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Effects of a continuous-combined regimen of low-dose hormone therapy (oestradiol and norethindrone acetate) and tibolone on the quality of life in symptomatic postmenopausal women: A double-blind, randomised study☆

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ABSTRACT

Objective: This study compared the effects of a continuous-combined regimen of low-dose hormone therapy (LD-HT) versus tibolone and supplemental calcium/vitamin D3 (control) on quality of life (QoL) in symptomatic postmenopausal women.
Design: This study was a prospective, randomised, double-blind, comparative trial with a control group.
Setting: The study was conducted in a climacteric outpatient clinic in the University Hospital of Federal University of Juiz de Fora, Brazil.
Population: A total of 174 postmenopausal women under 60 years of age who attended the climacteric outpatient clinic between June 2009 and June 2011 were recruited. These women complained of moderate or intense vasomotor symptoms and exhibited no contraindications for the use of hormone therapy.
Interventions: The patients were randomised into three groups: (1) daily treatment with 2.5 mg tibolone ($n = 64$), (2) 50 mg calcium carbonate + 200 IU vitamin D3 (Ca/Vit D3, $n = 54$) or (3) 1 mg oestradiol + 0.5 mg norethindrone acetate (E2/NETA, $n = 56$) for 12 weeks.
Primary outcome measures: The primary outcome was the evaluation of QoL using the Women's Health Questionnaire (WHQ) in all subjects at baseline and after 4, 8 and 12 weeks of treatment.
Results: A total of 130 women in the following groups completed the study: tibolone ($n = 42$), Ca/Vit D3 ($n = 44$) and E2/NETA ($n = 44$). An improved QoL based on the WHQ was observed at T0 (80.12 ± 14.04, 77.73 ± 15.3, 77.45 ± 15.4) and T12 (57.0 ± 15.5, 55.7 ± 16.7, 58.4 ± 12.6) for the tibolone, E2 + NETA and Ca/Vit D3 groups, respectively (p values <0.05). The three groups exhibited significantly different scores at T12 for sexual behaviour and vasomotor symptoms. The tibolone group exhibited better sexual function compared with the E2/NETA and Ca/Vit D3 groups (4.2 ± 26, 5.6 ± 2.8, 5.4 ± 2.8, respectively, p values <0.05). LD-HT was superior to tibolone and Ca/Vit D3 treatment for improvements in vasomotor symptoms (3.2 ± 1.5, 4.0 ± 1.8, 4.3 ± 2.0, respectively, p values <0.05). Adverse effects were few and mild.
Conclusions: An improved QoL was observed in the three study groups. Tibolone primarily improved sexual function, and E2/NETA exhibited a superior response for vasomotor symptoms.

1. Introduction

Vasomotor symptoms, vaginal atrophy, sexual dysfunction, urinary symptoms, and increased risk for cardiovascular disease and osteoporosis are all consequences of the hypoestrogenism that occurs during perimenopause. These signs and symptoms may reduce the quality of life (QoL) of climacteric women [1–3]. The interest in studying QoL has increased in several fields because an increase in life expectancy should be accompanied by an improved QoL. The physical, social, psychological, and spiritual domains of

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QoL should be evaluated [4]. Several factors are related to the QoL in postmenopausal women, including education; marital status; paid work; family income; morbidities; lifestyle; and marital, family, social, and sexual difficulties [5]. The symptoms that arise at this stage result from hypoestrogenism and may reduce the QoL of these women [2,6]. Hormone therapy (HT) using oestrogen or other drugs, such as tibolone, has been recommended to improve these symptoms [6–9]. The issue of QoL has not been widely studied in Brazil, despite its importance. Many studies have been conducted in other countries, but these results may not be valid for the population in Brazil because of cultural and socio-economic differences [10]. The importance of HT in the improvement of menopausal symptoms is indisputable, but the impact of HT on the QoL of postmenopausal women is controversial [11–20]. Previous studies use different oestrogens and progestins, as well as varying drug regimens, doses and routes of administration, resulting in conflicting results. This study compared the effects of a combined, continuous, low-dose hormone therapy (LD-HT) with the effects of tibolone and a control group on the QoL in symptomatic postmenopausal women.

2. Methods

2.1. Study design and population

This prospective, randomised, double-blind study with control group was conducted at the University Hospital of Federal University of Juiz de Fora (HU-UFJF), Minas Gerais, Brazil, from June 2009 to June 2011. The study population included 174 postmenopausal women who were selected from a group of women who were treated at a climacteric outpatient clinic.

The Ethics Committee in Research of the University Hospital of Federal University of Juiz de Fora (Brazil) – CEP-HU/UFJF – approved this research (protocol number 0046/09), and each subject provided written informed consent prior to any study-related procedures. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and applicable laws and regulations. The ethics committee's approval was obtained at each of the participating sites.

