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Effects of low-dose, continuous combined hormone replacement therapy on sleep in symptomatic postmenopausal women

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Abstract

Sleep disturbances in peri- and postmenopausal women may result from hormonal changes, vasomotor symptoms, and possibly psychological factors. Hormone replacement therapy (HRT) seems to diminish the disruption of sleep in climacteric women. The aim of this study was to determine the effects of a low dose of conjugated equine estrogens (CE) in combination with different progestins (LD-HRT) and evaluate differences between regimens on sleep in symptomatic postmenopausal women. Postmenopausal women were recruited and assigned to calcium–vitamin (control group) or to LD-HRT with 0.3 mg of CE associated with a daily administration at bedtime of a progestin (2.5 mg MPA, CE + MPA, $n = 20$), or 100 mg natural micronized progesterone (CE + P, $n = 20$). Subjective symptoms were evaluated by the Greene climacteric scale, and by a visuoanalogic graduated scale (0–10) at baseline and after 4, 8, and 12 weeks of study. Greene's scores for the control group were similar to those in LD-HRT group at baseline, and showed no significant modification at all subsequent measurements. Conversely, in LD-HRT group, a significant ($P < 0.05$) reduction in the scores of all Greene's domains was evident versus corresponding baseline and control group values. Conversely, in LD-HRT group, a significant ($P < 0.05$) reduction in the scores of all Greene's domains was evident with no difference in the scores of the two treated group. Both CE + MPA and CE + P significantly ($P = 0.05$) reduced the HF and sleep visuanalogic score in comparison to the control group. The score of sleep was significantly ($P = 0.05$) lower in the CE + P group in comparison to that measured in the CE + MPA group. No significant correlation between sleep and vasomotor score was found.

In conclusion, low estrogen dose may have a value in the treatment of menopausal women in which sleep disturbances may be a symptom of estrogen deprivation. Low-dose estrogen associated with low-dose micronized progesterone may especially benefit women who complain of disturbed sleep.

Keywords: Hormone replacement therapy; Estrogen; Progesterone

1. Introduction

Insomnia, disturbed sleep, and mood alterations are significantly more frequent in perimenopausal than in premenopausal women [1,2]. Perimenopausal sub-

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jects experience longer and more numerous arousals, resulting in significantly less sleep, with a significant correlation between sleep and mood changes [3–6]. The most common problems are frequent nocturnal awakenings with difficulty returning to sleep and sometimes difficulty falling asleep [7,8]. Sleep disturbances with reduced sleep efficiency and increased rapid eye movements (REM) sleep latency in peri-and postmenopausal women may result from hormonal changes, vasomotor symptoms, and possibly psychological factors [9–11]. Several studies indicate that estrogen therapy given during the perimenopausal or menopausal period can diminish not only hot flushes, but also anxiety, fatigue, depressive symptoms, enhancing mood and subjective sense of well being [12–20]. Improvement of psychological symptoms, cognitive functions, and sleep by hormone replacement therapy (HRT) could be the consequence of a decrease of vasomotor symptoms. Although many age-related conditions should be considered when treating postmenopausal sleep disorders [18], HRT seems to diminish the disruption of sleep in climacteric women [19]. Since the beneficial effects of estrogen on mood may be counterbalanced by concomitant administration of progestagens [18,19], the aim of this study was to determine the effects of a low dose of conjugated equine estrogens (CE) in combination with different progestins (LD-HRT) and evaluate differences between regimens on sleep in symptomatic postmenopausal women.

