THE COMPARISON OF EVENING PRIMROSE OIL, FRUCTUS AGNI CASTI, AND REASSURANCE IN THE TREATMENT OF MASTALGIA

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ABSTRACT

Background: Although many therapeutic options have been used in the treatment of mastalgia, none of those has a curative effect. Aim: In this study, we aimed to investigate the effects of evening primrose oil, Fructus Agni Casti and reassurance on mastalgia, in comparison to placebo. Methods: This is a prospective clinical study on the effectiveness of evening primrose oil, Fructus Agni Casti and reassurance in the treatment of mastalgia. One hundred twenty-eight female patients with mastalgia were placed randomly into four groups: (1) evening primrose oil, (2) Fructus Agni Casti, (3) reassurance, and (4) placebo, for the treatment of 3 months. The severity and type of mastalgia were evaluated according to the Breast Pain Questionnaire. Response to treatment was assessed by the Cardiff Breast Pain scoring system. Results: Fructus Agni Casti group had a more effective therapeutic response when compared with other groups. Reassurance and evening primrose oil groups had similar effects on reducing breast pain. The worst response to treatment was obtained in the placebo group. During follow-up, no serious adverse effect was observed. Conclusion: Fructus Agni Casti can be used in mastalgia patients with a high success rate and less adverse effect profile. Reassurance may be an important part of mastalgia management, due to the psychological basis of this entity.

KEYWORDS: Evening primrose oil, fructus agni casti, mastalgia, reassurance, treatment

Introduction

Mastalgia, also called as mastodynia or breast pain, is a common complaint among women, with a reported prevalence of up to 80% [1, 2]. Although mastalgia is considered as a feature of benign breast disorders, it can be also associated with breast cancer with a ratio of approximately 1% [2, 3]. Mastalgia has three different clinical patterns including cyclical mastalgia, non-cyclical mastalgia, and extramammary pain [4, 5]. Cyclical mastalgia, often described as premenstrual mastodynia, is the most frequent type of a close relationship to the menstruation and response to the hormonal therapies [6]. However, noncyclic mastalgia is characterized by intermittent or constant breast pain and does not seem to be associated with menstrual cycle. Additionally, the etiology of noncyclic mastalgia is usually unclear and appears to less likely to respond to hormonal therapies [5]. The third group, extramammary pain, is associated with various clinical disorders such as costochondritis, Tietze Syndrome, arthritis, slipping and clicking ribs [5, 7]. Although spontaneous healing is seen in the majority of patients with mastalgia, up to 22% of patients, have persistent pain that requires medical assistance [1, 5, 8]. However, there is no consensus about the drug of choice for treatment of mastalgia. Many hormonal agents such as tamoxifen, danazol, bromocriptine and LH-RH analog, and non-hormonal therapy modalities
including acetaminophen, non-steroidal anti-inflammatory gels, wearing a supportive and well-fitted brassiere have been used in the treatment of mastalgia [9]. Unfortunately, there isn’t any curative treatment today. In this paper, we evaluated the efficacy of three different therapeutic options including evening primrose oil (EPO), Fructus Agni Casti (FAC) and reassurance, in the patients with breast pain.

Patients and Methods

Study Design
Between 2014 and 2015, a placebo-controlled prospective study was started with 154 female patients suffered from breast pain, in a tertiary university hospital. A total of 26 patients (7 in EPO group, 4 in FAC group, 5 in reassurance group, and 10 in placebo group) who did not come regularly to control examinations or did not take medication correctly were excluded from the study, and hence, the statistical analysis was performed by using data of the remaining 128 patients who fulfilled the study principles. The presence of breast pain for at least three months and available with written informed consent were the inclusion criteria. However, exclusion criteria were as follows; (I) inability to fill the questionnaire, (II) age under 18 years, (III) having an organic breast disease such as cancer, abscess, infection, and others, (IV) previous breast surgery, (V) pregnancy, pregnancy wish, and lactation. Patients included in the study were divided into four groups: EPO group (group 1, n=31) who was given EPO capsule two times per day, FAC group (group 2, n=30) who received one FAC tablet/day, reassurance group (group 3, n=35), and placebo group (group 4, n=32) who received starch tablet 20 mg/day. Medication was given for three months. A detailed examination was performed by the same general surgeon and psychiatrist for each participant. Additionally, the radiological examination was performed if there was a need according to the clinical findings of the patients.

