Original Investigation

Ulusal Cer Derg 2014; 30: 34-38

DOI: 10.5152/UCD.2014.2409

Comparison of fructus agni casti and flurbiprofen in the treatment of cyclic mastalgia in premenopausal women

Tolga Dinç[1], Faruk Coşkun[2]

ABSTRACT

Objective: Cyclic mastalgia is described as a diffuse, periodic and bilateral breast pain that can not be localized. Although there are several methods of treatment, the most efficient treatment method is still controversial. The aim of this study is to determine, compare and discuss the results of the patients under 40 years old age with a complaint of cyclic mastalgia and without any clinical signs, family history and ultrasonography finding, treated with fructus agni casti extract or flurbiprofen.

Material and Methods: One hundred and fourteen premenapousal patients younger than 40 years old with a complaint of cyclic mastalgia and without any clinical, family or ultrasonography findings were analyzed prospectively. Fructus agni casti extract (Group 1) or flurbiprofen (Group 2) were administered to the patients. VAS scores were accepted as full recovery whit a score of zero, as significant healing when the score improved more than 50%, as mild-moderate healing when the improvement was less than 50% and as no healing in case of no improvement.

Results: The mean age in group 1 was 28.29±5.81, and in group 2 was 29.09±4.49. The mean number of days with pain was 6.0±1.70 days in group 1, and was 6.3±1.63 in group 2. There was no significant difference in VAS scores between the two groups after treatment.

Conclusion: Fructus agni casti extract and flurbiprofen are commonly used medications in the treatment of cyclic mastalgia. Both of these medications significantly reduce the complaints and have acceptable side-effects. There is no proven superiority over each other. Further clinical and laboratory studies are necessary to determine the ideal medication fort he treatment of cyclic mastalgia.

Key Words: Mastalgia, Vitex agnus castus, flurbiprofen

[1]Clinic of General Surgery, Dr. Sami Ulus Gynecology and Pediatrics Teaching and Training Hospital, Ankara, Turkey

[2]Department of General Surgery, Hitit University Faculty of Medicine, Çorum Teaching and Training Hospital, Çorum, Turkey

Address for Correspondence
Dr. Tolga Dinç

Clinic of General Surgery, Dr. Sami Ulus Gynecology and Pediatrics Teaching and Training Hospital, Ankara, Turkey
Phone +90 532 481 22 75
e-mail: tolga_dr@hotmail.com

Received: 21.10.2013
Accepted: 02.12.2013

Available online at www.ulusalcerrahidergisi.org

INTRODUCTION

Mastalgia has been first introduced in 1829 by Billroth, and is defined as breast distension, discomfort or pain (1). Clinically, according to its relationship with the menstrual cycle, it is classified as cyclic and non-cyclic mastalgia. Cyclic mastalgia is defined as diffuse, periodic breast pain that cannot be localized, and is often bilateral . Cyclic mastalgia, constitutes approximately 60% of all mastalgias and is most common in the 2nd and 3rd decades, and it continues from 4 to 7 days. Before starting treatment, a detailed history, physical examination and imaging systems should be used. A large majority (90%) responds well to treatment (2, 3). There are various non- standardized treatment protocols either pharmacological or not for the treatment of mastalgia (4, 5). The drug options used in treatment include bromocriptine, non-steroidal anti-inflammatory drugs, herbal fruit extracts (chaste tree extract), danazol , tamoxifen, luteinizing hormone -releasing hormone (LHRH) analogues, gamma linoic acid, testosterone, B6 and vitamin E. However, choosing the appropriate drug is usually difficult due to the diverse side effects of hormonal treatments and the lack of consensus regarding the most effective treatment method (6, 7). This study aimed to determine and compare the results of patients under 40 years old age with a complaint of cyclic mastalgia and without any pathologic clinical signs, family history and ultrasonography finding, who were treated with fructus agni casti (FAC) extract or flurbiprofen (FBP), and discuss these results with review of the literature.

