The treatment of menopausal hot flushes with oral administration of Clonidine

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A randomized, prospective, double-blind study was performed to evaluate the efficacy of orally administered clonidine hydrochloride in the treatment of menopausal hot flushes. The intensities of the flushing attacks before and after an 12 week treatment period were evaluated in 58 (after 2 patients dropped off) postmenopausal women received oral clonidine or calcium. The study group included 38 patients (mean age: 52.6±6.1, mean menopausal age: 6.4 ±6.5 yrs.) received oral clonidine. The control group was consisted of 20 patients (mean age: 51.7+7.2, mean menopausal age: 6.2±4.9 yrs.) who received only calcium supplementation. The difference between the pretreatment and the posttreatment intensities of the hos flushes was statistically significant (p<0.02) in the study group. [Turk J Med Res 1995, 13(1): 34-37]

Key Words: Menopause, Clonidine

Hot flushes are the most annoying symptoms of menopause. They are experienced by 75 to 85% of women going through menopause and some 25 to 50% of women experience them for 5 years or even longer. Estrogen replacement therapy is the most effective form of the treatment of menopausal hot flushes, but when the patient has a contraindication to estrogen or if she requests a nonhormonal therapy, alternate forms of therapy become essential (1,2).

One of these alternate forms is clonidine hydrochloride which is an alpha-2-adrenergic agonist agent. It is an imidazoline derivative and has been available in an oral form for the treatment of hypertension and for the prophylaxis against migraine (4,8). Because of its alpha adrenergic agonistic effects on the vasculature it has also been used for the relief of menopausal hot flushes (5).

In this study the efficacy of orally administered clonidine in the relief of menopausal hot flushes was evaluated.

MATERIALS AND METHODS

This randomized, prospective, double-blind study included 58 (after 2 patients dropped off from the study group) postmenopausal women who were admitted to our center for the treatment of their hot flushes.

40 of the patients received oral clonidine. These were the patients who did not want to receive hormonal therapy (n:31) or the patients who had contraindications for hormone replacement therapy such as breast cancer (n:6), thromboembolic phenomenon (n:2) and adenoma of the liver (n:1). 29 were natural and 11 were surgical postmenopausal women.

The control group was consisted of 20 postmenopausal patients who did not want to receive any type of medication except vitamins or minerals. They were instructed to receive only calcium supplementation to keep them under control until the end of the study period. 12 of these had undergone a natural and 8 a surgical menopause.

None of the patients had received any form of treatment for hot flushes until the study and none of them had a history of systemic disease such as cardiac, hepatic or renal disfunction.

At the beginning and at the end of a 12 week study period, the patients were questionned aboud the intensities of the hot flushes. Evaluation of the intensities by the patients was purely subjective.

The patients received oral clonidine were seen at semimonthly intervals with their home blood pressure recordings and also the resting blood pressures and resting pulse rates were checked at each visit. The

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mean hormonal levels were also evaluated in this group.

Dosages

Because of the antihypertensive effect of the clonidine the dosage was modified upon the beginning blood pressure of the patients between 75-100 mgr twice daily (Catapresan tb. Boehringer-Ingelheim).

The control group received a calcium supplementation, Ca gluconolactate 2.94 gr Ca carbonate 0.30 gr (Calcium Forte tb. eff.-Sandoz).

Assays

Estradiol (E_2) levels were measured by using double antibody RIA method with RSL direct 1125 estradiol 17 p kit (ICN Biomedicals Inc. Diagnostic Division, USA).

Follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels were measured with the magnetic separation method by using Amerlex-M FSH kit (Kodak Clinical Diagnostic Division, England).

Table **1.** Comparison of the characteristics of the study groups*

	Clonidine group (40)	Control group (20)
Age	52.6±6.1	51.7±7.2
Menopausal age (yr)	6.4±6.5	6.2+4.9
Gravidity	5.2+5.2	4.9±4.7
Parity	2.4+1.6	2.6±1.3
Body mass index	27.6+4.4	26.9±4.1

Ivalues are mean±SD

Table 2. The comparison of mean resting blood pressure and pulse rates before and after the treatment with oral clonidinef

	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Pulse Rate (beats/min)
Before	147.4±23.6	90.1 ±9.6	79.9±3.7
After	135.7±18.5	83.3+10.0	79.5±3.2

t: values are mean+SD

Prolactine (PRL) levels were measured with using Medgenix, IRMA-Immunoradiometric Assay kit (Belgium).

Statistical analysis was performed by the x^2 and Student's t tests.

RESULTS

There were no significant differences between the two study groups in age, menopausal age, gravidity, parity, body mass index (Table 1).

Two of the patients of clonidine group had dropped out of the study.

There were no significant differences between the mean resting systolic, diastolic blood pressure levels and the pulse rates before and after the treatment with clonidine (Table 2).

