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The effects of cinnarizine on menopausal symptoms in women

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ABSTRACT

Objective To evaluate the effectiveness and safety of cinnarizine in the treatment of menopausal symptoms.

Design A total of 100 climacteric and symptomatic women participated in a double-blind, placebo-controlled study. They were divided into two groups of the same size: Gcin, intake of 25 mg of cinnarizine every 12 h for 6 months ($n = 50$); and Gpla, placebo intake every 12 hours for 6 months ($n = 50$). Menopausal symptoms were evaluated according to the Kupperman menopausal index on the first visit and at 6 months of treatment. A total of 62 women completed the study: 27 from the Gcin group and 35 from the Gpla group.

Results Based on the Kupperman menopausal index, there were no statistically significant differences between the two groups before and after the treatment.

Conclusion Our data suggest cinnarizine is not effective on menopausal symptoms because it had no more efficacy than placebo.

INTRODUCTION

The climacteric is an uncomfortable time for many women. Endocrine, somatic, psychic and metabolic changes may cause various health problems in addition to climacteric symptoms, such as hot flushes, compromising the quality of life in up to 70% of all postmenopausal women[1,2].

As hormone treatments became much better at controlling menopausal symptoms, they began to be used on a large scale and were often prescribed indiscriminately. Undesirable side-effects, such as an increase in the relative risk of cardiovascular diseases and of breast cancer, led to reassessments that partially restricted their uses[3–5].

As a result, many women have discontinued using hormones to treat climacteric symptoms. A number of options have been studied like phytotherapy, homeopathy, and hypotensive drugs, the effects of which are similar to those of placebo[4–6]. On the other hand, antidepressants, tranquilizers, and acupuncture have produced better results than those of placebo[6–9]. These facts have encouraged research into other medications, such as cinnarizine, for treating climacteric symptoms.

Cinnarizine was discovered in 1953 and is used for neurological disorders. It has vasodilator action on the central nervous system and has achieved good results in the treatment of vertigo, cephalalgia, migraine and motion sickness[10–12]. Cinnarizine is a H1-blocker (antihistamine) and may influence the thermoregulatory system in the hypothalamus[13,14]. The action of this drug on the central nervous system could thus, at least theoretically, exert beneficial effects on the control of vasomotor symptoms. This assumption was tested by Fonseca and colleagues with a positive outcome[13,14]. However, their studies were neither randomized nor double-blind. The purpose of this study was to evaluate the effects of cinnarizine on the climacteric symptoms of postmenopausal women.

METHODS

This study was conducted at the Division of Endocrine Gynecology and Climacterium, General Hospital, School of Medicine, University of São Paulo. The selection of 100 participants from among 480 volunteers was based on the following criteria: (1) inclusion – amenorrhea for at least

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1 year; follicle stimulating hormone >40 ml/IU and estradiol <20 pg/ml; at least 50 hot flushes per week; and (2) exclusion – absence of hot flushes; presence of systemic diseases (systemic arterial hypertension, thyroid disorders, and diabetes mellitus) and of neoplasia or suspected neoplasia; use of hormonal or herbal drugs or any medications acting on the central nervous system; unwillingness to participate or to sign the informed consent statement. The study lasted from October 2008 to May 2010.

This study was approved by the Institutional Ethics Committee of the General Hospital, School of Medicine, University of São Paulo. All participants were evaluated by means of clinical history and physical examination as well as by laboratory and imaging tests before randomization.

This was a randomized, double-blind, and placebo-controlled study. Randomization was performed by drawing numbers from a randomization table at the Industrial Pharmacy Center (CIFAR), General Hospital, University of São Paulo. The length of treatment was 6 months.

After randomization, the 100 patients were divided into two groups: Gcin ($n = 50$), 25 mg of cinnarizine every 12 h for 6 months, and Gpla ($n = 50$), placebo every 12 h for 6 months. The tablets in both groups had the same shape, size and color. All recruited patients were advised to include regular exercise and adequate dietary habits in their lifestyles but to decrease sedentary time throughout the study.

An independent investigator was on call to evaluate the side-effects of the treatment. He had no clinical data or any information about the study protocol so as not to compromise masking.

