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CLINICAL ARTICLE

Effects of transdermal estradiol gel and oral tibolone on health-related quality of life after surgical menopause

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ABSTRACT

Objective: To study the effects of 6 months of treatment with transdermal estradiol gel versus oral tibolone on health-related quality of life (HRQOL) after surgical menopause. *Methods:* In a randomized single-blind trial, Indian women received either oral tibolone tablets (2.5 mg) or transdermal estradiol gel (0.06%) daily. Each woman scored herself on the Menopause Rating Scale (MRS) II at the beginning of the study and after 6 months. Independent *t* tests were used to determine the significance of changes in HRQOL. *Results:* In total, 31 (81.6%) women who received estradiol gel and 38 (100.0%) women who received tibolone completed treatment. Intent-to-treat analysis showed that, after 6 months of treatment, the total MRS score was significantly reduced in the tibolone group compared with the transdermal estradiol gel group (-9.5 ± 5.1 versus -4.9 ± 5.7; 95% confidence interval, 2.0–7.0; $P<0.01$). Significant improvements were also noted in the tibolone group in terms of somatovegetative ($P=0.04$) and psychologic ($P<0.01$) domains. *Conclusion:* Oral tibolone treatment was more effective than transdermal estradiol gel at improving HRQOL in Indian women with surgical menopause.

1. Introduction

Surgical menopause in younger women can cause major symptoms of estrogen deficiency, which can affect quality of life. Much attention has been paid recently to the concept of health-related quality of life (HRQOL), together with traditional assessments of morbidity and mortality. The concept of HRQOL is used to evaluate patients' satisfaction with certain levels of function, and represents the functional effects of a condition and its treatment, as perceived by the patients themselves [1]. The incorporation of HRQOL scales into routine clinical practices and studies is fast gaining popularity.

The Menopause Rating Scale (MRS) II was developed because there was a lack of standardized scales for measuring the severity of menopausal symptoms and their effect on HRQOL. The scale can be easily interpreted by patients, and has good reliability and validity, excellent applicability, and sufficient repeatability [2,3]. It lists 11 symptoms or complaints, each of which can be scored between 0 (no complaint) and 4 (severe complaint). Personal perceptions of symptoms are provided by checking 1 of the 5 boxes of severity for each item. The MRS II has 3 independent subscales, which relate to somatovegetative, psychologic, and urogenital symptoms.

Hormone replacement therapy (HRT) has long been used to treat menopausal symptoms and for the overall wellbeing of menopausal women. Tibolone is a selective tissue estrogenic activity regulator, which is used for the treatment of menopausal symptoms. It exerts its estrogenic effects on bone, vagina, and climacteric symptoms through its 3-α and 3-β hydroxy metabolites. Progestogenic and androgenic effects are mediated via the δ-4 metabolite [4].

Transdermal estradiol gel is another option for HRT. The estradiol is transported through intact skin into the systemic circulation via the dermal capillaries, thus bypassing the liver and avoiding metabolism to estrone; instead, there is a nearly 1:1 ratio of estrone:estradiol [5]. Ross and Alder [6] reported that estrogen might be more effective than tibolone as an HRT for the treatment of surgical menopause.

The aim of the present study was to evaluate, using the MRS II, the effects of 6 months of treatment with transdermal estradiol gel versus oral tibolone on the HRQOL of Indian women with surgical menopause.

2. Materials and methods

Indian women with surgical menopause (occurring 3–18 months after surgery) who presented with distressing menopausal symptoms at the S.C. Das Memorial Medical and Research Centre, Kolkata, India, between January 1, 2007, and July 31, 2009, were screened for enrollment. All women had undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy (performed by SMB) for benign gynecologic conditions such as fibroids, dysfunctional uterine bleeding, and endometriosis.

Approval for the study was obtained from the Ethics Committee of the S.C. Das Memorial Medical and Research Center. The study center

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is a small non-teaching private hospital, so Institutional Review Board approval was not applicable.

The following women were excluded: those who had already taken some form of estrogenic preparation in the preceding 3 months; those with severe medical disorders (e.g. renal disease, liver disease, cardiac disease, uncontrolled diabetes, uncontrolled hypertension, and history of venous thromboembolism); those with histologic results showing malignant or premalignant conditions of the genital tract; and those already on psychiatric treatments.

Women with distressing menopausal symptoms who were not excluded were counseled about the need for HRT. Written informed consent was obtained from all participants, who were then randomized. Half of the women received a daily dose of 0.06% estradiol gel (Oestrogel, Besins International, Paris; 2.5-g gel containing 1.5 mg of estradiol) transdermally using a ruler. The remaining women received oral 2.5-mg tibolone (Livial, Organon, Oss, The Netherlands) daily.

