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RESEARCH ARTICLE

COMPARATIVE STUDY OF HORMONAL AND NON-HORMONAL TREATMENTS FOR THE MANAGEMENT OF MENOPAUSAL SYMPTOMS

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ABSTRACT

Objective: This study was conducted with the objective of comparing safety and efficacy of hormonal treatment and non-hormonal alternatives for the management of menopausal symptoms.
Materials and Methods: A total of 40 patients suffering from menopausal symptoms were recruited to the study protocol and were divided into 4 groups according to the treatment they received, with 10 patients in each group. Group A received conjugated estrogen and medroxy progesterone acetate, Group B received Tibolone, Group C received Isoflavone and Group D received Vitamin E. Efficacy of the treatment was evaluated by improvement in symptomatic score and safety of the treatment was assessed on the basis of adverse effects reported and relevant laboratory investigations.
Results: Most of the symptoms were significantly improved in groups A and B ($p < 0.01$) while in groups C and D significant improvement was observed in hot flushes, sweating and insomnia ($p<0.05$). On comparative analysis there was no significant difference in the efficacy between groups A and B and between groups C and D. On the other hand significant difference was observed in the efficacy when groups A and B were compared with groups C and D ($p<0.01$). Only mild tolerable side effects were reported by the patients in all the groups with slightly higher incidence in groups A and B.
Conclusions: Hormonal treatment is very efficacious for the early relief of menopausal symptoms. Isoflavone and vitamin E can be considered as a satisfactory treatment alternative when for any reasons hormonal treatment cannot be used.
Key Words: HRT, Tibolone , Isoflavone, Menopausal symptoms

INTRODUCTION

Menopause is a natural process that occurs in a woman's life as a part of normal aging. Nowadays with better lifestyle, better health care facilities and longer life span more and more women live well past the age of menopause and survive to endure the consequences of menopause and it is estimated that by the end of 2015 there will be 130 million elderly women in India[1,2].

Menopause which is associated with decline in estrogen level may adversely affect the life of women. Though some women do not experience any menopausal symptoms, a considerable proportion suffer from wide range of climacteric symptoms like hot flushes, night sweats, insomnia, palpitation, depression etc. often starting several years before the final menstrual period [3]. This has a marked negative effect on the quality of life and prompts the menopausal women to visit health care professionals.

Systemic hormone replacement therapy (HRT) in the form of combination of estrogen and progesterone or estrogen alone has been available for over half a century for the management of menopausal symptoms. After the results of Women's Health Initiative (WHI) and the Heart and Estrogen/ Progestin Replacement Study (HERS) which reported an unfavorable balance of risks compared with benefits, there was a major shift in perspective on HRT and has led to a significant decline in the use of hormonal treatment [4,5].

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The constantly changing landscape regarding menopausal hormonal therapy has been challenging for providers caring for menopausal women. After a decade of fear and uncertainty regarding HRT, reanalysis of the WHI data and the results of recent studies have provided some clarity regarding the balance of risks and benefits of systemic menopausal HRT. Age and years since menopause are now known to be important variables affecting the benefit-risk profile. For symptomatic menopausal women who are under 60 years of age or within 10 years of menopause, the benefits of HRT generally outweigh the risks [6,7].

Other hormonal alternative is tibolone, which is a synthetic compound with weak hormonal properties, is equally effective in relieving menopausal symptoms as the conventional HRT but continues to have concerns over long term adverse consequences of hormone therapy [8,9].

Thus the apprehensions about safety and efficacy of hormonal treatments has led to the exploration of a number of non-hormonal alternative treatments like isoflavone, vitamin E, Black Cohosh, St. Johns Wort etc in perimenopausal and postmenopausal women for the control of menopausal symptoms. At present the data regarding efficacy and safety of these alternatives are limited, most of the studies are placebo controlled and none of the studies has compared these alternatives with the hormonal treatment particularly in Indian patients. Therefore, this study was planned to compare the efficacy and safety of hormonal and non-hormonal alternatives treatments used for the management of menopausal symptoms.

