies demonstrate median age of menopause as 48 years, while those from the west reveal the same to be about 51 years [1]. Surgical menopause is an artificially induced condition where the woman loses her so-long known attributes of womanhood, a motherhood. This gives rise to hormonal changes like—decrease level of estrogen, progesterone, DHEA, and inhibin and increase in levels of FSH, LH, and androgen.

This hormonal homeostatic turbulence leads to various menopausal symptoms like vasomotor symptoms, psychological symptoms, urogenital symptoms, breast, and osteoporotic changes, and cardiovascular-related problems. HRT has been advocated to prevent menopausal syndrome,

reduce fracture rate, for cardiac protection and to improve mood disorders and libido. Hysterectomy is one of the commonest gynecological operations. With this background information, the current investigation was designed to compare the efficacy, safety, and cost effectiveness of conjugated equine estrogen (CEE), tibolone, and DHEA for prevention of various menopausal symptoms, reduce fracture rate, and for cardiac protection in patients with surgical menopause.

Materials and Methods

This was a randomized controlled trial conducted in the Department of Obstetrics and Gynaecology of SMS Medical College Jaipur (2005), in which 100 patients were enroled, who had undergone TAH with BSO irrespective of age and indication of surgery. The inclusion criteria were asymptomatic patients as regards to menopausal symptoms, who had undergone TAH with BSO 3 days earlier. Patients with carcinoma endometrium, liver, breast or ovary, endocrine diseases (diabetes, thyroid), cardiovascular, cerebrovascular and peripheral vascular disease, hypertension, severe renal disease or liver disease, bone metabolic diseases, obesity (BMI > 30), smokers and alcoholics, and with history of thrombophlebitis or immunosuppressive drugs were excluded from the study. 25 patients did not receive HRT and were termed as control group. 25 patients received Premarin (CEE 0.625 mg OD orally) for 12 months; 25 patients received tibofem (tibolone 2.5 mg OD orally) for 12 months; and 25 patients received Evandra (DHEA 25 mg OD orally) for 12 months. The patients lost to follow up have been documented but excluded from the series. The control and cases were allotted to their respective groups randomly. Follow up of all the groups was done for 1 year.

A detailed clinical history of each patient was elicited to fulfill inclusion and exclusion criteria. Each patient was subjected to thorough physical examination including examination of breast, BP, weight, per abdomen, per speculum, and per vaginal examination. A systemic examination was done to rule out the presence of systemic illness.

As the patients who were included in the study had undergone TAH with BSO, 3 days earlier, after being fully investigated, the required investigations like CBC, LFTs, RFTs, FBS, ECG, USG whole abdomen, urine for complete examination, and PAP's smear were already available and were within normal limits. A lipid profile including S. cholesterol, S. triglyceride, S. HDL, S. LDL, and bone densitometry of lumbar spine and right femoral neck and baseline mammography were done.

Follow Up

A prospective follow up of 1 year was done for every patient. Check ups were done at the 1st month, 6th month, and at 12th month of therapy.

1st follow up Besides thorough examination, the patients were asked regarding the emergence of menopausal symptoms like hot flushes, night sweats, palpitations, tiredness, irritability, depression, poor concentration, lethargy, dyspareunia, loss of libido, bone and joint pain, vaginal dryness, pruritus vulva, vaginal discharge, and urinary symptoms. The patients were also inquired regarding the appearance of any side effects like nausea, vomiting, breast tenderness, weight gain, acne, hirsutism, hair loss, and deepening of voice.

2nd follow up Protocol was similar to that of the 1st follow up. In addition, a PAP's smear was done.

3rd follow up In addition to eliciting history and doing a proper examination, a PAP's smear, LFTs, RFTs, lipid profile, bone densitometry, and mammography were done.

As the patients were followed up at longer intervals, compliance was assured by checking drug purchase vouchers and empty drug blister packs.

Results

Frequency of vasomotor symptoms was the highest in control group followed by psychological symptoms and urogenital symptoms.

