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Original Research Article

Prospective and retrospective study of weekly intermittent hormone (estrogen and progesterone) replacement therapy in hysterectomised women

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ABSTRACT

Background: Estrogen therapy in younger postmenopausal women is associated with a decisive reduction in morbidity and mortality, but estrogen use in this population is low because of risk of side effects. Weekly intermittent therapy is a more patient friendly approach with reduced pill burden increasing compliance and adherence as well as reducing side effects. Therefore, authors wanted to study the effect of weekly intermittent fixed dose estrogen and progesterone (ultra-low dose) supplements in hysterectomised surgically menopaused women.
Methods: The present study was prospective and retrospective study. For retrospective study authors records of 100 hysterectomised women up to 45years of age with severe post-menopausal symptoms treated in authors Medicine Department of Hospital with once weekly MALA-D tablets were studied. For prospective study, all consecutive hysterectomised patients with severe post-menopausal symptoms attending medicine OPD were given once weekly MALA-D which contains ethinylestradiol 0.03mg and levonorgestrel 0.15mg tablets and followed up monthly with outcomes measured by Modified Kuppermann Index, visual analogue scale, and women's health questionnaires.
Results: Present retrospective study showed moderate degree of postmenopausal symptoms as indicated by Modified Kuppermann index of 19.57. Prospective study showed significant improvement in postmenopausal symptoms with weekly intermittent hormone replacement therapy as indicated by outcomes measured by Modified Kupperman index and Visual analogue scale. Women's health questionnaire also showed statistically significant improvement in 6 out of 8 dimensions.
Conclusions: Authors concluded that weekly estrogen progesterone hormone replacement therapy with mala-D tablet (ultra-low dose therapy) was 100% effective in relieving vasomotor symptoms and it is very effective in improving psychosomatic symptoms, urinary symptoms and quality of life with no obvious side effects and greater adherence.

Keywords: HRT, Post menopausal symptoms, Vasomotor symptoms

INTRODUCTION

Women reach menopause at the mean age of 50years and approximately every three out of four women experience menopausal symptoms, which can significantly deteriorate quality of life. Younger age at menopause associates with an elevated risk of cardiovascular disease, osteoporosis, and shorter life expectancy.[1-5]

Typical menopausal symptoms include-vasomotor hot flushes, night sweats, broken sleep, Mood swing, muscle and joint pain, impaired memory and concentration and urinary tract infections.[6]

Estrogen stabilizes the CNS thermoregulatory set point and leads to a normal thermoregulatory response. During menopausal transition, decreased estrogen levels lead to instability of the set point and an altered response to external thermal stimuli. pharmacological intervention with estrogen may stabilise the set point.[7] These post-menopausal women had been given hormonal supplements in the form of estrogen and progesterone tablets on daily basis.[4] There is no literature available regarding intermittent once a week estrogen and progesterone replacement (ultra-low dose). However intermittent therapies are used in the management of male hypogonadism using HCG, FSH, LH, GnRH hormones. Similarly, intermittent therapy is also used in treatment of various auto immune diseases using cyclophosphamide pulse therapy in SLE, psoriasis, pemphigus etc. long-term steroid therapy is also used intermittently. Similarly, methotrexate is used intermittently in management of rheumatoid arthritis.

Cancer chemotherapy is also given intermittently in management of various malignancies to give rescue time to healthy cells of the body to recover from the ill effects of the chemotherapeutic agents. Antitubercular medications are used intermittently alternate day. Ormeloxifene is a selective estrogen receptor modulator which is used intermittently bi weekly as an oral contraceptive agent and also used to in dysfunctional uterine bleeding. Estrogen and progesterone hormones are highly protein bound (98%).[8,9] Therefore they are suitable for dosing at longer interval. Weekly Intermittent therapy is a more patient friendly approach with reduced pill burden.