Visits

Menopausal symptoms were assessed through the Kupperman menopausal index before treatment (baseline visit) and after treatment (visit at the end of 6 months) (Figure 1). The interviews were conducted by the same investigator. The drop-out patients were recalled and the reasons for not remaining in the study were investigated. A 3-month follow-up of all patients was carried out to evaluate any late side-effects.

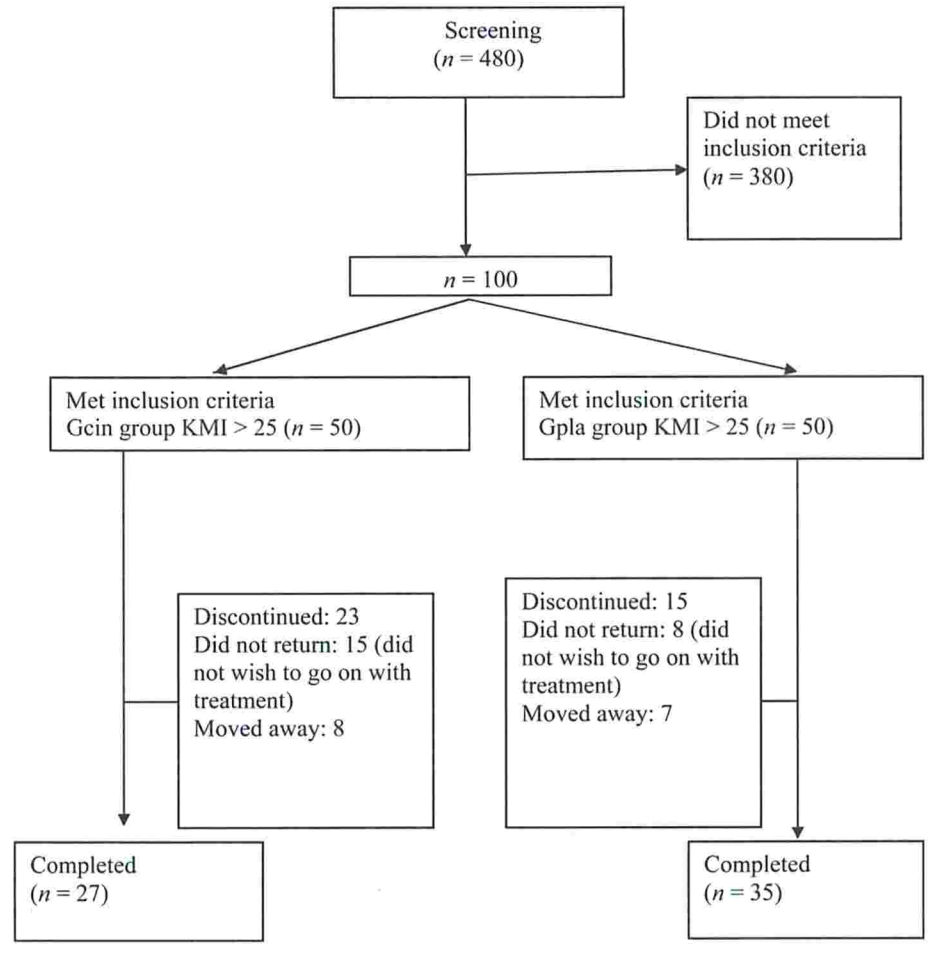

Figure 1 Patient follow-up throughout the study. KMI, Kupperman menopausal index; Gcin, group receiving cinnarizine; Gpla, group receiving placebo

Statistical analysis

The power calculation of 80% was based on vasomotor symptoms and a minimum number of 23 patients per group (46 patients in all).

A comparison of the two groups was made with the Mann–Whitney test for age, the Kupperman menopausal index, vasomotor symptoms, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia and myalgia, headaches, palpitations, and formication. A proportion comparison of race distribution was performed using Fisher's exact test. The Wilcoxon signed-rank test was applied to assess any differences between the pre- and post-treatment visits. The level of significance was set at 5% ($p < 0.05$). The Statistical Package for Social Sciences (SPSS 17.0) was used for results.