The intensity of the hot flushes before and after the treatment showed a statistically significant difference in the study group. The number and the percentage of the patients who expressed that their hot flushes' intensities were changed positively showed a statistically significant difference whereas no significant differences were observed for the control group (Table 3). Interestingly the patients expressed that sweatings were remained unchanged and only the component of feeling hot did changed.

The prevalence of the side effects in the study group was 65.8%, but these side effects were well tolerated by the patients (Table 4).

There were no statistically significant differences in hormonal levels before and after treatment with clonidine (Table 5).

DISCUSSION

Hot flushes which are the most common symptom of the climacteris are experienced by the majority of menopausal women (1). They are accompained by peripheral vasodilatation, tachycardia, decreased skin resistance and sweating. It has been hypothesized that a thermoregulatory disturbance is involved and hot flushes are triggered within hypothalamus and that central noradrenergic activity plays a role in their initiation (2,3).

Table 3. Comparison of the intensity of the hot flushes before and after the therapy'"

	Mild	Moderate	Severe	Total
Clonidine				
Before therapy	6/15.8	20/52.7	12/31.5	38/100
After therapy	22/57.0*	13/34.3*	3/7.8*	38/100
Control				
Before therapy	4/20	10/50	6/30	20/100
After therapy	5/25	8/40	7/35	20/100

': Values are number/per cent

*: p<0.02 Difference between the value reflecting the number and the per cent of the patients whose hot flushes was changed

Table **4.** The prevalence of the side effects in Clonidine group[1]

	n	%
Tiredness	13	34.2
Nausea	3	7.9
Irritability	3	7.9
Dry mouth	3	7.9
Drowsiness	7	18.4
Orthostatic hpotension	2	5.3
Headache	2	5.3

[1]: Values are number of the cases and percent

were no statistically significant differences between the mean systolic, diastolic blood pressure and resting pulse rate in the study group.

The results of our study let us to suggest that Clonidine is a beneficial agent in the treatment of hot flushes. Although there are some published trials failed to demonstrate a significant reduction in the intensity of flushing attacks and although the method used to grade the intensity of hot flushes was totally subjective, we concluded that Clonidine has a significant positive effect on the hot flushes and a valuable agent when the hormone replacement therapy is contraindicated.

Table 5. The differences between the hormonal levels in Clonidine group[1]

	Estradiol (pg/ml)	FSH (IU/L	LH (IU/L)	PRL(ng/ml)
Before therapy	14.4±7.4	64.9±18.6	52.9±25.7	4.1 ±1.8
After therapy	14.5±6.8	60.4±16.2	44.4±19.9	4.0±1.5

[1]: Values are mean±SD

Clonidine is an imidazoline derivative and has been available in an oral form for the treatment of hypertension since 1974 and also for the prophylaxis against migraine (4,8). It exerts alpha-mediated central and peripheral action on the vasculature and appears to reduce the sensitivity to both vasodilator and constrictor stimuli in abnormally stressed or hyperactive peripheral vessels (5). Because of these effects clondine has also been used for the relief of the postmenopausal hot flushes.

Indeed, in this study after the treatment with clonidine the number and the percentage of the patients who expressed that the intensity of their hot flushes were changed positively showed a statistically significant difference. Before the treatment 15.8% of the patients had mild hot flushes. This proportion was expanded and reached a value such as 57% after the oral administration of clonidine whereas the proportions of the patients with severe hot flushes before and after the therapy were 31.5% and 7.8% respectively.

It has also been demonstrated a significant decrease in plasma luteinizing hormone concentration in clonidine using patients (11). In an attempt to explain the possible mechanism of the action of clonidine, we compared the pre and posttreatment levels of gonadotropins in the study group, but we did not detect any difference.

The dose that is used for the treatment of menopausal flushing is lower than that is used for hypertension, because of possible side effects such as tiredness, irritability, mouth dryness, drowsiness, orthostatic hypotension and headache. However a way to reduce the side effects may be to increase the dosage gradually. In our study the prevalence of these effects was 65.8% but well tolerated by the patients and they might be temporary in a longer period There

Menopozdaki ateş basmalarının
Clonidin ile tedavisi

Menopozdaki ateş basmalarının tedavisinde oral olarak uygulanan clonidin hidrokloridin etkisini değerlendirmek için randomize, prospektif ve çift-kör bir çaiışma yapıldı. Oral clonidin veya kalsiyum alan 58 postmenopozal kadında tedaviden önce ve tedaviden 12 hafta sonra ateş basmalarının sıklığı incelendi. Çalışma grubu clonidin alan 38 hastadan (ortalama yaş 52.6±6.1, ortalama menopoz süresi 6.4 ±6.5 yıl), kontrol grubu ise yalnız kalsiyum kullanan 20 hastadan (ortalama yaş 51.7+7.2 ve ortalama menopoz süresi 6.2±4.9yıl) oluştu. Tedavi öncesi ve tedavi sonrası ateş basması sıklığı çalışma grubunda istatistiki olarak anlamlı bulundu (p<0.02).
[Turk JMed Res 1995; 13(1): 34-37]

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