Non-hormonal treatment for mastalgia-a topical non-steroidal anti-inflammatory agent versus Evening Primrose Oil: prospective comparative analysis

Mohammed Kamil Mohammed

CABS*

Abstract:

Aim of the study: to compare a topical non-steroidal anti-inflammatory drug (NSAID) and Evening Primrose Oil (EPO) regarding effectiveness, rapidity of response, safety, and patient compliance in the primary treatment of mastalgia.

Setting: Author's Private clinic**

Design: A prospective interventional non-blinded comparative clinical trial between the two drugs carried out over a period of 4 years.

Patients & Methods: seventy female patients with moderate to severe mastalgia were prospectively selected and given one of the two agents alternatively. Data pertaining to each patient were collected and analyzed at one month, two months and three months period.

Results: after three months of treatment, out of 35 patients treated with topical NSAI gel, 96.5% had clinically significant response compared with 45.7% of 35 patients treated with EPO. Two patients (5.7%) had side effects with EPO treatment while none had any side effects with NSAI gel treatment. Response to NSAI gel reported earlier than response to EPO. 82.8% of patients found the cost of NSAI gel treatment acceptable versus 85.7% for EPO.

Conclusions: Topical NSAIDs are effective, safe and acceptable mode of treatment for mastalgia.

Keywords: Mastalgia. Evening Primrose Oil (EPO). Topical NSAIDs.

Introduction :

About two-thirds of women may complain of mastalgia at some time during their active reproductive period [1,2]. Although only 7-8% of patients with operable breast cancer have mastalgia as the sole primary presenting symptoms, still, the vast majority of women complaining of mastalgia consult mostly for the fear of having an underlying breast cancer [2,3]. Minor premenstrual breast pain, with or without nodularity, is a common complaint which usually resolve with menstruation and can be considered as a normal physiological response to cyclical hormonal changes [4]. Moderate to severe breast pain and nodularity, which persist for most, if not all of the cycle, and interferes with patient's daily activities, is considered to be clinically relevant [4].

Cases of mastalgia are primarily evaluated by proper history and physical examination. Imaging modalities may be needed to exclude cancer. Subsequently; 85% of patients will require no further treatment while the rest 15% who have significant pain affecting the quality of their life will need further management [5].

The primary treatment usually includes psychological support, weight reduction, the use of well-fitting Bra, a decrease of dietary fat intake and discontinuation of oral contraceptives and any other hormone replacement therapy [5,6]. More specific treatment may be offered to patients who do not respond to these preliminary measures.

A range of hormonal and non-hormonal agents are usually prescribed to relieve symptoms, but many are ineffective and may have side effects that urge stopping the treatment, in addition, only a small number of these agents have been adequately assessed in randomized controlled trials and proved to be more effective than placebo [7].

Response to therapy and prognosis of symptoms might be unpredictable and it may follow a protracted course requiring long-term treatment, thus, prescribing a drug require taking in to account the efficacy, cost and side effects of that agent [8].

The present study evaluates a topical NSAID versus EPO in the primary non-hormonal treatment of mastalgia.

Patients & Methods:

Over a period of 4 years (Sep. 2005 till Sep. 2009), cases of moderate to severe mastalgia (Breast pain that significantly affect patient's social activities and sleep) attending the author's private clinic, were evaluated by history, physical examination and imaging modalities (Ultra-sound and Mammography) whenever indicated. Patients with discrete lump(s), nipple discharge and lactation with clinical evidence of mastitis, were excluded. Accordingly; seventy patients were selected and every patient was provided with a "Breast Pain Chart" (**Figure 1),** fully informed how to fill daily, and asked to submit for evaluation of the response at one month, two months and three months of the commencement of therapy.

The response to treatment was evaluated using Cardiff Breast pain Score (CBS) (**Table 1).**

Selected patients were allocated in to two groups alternatively; the first group was given topical Diclofenac Sodium (Olfen ^{TM}) 50 gm gel (10 mg/ 1 gm gel) and announced as "Topical NSAI gel" group. The patients were informed to apply the gel locally to the site of pain twice daily for three months. The second group was given EPO 500mg capsule, two capsules three times daily for three months and announced as "EPO group". EPO is an extract from primrose plant (5000 seeds= 500 gm of drug).