MATERIALS AND METHODS

This was a prospective observational study conducted in the Pharmacology department of Himalayan Institute of Medical Sciences, Dehradun over a period of six months. Subjects selected were patients attending outpatient department of Obstetrics and Gynaecology. The protocol was approved by the ethical committee of the institute and all study subjects gave their written informed consent. Eligibility for enrollment in the study was based on inclusion and exclusion criteria.

Inclusion Criteria

- Perimenopausal Women
- Postmenopausal women
- Surgical menopause
- Must be experiencing menopausal symptoms
- Age< 60 years
- Time of enrollment < 10 years since menopause

Exclusion Criteria

- Undiagnosed abnormal vaginal bleeding
- Women with active thromboembolic disease or thrombophlebitis or history of thromboembolic disease.
- Estrogen dependent neoplasm such as those of breast or endometrium.
- Women with active liver disease
- Sever cardiac disease
- Diabetes

Subjects fulfilling inclusion criteria were recruited to the study protocol. All women selected were otherwise healthy on the basis of routine clinical and laboratory examination, except for menopausal sign and symptoms. None of them had received any type of treatment or therapy for menopausal symptoms in the last 6 months before enrollment in the study.

Total number of 40 patients were enrolled in the study. 10 women were recruited to each of the following 4 groups according to the treatment they received.

Group A received Conjugated estrogen 0.625mg/day for 25 days and Medroxy Progesterone Acetate (MPA) from 16^{th}-25^{th} day of the month. Women who were hysterectomised did not receive MPA.

Group B received Tibolone 2.5mg/day. Only those patients were enrolled in this group who had ammenorrhoea of at least 1year.

Group C received Isoflovone 75mg/day.

Group D received Vitamin E 400 mg/day.

All the drugs were given orally for a period of 3 months. All study participants were required to make 3 follow up visits i.e after 1 week, I month and 3 months of treatment. Patients were examined on day 0 and at each follow up visit. Relevant investigations were done on day 0 and after 3 months. After 3 months mammography was done only in subjects of group A and group B.

Efficacy of the treatment was assessed by improvement in symptomatic score[8]. The symptoms complained by the patients were scored on a scale of 0-3 (0= none, 1= mild, 2= moderate, 3= severe) which was recorded on the day of enrollment (day 0) and at each follow up visit. Finally the symptom score at each follow visit was compared with the baseline values.

A check list was used to enquire about adverse effects at each visit by the patients. The patients were encouraged to describe their symptoms at each visit.

Statistical Analysis

The results were analyzed using student t test (paired and unpaired) and were expressed as mean ± SE.

OBSERVATIONS AND RESULTS

Out of the 40 patients enrolled in the study, 10 were perimenopausal and 30 postmenopausal (14 surgical and 16 natural menopause). Menopausal status in different treatment groups is given in (Table 1). Demographic parameters and other baseline characteristics were similar in all the 4 groups (table2). Mean age of menopause as analyzed from the 16 natural menopausal women in the study was 48.06 ± 0.93 years. Age of onset of menopause shows no relationship with education, diet, socioeconomic status, religion, menarche age, and OCP use.

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Table 1: Menopausal status in different treatment groups

Treatment Groups	Group A *n = 10*	Group B *n = 10*	Group C *n = 10*	Group D *n = 10*
Perimenopause	1	0	4	5
Natural menopause	4	4	4	4
Surgical Menopause	5	6	2	1

Table 2: Demographic parameters (mean ± SE) of perimenopausal and postmenopausal women in different treatment groups:

Group	Age in years	Religion*ƒ* H:M:O	Edu. *ƒƒ* Il:L	SES≅ H:M:L	Occ.≠ W:NW	Menarche Age in yrs	Parity	H/o OCP use	Marital History in years	Years since menopause
Group *A (n = 10)*	45.4 ± 1.70	7:2:1	2:8	0:10:0	1:9	13.1± 0.28	3.3± 0.47	2:8	28.8±2.01	3.5± 0.88
Group *B (n = 10)*	51.1 ± 1.93	9:1:0	3:7	1:8:1	0:10	13.7± 0.30	3.3± 0.34	1:9	32.8±1.44	4.7 ± 0.98
Group *C (n = 10)*	45.6 ± 2.07	9:1:0	3:7	1:8:1	1:9	13.5± 0.22	3± 0.62	1:9	29.4±1.56	5.0 ± 1.54
Group *D (n = 10)*	48.2 ± 1.68	10:0:0	2:8	0:9:1	1:9	12.7± 0.34	2.9± 0.38	1:9	30.6±1.84	5.0 ± 1.30