The recommendations for hormonal therapy (HT) also suggest treatment with the lowest effective dose for the shortest possible time.[10,11] After experiencing substantial improvement on HT, women should stick with the regimen for 6 to 12 months, then gradually taper off. A woman's age and time since menopause are likely to influence the outcomes of HT.[12,13]

Daily regimen has risk of breast carcinoma, endometrial carcinoma, gall bladder disease, DVT, pulmonary embolism etc.[14]

To nullify risk of endometrial hyperplasia and subsequent carcinoma we selected only hysterectomised women.

These tablets are available free of cost in our institute hospital with brand name of MALA-D which contains ethinylestradiol 0.03mg and levonorgesttrel 0.15mg. It can be used as an effective tool to improve patient compliance and adherence in patients with poor drug compliance. It may also be used to decrease the cost of treatment. Therefore, authors wanted to study the effect of weekly intermittent fixed dose estrogen and progesterone (ultra-low dose) supplements in hysterectomised postmenopausal women.

METHODS

- For retrospective study: records of 100 hysterectomised women up to 45years of age with severe postmenopausal symptoms treated in medicine department of our institution were studied.
- For prospective study: all consecutive hysterectomised patients with severe post-menopausal symptoms attending medicine OPD of authors' institution. Authors studied 100 such patients.

After taking proper consent, all enrolled women for prospective study were clinically examined for any systemic illness and Gynaecological examination were done in Department of Obstetrics and Gynaecology, including P/S and P/V at the time of enrollment and subsequently after 3 months and 6 months. Routine blood investigations including CBC, RFT, LFT, FBS, PPBS, LIPID PROFILE, TSH, HbA1c, Urine routine and microscopy, chest x-ray, abdominal sonography, ECG were done. Study population were followed monthly up to 6months for improvement in symptomatology with weekly estrogen and progesterone tablets with the brand name of MALA-D. These enrolled women of prospective and retrospective studies have already received first line therapy with calcium, vitamin D, protein, multivitamins supplement, reassurance, physiotherapy, life style modification therapy for the preceding 3months prior to enrollment in this study. There vasomotor symptoms and psychosomatic symptometology were not responding to this first line therapy and therefore this subset of women were considered for weekly estrogen progesterone hormone replacement therapy (ultra-low dose HRT) and therefore these study women themselves served as control group for this study.

Inclusion criteria

- Hysterectomised women up to 45years of age were included in both retrospective and prospective study.
- For retrospective study: only records with adequate information for patients contact, physical examination and investigations were analyzed.

Exclusion criteria

- Women suffering from any of the chronic illnesses - diabetes, hypertension, CKD, CAD, COPD, CVA, CLD, family history of breast cancer /ovarian cancer, smoking, BMI more than 30kg/m^2.
- For prospective study: women not willing for consent and follow up.

Outcome measures

Authors measured end points of present study with the following parameters.

Modified Kupperman index

The Kupperman Index (KI) is an example of a traditional menopause-related symptom list.[15] It measures symptoms as a menopausal index, a sum of symptom points weighted according to their prevalence (higher the score, the worse menopausal symptoms). In addition to the same 11 items included in the original KI the modified version adds urogenital symptoms, including urinary infection & sexual complaints. These 11 items includes sweating/hot flushes, palpitation, vertigo, headache, paresthesia, formication, arthralgia, and myalgia (categorized as somatic symptoms), fatigue, nervousness, & psychological symptoms. A scale ranging from 0-3 points is used to describe the severity of the complaints. The total score ranges 0 to 63, calculated as sum of all items by the weighting factor. Scores ranging from 0-6, 7-15, 16-30, >30 were used to rate the degree of severity as none, mild, moderate, and severe, respectively.

Visual analogue scale

Visual analogue scale is single item generic measure designed to assess aspects of life, not only those that are health related.[16,17] On a 10cm scale from 0 ("might as well be dead") to 100 ("perfect quality of life"), participants were asked "Which number best represents your overall quality of life over the past two weeks?"