2.1.1. Eligibility criteria for participants

The selected participants were between 45 and 60 years in age and were in the postmenopausal phase with moderate or pronounced vasomotor symptoms and a Blatt–Kupperman menopausal index (BKMI) that was equal to or greater than 20 points. Women outside of this age range were excluded if they had no vasomotor symptoms or had mild symptoms; used hormone, non-hormone, herbal, or isoflavone therapy or soy-based foods in the last 6 months; underwent surgery for breast and/or endometrial cancer; had a history of myocardial infarction or coronary artery disease; had a history of thromboembolism, acute or severe liver disease, renal failure, coagulopathy, decompensated thyroid disease, or intestinal disorders that might interfere with drug absorption; or exhibited abnormal genital bleeding of unknown cause, porphyria or any other contraindication for the use of HT. The diagnosis of postmenopausal phase was primarily clinical and was based on the patient's age. Menopause was characterised by the absence of menstruation for at least 12 months and was confirmed by an increase in follicle-stimulating hormone (FSH) to levels greater than 40 mIU/mL.

2.2. Data collection procedures

Data collection from the women was performed during scheduled patient clinic visits to the postmenopausal outpatient clinic at the HU-UFJF on the occasion of their inclusion in the trial. Women with appointments at the clinic between June 2009 and June 2011 who met the eligibility criteria and agreed to participate were included in the study. The purpose of this research and study participation was explained to each participant. Interviews were used to collect patient data. Participants answered questions on sociodemographic characteristics and clinical and life habits. The Blatt–Kupperman menopausal index (BKMI) and the Women's Health Questionnaire (WHQ) were applied. The same investigator administered all of the questionnaires. Complementary exams were requested after the clinical and gynaecological examinations, according to the protocol. A computer-generated list of random numbers was used to allocate the participants. The participants were randomly assigned to one of the three treatment groups using simple randomisation procedures: group 1 received Formula 1 capsules (2.5 mg tibolone); control group 2 received Formula 2 capsules (50 mg calcium carbonate and 200 UI vitamin D3) and group 3 received Formula 3 capsules (1 mg oestradiol + 0.5 mg norethindrone acetate). The Cavalieri Dispensing Chemists, Ltd. (Juiz de Fora – MG) was responsible for the handling and dispensing of the medications. Quality control was conducted of the raw material, the supplier and the finished product to ensure the uniform content of the hormones. All capsules appeared identical, which made distinguishing the contents impossible. The capsules were prepacked in identical boxes and consecutively numbered for each woman according to the randomisation schedule. The composition of the capsules was unknown to the researcher and the research participant. Only the pharmacist responsible for the handling of the capsules and Cavalieri Dispensing Chemists, Ltd., knew the capsule contents. The participants were instructed to take one capsule daily in the morning for a period of 4 weeks, take notes of any symptoms that occurred, communicate with the investigator when necessary, and return for scheduled evaluations. The BKMI and WHQ were administered after 4, 8 and 12 weeks of medication use.

2.2.1. Efficacy assessment

This study compared the effects of tibolone and LD-HT on the overall QoL in each study group from baseline to 12 weeks of treatment.

The secondary efficacy analysis compared the effect of these drugs in each WHQ domain in each group and between group pairs, from baseline to 12 weeks of treatment. The group pairs that exhibited a significant difference at the end of treatment were compared.

2.2.1.1. Women's Health Questionnaire. QoL was evaluated using the WHQ that was developed by Hunter [21] and modified by Dias [22] for the Portuguese language. The WHQ analyses physical changes and changes in the well-being of postmenopausal phase women.

The WHQ includes 36 questions that offer four possible alternatives responses. The questions are divided into nine groups, or domains, that assess the following categories of symptoms: depressed mood (questions 3, 5, 7, 8, 10, 12, 25), somatic symptoms (questions 14, 15, 16, 18, 23, 30, 35), cognitive difficulties (questions 20, 33, 36), vasomotor symptoms (questions 19, 27), anxiety (questions 2, 4, 6, 9), sexual behaviour (questions 24, 31, 34); sleep problems (questions 1, 11, 29), menstrual symptoms (questions 17, 22, 26, 28), and attractiveness (questions 13, 21, 32) [21].

Survey responses were interpreted according to a score that related to symptom severity [21,23].

The following scores were assigned for each of the possible answers: (1) no, not at all; (2) rarely; (3) yes, sometimes; and (4) yes, definitely. Thirty questions refer to an unfavourable issue, and 6 questions refer to a favourable issue. This study evaluated 32 questions of the WHQ. An improvement in the unfavourable WHQ items was noted as a lower score. An improvement in the favourable items was noted as a higher score. Symptom clusters (WHQ domains) and