2. Methods

The Ethical Committee of our Department approved the study protocol. Symptomatic postmenopausal women, attending our Clinic for symptoms, were recruited and assigned to calcium–vitamin- (control group) or LD-HRT-treated group, using a randomisation list. Postmenopausal women between the age of 45 and 55 were studied. Inclusion criteria were amenorrhea for at least 6 months, levels of follicle-stimulating hormone >40 IU/L and estradiol <20 ng/L, body weight within 30% of ideal, menopausal symptoms (hot flashes, night sweats, insomnia, anxiety, and mood swings). Exclusion criteria included past use of hormone/estrogen replacement therapy within 12 weeks of study enrollment, endocrinopathy, major psychiatric disease, use of medication likely to influence sleep or vigilance, such as benzodiazepines, psychostimulants, and antidepressants, and sleep disorders. No women with major depression or diagnosed psychological disorder were allowed. The control group received a daily supplement of calcium (1000 mg per day, $n = 20$). The LD-HRT group received with 0.3 mg of CE associated with a daily administration at bedtime of a progestin (2.5 mg medroxiprogesterone acetate (MPA), CE + MPA, $n = 20$), or 100 mg natural micronized progesterone (P), (CE + P, $n = 20$). No women in the LD-HRT group received any information about the two different progestins used in the study. Subjective menopausal symptoms were evaluated by the Greene climacteric scale [21] and by a visuoanalogic graduated scale (0–10). The questionnaires were performed at baseline after 4, 8, and 12 weeks of study. All the results are reported as mean ± S.E. of absolute values. Two-way analysis of variance for repeated measures and factorial analysis of variance were used to test the differences within and between the groups, respectively. The post hoc comparison was made by Scheffe *F*-test for factorial analysis of variance.

3. Results

Table 1 presents the baseline data for the study participants. There were no significant differences in age, BMI, hormone values, bone metabolism markers, and femur bone density in the control and LD-HRT groups

Table 1
Baseline characteristics of participants who completed the study

	Control	CE + MPA	CE + P
Age (years)	53 ± 4.4	53.6 ± 2.2	53.4 ± 2.6
YSM	2.7 ± 0.7	2.8 ± 1.3	2.5 ± 0.3
BMI (kg/m^2)	24.2 ± 0.8	24.0 ± 0.4	24.7 ± 0.8
FSH (IU/L)	73.4 ± 24.0	68.3 ± 14.0	58.9 ± 11.0
Estradiol (pg/mL)	14.1 ± 2.6	15.4 ± 4.4	16.2 ± 5.3

The results are reported as the mean (±S.D.). Control group: postmenopausal women receiving 1000 mg of calcium per day ($n = 20$); CE + MPA group: 0.3 mg of CE associated with a daily administration of 2.5 mg MPA ($n = 20$); CE + P group: 0.3 mg of CE associated with a daily administration of 100 mg natural micronized progesterone ($n = 20$). YSM: years since menopause; BMI: body mass index; FSH: follicle-stimulating hormone.

