

Comparison the effect of Different agents on Mastalgia in Fibrocystic Disease Patients

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ABSTRACT

Background : Breast pain, also called mastalgia, is a very common condition, especially among women aged 30 to 50. It affects roughly 70% of women at some point in their life. For mastalgia, acetaminophen or a nonsteroidal anti-inflammatory drug is usually effective. If pain is severe, a brief course of danazol or tamoxifen may be given.

Aim of the study: The aim of this study was to Compare of Different agents for Mastalgia in Fibrocystic Disease Patients.

Patients and 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 mars -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. **Conclusion :** 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

Fibrocystic breast changes are one of the most common benign lesions, which cause suffering to women. The cyclic breast pain mastalgia is the most common symptom of fibrocystic breast changes [1].

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 as controversial as it 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].

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 [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 of Different agents for Mastalgia in Fibrocystic Disease Patients.

PATIENTS AND 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.

Written informed consent was obtained from all patients and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University (International review board ZU-IRB #5107/11-5-2019). The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion Criteria: All patients encountered in breast outpatients clinics complaining of mastalgia with fibrocystic disease above age of 18 years old.

Exclusion Criteria: Pregnant or lactating patients. Patients were planning to conceive in near future. Patients who have history of breast cancer or family history of breast cancer. Patients who have dermatological or musculoskeletal disorder causing breast pain. Any previous breast surgery. Patients refusal to share in the study.

All patients were subjected to :

Demographic data and personal history including name, age, residence, occupation, marital status, special habits of medical importance, menstrual and obstetric history has been taking.

Careful history has been taking regarding to the mastalgia including onset, course and duration.

Clinical examination including general and complete breast examinations(CBE) .

Ultrasound breast has been requested to all cases at first visit and three months post treatment.

Precipitated patients were divided into four groups: First group: received evening primrose oil capsule 1000 mg once daily for period of three months. Second group: received danazol tablet 200mg once daily for period of three months. Third group: received Cabergoline tablet 0.5mg once weekly for period of three months. Fourth group: received tamoxifen 10mg once daily for period of three months.

Follow up:

Patients are followed up as outpatients monthly for 3 months. Patients seen monthly and their pain assessed by careful history to the pain and its intensity measured by pain analogue scale in each visit, any side effect of the drug developed has been sought and recorded ,Patients are also seen at the outpatient clinic instantly if they developed any new or concerning symptoms or side effects between their follow-up visits.

Parameters of evaluation:

Patient improvement and relief according to visual analogue scale ranging between 0 to 10 (0 experiencing no pain and 10 experiencing the worst unbearable pain).

Clinical improvement assessed by breast examination which requested at first visit then after three months to assess nodularity.

Reported drugs side effects which revised monthly till the end of period of trial.

Statistical analysis:

SPSS version 20 was used for statistical analysis, a description was given of the demographic variables in the overall sample, with measures of central tendency (mean) and standard deviation for the quantitative variables, and percentages for the categorical variables. A search was subsequently made for differences in variable distribution between the two study groups. A Student's t test was used for the quantitative variables, and a Chi-square test was used for the categorical variables. Measurement of the incidence of the outcome variables was then continued, after which the relative risk of prediabetes as a function of the outcome variables and the

corresponding confidence interval were estimated. Level of significance was considered for $P < 0.05$ and high significance $P < 0.001$.

RESULT

Table (1): Comparison between the studied groups regarding demographic data:

Demographic data	Groups				Test	
	Cabergoline group	Evening primrose oil group	Tamoxifen group	Danazol group	F/χ^2	P
	N=17 (%)	N=17 (%)	N=17 (%)	N=17 (%)		
Age: Mean \pm SD Range	35.12 \pm 10.66 24 – 54	32.29 \pm 6.62 20 – 40	40.35 \pm 5.51 34 – 48	39.47 \pm 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 (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 primrose groups. patients received tamoxifen and danazol were the oldest. There is statistically non-significant difference between the studied groups regarding marital status.

