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ORIGINAL ARTICLE

Comparison of Different Agents for Reducing Mastalgia in Fibrocystic Disease of Women

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ABSTRACT

Background: Mastalgia, or breast pain (or mastodynia), is globally a common symptom experienced by women of reproductive age; treatment for these conditions is not yet standardized. Most of the drugs used for mastalgia are expensive and have side effects, so, the aim of this study was to compare different agents for reducing mastalgia in fibrocystic disease of women in outpatient clinics at Zagazig University.

Methods: this prospective random comparative study has been carried out in Zagazig University out patients clinics specifically in breast clinic subjects in period between May-2019 to March -2020 on 68 patients enrolled with 3 months period of follow up.

Results: In EPO group 30% of patients showed complete resolution and 61% showed partial response. The danazol group received, 58% of patients showed complete resolution and 41% showed partial improvement. In Tamoxifen group 47% of patients showed complete resolution while 52 % showed partial improvement. In the cabergoline group 14% of patient showed complete resolution and 42% showed partial improvement.

Conclusions: Evening prime rose oil is effective in reducing the severity of mastalgia with minor tolerable side effects and should be used as first line of management. Danazol is the most effective agent but its side effects make it less favorable agent. Tamoxifen is the second most effective agent among the other agents with reversible tolerable side effects. Cabergoline is significantly decrease breast pain especially cyclic mastalgia, with notable side effects.

Keywords: Mastalgia; Fibrocystic breast disease; Fibrocystic breast changes

INTRODUCTION

One of the most prevalent benign lesions that hurt women is fibrocystic breast alterations. The most typical sign of fibrocystic breast alterations is periodic breast pain, or mastalgia [1].

Fibrocystic breast changes as well as mastalgia are common conditions that women suffer from. They may occur separately or in combination. The nature of these changes as well as the associated factors responsible for their development are not fully understood by many who treat patients suffering from breast pain. Unfortunately, mastalgia caused by fibrocystic breast changes is treated by breast specialists as well as by those not specialized in breast diseases. This results in patients receiving inappropriately strong medication with severe side effects, where simpler remedies could have done the job more efficiently [2].

Treatment of mastalgias is as controversial as its aetiopathogenesis. Non-medical therapy includes reassurance and good external breast support “sports brassier”. There are number of drugs which have been tried in the treatment of mastalgia such as bromocriptine, tamoxifen, danazol, evening primrose oil, topical as well as oral non-steroidal anti-inflammatory drugs and centchroman [3].

Evening primrose oil (EPO) is rich in essential fatty acids and contains gamma-linolenic acid (GLA) as much as 7% - 14%, which prevents the

synthesis of prostaglandins that potentially cause the breast pain [1].

Danazol is a derivative of the synthetic steroid ethisterone, a modified testosterone. It was approved by the U.S. Food and Drug Administration (FDA) as the first drug to specifically treat endometriosis in the early 1970s. It suppresses gonadotropin secretion, prevents luteinizing hormone surge, and inhibits ovarian steroid formation and is approved by the FDA for treatment of mastalgia [2].

Tamoxifen at a dose of 10 mg daily is reported to relieve cyclical and noncyclical mastalgia. Side effects at this low dose for 3 months are minimal and include irregular periods and hot flushes. Tamoxifen is the drug of choice for mastalgia in most breast clinics in the West. The patient must be told that tamoxifen is not being given for cancer [4].

Cabergoline has been widely used for hyperprolactinemia for several years but has not been used for mastalgia before, and the side effects seem to be much less compared to bromocriptine. We therefore hypothesized that cabergoline could be as effective as bromocriptine for the symptomatic treatment of mastalgia, with fewer adverse effects [5]. Cabergoline, another long-lasting, potent, dopamine, has been demonstrated to be as effective as bromocriptine with fewer side effect [6]. The aim of this study was to compare different agents for reducing mastalgia in fibrocystic disease of women in outpatient clinics at Zagazig University

METHODS

This prospective random comparative study has been carried out in Zagazig university outpatient clinics specifically in breast clinic subjects in period between May-2019 to March-2020 on 68 patients enrolled with 3 months' period of follow up.