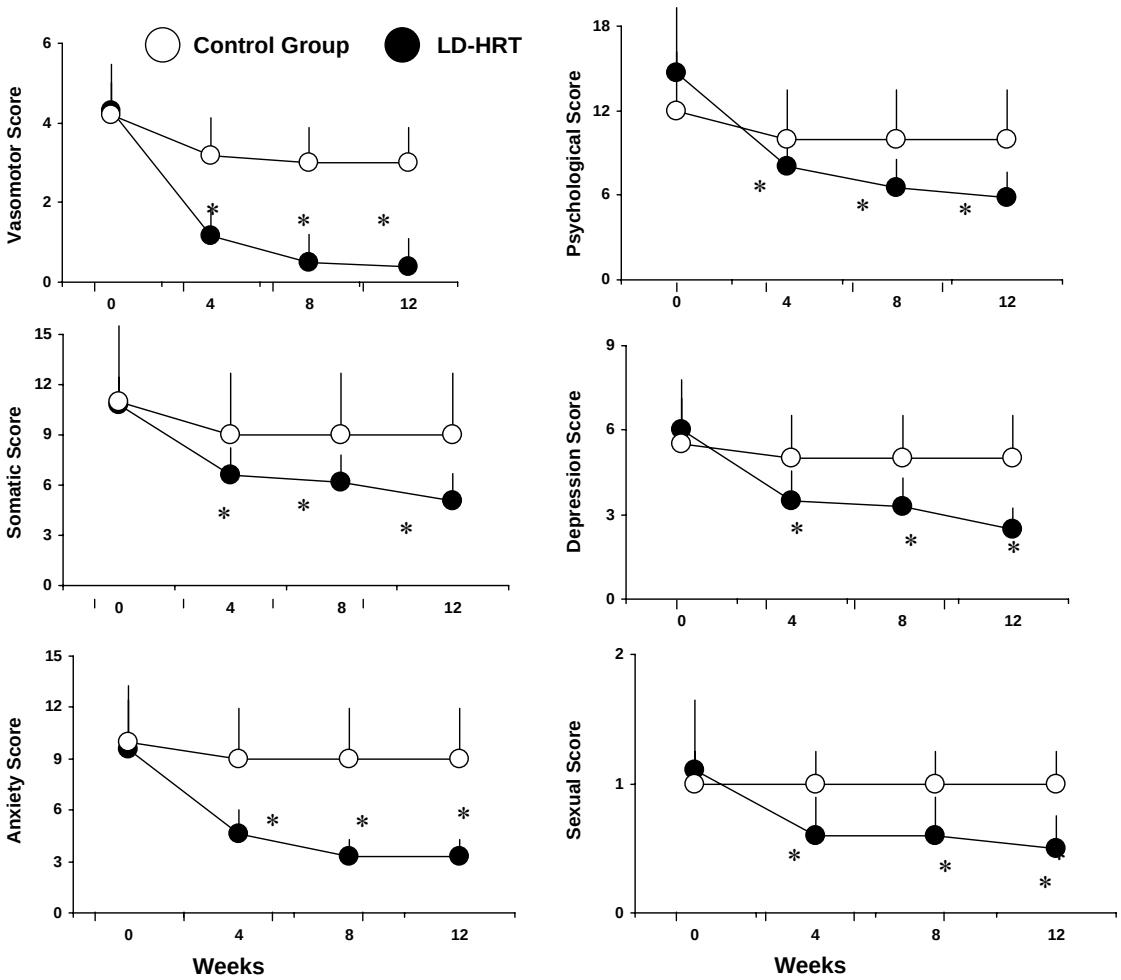

Fig. 1. Clinical symptoms (mean ± S.E.) evaluated by the Greenee climacteric scale at baseline (0 weeks), 4, 8 and 12 weeks in postmenopausal women in the calcium-treated control group ($n = 20$) and in the LD-HRT group ($n = 40$). *$P < 0.05$ vs. corresponding baseline levels.

before the study. No differences in smoking habits, blood pressure, education, life style, family history of breast cancer, osteoporosis, and cardiovascular diseases were present in the two groups (data not shown). The two groups were also comparable with respect to symptoms at baseline (Fig. 1). About 15% of patients of LD-HRT groups report spotting lasting in the first 4–6 months (data not shown). No cases of bloating, headache, weight gain, and water retention were reported (data not shown).

Fig. 1 depicts the pattern of subjective symptom scores grouped in the Greene's domains. Symptom scores for the control group showed no significant modification during our observation. There was no difference in any domain in the two groups of women treated with low-dose CE and progestin or micronized progesterone, and there was no group interaction for any of the menopausal symptoms, indicating that both groups improved in a similar fashion on all symptoms after treatment. Therefore, the Greene's data are reported together. In LD-HRT group, a significant ($P < 0.05$) reduction in the scores of all Greene's domains was evident versus corresponding baseline and control group values (Fig. 1). As shown in Fig. 2, both CE