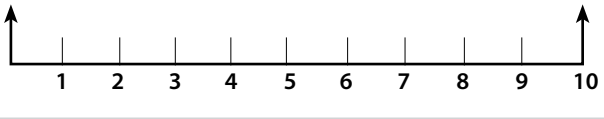
MATERIAL AND METHODS

One hundred and fourteen premenapousal patients younger than 40 years old who presented to Dr. Sami Ulus Gynecology and Pediatrics Teaching and Training Hospital between 01.09.2012 and

01.06.2013, with a complaint of cyclic mastalgia and without any pathologic clinical, family history or ultrasonography findings were analyzed prospectively. Ten patients who were lost to follow-up were excluded from the study. All patients received a detailed medical history, general medical evaluation, breast examinations, and breast ultrasound (with 10 - MHz ultrasound probe in SSA- 240 USG device, Toshiba, Japan). Pain assessment was done by visual analog scale (VAS). In this evalation, on a 10-cm line the minimum and maximum definitions of the evaluated parameter were written on both ends (I do not have any=0, I have a very severe pain=10) and the patients were asked to indicate their own state on this line by putting a mark on the corresponding value. A previously prepared template was used for detection of the values on the line (Figure 1) (8). In the treatment of breast pain, FAC and FBP were selected as two options and were applied to the patients included in the study. FAC 40 mg was administered as 1 tablet daily, and FBP was prescribed in a total dose of 200 mg/day in two divided portions for 3 months. After three months of treatment, patients were re-evaluated and their current pain was re-scored with VAS. At the end of three months, VAS value of 0 was accepted as full recovery, greater than 50% reduction in VAS values was defined as significant improvement, less than 50% reduction as mild-moderate improvement, and no change in the VAS value was accepted as no improvement. Among these patients, those treated with FAC were named Group 1, and those treated with FBP as Group 2. An approval was obtained from the Ankara Numune Education and Research Hospital Ethics Committee and informed consent was obtained from all the patients, and the criteria of Declaration of Helsinki were adhered to. The following data were recorded for Group 1 and 2; mean age, the duration of pain in the menstrual cycles, VAS scores before and after treatment and medication side effects were recorded.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 20 was used for recording and evaluation of the data. Descriptive statistical methods (mean, standard deviation) were used as well as independent Student's t test for the comparison of quantitative data and Fisher's chi-square test for comparison of qualitative data between groups. Results were evaluated at 95% confidence interval and significance set at $p<0.05$ level.



Figue 1. Numbered Visual Analogue Scale (VAS)

RESULTS

Ten out of 114 patients were excluded from the study since they were lost to follow-up, remaining 104 patients in the study. Of these patients, 51 patients who were treated with FAC constituted Group 1, while 53 patients treated with FBP were classified as Group 2. The mean age of overall patients was 28.70±5.17 years, this value was 28.29±5.81 years for Group 1, and 29.09±4.49 years for Group 2. The difference in mean age was not found to be statistically significant between the two groups (p=0.438). The mean number of painful days during menstrual cycles in all patients was calculated as 6.16±1.66 days, it was found as 6.0±1.70 days in Group 1 and as 6.3±1.63 days in Group 2. Number of painful days did not differ significantly between the two groups (p=0.329) (Table 1). The VAS scores on admission was compared between the groups and no statistically significant differences were detected, the pain scores for both groups were similar (p=0.852) (Table 2). When pre-treatment and post-treatment mean VAS were compared between the groups, it was determined that treated patients expressed similar amounts of decrease in pain (p=0.985, p=0.249) (Table 3). Each of these drugs was observed to be effective in treating mastalgia (p=0.485) (Table 3). Regarding the post-treatment VAS assessment results; the number of patients with full recovery, significant improvement, mild-moderate improvement and no improvement did not show a statistically significant difference between the two groups (p=0.945) (Table 4). The side effects of drugs also did not show a statistically significant difference (p=0.945) (Table 5).

DISCUSSION

Cyclic mastalgia constitutes 2/3 of patients who present with breast pain, and is defined as diffuse, periodic breast pain that cannot be localized, that lasts from 4-7 days and is often bilateral (9). It is seen more often in the second and third decades of life (2, 3). The mean age of patients in our study was calculated as 28 years and is consistent with the literature. In addition, the mean number of painful days has been identified as 6 days in our study that is also parallel to the literature.