All participants' parents or other family members provided written informed consent, and the research ethics committee of Zagazig University's Faculty of Medicine authorized the study. The work has been finished in accordance with the World Medical Association's Declaration of Helsinki code of ethics for human subjects' research.

All patients seen in breast outpatient clinics who was older than eighteen, complained of mastalgia with fibrocystic illness and only patient with pain characters consistent with cyclic mastalgia were included.

Patients who are breast feeders or pregnant, those who planned to become pregnant soon, those who have had breast cancer in the past or in their family, those who have had breast surgery in the past, those who have a history of breast cancer, those who refuse to participate in the study and any female with breast mass and psychic disorders were excluded from this study

All patients were subjected to menstrual and obstetric history, as well as demographic information such as name, age, place of residence, employment, marital status, and any unique medically significant behaviors, have been recorded. The onset, course, and duration of the mastalgia, along with any co-morbidities and the cyclic or noncyclic nature of the breast pain, have all been carefully documented in the medical history.

Clinical evaluations that include thorough and general breast exams (CBE) to assess breast size, tenderness, nipple changes or discharge, lumpiness or localized nodularity and any hotness redness and thorough examination to the axillary lymph node.

Every case has had a breast ultrasound requested at the initial visit and three months after therapy to assess nodularity and the response to treatment regarding to nodularity and to discover any other breast mass which may not be seen by clinical examination.

Patients were randomized employing sequentially numbered opaque sealed envelopes with computer-generated randomization lists and cards with the allocation information written on them. A research nurse opened envelopes one by one to place patients in their designated groups. Participated utilizing consecutively numbered opaque sealed envelopes with the allocation information written on a card, together with a computer-generated randomization list for each patient, the study's participants were randomized. A research nurse opened envelopes one by one to assign patients to four groups after requesting breast ultra-sound for all of them at first visit and after three months, all of them have their pain intensity assessed by visual analogue scale at time of presentation and monthly ever since.

For period of three months, first group was given a 1000 mg evening primrose oil capsule once a day, second group was given a 200 mg daily danazol tablet, and third group was given cabergoline tablet 0.5mg once weekly and fourth group received tamoxifien 10mg once daily.

Patients were followed up at outpatients once a month for three months. During each visit, the patients' pain levels were assessed using a pain analogue scale, and any side effects that arose

from the medication were sought out and documented. Patients were also seen right away in between follow-up visits if they noticed any new or concerning side effects or symptoms at the outpatient clinic appointments.

Parameters of evaluation are patient comfort and improvement as indicated by a visual analog scale that ranges between 0 to 10 (0 experiencing no pain and 10 experiencing the worst unbearable pain) which shown to each patient as numerical scale and explained to each patient individually as the main goal of our study is to control mastalgia.

Every appointment should include a breast examination to measure clinical progress, and nodularity should be reviewed after three months, although most of patients came to our clinic complain of mastalgia rather than nodularity or lumpiness which are not uncommon among patients with fibrocystic diseases.

The side effects of medications were updated every month until the trial's conclusion. Side effect of each drugs was explained to each patient in simple language and reported in every monthly visits.

statistical analysis:

SPSS version 20 was used for statistical analysis; The demographic variables in the sample as a whole were described, and the quantitative variables (mean and standard deviation) and categorical factors (percentages) were presented. Following that, a look for variations in variable distribution between the two research groups was conducted. For the quantitative variables, A Student's t test and a Chi-square test were used to analyze the categorical variables. Next, the relevant confidence interval and the relative risk of prediabetes were calculated as functions of the outcome parameters. Next, the outcome variables' incidence was calculated. Level of importance was taken into account for $P < 0.05$ and high significance $P < 0.001$.

