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Comparison of *Vitex Agnus Castus* with Meloxicam and Placebo in Treatment of Patients with Cyclical Mastalgia

Siklik Mastaljili Hastaların Tedavisinde *Vitex Agnus Castus* Preperatının Meloksikam Ve Plasebo İle Karşılaştırılması

ABSTRACT

Background: Mastalgia is classified as cyclic and non-cyclic. Cyclical one constitutes approximately 60-70% of mastalgia. It is seen between 2 to 3 decades of age, and it usually responds to treatment.

Objectives: To compare efficacy of *vitex agnus castus* (VAC) preparation with meloxicam and placebo in treatment of mastalgia.

Methods: The study was designed as prospective and placebo-controlled clinical trial. Three groups were constituted. Before grouping, prolactin level was tested for every patient. The group1 enrolled the patients with cyclical mastalgia and high level prolactin. VAC was administered to patients from study group1. The second group enrolled the patients with cyclical mastalgia along with normal prolactin level, and to which meloxicam was given. Third group was placebo group, and placebo was applied. Before treatment, VAS (Visual analogue scale) scoring was applied to every patient. Prolactin level was tested for patients from group 1. After 3 months of study, VAS scoring was applied to every patient, but only prolactin levels were re-evaluated in patients from group1.

Results: 95 patients were analyzed; enrolling women aged 19 to 54 years. Intensity of mastalgia diminished in VAC group 1, 2 more than in placebo group ($p<0.0001$). In addition to VAS scoring, prolactin level in group 1 after treatment was significantly reduced, comparing with before treatment ($p<0.0001$). In conclusion, we found that VAC preparation was effective in the treatment of mastalgia and hyperprolactinemia, with good tolerability.

Key Words: Mastalgia, *vitex agnus castus*, prolactin.

ÖZET

Giriş: Mastalji meme ağrısı olup klinik olarak siklik ve siklik olmayan şekilde sınıflandırılır. Siklik mastalji mastaljilerin yaklaşık %60'ını kapsar. Siklik mastaljiler en sık 20 ve 30 yaşlarda görülür ve genellikle tedaviye iyi cevap verir.

Amaç: *Vitex Agnus Castus* preparasyonunun (VAC) mastalji ve hiperprolaktinemi üzerine olan etkinliğinin araştırılması amaçlandı.

Metot: Araştırma prospektif ve palsebo kontrollü klinik çalışma olarak yapıldı. Hastalar gruplara ayrılmadan önce her hastadan prolaktin seviyesine bakıldı. Hastalar gruplara ayrıldıktan sonra her hastaya tedavi öncesi VAS uygulandı. Grup 1 siklik mastaljisi ve hiperprolaktinemisi olan hastalardan oluştu. Bu hastalara VAC (agnucaston) başlandı. Grup 2 siklik mastaljisi ve normal prolaktin seviyesi olan ve meloksikam 15 mg/gün başlanan hastalardan oluşmuştur. Placebo grubu mastaljisi olan ve prolaktin seviyesi normal olan hastalardan oluştu. 3 aylık tedavi sonrası her hastaya VAS ve grup 1 için prolaktin seviyesine bakıldı.

Sonuçlar: Toplam 19–54 yaş arası 95 hastanın analizi yapıldı. VAC alan grupta mastaljinin yoğunluğu plasebo grubundan anlamlı ölçüde azaldığı gözlemlendi ($p<0.0001$). VAS skoruna ilaveten, prolaktin seviyesinde tedavi öncesine göre anlamlı azalma tespit edildi ($p <0.0001$). Sonuç olarak, VAC preperasyonunun mastalji ve hiperprolaktinemi tedavisinde iyi tolerabilite ile birlikte etkin olduğunu bulduk.

Anahtar Kelimeler: Mastalji, *vitex agnus castus*, prolaktin

INTRODUCTION

Mastalgia is a painful condition originated from breast tissue, and clinically is classified into two types as cyclical and non-cyclical one. Cyclical one can be

described as middle to severe level breast pain lasting approximately 5 days, or more. Cyclical mastalgia is commonly seen between 20 to 30 years of age, but it can be seen after menopause. It comprises 60-70 % of mastalgia. Approximately 90% of cyclical mastalgia respond to treatment. It occurs mainly during menstrual period, so it is considered to be associated with hormonal change. Non-cyclical mastalgia comprises 20-30 % of cases, and is more severe and resistant to treatment, comparing with cyclical one (1, 2).