ƒ Religion : H = Hindu ; M = Muslim; O = Others
ƒƒ Edu. = Education; Il = Illiterate ; L = Literate
≅ SES = Socio-economic status : H = High ; M = Middle ; L = Low income group (according to B G Prasad classification)
≠ Occ. = Occupation ; W = Working ; NW = Non-working

Table 3: Symptomatic score in different treatment groups (mean±SE) at time of enrollment

Symptoms	Treatment Groups			
	Group A	Group B	Group C	Group D
Hot flushes	2±0.37	0.2±0.25	1.8±0.32	2.1±0.27
Sweating	1.5±0.42	1.9±0.31	1.3±0.36	1.3±0.3
Dizziness	0.4±0.22	0.4±0.22	0.4±0.26	0.2±0.2
Anxiety	0.3±0.21	0.3±0.21	0.2±0.13	0.3±0.21
Insomnia	1.6±0.30	1.6±0.16	1.6±0.37	1.6±0.30
Depression	1.2±0.33	1±0.29	0.8±0.32	0.4±0.26
Loss of libido	1.1±0.23	1.3±0.15	0.8±0.24	0.8±0.24
Headache	0.8±0.20	0.8±0.24	1.2±0.29	0.7±0.30
Tiredness	0.4±0.16	0.7±0.21	0.7±0.30	0.7±0.26
Mood swing	0.8±0.32	0.6±0.30	0.4±0.26	0.6±0.26
Irritability	0.6±0.26	0.9±0.27	0.6±0.26	0.4±0.22
Nervousness	0.6 ± 0.30	0.8±0.32	0.8±0.29	0.6±0.30
Tendency to be ill	0.6±0.26	0.8±0.29	0.6±0.22	0.6±0.30
Osteoarticluar pain	1.15±0.26	1.5±0.22	1.3±0.26	1.1±0.23
Dyspareunia	0.7±0.21	1±0.21	0.5±0.22	0.8±0.29

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At the onset of study symptoms encountered were comparable in all the 4 groups and the difference was not significant (Table 3). Table 4 depicts reduction in symptomatic score over 3 months period between the treatment groups. At the end of 3 months there was significant decrease in symptomatic score ($p< 0.01$) for most of the symptoms in groups A and B except dizziness, anxiety, tiredness and nervousness. In group B mood disorders, loss of libido, dyspareunia and osteoarticular pain were better relieved when compared to group Although the difference was not significant. Improvement in symptoms in both the groups was observed even as early as 1 month follow up and improvement was maintained and further improved thereafter.

In groups C and D significant improvement was observed in hot flushes, sweating and insomnia ($p < 0.05$) but the improvement was much less as compared to groups A and B ($p < 0.01$). Significant improvement was observed in headache in group C and dyspareunia in group D. Most of these improvements were observed at around 3 months of therapy. There was no statistically significant difference in improvement of symptoms in between groups A and B and in between groups C and D.

Comparative analysis of groups A and B with groups C and D reveals statistically significant difference in each symptomatic score which were significantly decreased at 1 month and 3 months of follow up visit in groups A and B ($p<0.01$) (Table 4).

Table 4: Comparison of symptomatic improvement in different treatment groups as assessed by symptomatic score (mean±SE) at 1and3 months of follow up.