RESULTS

Table (1) showed that there is statistically significant difference between the studied groups regarding age. On LSD comparison, the difference is significant between Tamoxifen group and both Evening primrose oil and Cabergoline groups. Similarly, the difference is significant between danazol and evening primerose groups. patients received tamoxifen and danazol were the oldest. There is statistically non-significant difference between the studied groups regarding marital status. Table (2) showed that there was no statistical significant difference between the studied groups regarding baseline ultrasonographic findings. There was a statistical significant difference between the studied groups regarding ultrasonographic finding at 3 months with significant difference between Cabergoline group and both Tamoxifen and Danazol groups. Table (3) showed that there was no statistical significant difference between the studied groups regarding baseline VAS score. There was statistically significant difference between the studied groups regarding VAS score in the second month (Cabergoline group had the most significant higher VAS score in comparison with each other group). Also, there is statistically significant difference between the studied groups regarding VAS score in the third month (Cabergoline group had the most significant higher VAS score in comparison with each other group). There is also significant difference between Danazol, Tamoxifen groups and both Cabergoline group and evening Primeroe group). Table (4), showed that there was a statistically significant difference between the studied groups regarding percent decrease in VAS score with Cabergoline group had the least value. Danazol showed the highest percent of pain improvement followed by tamoxifen then evening primrose oil. Table (5), showed that there was statistically significant difference between the studied groups regarding occurrence of adverse effects with significant difference between tamoxifen and both evening primrose oil and Danazol groups.

Table (1): Demographic data among the studied groups

Demographic data	Groups				Test	
	Cabergoline group	Evening primerose oil group	Tamoxifen group	Danazol group	F/ χ^2	P
	N=17 (%)	N=17 (%)	N=17 (%)	N=17 (%)		
Age: **Mean ± SD** **Range**	35.12 ± 10.66 24 – 54	32.29 ± 6.62 20 – 40	40.35 ± 5.51 34 - 48	39.47 ± 4.8 34 – 48	4.608	0.006*

Marital status: **Married** **Single**	17 (100) 0 (0)	16 (94.1) 1 (5.9)	13 (76.5) 4 (23.5)	13 (76.5) 4 (23.5)	6.531	0.113

*p<0.05 is statistically significant

Table (2) Ultrasonographic findings at presentation and after the third month among the studied groups.

Ultrasonographic findings	**Groups**				Test	
	Cabergoline group	**Evening primerose oil group**	**Tamoxifen group**	**Danazol group**	χ^2	P
	N=17 (%)	**N=17 (%)**	**N=17 (%)**	**N=17 (%)**		
At time of presentation: **Fibroadenosis** **Normal study**	 14 (82.4) 3 (17.6)	 13 (76.5) 4 (23.5)	 17 (100) 0 (0)	 17 (100) 0 (0)	8.122	0.055
At third month: **Fibroadenosis** **Partial resolution** **Complete resolution**	 6 (35.3) 6 (35.3) 5 (29.4)	 1 (5.9) 8 (47.1) 8 (47.1)	 0 (0) 9 (52.9) 8 (47.1)	 0 (0) 7 (41.2) 10 (58.8)	16.455	0.010*

*p<0.05 is statistically significant

Table (3): Comparison between the studied groups regarding VAS score at the first, second and third months:

VAS	**Groups**				**Test**	
	Cabergoline group	**Evening primerose oil group**	**Tamoxifen group**	**Danazol group**	**F**	**P**
	N=17 (%)	**N=17 (%)**	**N=17 (%)**	**N=17 (%)**		
1st month: **Mean ± SD** **Range**	 8.059 ± 0.827 7 – 9	 8.412 ± 0.795 7 – 9	 8.471 ± 5.145 8 - 9	 8.647±0.493 8 – 9	2.269	0.089
2nd month: **Mean ± SD** **Range**	 6.941 ± 0.748 6 – 8	 5.765 ± 1.091 4 – 7	 5.471 ± 1.179 4 - 7	 5.529±0.943 4 – 7	7.995	<0.001** *
3rd month: **Mean ± SD** **Range**	 4.353± 1.169 3 – 6	 3.118 ± 1.111 2 – 5	 2.471 ± 0.514 2 – 3	 2.176±0.728 2 – 3	18.678	<0.001** *

*p<0.05 is statistically significant

Table (4): Comparison between the studied groups regarding percent change in VAS score at the third months:

% change in VAS	**Groups**				**Test**	
	Cabergoline group	**Evening primerose oil group**	**Tamoxifen group**	**Danazol group**	**KW**	**P**
	N=17 (%)	**N=17 (%)**	**N=17 (%)**	**N=17 (%)**		
Third month: Mean ± SD Range	 45.763 ±14.19 25 – 66.7	 62.27 ± 14.53 37.5 – 77.78	 70.75 ± 6.36 62.5 – 77.78	 74.75±8.55 62.5 – 88.89	28.719	<0.001**