It is one of the most common symptoms of female patients seeking health care at both primary health clinics and breast referral centers. Its prevalence is not exactly known, but is estimated to be seen as 66% in community-based screening and 50% in outpatient clinic (3). 50% to 80% of women are estimated to have experienced with mastalgia at some point in their life, but in only 1% of patients is mastalgia a symptom of breast cancer (4,5).

Today's, we have several options to treat mastalgia as pharmacologic and non-pharmacologic, but these are not standardized therapies. Firstly, it should be evaluated carefully for its reasons. History taking, physical examination and imaging methods such as mammography and ultrasonography should be performed before deciding treatment. Bromocriptine, danazol, tamoxifen, LNRH analogues, gamma linoleic acid, testosterone, gestrinone, goserelin, vitamins such as B6 and E, and analgesic agents (6,7,8,9). However, hormonal therapies such as bromocriptine, danazol, LNRH analogues have severe side effects. Nevertheless, efficacy of any treatment modality is not superior to each other.

VAC has been also used in the treatment of female conditions such as premenstrual syndrome, corpus luteum insufficiency, menstrual disorders, hyperprolactinemia and menopause. *Agnus castus* is thought to be effective in the management of mastalgia because of its dopaminergic effects. It could be helpful in the management of mastalgia may be because of its effect on latent hyperprolactinemia, estrogen receptors or other unknown mechanisms (10).

The aim of study presented here was to compare efficacy of *Vitex agnus castus* (VAC) preparations with meloxicam and placebo in the treatment of patients with cyclical mastalgia.

MATERIAL and METHODS

Study Population

The study was prospective, placebo-controlled clinical trial, enrolling consecutive female patients presenting with mastalgia to our clinic, general

surgery out-patient clinic, Karadeniz Technical University, School of Medicine, and Trabzon, Turkey. On admission, the patients suffering from mastalgia were classified into cyclical and non-cyclical form. Among them, 108 women were enrolled into study by taking their informed consent. The study was approved by ethical committee of our institution.

Study Protocol

For every patient, prolactin level was measured before grouping. Visual Analogue Scale (VAS) for scoring breast pain was performed for every patient before arranging into groups. Group 1 consisted of subjects with cyclical mastalgia and hyperprolactinemia, group 2 consisted of those with cyclical mastalgia and normal prolactin (3.4 ng/mL-24.1 ng/mL, radioimmunoassay method), and placebo group consisted of those with cyclical mastalgia and normal prolactin. Mammography for patients over 35 years of age and ultrasonography for those less than 35 years of age were performed for every subject to rule out malign conditions. Cyclical mastalgia during at least 5 days of menstrual cycle before grouping was the strict inclusion criteria. The patients with non-cyclical mastalgia, history of breast cancer and family history of breast cancer, being male, medical conditions requiring mammary biopsy, doubtful positive signs on imaging, prolactin level over 120 ng/mL (high probability sign for intracranial pathology), and the patients who rejected to participate in study were excluded. Other exclusion criteria are Granulomatous infiltration of the hypothalamus, severe head trauma, primary hypothyroidism, renal failure.

Visual Analogue Scale (VAS) was used for breast pain scoring. The patients were asked to fill VAS scale. VAS was degreeed from one to ten degree according to severity of pain. One degree referred very light pain, and ten referred very severe pain on VAS. Very light pain (VAS 1) indicated painful condition on resting state and without working. Very severe pain (VAS 10) indicated that it awaked the patient from sleep, and interrupted her daily activities. Score of middle pain indicated that interrupted her daily activities but not awaked her.

Clinical and demographic features of patients, including, age, marital and educational state, smoking and alcohol drinking, co-morbid diseases, medicines, and occupation were recorded by medical notes and semi-structured interview with them. *Vitex Agnus Castus* preparation (Agnucaston 40 mg a day in a single dose, Biomeks) was administered to patients from group 1. Meloxicam 15 mg/day (Mobic tablet in a single dose, Boehringer Ingelheim) was given to patients from group 2. For group 3, placebo (a day in a single dose) was applied. The patients from 3 groups

have been followed for three menstrual cycles. They were also recruiting to re-evaluate for tolerability and efficacy of VAC preparation at the end of 1st and 3rd month. VAS scoring was re-applied at the end of 3rd month. Serum Prolactin level of patients from group 1 was measured at the end of third month of treatment.

Statistical Analysis

Data were analyzed using Statistical Package for Social Science for Windows (SPSS) version 10.0. The results are presented as mean ± standard deviation for scale variables, and stated as median and range for nominal variables and percentages for proportions. For parametric two-dependent variables, paired Student-t was used, but Wilcoxon Signed Ranks Test test for non-parametric ones. Analysis for non-scale variables was done using X2-test (Fischer’s exact test). Comparisons of VAS scoring between groups are computed by using one-way ANOVA with post-hoc Bonferroni test.