Several studies have been conducted with the aim of explaining the cause of breast pain and different opinions have been reported. Excess of estrogen (10), progesterone deficiency (11), imbalance of progesterone/estrogen ratio (12), deficiency of γ -linolenic acid and essential fatty acids that alters progesterone receptor sensitivity (13), mismatch in FSH

Table 1. Mean age and number of painful days during menstrual cycle

	FAC (Group I)	±SD	FBP (Group II)	±SD	p
Patient's mean age	28.29 (19-39)	5.818	29.09 (22-38)	4.498	0.438
Pain duration (day)	6.00 (3-10)	1.708	6.328 (3-10)	1.629	0.329

FAC: Fructus Agni-Casti; FBP: Flurbiprofen

Table 2. Pre-treatment VAS scores (number of days)

VAS Scores	FAC (Group I) %	FBP (Group II) %	p
5	4 (7.8)	5 (9.4)	
6	11 (21.6)	10 (18.9)	
7	17 (33)	18 (34)	0.852
8	13 (5.5)	11 (20.8)	
9	4 (7.8)	8 (15.1)	
10	2 (3.9)	1 (1.9)	

VAS: Visual Analogue Scale; FAC: Fructus Agni-Casti; FBP: Flurbiprofen

Table 3. Comparison of pre- and post-treatment VAS scores and treatment efficiency

	FAC (Group 1) Mean (SD)	FBP (Group 2) Mean (SD)	p
Pre-treatment VAS	7.156 (1.206)	7.188 (1.244)	0.895
Post-treatment VAS	3.159 (2.221)	3.585 (2.249)	0.249

VAS: Visual Analogue Scale

Table 4. Treatment results as determined by VAS scores by group

	FAC (Group 1) %	FBP (Group 2) %	p
Full recovery	11 (21.6)	9 (17)	
Significant improvement	22 (43.1)	24 (43.3)	0.945
Mild-moderate improvement	13 (25.5)	14 (26.4)	
No improvement	5 (9.8)	6 (11.3)	

FAC: Fructus Agni-Casti; FBP: Flurbiprofen

Table 5. Comparison of side effects between groups

	FAC (Group 1) %	FBP (Group 2) %	p
None	47 (92.2)	46 (86.8)	
Confusion	2 (3.9)	0	
Rash	2 (3.9)	0	0.062
Diarrhea	0	1	
Dispepsy	0	5 (9.4)	
Tinnitus	0	1 (1.9)	

FAC: Fructus Agni-Casti; FBP: Flurbiprofen

and LH release (14), low levels of androgens and generalized hypothalamic-pituitary abnormalities that cause prolactin levels to rise (14, 15), and excessive consumption of CNS stimuli like caffeine and xanthine (16, 17) have all been reported in its etiology. However, other investigators (18-20) have not confirmed some of the results of these researches. Thus, it cannot be stated that causes of breast pain are completely clarified. As we are unable to clarify the exact cause of mastalgia, there is not any optimal treatment. Drug options used in the treatment include bromocriptine, nonsteroidal anti-inflammatory drugs, herbal fruit extracts, danazol, tamoxifen, luteinizing hormone -releasing hormone (LHRH) analogues, gamma-linoleic acid, testosterone, B6 and vitamin E. However, choosing the appropriate drug is usually difficult due to the diverse side effects of hormonal treatments and the lack of consensus regarding the most effective treatment method (6, 7). That is why our study was designed to evaluate the effectiveness of the commonly used FAC that ensures normal estrogen-gestagen equilibrium by regulating gonadotropin secretion and FBP that plays a role in the inflammatory process by blocking cyclooxygenase enzymes in the treatment of mastalgia and their superiority over each other.

There are many studies in the literature on the use of FAC in the treatment of mastalgia. Frisch examined 646 cases treated with FAC during 10 years of experience, and observed complete remission in 420 patients (65%), temporary improvement requiring re-treatment in 220 patients (32%), and in 23 patients (3%) a marked improvement was not determined (21). Roeder, in 1976, treated 480 patients with FAC, in 81.5% of the patients symptoms have permanently resolved and 12% satisfactory but non-persistent improvement had been achieved and the treatment had to be repeated (22). In this study, short -term treatment results were satisfactory, but these results were not permanent. In our study, full recovery was detected in 21.6% of patients, significant improvement in 43.1%, mild-to-moderate improvement in 25.5% and no improvement was detected in 9.8% of patients. Varying degrees of improvement is observed in up to 90% of patients with FAC use.

The analgesic activity rates were consistent with the literature. It is emphasized that the optimal duration of FAC treatment is 12 weeks. In our study, treatment was administered for 12 weeks and no improvement was detected in only 9.8% of patients.