Table (5): Comparison between the studied groups regarding occurrence of adverse effects:

Adverse effects	Groups				Test	
	Cabergoline group	Evening primerose oil group	Tamoxifen group	Danazol group	χ^2	P
	N=17 (%)	N=17 (%)	N=17 (%)	N=17 (%)		
No	13 (76.5)	16 (94.1)	9 (52.9)	11 (64.7)		
Yes	4 (23.5)	1 (5.9)	8 (47.5)	6 (35.3)	20.09	<0.001**

*p<0.05 is statistically significant

DISCUSSION

In the present study, we assessed the various forms of therapy to control cyclic mastalgia. Currently various treatment modes are in practice for the management of cyclic mastalgia but most are insufficient. This study was conducted with the aim of evaluating effectiveness, compliance and adverse effects of evening primerose oil (EPO), danazol, tamoxifen and cabergoline. The study included 68 patients with age range between 20 - 48 years where the median age was 37 years that matches with the study conducted by Aydin et al [5] where the mean age of the patients in their study was 38years.

Although there was no placebo group in our investigation, we can roughly calculate the placebo effect from other research in which placebo effect ranged from 25 to 50 % as Aydin et al [5] stated in their study depending on reviewing the literature.

There was statistically significant difference in the mean age between the four different groups where danazol and tamoxifen group had the oldest patients.

Regarding the baseline ulatrasonography results at the time of presentation, no statistically significant distinction existed between the tested groups, which was consistent with the results and information provided by Jain et al., [7] research pertaining to baseline findings from ultrasonography.

Regarding to the ultrasonography findings, 3 months post treatment, we found that, in the cabergoline group (14%) of the patients achieved complete resolution, and (42%) showed partial improvement in the degree of fibroadenosis compared to the base line ultrasound and (43%) showed no changes at all and that the data available in study conducted by Memon et al [8] which showed that 73% of cyclic nodularity reduced using cabergoline , but they used dose of 1.5mg over period of three month.

Although thirty percent of the patients treated with evening primrose oil demonstrated complete remission, sixty-one percent had varying degrees of response, and one patient displayed almost no change. The outcome nearly reflects what Khadka et al., [9] has been stated in their study.

Patients treated with tamoxifen showed complete resolution in 47% of total group and 52% patients responed by different degree of improvement in fibroadenosis changes and no recent study found regarding to the effect of tamoxifen on cyclic nodularity but the role of tamoxifen in reducing nodularity need to be evaluated, as most studies concentrate on its effect on pain control.

Patients have been treated with danazol showed complete resolution in 58% of patients and 41% have been improved radiologicaly comparing to the first ultrasound, in study conducted by kumar et al. [10] showed that 85% of resolution can be achieved in breast nodularity which near match the result of current study.

The main goal of this study was to control mastalgia in the first place measuring the pain by visual analogue scale which has been assessed by the patients in monthly visits.

All patient included in the four groups of our study had cyclic mastalgia with VAS more than 7 where the patient with non-cyclic breast pain has been excluded and this does not typically match the study conducted by Aydin et al [5] whose patients included in the study had cyclic mastalgia with visual analogue scale above 4 which considered moderate mastalgia.

The four drugs groups showed significant difference alleviating the pain of cyclic mastalgia, where Patients in the group treated with danazol had experienced the greatest degree of reduction in the VAS of pain followed by tamoxifen, evening primerose oil and then cabergoline.

The patients of cabergoline group at time of presentation had a cyclic mastalgia with VAS of (7-9) that decreased to (6-8) after 1 month of treatment and further decreased to (3-6) after 3 months post treatment.While patients in evening primerose oil group had (7-9) VAS which

decreased to (4-7) and down to (2-5) over period of three month of treatment.

The VAS of patients in tamoxifen group at first visit was (8-9) and decreased with treatment to (4-7) in second month and (2-3) after 3 months of treatment. In danazol group all patients had VAS ranged between (8-9) which decreased to (4-7) in the second month of treatment and further decreased to (2-3) at the end of follow up period.

The difference in VAS between firs visit and after first months of treatment was insignificant in all four groups, the baseline parameters and initial pain score of the four groups did not differ in a way that was statistically significant.