At admission, breast pain levels of the patients were assessed by Breast Pain Questionnaire (BPQ) which is a derived form of the McGill Pain Questionnaire. A final breast pain score (%totalBP) which were composed of four individual scores including %Qtotal, %PPI, %VAS and %QOL was obtained from each patient. %Qtotal is the sum of sensory and affective scores obtained from each sensory and affective descriptor. %PPI means the present pain index calculated as a percentage. %VAS is a score obtained from visual analag scale, and %QOL consisted of the score for quality of life questions. Finally, the total breast pain was classified as mild (0-100), moderate (101-200), and severe (>200).

All patients were evaluated at regular intervals regarding response to treatment and possible adverse effects. Response to treatment was assessed by Cardiff Breast Pain Score (CBS) [10] (Table 1). Grade 1 and 2 were evaluated as ‘effective respond to treatment’. Treatment modality did not change before three months of treatment. However, changes in medication were performed if the patient did not benefit from 3 months of treatment.

The participants were informed about the treatment and study design, and the written informed consent form was obtained from all.

Statistical analysis
This clinical study was focused on the assessment of the response to three different therapeutic modalities, EPO, FAC, and reassurance, with a comparison to placebo. The Statistical Package for the Social Sciences, version 21 was used for statistical analysis. Descriptive analysis was done for sociodemographic data and pain characteristics, and the statistical results were presented as mean ± SD/percentages for continuous variables and number/percentage for categorical variables. To investigate the homogeneity of groups, one-way ANOVA test was used for the homogeneity of groups according to age and breastfeeding variables. A significant value less than 0.05 was considered as statistically significant. Mann–Whitney U test and Chi-square test were used for investigating the differences between groups according to categorical variables.

Results
A total of 128 female patients with a median age of 35.1 y (range 18 to 60 y) were completed the study. The study groups were found to be homogeneous according to age (p=0.879) and duration of breastfeeding (p=0.856) in one-way ANOVA test. Additionally, the groups were homogeneous regarding sociodemographic data, including marital status (p=0.802), educational status (p=0.693), the number of pregnancies (p=0.897), the pattern of breast pain (p=0.633), the severity of breast pain (p=0.975) and reproductive status (p=0.919), in the Chi-square test. The baseline characteristics of each group are summarized in Table 2.

In the assessment of breast pain with BPQ, the majority of patients had a cyclic form of mastalgia (n=86, 67.2%), and there were no significant differences in the mean of ‘type of mastalgia’ between each group (p=0.633). Also, statistical analysis was performed between all groups regarding the scores that were obtained from BPQ. No significant differences were found in these scores, including %Qtotal (p=0.498), %PPI (p=0.599), %VAS (p=0.313), %QOL (p=0.247), and %totalBP (p=0.437). Additionally, ‘the severity of pain’ was similar between each group statistically (p=0.975). Table 3 shows the pain characteristics and response status to the treatment of four study groups.