RESULTS

The patients from both groups had similar demographic data as can be seen in Table 1. The variables included weight, height, body mass index, systolic blood pressure, waist circumference and hip circumference.

Table 2 displays the pretreatment and post-treatment data from both groups, enabling a comparison of the two observation times within each group and between the groups. Before treatment, the two groups were not significantly different from each other on any of the items of the Kupperman menopausal index. After treatment, both groups showed improvement in all of the Kupperman menopausal index items. Again, there were no statistical differences between the two groups according to the Kupperman menopausal index, except for palpitation, with the placebo group having fewer episodes than the cinnarizine group ($p < 0.05$).

A total of 23 patients (15 from the placebo group and eight from the cinnarizine group) chose to discontinue treatment due to the lack of therapy efficacy on their vasomotor symptoms (Figure 1). At the end of the study, patients complained about vaginal dryness (12 from the placebo group and ten from the cinnarizine group), lack of libido (seven from the placebo group and eight from the cinnarizine group), and mild headaches (four from the placebo group and three from the cinnarizine group).

DISCUSSION

The clinical manifestations of menopause, especially vasomotor symptoms, are a source of great discomfort, and they interfere negatively in women's quality of life[7–8]. Nelson[1] observed that over 40% of women presented neurovegetative symptoms, like hot flushes and insomnia, in varied degrees. In most studies, estrogen therapy proved to be the most effective[15–18]. However, some clinical studies pointed to an increase in the relative risk of adverse events (thromboembolic phenomena, cardiovascular disease, breast cancer, and breast density), warning doctors and women about the risks of hormone treatment[3–5].

The initial impact caused women to reassess risks and benefits. As a consequence, they searched for non-hormonal treatments for the menopausal syndrome, such as phytohormones, antidepressants (gabapentin, fluoxetine, paroxetine and venlafaxine), antihypertensives (clonidine), cyclophenil, homeopathy and acupuncture, all of which had varied results[7,9,19–22]. Hence, further research is being conducted.

The literature review carried out by Cheema and colleagues[8] produced similar results to the surveys undertaken by others. Evaluations were made of the effectiveness and tolerability of clonidine, paroxetine, venlafaxine, gabapentin, *Cimicifuga racemosa* (black cohosh), fluoxetine, *Trifolium pratense* (red clover), soy isoflavones, *Panax ginseng*, *Oenothera biennis* (evening primrose), *Angelica sinensis* (*dong quai* or female ginseng), and vitamin E. The authors also concluded that results were still unclear and thus further research with a larger number of participants and more rigorous methodology was necessary to achieve more consistent outcomes.

Table 1 Description of the demographic variables according to observation times and groups

	Gcin		*Gpla*	
Variable	*Before* ($n = 27$)	*After* ($n = 27$)	*Before* ($n = 35$)	*After* ($n = 35$)
Age (years)	53.96 ± 4.25		54.7 ± 3.88	
Weight (kg)	67.09 ± 11.11	68.23 ± 10.01	69.72 ± 12.82	69.73 ± 12.27
Height (m)	1.57 ± 0.06	1.57 ± 0.06	1.57 ± 0.05	1.57 ± 0.05
Body mass index (kg/m^2)	27.06 ± 4.09	27.50 ± 3.52	28.59 ± 4.85	28.22 ± 4.44
Systolic blood pressure (mmHg)	121.69 ± 20.32	125.19 ± 17.96	123.91 ± 15.58	121.71 ± 14.40
Diastolic blood pressure (mmHg)	71.87 ± 17.95	75.85 ± 11.97	77.00 ± 13.19	75.26 ± 8.98
Waist circumference (cm)	85.62 ± 12.41	86.60 ± 10.84	88.76 ± 10.4	88.94 ± 9.54
Hip circumference (cm)	96.69 ± 12.23	98.44 ± 12.44	98.82 ± 10.72	99.15 ± 10.52
Race				
White	$n = 14$ (51.9%)		$n = 20$ (57.2%)	
African Brazilian	$n = 9$ (33.3%)		$n = 11$ (31.4%)	
Mulatto	$n = 4$ (14.8%)		$n = 4$ (11.4%)	