Gregl'n treated 444 patients with FAC, and the complaints disappeared in 57.8%, while a significant improvement in symptoms was not achieved in 25% (23). Beles et al. (24) included 97 patients with breast pain for at least 5 days in each cycle in their randomized, double- blind, placebo-controlled study. Half of the patients (n=48) received FAC extract, and the other half (n=49) received placebo. The treatment was continued for three cycles, and the participants were asked to record the intensity of breast pain according to the visual analog scale (VAS). After one cycle of treatment, decline in pain intensity was 2.1 cm (30%) in the FAC group, whereas the decline in the placebo group was 1.0 cm (11%). After the second cycle, breast pain was reduced by 53% by FAC, this rate was only 25% in patients on placebo. In this study, treatment success with FAC was largely achieved after two cycles. In 71.4% of respondents in the group treated with FAC, symptoms either fully resolved or significantly improved. In our study, patients in both groups used FAC and FBP for three cycles, in both groups the rate of full or partial recovery was close to 90%.

Wuttke et al. (25) evaluated 104 patients with mastodynia at least in 3 cycles and at least for 3 days in each cycle in a randomized, placebo-controlled, double blind study. Thirty-four patients received a solution containing FAC extract, 32 were given pills containing the same dose of FAC and 38 received placebo. This research was carried out for three cycles and participants were asked to record their breast pain intensity according to VAS. The difference in pain intensity before and after treatment was 36.5 mm for FAC extract solution, 36.7 mm for pills containing FAC extract, and was only 20.8 mm for placebo. In our study, three cycles of FAC and FBP were used but the effectiveness of the two drugs showed significant similarity.

Roeder (22), Frisch (21), Meyl (26), Kubista (27), Karting (28) and van-Die (29) have reported no side effects, whereas in our study in FAC patients 2 developed rashes and 2 had confusion. In patients receiving FBP, dyspepsia was detected in 5 patients, 1 patient had tinnitus, and 1 patient experienced diarrhea. The disruption of mucus barrier in the stomach by FBP is thought to be caused by secondary gastric acidity.

Many drugs have been used in solving the problem of mastalgia that cause discomfort in women's life. In the study by Saydam et al. (30), cyclic and non-cyclic mastalgia patients had been treated with tamoxifen and they did not significantly differ from the placebo group. Studies aiming to resolve mastalgia efficiently will be continued in the future.

Breast pain is accepted as a major problem in terms of women's health, with its risk of breast cancer, although low, causing anxiety, and depression. Clinical experience shows that women with breast pain mostly fear of having breast cancer (31). In the majority of patients, explaining that there is not any pathology that causes breast pain and in particular, the exclusion of breast cancer, and initiation of additional medical treatment is important.

Study Limitations

In our study, the results of FAC and FBP treatment and their superiority to each other were evaluated. The follow-up period was limited to three months. Restriction of our study is the need for long term results.

CONCLUSION

Fructus agni casti and FBP are commonly used ingredients in patients with complaint of mastalgia. Both of these agents significantly reduce mastalgia with acceptable side effects, and they were not shown to have significant advantages over each other. Nevertheless, further clinical and laboratory studies are required to identify the ideal drug that will improve mastalgia, completely and permanently, without any side effects.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Numune Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.D., F.C.; Design - T.D.; Supervision - F.C., T.D.; Funding - F.C., T.D.; Materials - T.D.; Data Collection and/or Processing - T.D.; Analysis and/or Interpretation - F.C., T.D.; Literature Review - F.C.; Writer - T.D.; Critical Review - T.D., F.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Ader DN, South-Paul J, Adera T, Deuster PA. Cyclical mastalgia: Prevelance and associated health and behaviuoral factors. J Psyhosom Obstet Gynecol 2001; 22: 71-76. [CrossRef]
2. Plu-Bureau G, Thalabard JC, Sitruk-Ware R. Mastalgia. J Obstet Gynaecol Can 2006; 28: 49-71.
3. Antonio VM, Frederick MD. Clinical management of breast pain: A review. Obstet Gynecol Surv 2002; 57: 451-461. [CrossRef]
4. Halaska M, Beles P, Gorkow C, Sieder C. Treatment of cyclical mastalgia with a solution containing a Vitex agnus castus extract: results of a placebo-controlled double-blind study. Breast 1999; 8: 175-181. [CrossRef]
5. Gorkow C, Wuttke W, März RW. Effectiveness of vitex agnus castus preparations. Wien Med Wochenschr 2002; 152: 364-372. [CrossRef]
6. Carmichael AR. Can Vitex agnus castus be used for the treatment of mastalgia? What is the current evidence? Evid Based Complement Alternat Med 2008; 5: 247-250. [CrossRef]
7. Holland PA, Gateley CA. Drug therapy of mastalgia. What are the options? Drugs 1994; 48: 709-716. [CrossRef]
8. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health 1990; 13: 227-236. [CrossRef]
9. Wuttke W, Jarry H, Christoffel V. Chaste tree (Vitex agnus-castus) pharmacology and clinical indications. Phytomedicine 2003; 10: 348-357. [CrossRef]
10. Fechner RE. Benign breast disease in women on estrogen therapy. Cancer 1972; 29: 273-279. [CrossRef]
11. Mauvais-Jarvis P, SitruckWare AR, Kutten F. Luteal insufficiency: a common pathophysiologic factor in the development of benign and malignant breast disease. In: Bulbrook RD, Taylor DJ, eds. Commentaries on research in breast disease. New York, 1975.p.25.
12. Sitruk-Ware AR, Sterkers N, Mowiszowicz I. Inadequate corpus luteum function in women with benign breast disease. J Clin Endocrinol Metabol 1977; 44: 771-775. [CrossRef]
13. Horrobin DF. The effects of gamma-linoleic acid on breast pain and diabeticneuropathy: possible non-eicosanoid mechanism. Prostaglandin Leuko Esent Fatty Acids 1993; 48: 101-104. [CrossRef]
14. Kumar S, Mansel RE, Scanlon MF. Altered responses of prolactin, luteinizing hormone and follicle stimulating hormone secretion to thyrophin releasing hormone/gonadotrophin releasing hormone sitimulation in cyclical mastalgia. Br J Surg 1984; 71: 870-873. [CrossRef]
15. Cole EM, Sellwood RA, England PC. Serum prolactin concentrati-

