Efficacy of pulsed estrogen therapy in relatively younger patients with surgically induced menopause

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BACKGROUND: Pulsed estrogen therapy is a new approach in estrogen replacement therapy. We carried out a prospective study to evaluate the efficacy of pulsed estrogen therapy in relatively younger patients with surgically induced menopause. METHODS: Patients (n = 138) <45 years old and suffering from severe vasomotor symptoms secondary to surgically induced menopause were included in the study. After the initiation of pulsed estrogen therapy (300 mg/day), the patients were re-evaluated every 4 weeks. The dose was increased at each follow-up, if necessary (to a maximum of 600 mg/day). The patients who preferred another method after the first 12 weeks were prescribed oral conjugated estrogen (0.625 mg/day) and at the end of the second 12 weeks their satisfaction levels were assessed. RESULTS: At the end of the first 12 weeks, 26 patients were completely satisfied (18.8%) and 47 were moderately satisfied (34.1%), whereas 65 concluded that the pulsed estrogen therapy they received was ineffective (47.1%). At the end of the second 12 weeks, all the patients were completely satisfied. CONCLUSION: Pulsed estrogen therapy for 12 weeks reduced the frequency of hot flushes in relatively younger patients with surgically induced menopause; however, 81.2% of patients were not completely satisfied at the end of this period.

Key words: menopause/pulsed estrogen therapy/surgically induced menopause

Introduction

Oestrogen replacement therapy is effective in reducing the vasomotor symptoms of the menopause (Belchetz, 1994; Greendale et al., 1999; Lopes et al., 2000). The two most commonly used methods for the administration of estrogen supplementation are the oral and transdermal routes, but both have several disadvantages. Oral estrogen is subject to substantial intestinal and hepatic first-pass metabolism (De Lignieres et al., 1986; O’Connell, 1995), necessitating relatively high doses. On the other hand, transdermal estrogen administration is associated with variable absorption rates between women (Stanczyk et al., 1986), local skin irritation (Frenkel et al., 1994) and the loss of patches in 4–8% of cases due to poor adhesion (The Transdermal HRT Investigators Group, 1993).

There is a substantial need for a new well-tolerated route of estrogen replacement that bypasses the liver, but that is efficient enough to relieve the vasomotor symptoms of menopause. In particular, the severe vasomotor symptoms secondary to surgical menopause in relatively early years of life constitute a serious health problem. Pulsed estrogen therapy represents a new approach for the treatment of menopausal symptoms. In this therapy an aqueous solution of the natural 17β-estradiol (E2) is used and it is delivered by a pump intranasally. After nasal administration, plasma E2 levels rise rapidly and fall to 10% of their peak level within 2 h (Devisaguet et al., 1999), unlike both oral and transdermal administration, which produce prolonged or plateau estrogen levels (Scott et al., 1991). The efficacy of pulsed estrogen therapy in reducing postmenopausal symptoms has been demonstrated in a prospective randomized placebo-controlled study (Studd et al., 1999) and 300 μg/day was identified as an appropriate initial dose. However, the efficacy of pulsed estrogen therapy has not been evaluated in the treatment of the severe vasomotor symptoms of relatively young patients who have undergone total hysterectomy and bilateral oophorectomy.

We carried out a prospective open-labelled multicentre study to evaluate the efficacy of pulsed estrogen therapy in patients <45 years old with surgically induced menopause.

Materials and methods

Locations

This clinical trial was carried out at Zübeyde Hn. Women’s Hospital and Ankara Research and Training Hospital, Ankara, Turkey.