Women's health questionnaire (WHQ)

Authors measured the HRQL with the WHQ, which is a reliable and well documented tool to assess a wide range of physical and emotional symptoms and possible health changes in middle-aged women.[18] It is a self-administered questionnaire composed of 36 items capturing 9 domains of women's health: vasomotor symptoms (two items), somatic symptoms (seven items), anxiety and fears (four items), depression (seven items), sleep problems (three items), sexual behavior (three items), memory and concentration (three items), menstrual cycle related symptoms (four items) and attractiveness (two items). Each item is answered on a four-point scale (1-4) and then reduced to a binary scale (1 and 2=0, 3 and 4=1) for scoring. A mean score (between 0&1) was calculated for each domain (corresponding items), and thus higher the score, better the quality of life.[19]

Statistical analysis

Statistical test of significance ANOVA was applied to analyze the difference between the means at the time of enrollment, at 3 months and 6 months.

RESULTS

Hot flushes were the most common symptom both in prospective and retrospective study (100% and 95% respectively).

Next most common symptom was fatigue in both studies (90% and 90% respectively) as shown in Figure 1 and 2 respectively.

Hot flushes, night sweats, dyspareunia and urinary tract symptoms and infections resolve in almost 100% women after the use of weekly intermittent hormone replacement for 6 months in prospective study as shown in Figure 1.

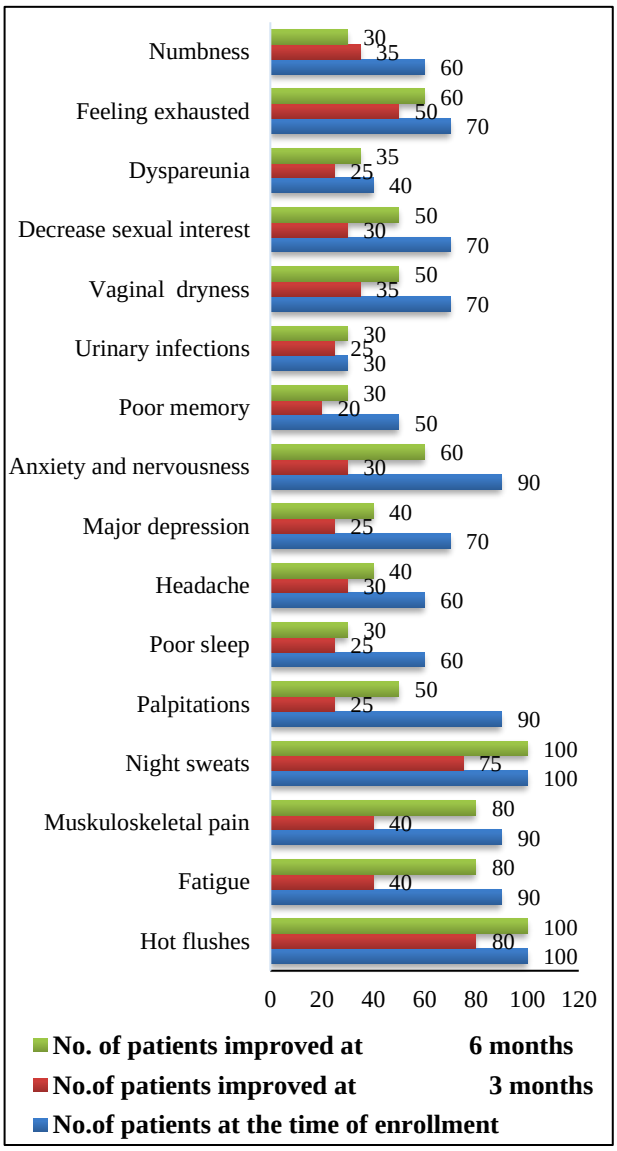

Figure 1: Common symptoms of menopause prospective patients.

Outcome measures

Retrospective study

Number of patients with Modified Kupperman index (K.I.) is shown in Table 1.

Mean Modified Kupperman Index was 19.57 indicating moderate degree of symptoms.

Prospective study

Modified Kupperman index (K.I.)