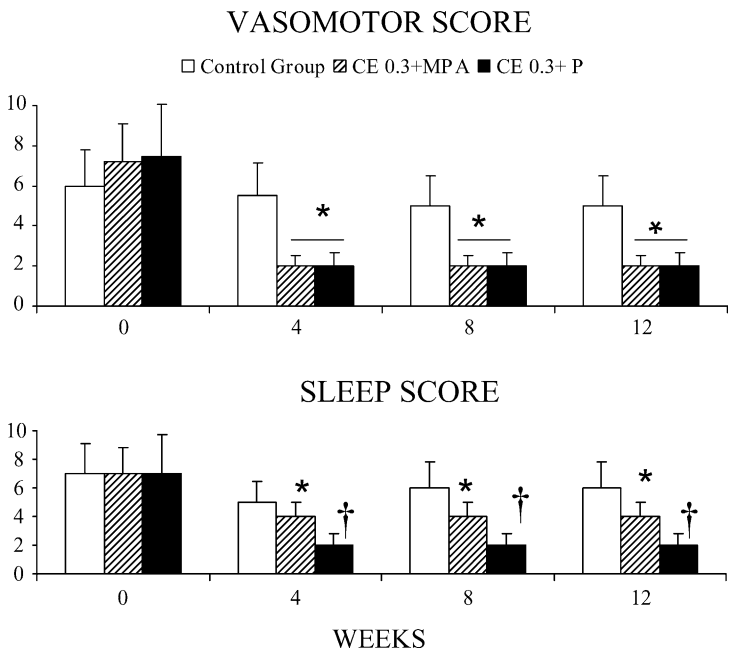

Fig. 2. Visuonalogic scores (VAS, mean ± S.E.) for hot flushes (HF, upper panel) and sleep disturbances (lower panel) evaluated at baseline and after 4, 8 and 12 weeks in postmenopausal women in the calcium-treated control group ($n = 20$) and in the LD-HRT groups (0.3 mg of CE associated with a daily administration at bedtime of a progestin (2.5 mg MPA, CE + MPA, $n = 20$), or 100 mg natural micronized progesterone (CE + P, $n = 20$)). $^{*}P < 0.05$ vs. corresponding baseline and control group levels; $^{\dagger}P < 0.05$ corresponding control and CE + MPA group values.

+ MPA and CE + P significantly ($P = 0.05$) reduced the HF and sleep visuanalogic score in comparison to the control group (Fig. 2). The score of sleep was significantly ($P = 0.05$) lower in the CE + P group in comparison to that measured in the CE + MPA group (Fig. 2).

Table 2 presents data about the correlation between the variation in sleep and vasomotor score in all subjects at each visit and in each group at each visit. No statistically significant correlation has been found between the variation in sleep and vasomotor score at each visit in all groups.

4. Discussion

To our knowledge, this is the first report on the effects of low-dose HRT on sleep disturbances in symptomatic postmenopausal women. Present data confirm that low-dose HRT is effective in the treatment of climacteric symptoms in early postmenopausal women [22,23]. Lower doses of CEE and progestin can alleviate the symptoms of younger menopausal women, reducing annoying side-effects [22,24] and maintaining the bone-sparing effects of higher doses [23,25]. In addition, present results show that low-dose CE in association with natural micronized progesterone resulted in a more positive effect on sleep disturbances than the CE + MPA combination. Conflicting results have been reported concerning the effect of different forms of HRT on sleep quality, efficiency, and various sleep architecture variables [26–34]. However, recently it has been reported that the standard conjugated estrogen dose (0.625 mg/day), in association with micronized progesterone, induces a better improvement of the quality of sleep than the same estrogen dose associated with medroxyprogesterone acetate [35]. Our data appear in accordance with these results, suggesting that even a lower estrogen dose may have a value in the treatment of menopausal women with sleep disturbances. In our study, the effects of low-dose HRT were evaluated with subjective method and not with stan-

Table 2
Correlation between absolute change in vasomotor (ΔHF) and sleep (Δsleep) score

	Correlation	*P*-value	
All subjects ($n = 60$)			
$\Delta HF_4/\Delta sleep_4$	−0.056	0.6720	ns
$\Delta HF_8/\Delta sleep_8$	−0.092	0.4863	ns
$\Delta HF_{12}/\Delta sleep_{12}$	−0.090	0.4966	ns
Controls ($n = 20$)			
$\Delta HF_4/\Delta sleep_4$	−0.01	0.9963	ns
$\Delta HF_8/\Delta sleep_8$	0.052	0.8287	ns
$\Delta HF_{12}/\Delta sleep_{12}$	0.22	0.3571	ns
CE + MPA ($n = 20$)			
$\Delta HF_4/\Delta sleep_4$	0.10	0.6775	ns
$\Delta HF_8/\Delta sleep_8$	0	0.9999	ns
$\Delta HF_{12}/\Delta sleep_{12}$	0.061	0.8022	ns
CE + P ($n = 20$)			
$\Delta HF_4/\Delta sleep_4$	−0.083	0.7316	ns
$\Delta HF_8/\Delta sleep_8$	−0.051	0.8317	ns
$\Delta HF_{12}/\Delta sleep_{12}$	−0.11	0.6457	ns