Study design

The Kupperman Index (KI) was 30.3 ± 2.2 in the patients at the beginning of the study (Table I). The patients had no contraindications
for estrogen replacement therapy. Smokers were not included in this study. The mean body mass index (BMI) of the patients was 25.5 ± 4.3 (mean ± SD). All the patients were of low socio-economic status. The expense of both therapies was covered by the national health insurance, since this study was not financially supported by any commercial body. Pulsed estrogen therapy (Aerodiol®, nasal spray; Les Laboratories Servier, France) became available in April 2002 in Turkey and the study was started the following month. Since it was shown to be safe, well accepted and effective in doses ranging from 100 to 600 mg/day, and while 900 mg/day produced excessive estrogenization (Pelissier et al., 2001), an initial dose of 300 mg/day was administered in accordance with the results presented by Studd et al. (1999). The dose was raised to a maximum of 600 mg/day, if menopausal symptoms persisted at each follow-up, if necessary. In all patients, the dose was increased to 450 and 600 µg after 4 and 8 weeks, respectively. The doses of 450 and 600 µg were prescribed as two puffs in the morning/one puff in the evening and as two puffs in the morning/two puffs in the evening, respectively. After using pulsed estrogen therapy for 12 weeks, patients were invited back for the third time and the KI was re-calculated, and they were asked the following questions: Do you find the medication you have just used effective in terms of relieving your hot flushes? Do you want to continue using this method of hormone replacement or would you prefer to try another method? The responses of the patients to the first question were recorded as 1–3 (completely = 1, moderately = 2, ineffective = 3). The patients who preferred another method at the end of the first 12 weeks were prescribed oral conjugated estrogen (Premarin® tablet, 0.625 mg, 1 tablet/day; Wyeth, Istanbul, Turkey) (Figure 1). The patients were re-evaluated clinically at the out-patient departments every 4 weeks. At the end of the second 12 weeks, they were invited back for the last time. They were asked the same questions again as those asked after they had been using pulsed estrogen therapy for 12 weeks.

The statistical analysis was performed by two-way analysis of variance and by Wilcoxon signed-ranks test. Data are presented as means ± SD.

Results

At the end of the first 12 weeks, 26 patients were completely satisfied (18.8%) and 47 were moderately satisfied (34.1%), whereas 65 concluded that the pulsed estrogen therapy they received was ineffective (47.1%). The patients (n = 112) who were moderately satisfied and those who thought that the therapy was ineffective wanted to use another route of estrogen replacement therapy (81.2%) after the first 12 weeks. All these patients' preferences.

Figure 1. Study design and the results in summary. All the patients received pulsed estrogen therapy during the first 12 weeks. After the initial 12 weeks of treatment, moderately satisfied and unsatisfied patients received oral conjugated estrogen according to their preferences, whereas completely satisfied patients continued using pulsed estrogen therapy until the end of 24 weeks (P < 0.0001, week 0 versus 12, 0 versus 24 and 12 versus 24 in all groups).

Table I. Hot flushes and KI at the beginning and during the course of treatment (means ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Completely satisfied patients at the end of 12 weeks (n = 26)</th>
<th>Moderately satisfied patients at the end of 12 weeks (n = 47)</th>
<th>Unsatisfied patients at the end of 12 weeks (n = 65)</th>
<th>Total (n = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
<td></td>
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<tr>
<td>Week 0</td>
<td>12.04 ± 1.03</td>
<td>11.94 ± 0.99</td>
<td>12.00 ± 1.06</td>
<td>11.96 ± 1.01</td>
</tr>
<tr>
<td>Week 12</td>
<td>3.96 ± 0.66</td>
<td>7.404 ± 0.45</td>
<td>7.569 ± 0.45</td>
<td>6.833 ± 0.67</td>
</tr>
<tr>
<td>Week 24</td>
<td>3.00 ± 0.69</td>
<td>3.00 ± 0.69</td>
<td>3.031 ± 0.68</td>
<td>2.993 ± 0.67</td>
</tr>
<tr>
<td>KI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>30.80 ± 2.25</td>
<td>30.60 ± 2.09</td>
<td>30.37 ± 2.21</td>
<td>30.33 ± 2.23</td>
</tr>
<tr>
<td>Week 12</td>
<td>13.92 ± 1.87</td>
<td>26.79 ± 1.86</td>
<td>28.91 ± 2.19</td>
<td>25.36 ± 5.96</td>
</tr>
<tr>
<td>Week 24</td>
<td>12.08 ± 1.94</td>
<td>12.40 ± 1.90</td>
<td>12.54 ± 1.79</td>
<td>12.36 ± 1.84</td>
</tr>
</tbody>
</table>

P < 0.0001, week 0 versus 12, 0 versus 24 and 12 versus 24 in all groups.
patients were using 600 μg/day of pulsed estrogen therapy. They were prescribed oral conjugated estrogen and they did not want to change their medication after the second 12 weeks.