Modified K.I. and mean Modified K.I. at the time of enrolment, 3 months and 6 months is shown in Table 2 and Table 3 respectively. Mean modified K.I. at the time of enrollment in prospective study was 19.8 indicating moderate degree of menopausal symptoms.

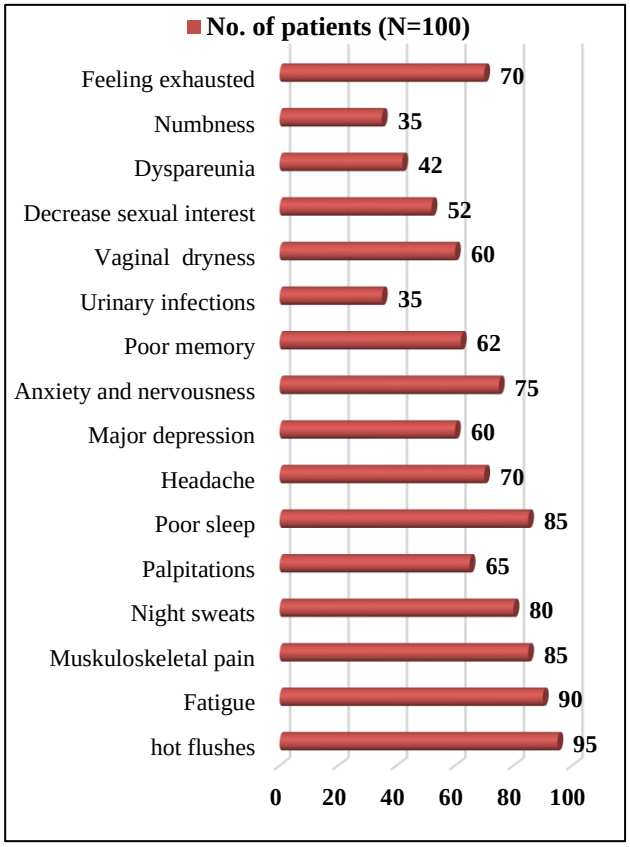

Figure 2: Common symptoms of menopause retrospective patients.

Mean modified K.I. at the end of 3months of weekly intermittent hormone replacement therapy was 15.80 and at the end of 6months was 11.65 which are statistically significant with p <0.05 indicating significant improvement in post-menopausal symptoms with weekly intermittent hormone replacement therapy.

Table 1: Modified Kupperman score (retrospective patients).

Modified K.I. (raw score)	No. of patients (N =100)
0-6	0
7-15	25
16-30	68
>30	07

Table 2: Modified Kupperman score (prospective patients).

Modified K.I. (raw score)	No. of patients at the time of enrolment (N =100)	3 months	6 months
0-6	00	15	39
7-15	21	51	41
16-30	70	29	20
>30	09	05	00

Table 3: Modified K.I. mean score (n=100).

	Enrollment	3 months	6 months
Modified K.I (n=100)	19.8	15.80	11.65

Visual analogue scale

Visual analogue scale also showed significant improvement in quality of life women with mean score 74 at the time of enrollment and 40 at the end of 6 months as shown in Table 4.

Table 4: Visual analogue scale.

	Enrollment	3 months	6 months
VAS (mean) n=100	74	53	40

Table 5: WHQ score (prospective patients).

WHQ dimension	WHQ score Mean±SD at the time of enrollment	WHQ score Mean±SD 3months follow up	WHQ score Mean±SD 6months follow up	P value
Vasomotor symptoms	0.925±0.1794	0.515±0.434	0.420±0.430	<0.05
Depression	0.794±0.093	0.688±0.164	0.498±0.342	<0.05
Anxiety/fears	0.585±0.244	0.515±0.218	0.490±0.218	<0.05
Memory/ concentration	0.663±0.260	0.646±0.24	0.579±0.257	<0.05
Sleep problem	0.599±0.250	0.407±0.316	0.258±0.311	<0.05
Somatic problems	0.595±0.19	0.485±0.196	0.423±0.189	<0.05
Sexual dysfunction	0.499±0.224	0.495±0.203	0.462±0.221	>0.05
Attractiveness	0.895±0.040	0.88±0.034	0.84±0.031	>0.05