Control group: postmenopausal women receiving 1000 mg of calcium per day ($n = 20$); CE + MPA group: 0.3 mg of CE associated with a daily administration at bedtime of 2.5 mg MPA ($n = 20$); CE + P group: 0.3 mg of CE associated with a daily administration at bedtime of 100 mg natural micronized progesterone ($n = 20$). ΔHF_x: variation in hot $flush_{weeks}$; $\Delta sleep_x$: variation in $sleep_{weeks}$.

dard psychiatric instruments. However, the improvement in the subjective evaluation of sleep by questionnaires was reported to correspond to a significant increase in sleep efficiency measured in the sleep laboratory [36]. In the present study, we did not correlate the variations of sleep disturbances to hormonal values. On the other hand, the preparation used does not allow the measurement of a single estrogen in the blood stream, being a mixture of different equine estrogens. In addition, conflicting data are reported on possible correlation between any serum hormone levels and severity or presence of mood symptoms [37].

Our data suggest that the choice of progesterone/progestin is crucial for the ultimate action of HRT on sleep disturbances. It must be noted that the pretreatment sleep score values for the estrogen + MPA group were similar to those for subjects treated with estrogen + micronized progesterone. There is a rationale to explain why micronized progesterone will be superior to progestogens in restoring a better sleep. Progesterone is one of several steroids that target the brain, and progesterone metabolites (not found in synthetic progestogens), allopregnanolone, and pregnanolone are potent neurosteroids [38–40]. These compounds have profound effects on brain functions, inducing anxiolytic and hypnotic effects [38,39]. These effects are mainly exerted through the modulation of neuronal firing through interactions with cell surface receptors for gamma-amino-butyric acid (GABA) [40]. The GABA-mimetic action of natural progesterone and its metabolites suggests that these neurosteroids act as inhibitory neurotransmitters that modulate specific neuronal functions, involved in the control of sleeping, eating, anxiety, and aggression [39,40]. On the contrary, the recent large placebo-controlled randomised trials Women Health Initiative (WHI) [40] seems to demonstrate that HRT does not induce any clinically meaningful effect on health-related quality of life [41]. However, the WHI has been performed in a population of barely symptomatic women. Therefore, it is difficult to predict in this population any significant improvement. Thus, our data may differ regardless the study sample size since our patients are younger and symptomatic. It can be argued that the reduction in hot flushes score could explain the improvement on sleep pattern. However, the change in hot flushes score were similar to the two treated groups, while the change in CE + P group was greater than the CE + MPA group. Moreover, the change in sleep score did not correlate with the change in hot flushes score. The positive effects of HRT on nocturnal hot flushes can improve the sleep pattern [42]. However, the different effects obtained with the two regimens reinforce the contention that neuroendocrine action of progesterone metabolites “per se” may explain the better improvement of sleep pattern in the CE + P group. Further studies are needed for better explaining the interaction among sleep mechanism and estrogen fall in postmenopausal women.

In conclusion, this study suggests that low-dose HRT using micronized progesterone may improve sleep disturbances associated with menopause. Since the key point of an improved use and compliance of HRT is the personalization of schemes, doses, and type of hormones prescribed, as clinicians, we should bear in mind that all progestagens have different characteristics and biological actions. Present results show that low-dose estrogen associated with low-dose mi-

cronized progesterone may especially benefit women who complain of disturbed sleep. However, because the power of this study is limited by small size, confirmation by larger controlled studies is necessary.

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