The percentage of decrease of the VAS been significant after the completion of the third month where the percentage of decrease in VAS in cabergoline group was 45.67% who received 0.5 mg/week over three months and that different from the study conducted by Aydin et al., [5] who achieved 66.2% with 70 patients enrolled in cabergoline group with the dose similar to what has been used in our current study.

Evening prime rose oil group had 62 % decrease in VAS in the third month comparing to 50% which was achieved in study Conducted by Nigam et al., [11] on 98 patients in which 62 patients had cyclic mastalgia treated by 1000 mg once daily dose, another study carried out by parveen et al [12] achieved 68% decrease in the VAS after 12 weeks which in concordance with our current study.

Patients in tamoxifen group who have been on 10mg/day tablets over 3 months, showed 70.75% decrease in their VAS at the third months, in disagreement with prospective randomized control trial conducted by Gupta et al., [13] where the response achieved in the tamoxifen group was 33.3% in study include 72 patients in which cyclic mastalgia constitute 66.67% of total number of patients complaining of mastalgia but in their study the dose was 20mg and the follow up period was 18 months. In another study conducted by Khadka et al [9] which include 106 patients received 10mg tamoxifen over 3 months' period, which resemble our parameters in our present study, the decrease in VAS was 60 % which near match our current study, while Jain et al. [7] reported decrease in the cyclic pain around 71% of total group.

Meanwhile, the VAS showed that patients in the danazol group had significantly reduced their cyclic pain, with a 75% reduction at the conclusion of the follow-up period. These results appear to be consistent with those of a prospective randomized research carried out by Kumar and hasan [14]. This displayed 71% and had 64 patients. In a different trial by, patients treated with danazol 200mg for 12 weeks with adverse effects showed 30% improvement Gupta et al [13]. The results of our current study are corroborated by another study by Cornell et al. which found a 77% reduction in pain in the VAS and a 71% decrease in VAS attained.

Additionally, the patients in the four groups of our thesis reported varying side effects.

In the case of the cabergoline group, headache was reported in 1 patient (5.9) and dizziness was noted as a side effect in 3 out of 17 individuals (17.6%) Aydin et al., [5] who reported a 16.4% incidence of dizziness during the research comprised 70 individuals in the group receiving cabergoline.

One patient (6%) in evening primerose oil group reported side effect represented in minor tolerable GIT upset and this correlate with data in study conducted by Nigam et al. [11] which showed insiginicant side effect of the study included 45 patients and reported safe profile of this drug, Sarayloo et al [15] stated that no side effects of evening prime rose oil, where Parveen et al [12] reported 8% of side effects occurrence.

In the tamoxifen group 9 patients (52.9%) had no side effect at all while 5 patients (29.41%) had hot flashes and 3 (17.6%) Over the course of three months, patients had sporadic vaginal discharge that is not precisely correlated with the findings by Mukherjee et al.[16] Approximately 58.28% of reversible side effects, primarily heat flashes, are reported.

Danazol group had 2 patients (11.8%) had delayed menses and 1 patient (5.9%) had scanty menses and 1 patient (5.9%) had urticaria and 1 (5.9%) had vaginal discharge and 11 patients out of 17 (64.7%) had no significant side effect at all, in study conducted by Parveen et al [12] they reported 32 % occurrence of side effects among patients in danazol group which near match our result.

Again the difference between the four drugs regarding to the occurrence of the side effect was significant with tamoxifen has higher incidence of side effect followed by danazol, cabergoline and lastly the evening primerose oil, which has the less incidence.

CONCLUSIONS

As a first line of treatment, evening prime rose oil can effectively lessen the severity of mastalgia while having mild, manageable side effects. Although it is the most effective agent, danazol

has unfavorable side effects. In addition to the other therapies having tolerable, transient side effects, tamoxifen is the second most effective. With noteworthy side effects, cabergoline dramatically reduces breast discomfort, particularly cyclic mastalgia.

Recommendations:

Further studies should be carried out with larger groups of patients and with period extended more than 6 months to one year as we need to assess the recurrence of breast pain after 3 months. Hopefully, the results obtained by our study will pave the way for additional research and a treatment strategy for this widespread issue that many women experience.

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