Gcin, Group taking cinnarizine; Gpla, group taking placebo

Table 2 Mean and standard deviation of the Kupperman menopausal index data of patients in the study

	Gcin ($n = 27$)		*Gpla* ($n = 35$)	
	Baseline	*After 6 months*	*Baseline*	*After 6 months*
Vasomotor symptoms	11.26 ± 1.93	4.15 ± 2.60*	10.74 ± 2.87	4.59 ± 2.44*
Flushes per day	9.40 ± 1.51	3.45 ± 2.21*	9.05 ± 1.39	3.83 ± 2.01*
Paresthesia	2.54 ± 2.37	0.96 ± 1.16*	2.91 ± 2.76	1.29 ± 1.55*
Insomnia	4.3 ± 2.58	1.26 ± 1.48*	3.26 ± 2.79	1.29 ± 1.77*
Nervousness	3.00 ± 2.62)	1.44 ± 1.67*	2.80 ± 2.53	1.41 ± 1.74*
Melancholia	1.11 ± 1.28	0.41 ± 0.69*	0.97 ± 1.19	0.50 ± 0.83*
Vertigo	0.81 ± 1.04	0.48 ± 0.85*	0.59 ± 1.02	0.35 ± 0.69*
Weakness	0.59 ± 0.84	0.30 ± 0.54*	0.63 ± 1.03	0.29 ± 0.63*
Arthralgia/myalgia	1.89 ± 1.09	1.56 ± 1.12	1.74 ± 1.25	1.18 ± 1.11*
Headaches	1.33 ± 1.24	0.89 ± 1.05*	1.11 ± 1.21	0.59 ± 0.89*
Palpitation	0.85 ± 0.95	0.52 ± 0.58*	0.51 ± 0.66	0.24 ± 0.5*,†
Formication	0.85 ± 0.91	0.48 ± 0.58*	0.86 ± 1.00	0.50 ± 0.66*
Total	28.22 ± 7.11	12.19 ± 5.2*	26.29 ± 8.86	12.35 ± 8.18*

*, $p < 0.05$ compared to baseline; †, $p < 0.05$ compared to Gcin at the end of treatment
Gcin, Group taking cinnarizine; Gpla, group taking placebo

Cinnarizine is a drug that has long been employed in clinical indications, such as acute vertigo, chronic migraines, microcirculatory disorders in the brain, etc.[10–15,23], and for the control of menopausal symptoms, with favorable results[13,14]. The use of cinnarizine for treating climacteric symptoms is based on its action on the central nervous system in the areas involved in these clinical manifestations.

The first observational study was conducted by Fonseca and colleagues[13], who, in an open study, analyzed 57 patients to evaluate menopausal symptoms after cinnarizine treatment. They observed a positive effect, i.e. the mitigation of neurovegetative symptoms, especially of vasomotor symptoms, paresthesia and the vertigo sensation.

In 1987, Fonseca and colleagues[14] undertook a new study with 40 postmenopausal women, using similar methodology, and found that cinnarizine reduced menopausal symptoms with just one 25 mg tablet twice a day via the oral route. Minor side-effects were observed, such as shivering, dry mouth, and drowsiness. In our study, none of these side-effects was present.

Our choice of the Kupperman menopausal index was based on a study of women with the symptoms – as measured by the Kupperman menopausal index – and their influence on the quality of life of these women. This is why we applied the Kupperman menopausal index. One possible reason for the lack of differences between the two groups at the end of the study is the high number of drop-outs. Another is that cinnarizine may not have any effects on menopausal symptoms.

It is important to emphasize that psychological aspects may have influenced our results in both groups. This might be due to the assistance offered the women by the researcher himself, who provided them with information on the research and on habits and lifestyles. It should also be stressed that Fonseca and colleagues[13,14] did not carry out any comparative studies, which might explain such divergent outcomes. The improvement in vertigo in women with other climacteric symptoms is undoubtedly a favorable result, suggesting that women with similar clinical conditions might benefit from cinnarizine since none of the symptoms improved in the placebo group.

CONCLUSION

Cinnarizine and placebo produced similar results in the treatment of climacteric symptoms as measured by the Kupperman menopausal index.

Conflict of interest The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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