Among the total 128 patients, CBS score was found as grade 1+2 for 92 (%71,9) patients and as grade 3+4 for 36 (%27,1) pa-

Table 1 Cardiff Breast Pain Scoring (CBS) System [10].

| Grade | Explanation |
|-------|-------------|
| Grade I | An excellent response leaving no residual pain |
| Grade II | A substantial response leaving some residual pain but considered by the patient to be easily bearable |
| Grade III | A poor response leaving substantial residual pain |
| Grade IV | No response |
Table 2 The summary of the sociodemographic data of each group.

| Characteristics of the patients | EPO group (n=31) | FAC group (n=30) | Reassurance group (n=35) | Placebo group (n=32) | P |
|--------------------------------|-----------------|-----------------|-------------------------|---------------------|---|
| Mean age (year)                | 35.0±9.1        | 36.3±9.9        | 34.7±9.0                | 34.5±9.2            | 0.879 |
| Marital status                 |                 |                 |                         |                     | 0.802 |
| Single                         | 5 (16.1%)       | 5 (16.7%)       | 7 (20%)                 | 8 (25%)             |     |
| Married                        | 26 (83.9%)      | 25 (83.3%)      | 28 (80%)                | 24 (75%)            |     |
| Reproductive status            |                 |                 |                         |                     | 0.919 |
| Premenopausal                  | 29 (93.5%)      | 27 (90%)        | 31 (88.6%)              | 29 (90.6%)          |     |
| Postmenopausal                 | 2 (6.5%)        | 3 (10%)         | 4 (11.4%)               | 3 (9.4%)            |     |
| Number of pregnancy            | 1.9±1.1         | 1.87±1.2        | 1.74±1.3                | 1.81±1.4            | 0.897 |
| Duration of breast feeding     | 22.8±18.2       | 23.97±22.6      | 20.43±21.6              | 20.81±20.1          | 0.856 |
| Educational status             |                 |                 |                         |                     | 0.693 |
| Elementary school              | 13 (41.9%)      | 9 (30%)         | 8 (22.9%)               | 10 (31.3%)          |     |
| High school                    | 13 (41.9%)      | 12 (40%)        | 15 (42.9%)              | 12 (37.5%)          |     |
| Collage                        | 5 (16.1%)       | 9 (30%)         | 12 (34.3%)              | 10 (31.3%)          |     |

Patients. The best response to therapy (grade 1+2) was seen in FAC group (90%); however, the placebo group had the worst therapeutic response (56.3%). On the other hand, the patients in EPO and reassurance groups had similar response rates at the period of 3 months. There was a significant difference between groups according to the CBS scores (p=0.033). However, there was no significant difference between EPO, reassurance, and placebo groups according to the CBS scores when FAC group was eliminated from the statistical evaluation (p=0.339). Hence, FAC therapy was seen to be more effective than other treatment groups. Additionally, the grade 1+2 response to therapy in FAC group was found to be significantly higher when other three groups converted into a single group (p=0.008).

All patients were also divided into cyclic and non-cyclic groups, and the response rates to therapy of these two groups were analyzed between four study groups. There was no significant difference between groups according to CBS scores in between cyclic group (p=0.283) and non-cyclic group (p=0.078). Additionally, the statistical evaluation of the response to therapy between cyclic and non-cyclic patients was done within each study groups. No significant differences were determined, with p-values of 0.606, 0.653, 0.380, and 0.205 for EPO, FAC, reassurance and placebo groups, respectively.

Finally, no serious adverse effects were seen in patients during the study period. In a few patients, non-specific and mild symptoms such as nausea and epigastric discomfort were observed, but none of those was enough to discontinue treatment.

Discussion

Mastalgia is a common and worrying clinical entity among both premenopausal and postmenopausal women, and can lead to severe impacts on quality of life. Its adverse effects on sexual, social and routine daily activities are perspicuous in working and young women. Therefore, this condition leads to depression, helplessness, unhappiness, and a significant socioeconomic problem. In a study by Ader and Browne [11], it was shown that sexual, physical and social issues were appeared in women with severe mastalgia with a ratio of 48%, 36%, and 13% respectively. Also, breast pain is considered as a sign of cancer by the majority of women, and this belief leads to a big stress. In fact, breast pain is rarely a sign of underlying malignancy, and 0.05% risk of occult cancer was found in mastalgia patients with normal clinical and radiological finding [12, 13]. As a consequent, approximately two-thirds of women suffer from mastalgia throughout their reproductive lives, and, therefore, most of those have to seek medical assistance [3].