Women's health questionnaire

Maximum mean score (0.925) of WHQ was also seen in vasomotor dimension of the questionnaire which decreased to 0.51 and 0.42 over 3 and 6 months of weekly hormone replacement therapy. Six out of 8 WHQ dimensions shows statistically significant improvement in mean WHQ score (with $p < 0.05$). These include vasomotor symptoms, sleep problems, somatic problems, anxiety and fear, sexual dysfunctions, memory and concentration, attractiveness and depression. WHQ dimension sexual dysfunction and attractiveness also showed improvement in mean score but it was not statistically significant (Table 5).

Investigations, clinical examination and compliance

There was no statistically significant difference in the investigations performed at the time of enrollment and subsequently at the end of 3 month and 6 months. Fifteen patients did not come for follow up, so they were not included in the further study. Overall compliance of the hormonal therapy was very good and no clinically significant side effect occurred during examination in follow up period.

DISCUSSION

Estrogen replacement therapy in younger postmenopausal women is associated with a decisive reduction in all-cause mortality, but estrogen use in this population is low and continuing to fall.[20] This is probably because of possible risks associated with hormonal replacement therapy (HRT).[14] The Women's health initiative data suggest that more lives may be saved by rational use of HRT in a subset of age defined subgroups of postmenopausal women who have undergone hysterectomy.[20] Guidelines also recommend estrogen as the most effective treatment to alleviate vasomotor symptoms and other menopausal complaints.[10.11] Estrogen and progesterone hormones are highly protein bound hormones (98%) which makes them suitable for dosing at higher interval but there is paucity of studies on intermittent dosing of these hormones as HRT. Clinical trials have demonstrated that lower HT doses provide menopausal symptom relief and osteoporosis prevention with greater tolerability than standard HT doses. Marco Gambacciani et al, have found in their study that in relatively young postmenopausal women treated with daily regimen of either low dose HRT (LD-HRT) and ultra-low dose HRT (Ultra-LD-HRT), significant improvement in vasomotor symptoms was evident. Ultra-LD-HRT is effective in improving menopausal symptoms and can prevent the bone loss related to the estrogen deprivation.[21] Speroff et al, also studied menopausal women with hot flushes and treated them with esterified estradiol/norethindrone acetate 0.01/0.2mg/d, 0.025/0.5mg/d, 0.05/1mg/d, or 0.1/1mg/d and found significant reduction in hot flushes at the end of 4 weeks.[22]

Present study results were also consistent with the above studies and shows that even weekly ultra-low dose estrogen and progesterone therapy (Ultra-LD-HRT) was very effective in controlling hot flushes and other menopausal symptoms.

In some previous studies, women using low dose HRT had reduced likelihood of experiencing breast tenderness, compared with women using standard doses of therapy.[23] Lower HT doses may also have a reduced effect on venous thromboembolism risk compared with standard-dose therapy.[24]

Nurses' Health Study have found that the estrogen dose affected the risk of stroke associated with HT. In this analysis, conjugated equine estrogen (CEE) doses 0.625mg/day were associated with a significantly increased risk of stroke compared with no therapy whereas CEE dosed at 0.3mg/day was not linked to an increase in stroke risk.[25]

Authors also did not find any significant clinical side effect, and this may be because of use of weekly ultra-low dose estrogen and progesterone. There was significant improvement in health-related quality of life as indicated by Kupperman Index, WHQ score and VAS score.

This research work may be considered as a pilot study of fixed dose once weekly intermittent hormone replacement therapy in hysterectomised postmenopausal women. Present study may favor such a protocol. However, for regulatory purposes and for its wider use in the clinical practice, this requires confirmation with larger multicentric randomized controlled trials.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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