Symptoms	*Treatment Groups*							
	Group A		Group B		Group C		Group D	
	1 month	3 months	1 month	3 months	1month	3months	1month	3months
Hot flushes	1.20±0.25*τ#	0.50±0.17!τ#	1.4±0.22*τ#	0.8± 0.2!τ#	1.7±0.28	1.4 ± 0.30*	2.1±0.27	1.4± 0.22*
Sweating	0.9 ± 0.28*τ#	0.4 ± 0.16*τ#	1.6 ± 0.26	0.9± 0.23*τ#	1.3±0.36	0.9 ± 0.27*	1.3±0.3	1.2 ± 0.29*
Dizziness	0.4 ± 0.22	0.2 ± 0.3	0.4 ± 0.22	0.1 ± 0.1	0.4±0.26	0.4 ± 0.26	0.2±0.2	0.2 ± 0.2
Anxiety	0.2 ± 0.13	0.1 ± 0.1	0.3±0.21	0.2 ± 0.13	0.2± 0.13	0.2 ± 0.13	0.3±0.21	0.2 ± 0.2
Insomnia	1.1 ± 0.23*τ#	0.5 ± 0.16*τ#	1.1 ± 0.17*τ#	0.6±0.16*τ#	1.6±0.37	1.2 ± 0.32*	1.6±0.30	1.4± 0.30*
Depression	0.8 ± 0.24*τ#	0.5 ± 0.17*τ#	1±0.29	0.6 ± 0.16*τ#	0.8±0.32	0.7 ± 0.30	0.4±0.26	0.3 ± 0.21
Loss of libido	0.9 ± 0.18	0.4 ± 0.16*τ#	0.9±0.15	0.4 ± 0.16*τ#	0.8±0.24	0.7 ± 0.21	0.8±0.24	0.8±0.24
Headache	0.6 ± 0.16	0.2 ± 0.13*τ#	0.8 ± 0.24	0.2± 0.13*τ#	1.2± 0.29	0.8 ± 0.24*	0.6±0.26	0.5 ± 0.22
Tiredness	0.4±0.16	0.1 ± 0.1	0.7 ± 0.21	0.5 ± 0.16	0.7±0.30	0.6 ± 0.26	0.7±0.26	0.6 ± 0.22
Mood swing	0.5 ± 0.22	0.4 ± 0.16	0.4 ± 0.22	0.2± 0.15*τ#	0.4±0.26	0.4±0.26	0.6±0.26	0.5 ± 0.22
Irritability	0.6 ± 0.26	0.2 ± 0.13*τ#	0.9±0.27	0.4± 0.16*τ#	0.6±0.26	0.5 ± 0.22	0.4±0.22	0.2 ± 0.13
Nervousness	0.4 ± 0.22	0.3 ± 0.15	0.6 ± 0.26	0.4 ± 0.16	0.8±0.29	0.7 ± 0.26	0.6±0.30	0.6±0.30
Tendency to be ill	0.5 ± 0.22	0.3 ± 0.15	0.7 ± 0.26	0.3 ± 0.15*τ#	0.6±0.22	0.4 ± 0.16	0.6±0.30	0.5 ± 0.26
Osteoarticluar pain	1.1 ± 0.23	0.6 ± 0.16*τ#	1.3 ± 0.21	0.5 ± 0.16*τ#	1.3±0.26	1 ± 0.25	1.1±0.23	1 ± 0.25
Dyspareunia	0.6 ± 0.16	0.3 ± 0.15*τ#	0.9 ± 0.17	0.5 ± 0.16*τ#	0.5 ± 0.22	0.4 ± 0.22	0.8±0.29	0.6 ± 0.26*

** = p < 0.05 vs 0 day value in the same group, ! = p < 0.01 vs 0 day value in the same group, τ= p < 0.01 vs group C, # = p < 0.01 vs group D*

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Table 5 shows adverse effects encountered in different groups during follow up visits. Adverse effects were more common among the patients who received the hormonal treatment. Most common adverse effect reported was irregular breakthrough vaginal bleeding which was seen in 3 patients of group A out of the 5 nonhystrectomised patients. Next in order was GI upset which was seen in approximately 1% of the total enrolled women. Besides these there were few others but all these reported adverse effects were mild and tolerable and none of the patient withdrew from the study due to adverse effects, at any time of the study period.

Table 5: Adverse drug effects reported by number of patients in different treatment groups

Reported events	Group A *n = 10*	Group B *n = 10*	Group C *n = 10*	Group D *n = 10*
Bleeding	3	0	0	0
Headache	1	1	0	0
Nausea	3	1	1	0
Hirsutism	0	1	0	0
GI upset	0	1	2	0

Haemoglobin, blood sugar, lipid profile, urine analysis did not show any significant change at the end of the study. Ultrasonographic reports were normal both at the start of the treatment and at the end of study and no patients showed any detectable endometrial proliferation. Mammography scans were done at the end of study only in the women of groups A and B and were found to be normal.