on in benign breast disease throughout the menstrual cycle. Eur J Cancer Clin Oncol 1977; 13: 597-603.
16. Klimberg VS. Management of breast disorders, etiology and management of breast pain, disease of the breast. Lippincott-Raven 1996: 99-106.
17. Tavassoli F. Benign lesions. In: Tavassoli F eds. Pathology of the breast. Norwolk, Connecticut, Appleton Lange 1992: 79-227.
18. Maddox PR, Harrison BJ, Mansel RE. Non-cyclical mastalgia: improved classification and treatment. Br J Surg 1989; 76: 901-904. [CrossRef]
19. Ambramson DJ. Lateral extra mammary pain syndrome. Breast 1980; 6: 2-5.
20. LaBan MM, Meerschaert JR, Taylor RS. Breast pain: symptom of cervical radiculopathy. Arch Phys Med Rehail 1979; 60: 315.
21. Frisch H. On the treatment of mastodynia and mastopathy with Mastodynon R. Therapiewoche 1968; 34: 1354-1355.
22. Roeder D. On the of treatment mastodynia and mastopathy with Mastodynon R. Med Welt 1976; 27: 591-592.
23. Gregl A. Conservative treatment of mastopathy (Mastodynia). Die Med Welt 1979; 7: 264-268.
24. Beles P, Halaska M, Gorkow C, Sieder C. Treatment of cyclical mastalgia with a solution containing a Vitex agnus castus extract: results of a placebo-controlled double-blind study. The Breast 1999: 4: 175-181.
25. Wuttke W, Gorkow C, Jarry H. Phytotherapy in gynaecology. ZAN: Arztezeitschrift fur Naturheilverfahren 1996; 8: 587-592.
26. Meyl CH. Therapy of the premenstrual syndrome. Comprasion between a combined treatment of mastodynon R with vitamin E and vitamin E mono-therapy. Therapeutikon 1991; 5: 518-525.
27. Kubista E, Muller G, Spona J. Treatment of mastopathy with cyclic mastodynia clinical results and hormone profiles. Gynak Rdsch 1986; 26: 65-79.
28. Karting T. Vitex agnus castus-monk's pepper or chastity tree. A medicinal plant with an indirect luteotropic action. Zeitschrift Fur Phytoterapie 1986; 7: 119-122.
29. van Die MD, Burger HG, Teede HJ, Bone KM. Vitex agnus-castus extracts for female reproductive disorders: a systematic review of clinical trials. Planta Med 2013; 79: 562-575.
30. Saydam S, Bora S, Karaaslan M, Harmancıoğlu Ö, Bakır H, Astarcıoğlu K. The role of tamoxifen in cyclic and non-cyclic mastalgia. Ulusal Cer Derg 1994; 10: 185.
31. Yakut ZI, Karaoglanoglu M, Koktener A, Duvan CI. A new radiological approach to cyclic mastalgia: venous Doppler ultrasound. Breast 2009; 18: 123-125. [CrossRef]