The primary outcome measure was an absolute improvement in participants' HRQOL (total MRS II score and scores for the 3 subscales) after 6 months of treatment. The MRS II was used to assess HRQOL in both groups. Each woman scored herself at the beginning of the study and after 6 months, with body weight recorded on both occasions.

The sample size estimate was based on the results of a previous study (Bhattacharya SM, unpublished data) in which treatment with tibolone for 3 months led to a decrease of 9.9 ± 4.7 in total MRS score, compared with a decrease of 7.0 ± 4.5 with transdermal estradiol gel. The sample size was calculated using n-Master version 1.0 (Department of Biostatistics, Christian Medical College, Vellore, India). A sample size of 38 patients in each group provided 80% power and a 2-sided α value of 0.05.

Participants were randomized, using computer-generated randomization tables, in a 1:1 ratio. The interventions were sealed in sequentially numbered identical containers according to the allocation sequence. Participants were blinded to their treatment.

Primary analysis was intent to treat, which included all women who received at least 1 dose of medication and had 1 post-intervention visit to the clinic. The missing values were imputed by carrying the last observation forward. Independent *t* tests were used to determine the 2-tailed significance of the mean change in HRQOL between the 2 groups. $P<0.05$ was considered to be statistically significant. The 95% confidence interval (CI) of the mean difference in HRQOL score at 6 months was also calculated. All analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL, USA).

3. Results

In total, 119 women were assessed for eligibility, of whom 76 satisfied the eligibility criteria and were randomly assigned to 1 of the 2 groups (38 to each group) (Fig. 1). Of the 76 participants, 69 completed 6 months of treatment. All of the women who discontinued prematurely were in the transdermal estradiol gel group: 4 withdrew because of adverse events (1 because of leg swelling, 2 because of mastalgia, and 1 because of chest discomfort and persistent headache); 1 was excluded owing to protocol violation; and 2 were unwilling to continue. Thus, 100.0% patient compliance occurred in the tibolone group, compared with 81.6% in the transdermal estradiol gel group.

Patient-reported adverse effects for both treatments were assessed. There was a fear of long-term side effects, despite all assurances (2 cases in the tibolone group versus 3 cases in the estradiol gel group). At least

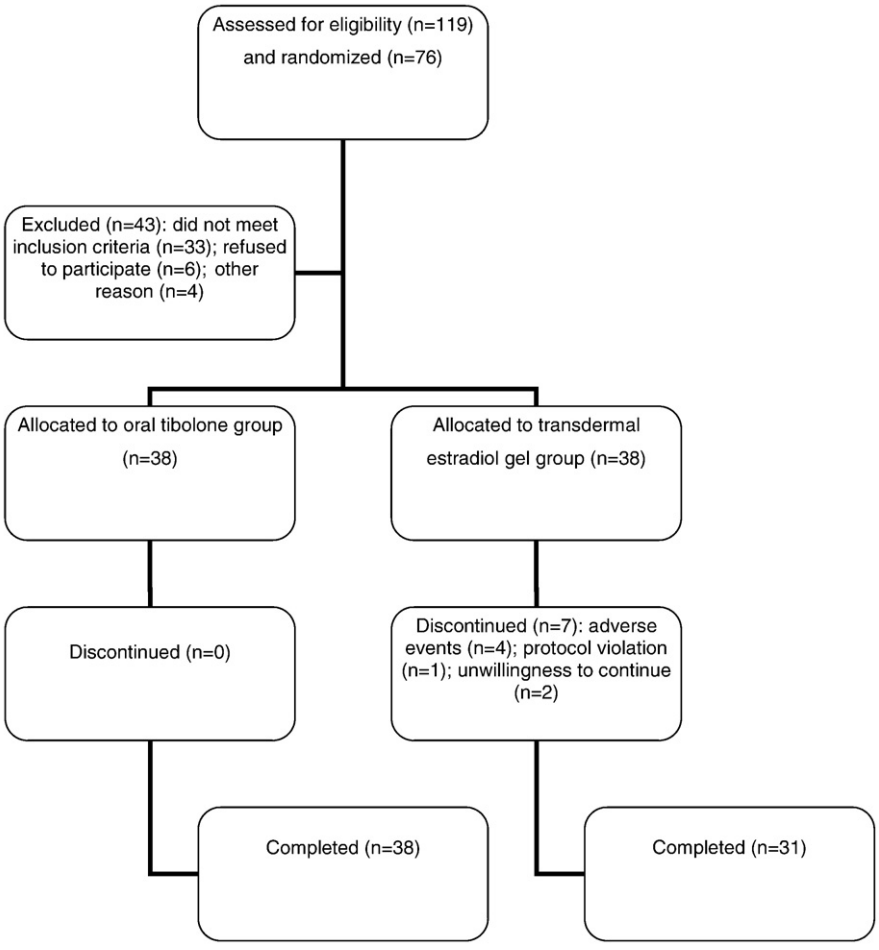

Fig. 1. Flow of subjects through the study.