To date, many therapeutic options have been used in the treatment of mastalgia. However, none of these had a curable
Table 3  Pain characteristics and response status to treatment of each group.

|                             | EPO group (n=31) | FAC group (n=30) | Reassurance group (n=35) | Placebo group (n=32) | P  |
|-----------------------------|------------------|------------------|--------------------------|---------------------|----|
| Type of pain                |                  |                  |                          |                     |    |
| Cyclic                      | 20 (64.5%)       | 18 (60.0%)       | 24 (68.6%)               | 24 (75%)            | 0.633 |
| Non-cyclic                  | 11 (35.5%)       | 12 (40.0%)       | 11 (31.4%)               | 8 (25.0%)           |    |
| %Qtotal (mean)              | 35.2±21.5        | 30.2±16.5        | 34.6±18                  | 29.1±16.5           | 0.498 |
| %PPI (mean)                 | 18.02±8.4        | 15.5±7.4         | 16.4±6.9                 | 14.9±6.9            | 0.599 |
| %VAS (mean)                 | 48.06±18.6       | 50±17.4          | 55.7±16.5                | 50.3±16.9           | 0.313 |
| %QOL (mean)                 | 33.5±21          | 26.8±16.9        | 36.5±22                  | 29.5±21.6           | 0.247 |
| %totalBP (mean)             | 134.9±62.7       | 122.7±51         | 143.3±57.6               | 124.2±56.6          | 0.437 |
| Severity of pain            |                  |                  |                          |                     | 0.975 |
| Mild                        | 13 (41.9%)       | 11 (36.7%)       | 11 (31.4%)               | 13 (40.6%)          |    |
| Moderate                    | 12 (38.7%)       | 14 (46.7%)       | 17 (48.6%)               | 14 (43.8%)          |    |
| Severe                      | 6 (19.4%)        | 5 (16.7%)        | 7 (20.0%)                | 5 (15.6%)           |    |
| Response to therapy         |                  |                  |                          |                     | 0.033 |
| Grade 1+2 (CBS)             | 22 (71.0%)       | 27 (90.0%)       | 25 (71.4%)               | 18 (56.3%)          |    |

effect. This situation may be explained by the presence of various etiologic factors in a woman at the same time. To rule out the presence of breast cancer usually resolves the patient’s pain. However, mastalgia remains as a problem in a few patients, and medical assistance is especially needed for this group [14, 15].

Non-steroidal anti-inflammatory drugs and hormonal agents such as tamoxifen, danazol, bromocriptine and LH-RH analog have all demonstrated efficacy in the therapy of mastalgia, but potential side effects limit their extensive use in daily practice [3].