There was significant reduction in the occurrence of vasomotor, psychological, sexual, and genitourinary symptoms in case groups as compared with controls. No difference was found among the effectiveness of three drugs as far as vasomotor symptoms are concerned. However, on comparison, tibolone was found as effective as CEE in reducing psychological symptoms, but found less effective than DHEA. Effects of tibolone and DHEA on sexual interest and activity were found similar but better than those of CEE. Effects of tibolone were found better than that of DHEA and CEE on genitourinary symptoms (Table 1). CEE showed beneficial effect on lipid profile by reducing total cholesterol and increasing HDL and TG, while tibolone caused reduction in total cholesterol, HDL, and TG. Effect of DHEA on lipid variables was not found significant (Table 2). There was significant reduction in bone density of control group. Percentage gains in BMD were 2.8 and 2 % with CEE at lumbar spine and femoral neck, respectively, which was greater than that caused by DHEA and Tibolone, but this difference was not statistically significant (p value > 0.05) (Table 3).

Table 1 Distribution of menopausal symptoms in various groups

Symptoms	Control	CEE	Tibolone	DHEA
Tiredness	15 (60 %)	5 (20 %)	5 (20 %)	6 (24 %)
Hot flushes and palpitation	9 (36 %)	3 (12 %)	3 (12 %)	4 (16 %)
Night sweats	10 (40 %)	3 (12 %)	4 (16 %)	3 (12 %)
Insomnia	5 (20 %)	–	–	–
Depression	4 (16 %)	1 (4 %)	–	–
Loss of libido	9 (36 %)	1 (4 %)	–	–
Vaginal dryness	4 (16 %)	1 (4 %)	–	1 (4 %)
Pruritis vulvae	4 (16 %)	1 (4 %)	–	1 (4 %)
Urethral syndrome	5 (20 %)	2 (8 %)	1 (4 %)	1 (4 %)

Table 2 Effects of HRT on various lipid variables

Variable	Control	CEE	Tibolone	DHEA
T. cholesterol				
Pretreatment	231 ± 1.4	224 ± 2.5	208 ± 5.1	228 ± 20.1
After 1 year of treatment	235 ± 11	211 ± 7.4	174 ± 4.0	235 ± 1.1
p value	0.0000	0.0000	0.0000	0.094
LDL cholesterol				
Pretreatment	156 ± 4.8	148 ± 3.8	134 ± 2.1	156 ± 4.8
After 1 year of treatment	159 ± 4.9	130 ± 4.3	134 ± 2.2	160 ± 5.2
p value	0.0343	0.0000	1.0000	0.071
HDL cholesterol				
Pretreatment	47 ± 1.9	47 ± 1.7	51 ± 1.8	47 ± 1.9
After 1 year of treatment	48 ± 1.5	51 ± 2.4	36 ± 1.8	48 ± 1.8
p value	0.0441	0.0000	0.0000	0.0618
Triglycerides				
Pretreatment	139 ± 6.1	145 ± 3.3	118 ± 2.0	139 ± 6.1
After 1 year of treatment	140 ± 5.4	162 ± 4.8	91 ± 1.4	140 ± 7.0
p value	0.5447	0.0000	0.0000	0.5930

CEE caused significant side effects in the form of headache (40 %) and nausea (28 %). Side effects with Tibolone were rare, and DHEA mainly caused androgenic side effects like acne and hair loss (Table 4).

Stopping rate for HRT was 2 % at 1 month and another 2 % at 6 months. Only 6 % women were aware of HRT at the time of surgery. In CEE group, 24 % patients were highly satisfied, and 76 % of the patients were, although satisfied, worried about the side effects, and only 1 patient was not satisfied at all with the therapy. In tibolone group, 60 % patients were highly satisfied, and 20 % of the patients were, although satisfied, worried either about side effects or about the cost of the therapy. In DHEA group, 44 % patients were highly satisfied; 24 % patients were satisfied but worried about the cost; and only one patient was not satisfied at all.

Discussion

This study compared the efficacy, side effects, acceptability, and cost effectiveness of CEE, tibolone, and DHEA on menopausal symptoms, lipid profile, and bone density.