The number of hot flushes was 11.96 ± 1.01 at the beginning of the study (week 0, n = 138) and 8.83 ± 0.67 and 2.99 ± 0.67 after 12 and 24 weeks, respectively (n = 138; P < 0.0001, week 0 versus 12, 0 versus 24 and 12 versus 24). In the completely satisfied patients, the number of hot flushes was 12.04 ± 1.09, 3.96 ± 0.66 and 3.00 ± 0.69 at weeks 0, 12 and 24, respectively (P < 0.0001, week 0 versus 12, 0 versus 24 and 12 versus 24). In the patients who were moderately satisfied at the end of week 12 (n = 47) the number of hot flushes was 11.94 ± 0.99, 7.40 ± 0.47 and 3.00 ± 0.69 at weeks 0, 12 and 24, respectively (P < 0.0001, week 0 versus 12, 0 versus 24 and 12 versus 24 and 12.00 ± 1.06, 7.57 ± 0.45 and 3.03 ± 0.68 in the unsatisfied patients (n = 65) at weeks 0, 12 and 24, respectively (P < 0.0001, week 0 versus 12, 0 versus 24 and 12 versus 24) (Table I and Figure 2).

At the beginning of the study (week 0), the KI was 30.33 ± 2.23 (n = 138), and 25.36 ± 5.96 and 12.36 ± 1.84 after the first and second 12 weeks, respectively (n = 138) (P < 0.0001, week 0 versus 12, 0 versus 24 and 12 versus 24). The KI was 30.80 ± 2.27, 13.92 ± 1.87 and 12.08 ± 1.94 in the completely satisfied patients at weeks 0, 12 and 24, respectively (n = 26) (P < 0.0001, week 0 versus 12, 0 versus 24 and 12 versus 24). In the patients who were moderately satisfied at week 12 the KI was 30.60 ± 2.092, 26.79 ± 1.86 and 12.40 ± 1.90 at weeks 0, 12 and 24, respectively (n = 47) (P < 0.0001, week 0 versus 12, 0 versus 24 and 12 versus 24), and 30.37 ± 2.21, 28.91 ± 2.19 and 12.54 ± 1.79 in the unsatisfied patients at weeks 0, 12 and 24, respectively (n = 65) (P < 0.0001, week 0 versus 12, 0 versus 24 and 12 versus 24) (Table I and Figure 3).

Mastalgia was reported by five patients in the pulsed estrogen therapy group (3.6%) and by seven patients in the oral estrogen replacement therapy group (6.3%) (P > 0.05). Headache (n = 3, 2.1%) and runny nose (n = 2, 1.4%) were the other complaints of patients using pulsed estrogen therapy. No side-effects other than mastalgia were observed in the oral estrogen replacement therapy group. A complaint expressed by all the patients using pulsed estrogen therapy at doses over 300 μg/day concerned the medication’s pump system. Since it did not have a numerator, it was difficult to predict when the tube would finish.

**Discussion**

To the best of our knowledge, this is the first prospective study carried out to evaluate the efficacy of pulsed estrogen therapy in patients <45 years old and suffering from severe vasomotor problems caused by bilateral oophorectomy. In different studies, pulsed estrogen therapy was shown to be effective for menopausal symptoms (Lopes et al., 2000; Pelissier et al., 2001). However, the efficacy of pulsed estrogen therapy to relieve the severe vasomotor symptoms of relatively younger patients (<45 years old) with surgically induced menopause has not been studied. When patients <45 years old undergo bilateral oophorectomy, the blood estrogen level decreases sharply and these patients start suffering from severe vasomotor symptoms within a few weeks. In the process of natural menopause, the estrogen level decreases gradually so that the organism can have enough time to adapt to the new hormonal status. In the surgically induced menopause of relatively older patients (e.g. >50 years old), the vasomotor symptoms are not so severe in general. With respect to the severity of vasomotor symptoms, relatively younger patients with surgically induced menopause are clinically different from other menopausal patients. This is why we carried out this study to evaluate the efficacy of pulsed estrogen therapy in this patient group.