Table (2) Comparison between the studied groups regarding change in ultrasonographic findings:

Change in ultrasonographic features in fibroadenosis	Groups				Test	
	Cabergoline group	Evening primrose oil group	Tamoxifen group	Danazol group	χ^2	P
	N=14 (%)	N=13 (%)	N=17 (%)	N=17 (%)		
Third month: No change Partial resolution Complete resolution	6 (42.9) 6 (42.9) 2 (14.3)	1 (7.7) 8 (61.5) 4 (30.8)	0 (0) 9 (52.9) 8 (47.1)	0 (0) 7 (41.2) 10 (58.8)	21.24	<0.001**

** $p \leq 0.001$ is statistically highly significant

Table (2), showed that there was statistically significant difference between the studied groups regarding change in fibroadenosis among the studied patients. The difference is significant between Cabergoline group and both danazol and tamoxifen groups.

Table (3): Comparison between the studied groups regarding percent change in VAS score at the third months:

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

Table (5), 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 (4): Comparison between the studied groups regarding occurrence of adverse effects:

Adverse effects	Groups				Test	
	Cabergoline group	Evening primrose 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)	20.09	<0.001**
Yes	4 (23.5)	1 (5.9)	8 (47.5)	6 (35.3)		

*p<0.05 is statistically significant

Table (6), 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.

DISCUSSION

In 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 aim of evaluating effectiveness, compliance, and adverse effects of evening primrose 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 is match the study conducted by **Aydin et al [5]** thesis where the mean age of the patients in their study was 38 years.

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

There was no statistically significant difference between the studied groups regarding the base line ultrasonography findings at time of presentation. That was in concordance with findings and data available by **Jain et al., [7]** study regarding baseline ultrasonography findings.

However 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 near match 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.

While the patients treated with evening primrose oil showed complete resolution in 30% of total group and 61% showed different degree of response and 1 patient showed no change at all, The finding that near match what **Khadka et al., [9]** has been stated in his their study.

Patients treated with tamoxifen showed complete resolution in 47% of total group and 52% patients responded 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 radiologically comparing to the first ultrasound, in study conducted by **kumar et al., [10]** who showed that 85% of resolution can be achieved in breast nodularity which near match the result of current study.

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., 2018 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 [11]** 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 month, showed 70.75% decrease in their VAS at the third months, in disagreement with prospective randomized control trial conducted by **Gupta et al., [12]** 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.

In the meanwhile patients in danazol group had achieved the most significant percentage of the decrease on cyclic pain according to the VAS which reached to 75% at the end of follow up period and that seem to be similar to results obtained by prospective randomized study conducted by **Kumar and hasan [13]** which included 64 patients and showed 71%. improvement in patients treated by danazol 200mg over 12 weeks with side effect reached 30%, in another study conducted by **Gupta et al [12]** in which the decrease in VAS achieved was 71% supported by another study conducted by cornell et al.,2016 reported 77% reduction of pain in VAS which all support the results of our current study.

Moreover, there was different side effects noticed in the four groups of our thesis reported by the patients.

Regarding the cabergoline group, dizziness was noticed an associated side effects in 3 out of 17 patients (17.6%) And 1(5.9) patient had headache and this in agreement of **Aydin et al., [5]** who mentioned (16.4 %)occurrence of dizziness in study included 70 patients in cabergoline group.

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. [14]** which showed insignificant 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 [11]** 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%) patients had vaginal discharge intermittently over three months that does not exactly correlate with the results obtained by **Mukherjee et al. [16]** where they report 58.28% occurrence of reversible side effects mainly hot flash.

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 [11]** they reported 32 % occurrence of side effects among patients in danazol group which near match our result .

Conclusion : 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.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Conflicting Interest (If present, give more details): No Conflict of Interest

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Not applicable

Declarations

-Ethics approval and consent to participate

Written informed consent was obtained from all patients and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University (International review board ZU-IRB #5107/11-5-2019). The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

-Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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