RESULTS

The study was employed between April 2005 and September 2005. Initially, 108 female patients were enrolled, but data of 60 patients (n= 30 for group 1, n= 30 for group 2, and 35 group placebo) were analyzed. Out of 108 patients, 13 ones left the study. Overall, the study sample consisted of 95 subjects aged from 19 to 54 years, averaging 36.31±8.92 yrs. Based on results, cyclical mastalgia was commonly observed after 30 years of age. Average age for group 1, group 2 and group 3 (placebo) was 43.47±8.71, 35.38±9.05 and 37.38±7.77 respectively. In study, were not any patients having consumed alcohol. Only the patients with current smoker were recorded. Most of them have had informal education. They were mostly married and housewife. Before treatment, there were not significant differences for age, VAS scoring, marital status, education level, occupation, mammographic and ultrasonographic findings, and smoking situation between groups (Table 1).

In group 1, two patients for hypertension and one for asthma had been using medicine. On the other hand, 4 patients from group2 had been using medicine for hypertension. In placebo group, two patients for hypertension had been using medicine. Mammography was performed for 14 (46%), 12 (%40), and 15 (50%) patients from groups, respectively. Ultrasonography was applied to 16 (53%), 18 (%60), and 12 (40%) patients of group 1, 2, and 3, respectively. Comparing findings on USG and mammographic examination, there were similar results between groups (p>0.05) (table 1).

Median of VAS scoring for groups 1 before initiating treatment was 6. After treatment with Vitex Agnus

Table 1. Basic features of subjects according to groups.

| | Group1 (n=30, %) | Group 2 (n=30, %) | Group 3 (n=35, %) | p |
|-------------------|---------------------|----------------------|----------------------|-------|
| Age | 43.47 ±8.71 | 35.38 ±9.05 | 37.38 ±7.77 | >0.05 |
| VAS before | 6 (20) | 6 (20) | 7(20) | >0.05 |
| Smoking | 3 (10) | 1 (33.3) | 0 | <0.05 |
| Marital status | 22 (73.3) | 23 (76.6) | 23 (65.7) | >0.05 |
| Occupation | 8 (26.6) | 10 (33.3) | 13 (37.1) | >0.05 |
| Mammography | 14 (46.6) | 12 (40) | 17 (48.6) | >0.05 |
| Ultrasonography | 16 (53.4) | 18 (60) | 18 (51.4) | >0.05 |
| Co-morbid disease | 3 (10%) | 4 (13.3) | 2 (5.7) | >0.05 |
| Education | | | | |
| Illiterate | 7 (23.3) | 11 (36.7) | 8 (22.8) | >0.05 |
| 1° and 2° school | 14 (46.6) | 12 (40) | 15 (42.9) | |
| High school | 7 (23.3) | 5 (16.7) | 7 (20) | |
| University | 2 (6.6) | 2 (6.6) | 5 (14.3) | |

Castus, median of VAS scoring was 1.5. It was statistically significant (p<0.0001). Median VAS scoring before and after in group 2 treated with meloxicam 15 mg7day was 6 and 2, respectively. It is also significant. For placebo group, median VAS scoring before and after treatment was almost similar and not significant (VAS before: 7, VAS after: 6) (p=0,052). 30% of patients treated with responded completely to therapy, 56% of them were affirmative, and remaining was unresponsive (Table 2). Average prolactin level of patients from group 1 was 38.93±19.57 ng/mL at initial (min: 25.0 ng/mL, max: 113.0 ng/mL). After treatment, it was measured as 21.90± 10.76 ng/mL (p<0.0001) (Figure 1). moreover, we did not observed any side effects due to vitex agnus castus administration, but one patient from group 2 specified gastrointestinal discomfort, but not severe.

Comparing VAS scoring of group 1 with group 2 was not significant, but it was significant with that of placebo after third month of treatment administration (p<0.0001). Median VAS scoring of group 2 after treatment was significant with placebo, but not with group 1.