The initial dose of pulsed estrogen therapy was 300 μg/day in our study as it was identified as an appropriate initial dose by Studd et al. (1999). The maximum dose was 600 μg/day, since Pelissier et al. (2001) concluded that pulsed estrogen was safe, well accepted and effective in doses ranging from 100 to 600 μg/day in their dose-finding study. In the same study (Pelissier et al., 2001), estrogenization was excessive for a daily dose of 900 μg/day. In addition to excessive estrogenization, another problem related to the use of 900 μg/day of pulsed estrogen is the expense of such a high dose; it is 5–6 times the cost of oral HRT in Turkey.

The patients were evaluated by the investigators taking into account the severity of vasomotor symptoms. The subjective measurements of hot flushes might be considered a limitation of this study, but it is widely known by clinicians that the evaluation of various symptoms is more useful than E2 plasma levels when adjusting the dose of estrogen replacement therapy in daily practice. The dose of pulsed estrogen was increased according to the clinical findings in our study. The final
decision about the efficacy of estrogen replacement therapy was made at the end of 12 weeks, which was considered a sufficient evaluation period (Pelissier et al., 2001). The difference between our findings in hysterectomized women and those reported by Pelissier et al. in women also receiving a progestin for 10–14 days of the month may stem from addition of a progestin. Moreover, the homogeneous and highly symptomatic patient population included in our study might play a role in this difference. Our data are in accordance with those reported by Steingold et al. (1985) concerning highly symptomatic women. They carried out a dose–response study of the effects of transdermal E₂ on the frequency of hot flushes in highly symptomatic postmenopausal women and reported that the standard dose of transdermal E₂ (0.050 mg/day) reduced the frequency of hot flushes by 50%, but the complete elimination of hot flushes required a dose of E₂ which was 4 times higher (0.200 mg/day).

In our study, 112 of 138 patients (81.2%) using 600 μg/day of pulsed estrogen therapy were dissatisfied and they wanted to change the medication at the end of the first 12 weeks. The patients who preferred another method at the end of the first 12 weeks were prescribed oral conjugated estrogen since it is the most widely prescribed estrogen replacement therapy medication in Turkey. It is easily available and much cheaper than transdermal estrogen replacement patches. Moreover, the major problem related to the use of transdermal patches in Turkey is adhesion, particularly during hot summer months (unpublished data). The administration of E₂ as a cutaneous gel represents an option comparable to the patch in estrogen replacement therapy (Hirvonen et al., 1997). However, transdermal estrogen gel was not an option since it only became available in Turkey after the beginning of this trial.

In another group of Turkish women, Ozsoy et al. (2002) showed pulsed estrogen therapy to be safe, easy to use and highly efficient in alleviating postmenopausal symptoms at a dose of 300 μg/day. However, their data was from a patient population which was not as homogeneous or highly symptomatic as the population included in our study (e.g. numbers of moderate to severe hot flushes per day at the beginning of the study in the two groups were 7.0 ± 4.9 and 7.1 ± 4.0).

Mastalgia was reported less frequently in the pulsed estrogen therapy group (n = 138) than in the oral estrogen replacement therapy group (n = 112) (3.6 versus 6.3%, P > 0.05). In the pulsed estrogen therapy group, mastalgia was reported only by the patients using 600 μg of pulsed E₂ daily. The incidence of moderate or severe mastalgia was reported as 7.2% by Lopes et al. (2001) in patients using pulsed estrogen therapy. In the same study, one woman out of 176 patients discontinued treatment prematurely as a result of mastalgia (Lopes et al., 2001). In our study, no women dropped out because of mastalgia.

In conclusion, pulsed estrogen therapy administered for 12 weeks significantly reduced the frequency of hot flushes in patients <45 years old with surgically induced menopause and suffering from severe vasomotor symptoms. However, 81.2% of patients were not completely satisfied at the end of this period. Further studies are needed to compare the efficacy of pulsed estrogen therapy and other estrogen replacement therapies in highly symptomatic women with surgically induced menopause.

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References


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