However, herbal medicines including EPO and FAC, are non-hormonal agents that are frequently used in mastalgia treatment, with less side effect profiles. EPO is obtained from the seeds of the evening primrose plant and is a rich source of omega-6 essential fatty acids including linoleic acid and gamma-linolenic acids. It is mostly used in the treatment of atopic dermatitis and rheumatoid arthritis. Also, clinically improvement has been shown in patients with multiple sclerosis, according to its immunomodulatory effects [16]. EPO effects by providing a balance between essential fatty acids and saturated fatty acids, and thus reduces the sensitivity of the breast against prolactin and prostaglandins by its indirect effect on the synthesis of eicosanoids, particularly in women with cyclic mastalgia [17]. However, FAC, commonly known as chasteberry, decreases the serum prolactin level in the premenstrual period by activating the dopamine receptors in lactotroph cells of the anterior pituitary, and thus many premenstrual symptoms such as headache, irritability, emotional lability, and mastalgia improve [18]. The activation of some opioid receptors is considered to be the other mechanism on the effect of FAC [19]. It is well known that FAC is one of the most popular herbal medicine in the treatment of premenstrual syndrome. In a large-scale study reported from China, the therapeutic effect of FAC was found to be high in patients with moderate to severe premenstrual syndrome [20]. Also, the dose-dependent efficacy of this herb in relieving symptoms of PMS was demonstrated in a recent study [21]. In our study, the effects of EPO, FAC, and reassurance in mastalgia patients with no organic breast-related problem were evaluated in comparison with placebo. The response in therapeutic modalities was assessed by CBS, and the best results were obtained from FAC group similar to the literature [18, 22]. The response rate of FAC therapy in our study may be seen as quite high, however in a large multi-centric study, 85% reduction in breast pain levels was reported with FAC therapy [23]. In a prospective study involved 40 women with cyclic mastalgia and 40 women with mild hyperprolactinemia, lower levels of serum prolactin and significantly fewer pain scores were obtained from both groups after FAC therapy [24]. This condition was explained with reduced prolactin levels during a premenstrual period in that study by the authors. Similarly, Wuttke [25] reported that premenstrual mastalgia is associated with latent prolactinoma. Also, in a review by Carmichael [2], FAC was recommended as an effective phytotherapeutic drug in the treatment of mastalgia with a safe side effect profile. Similar
to other reports, we recorded no significant side effect associated with FAC using [26]. However, the most reported adverse effects of FAC are nausea, headache, itching, and erythematous rash [2]. The other herbal medicine investigated in the present study, EPO, has been also commonly used in the treatment of mastalgia. However its efficacy is seemed to be less than the other herbal drugs [8, 27]. Furthermore, there are several studies on the insufficiency of EPO in patients with mastalgia [28]. Of those, Tejwani et al. [29] reported that EPO had a lack of benefit over placebo, and offered an antiestrogen agent, ormeloxifene, as an efficient and safe drug for the treatment of mastalgia. The reported adverse effects of EPO are a headache and minor gastrointestinal findings including abdominal pain, nausea, and diarrhea [30]. Similar to the literature, no significant side effect was developed in our patients treated with EPO. To the best of our knowledge, there is no prospective clinical study which compares the effectiveness of FAC and EPO. However, FAC was found superior to EPO and reassurance, particularly in patients with mild to severe cyclic mastalgia in our study, consistent with the literature. Interestingly, reassurance group had a mildly increased rate in effective response to therapy when compared with EPO group. In our opinion, this was because the patients in reassurance group had a psychiatric interview, and took medicine for depression, anxiety or other psychologic problems if was required. The therapeutic role of reassurance in the treatment of mastalgia has been investigated in several studies. In a study by Baros et al. [15], a success rate of 70.2% was obtained from the patients treated with reassurance. In fact, a relationship between mastalgia and psychiatric conditions or unexplained pain syndromes is a well-known issue. In a study by Genc et al. [31], mastalgia was found in 42% of the fibromyalgia patients. However, 36% of mastalgia patients fulfilled the criteria for fibromyalgia. Additionally, the authors defined these two clinical entities as unexplained pain syndromes. Colegrave et al. [32] also reported the association between mastalgia and psychological symptoms such as depression, anxiety and somatization. As a result, mastalgia seems to be associated with high-stress levels [33]. Therefore, reassurance alone may be helpful in selected cases, especially in patients with resistance to drug therapy, or can be considered as an additional therapy to other treatment options. In this respect, psychiatric evaluation and supportive therapy can be a choice of treatment for mastalgia patients with no related organic breast disease.

Conclusion
In conclusion, we suggest that FAC is a well-acceptable choice of treatment in both cyclic and noncyclic mastalgia with a safe adverse effect profile. Also, psychiatric assistance may be considered as a complementary therapeutic option to other medications, due to the psychological basis of mastalgia.

Authors’ Statements
Competing Interests
The authors declare no conflict of interest.

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