There was significant reduction in the occurrence of hot flushes, palpitation, night sweats in patients receiving any of the HRT as compared with controls (Table 1). In a similar study, Kokcu [2] 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, but both of these drugs were found less effective than DHEA (Table 1). Davis [3] also reported that tibolone has positive effects on mood and alleviates several adverse mood parameters to a similar

Table 3 Effect of HRT on bone densitometry

Site	Control	CEE	Tibolone	DHEA
Lumbar spine BMD (g/cm^2)				
Pretreatment	1.177 ± 0.004	1.168 ± 0.009	1.166 ± 0.007	1.166 ± 0.007
After 1 year of treatment	1.159 ± 0.004	1.200 ± 0.01	1.190 ± 0.008	1.182 ± 0.004
% difference	−1.46	+2.8 %	+2.09	+1.80
p value	0.0000	0.0000	0.0000	0.0000
Femur neck BMD (g/cm^2)				
Pretreatment	0.990 ± 0.009	0.989 ± 0.008	0.987 ± 0.007	0.987 ± 0.007
After 1 year of treatment	0.978 ± 0.009	1.008 ± 0.008	0.995 ± 0.006	0.992 ± 0.007
% difference	−1.12	+2 %	+0.89	+0.6
p value	0.0000	0.0000	0.0002	0.0204

Table 4 Distribution of cases according to side effects

Side effects	CEE	Tibolone	DHEA
Nausea	7 (28 %)	2 (8 %)	2 (8 %)
Headache	10 (40 %)	2 (8 %)	–
Leg cramps	–	–	–
Breast tenderness	5 (20 %)	1 (4 %)	–
Bloating	4 (16 %)	2 (8 %)	–
Weight gain	4 (16 %)	2 (8 %)	–
Hair loss	–	–	4 (16 %)
Acne	–	–	6 (24 %)

extent as conventional HRT. Effects of tibolone and DHEA on libido were found to be similar, but statistically better than that of CEE (Table 1). This finding is supported by Arlt [4] who reported that DHEA significantly increases the frequency of sexual desire. No patient in tibolone group developed genital symptoms, which proves its better effect on genitourinary symptoms as compared with other two drugs, and supported by Davis [3].

Table 2 demonstrates that CEE reduces total cholesterol and increases HDL cholesterol and triglycerides after 1 year of therapy. Peter Alexander [5] also found beneficial effects of estrogen on lipid profile in his study.

When the effectiveness features of three drugs were compared, it was found that % gains in BMD were 2.8 and 2 % with CEE at lumbar spine and femoral neck, respectively, which were greater than those caused by DHEA and Tibolone, but the difference was not statistically significant ($p > 0.05$) (Table 3). In a similar study, Gallagher [6] observed a net increase of approximately 2.6 % in lumbar spine BMD, and an increase of approximately 1 % in femoral neck BMD with tibolone therapy.

Table 4 shows that frequencies of nauseas, headache, breast tenderness, and weight gain were significantly higher in CEE group as compared with tibolone and DHEA ($p < 0.05$). In a similar study, Egarter [7] concluded that tibolone very effectively alleviates complaints that are normally attributed to ERT, e.g., headache, breast tenderness, and edema. In the current study, DHEA caused mainly androgenic side effects. Morales [8] also reported side effects like acne, deepening of voice, hirsutism, and hair loss after use of DHEA in women of advancing age.

Conclusion

One third of women's life is spent in an estrogen deficient state. HRT improves the quality of life spent in this period by reduction of osteoporotic fractures and coronary artery disease and relieving the menopausal symptoms. CEE is very effective in alleviating early and late climacteric symptoms, has beneficial effects on lipid and bone, and is low cost drug although frequently it causes side effects. Tibolone is a synthetic steroid, which exerts a unique tissue-specific action. It provides the efficacy of estrogen in controlling early and late climacteric symptoms, preventing bone loss without stimulation of endometrium and breast tissue and offering additional beneficial androgenic effects on mood and libido. Side effects do occur in the minority of women with tibolone; however, the major deterrent factor for its use is the cost, due to which it has to be used in selected patients, although it comes very close to ideal HRT. DHEA fortifies life after the age of 45 by alleviating early and late climacteric symptoms, especially improving symptoms of depressed mood, allaying fatigue, improving libido, and restoring sense of well-being. However, its cost and its androgenic side effects impose limits on its use as long-term HRT. Individual counseling both before and after starting treatment is essential to achieve good continuance with HRT. It is important to provide each woman with realistic expectations of the therapy, so that she understands the side effects, the duration of time required for symptoms control, and

maximum benefits. In spite of all the information provided, there will still be women who choose not to take HRT. In all such cases, importance of alternative therapies and changes in diet and lifestyle must be offered.

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