Table 2. Comparison of VAS scoring between groups before and after treatment.

| | Group 1 | Group 2 | Group 3 | p |
|------------|---------|---------|---------|--------|
| VAS before | 6 | 6 | 7 | p>0.05 |
| VAS after | 1 | 2 | 6 | * |
| p | <0.0001 | <0.0001 | 0.052 | |

* Group 1: not significant with group 2, but group 3 (ANOVA, Bonferroni)
 * Group 2: not significant with group 1, but group 3 (ANOVA, Bonferroni)

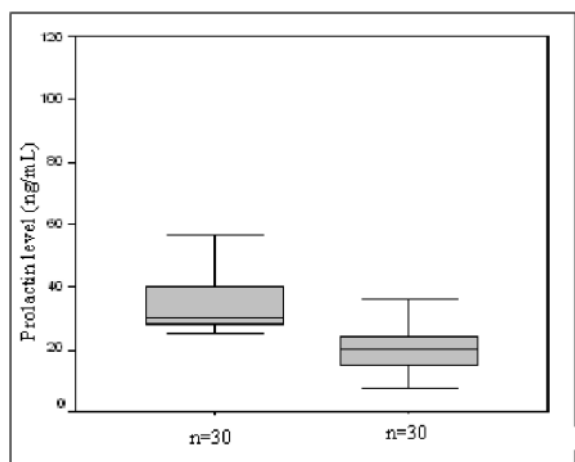


Figure 1. Serum prolactin level before and after treatment with Vitex Agnus Castus

DISCUSSION

Cyclical mastalgia is diffuse and transient or periodic, non-localized and usually bilateral breast pain. Cyclical mastalgia is seen commonly between second and third decades. Careful evaluation of patients presenting with mastalgia lights the way for efficacy and harmony of treatment, because most patients spontaneously improve without treatment after they are ensured that it would be not due to cancer (11). 44% of Mastalgia can be continued until menopausal period. Spontaneous regression can be seen in 22% of patients (12).

Patients with cyclical and non-cyclical mastalgia responded to anti-prolactin therapy in different results (12). Gatalay and et al. (13) obtained 47% and 20% respond in cyclical and non-cyclical mastalgia respectively after anti-prolactin treatment in their study. In another study, they also reported that the patients responded as 54% in cyclical and 33% in non-cyclical mastalgia after anti-prolactin therapy (14). In our study, 30% of patients from group 1 completely responded, and 50% of them affirmatively (decrease in VAS scoring as 50% and more) responded after Vitex Agnus Castus administration. It was statistically significant, comparing with placebo results. Generally response ratio change between 20 and 40% in literatures (15, 16). For our patients, response was obtained higher, comparing with previous studies.

Although mastalgia improved in a few subjects from our placebo group, intensity of mastalgia mostly remained during 3 three menstrual cycles, and small number of patients specified that intensity of their mastalgia increased. When the patients are satisfied that their mastalgia is due to benign conditions, after complete assessment and work-up, intensity of

mastalgia improves in most cases, remains in a few cases.

Results of the double-blind, placebo-controlled clinical trial which conducted by Halaska et al. (17) were almost consistent with our results. They included 97 patients were into their study (VACS: n = 48, placebo: n = 49). They found that Intensity of breast pain diminished quicker with VACS group, the tolerability was satisfactory. They stated that VACS was useful in the treatment of cyclical breast pain in women. In other hands, we investigated change in prolactin level in group 1. It was significantly different from level before treatment administration. Van Die et al. (28) concluded in their study that, while evidence from rigorous randomized controlled trials is lacking for the individual herb in this context, emerging pharmacological evidence supports a role for Vitex Agnus Castus in the alleviation of menopausal symptoms. Vitex Agnus Castus extract is considered to be dopaminergic effect. Efficacy of VAC is between 70-90% in mastalgia. In recent clinical trial, improvements in 53-67% of symptoms have been reported (11, 19-21).

In several studies, spontaneous improvements in mastalgia were reported after the patients was inspired confidence about whose breast pain was not commonly resulted from breast cancer and it would be benign conditions. Although mastalgia improved in a few subjects from our placebo group, intensity of mastalgia mostly remained during 3 three menstrual cycles, and small number of patients specified that intensity of their mastalgia increased. When the patients are satisfied that their mastalgia is due to benign conditions, after complete assessment and work-up, intensity of mastalgia improves in most cases, remains in a few cases. We estimated that improvement in mastalgia of our patients was quenched about their medical problems related mastalgia. This result was consistent with previous reports (22, 23).

In conclusion, patients with mastalgia should be carefully evaluated for breast cancer. On inquiring, mastalgia should be classified into cyclic and non-cyclic. If necessary, blood prolactin should be obtained. Due to effectiveness, tolerability and usefulness of Vitex Agnus Castus might be chosen as first-line therapy for patients as well as non-steroidal anti-inflammatory agents due to high its efficacy and good tolerability. It is also used to reduce prolactin level over normal.

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