DISCUSSION

Despite the fact that most of the women in some way face the short- and long-term health consequences of menopausal estrogen deficiency, many avoid HRT, primarily because of concerns related to safety and side effects. To date, even clinicians have been limited in their ability to address these concerns and besides this there is dilemma related with the use of alternative medications because of the limited safety and efficacy data.

This study shows that short course HRT is an efficacious modality with few tolerable side effects, for the management of menopausal symptoms. This is in accordance with the various earlier studies [5,8,9]. Reanalysis of the earlier published studies (WHI, HERS) including the Kronos Early Estrogen Prevention Study and Danish Osteoporosis Prevention Study suggest that HRT is primarily beneficial when initiated in younger women closer to the onset of menopause, but harmful when initiated later in life or further from the onset of menopause [6,7].

According to the present study Tibolone and conventional HRT have similar efficacy in alleviating most of the menopausal symptoms. The only difference observed was in symptoms like mood swings, loss of libido, dyspareunia and osteoarticular pain which were better relived in group B as compared to group A, although the difference was not statistically significant. A double blind comparative study conducted in 437 postmenopausal women with climacteric complaints done over a period of one year showed that both tibolone and combined estrogen progesterone therapy reduced climacteric symptoms to a similar extent[10]. In another comparative study done in 129 postmenopausal women, tibolone was more effective in improving the mood disorders and loss of libido after six months of therapy[8]. The reason for mood elevating effect of tibolone may be an increase in plasma endorphin levels[11]. Usually menopause is associated with reduction in endorphin levels, which is believed to be involved in the pathogenesis of mood disorders. The benefit in loss of libido observed in group B could be due to its androgenic effects[11]. Therefore this study confirms in many respects the results of other previous comparative studies.

In the non-hormonal alternative groups, the study demonstrates significant improvement in hot flushes, sweating and insomnia with isoflavone and vitamin E treatment. The use of isoflavone to modify the symptoms of estrogen deficiency has been addressed in small studies with conflicting results regarding the efficacy. In a metaanalysis of 14 trials, 11 showed significant improvement in the isoflavone group compared to placebo while 3 trials failed to show any benefit[12]. Epidemiological studies have also shown that the population in which soy isoflavone intake is higher, have lesser prevalence of vasomotor symptoms[13]. Possible explanation for this reduction is estrogenic component of isoflavone. Besides, it also has antioxidant effect which may have beneficial effect in slowing the degeneration of graffian follicles which will prevent the abrupt fall in estrogen levels[14]. The beneficial effects of isoflavone observed in our study can be attributed to the similar reasons as mentioned above.

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As with isoflavone, there are very few studies which have addressed vitamin E for the control of menopausal symptoms. In one study involving 120 patients vitamin E in the dose of 800 IU was more effective than placebo (32% vs 29%; p <0.05) for the control of menopausal vasomotor symptoms[15]. In yet another placebo controlled study of vitamin E showed greater reduction of hot flushes than observed with placebo (30% vs 25 %) over basal symptoms[16]. The mechanism for small reduction of hot flushes is unknown apart from possible placebo effects. Most of the studies have used 800 I.U of vitamin E but even by use of 400 IU for 12 weeks have also led to significant improvement in clinical outcome[17]. The reason for this meagre beneficial effect have not been yet elucidated apart from the possible placebo effect and hence further studies are needed.

CONCLUSIONS

The above results suggest that conventional HRT and tibolone are very efficacious with only few tolerable side effects when used for short period. Despite the fact that alternative treatments like isoflavone and vitamin E are less efficacious as that of conventional HRT and tibolone but can serve as a satisfactory treatment option when either hormonal therapy is contraindicated or there is risk associated with hormonal use or when woman is not in favour of hormonal treatment.

Limitations: The present study has certain limitations such as short duration and small sample size so, caution should be exercised while extrapolating the results.

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