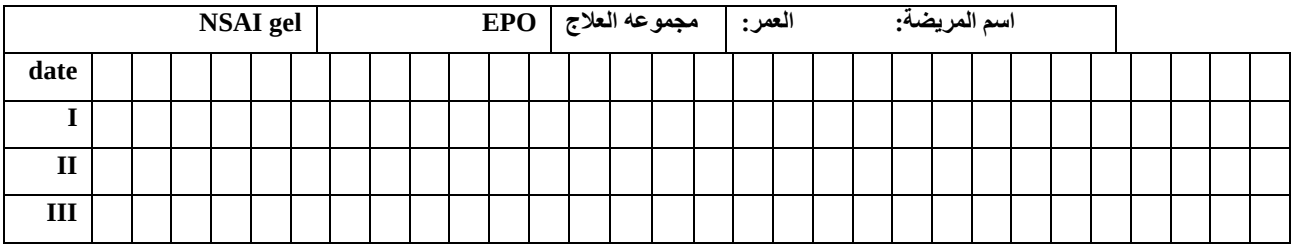
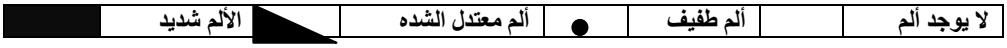


Figure 1: The "Breast Pain" Chart distributed to the patients



Adapted and modified from: Mansel RE; Fenn NJ; Davis EL. Benign breast disease and its management. In: Johnson CD; Taylor I. editors. Recent advances in surgery 21. Edinburgh: Churchill Livingstone; 1998, P. 75.

Table (1): Cardiff Breast pain Score (CBS)

CBS 1	An excellent response with no residual pain
CBS 2	A substantial response but with some residual pain, considered by the patient to be bearable
CBS 3	A poor response with substantial residual pain
CBS 4	No beneficial response at all

Adapted from: Mansel RE; Fenn NJ; Davis EL. Benign breast disease and its management. In: Johnson CD; Taylor I. editors. Recent advances in surgery 21. Edinburgh: Churchill Livingstone; 1998, P. 76.

Every patient in both groups was given the oral analgesic Paracetamol (Panadol ^{gsk}) 500 mg tablet, two tablets three times daily for one week only, to cover the early period where some delay in the action of the two drugs used is expected, and advised no oral analgesic thereafter but to report if the pain become intolerable.

At each follow-up visit, the patients are asked about any side effects, willingness to continue treatment and the compliance. No matter what the response, no drug was changed before three months of therapy. In any of the two groups, Patients who reported CBS 3 and CBS 4 response after 3 months of treatment were given supplementary oral Diclofenac Sodium 50 mg tablet twice daily after meals for an additional one month and the outcome of this additional therapy was not included in the evaluation of the results of this study.

After collecting data, results were compared and data analyzed by chi-square test.

Results:

Included in this study, 70 female patients aged 17-48 years (mean of 31 years). Out of 35 patients who used EPO, none showed a CBS 1 response at one month (**Table 2);** only one (2.9%) patient demonstrated a CBS 2 response and 12(34.3%) patients recorded a CBS 3 response at the end of one month period.

At the end of 3 months treatment, 7(20%) patients reported an excellent response with no residual pain (CBS 1) for EPO, while 7(20%) patients showed no beneficial response at all (CBS 4) for EPO (**Table 2).**

Two (5.7%) patients complained of nausea and altered taste during treatment with EPO.

Among the 35 patients in the "Topical NSAI gel" group, 2(5.7%) patients had a CBS 1 response at the end of first month treatment while 6(17.2%) patients reported a CBS 2 response at the end of the same period (Table 2). At the end of three months course of Topical NSAI gel treatment, 30(85.8%) patients and 2(5.7%) patients reported a CBS 1 and CBS 2 response respectively. No patient reported any side effect with Topical NSAI gel treatment.

5(14.3%) patients found EPO course costly versus 6(17.2%) in the Topical NSAI gel group.

Overall effectiveness (CBS 1+CBS 2 response at end of three months), rapidity of response (CBS 1+CBS 2 response at end of one month), side effects and acceptability of the cost, were compared for both groups and statistically evaluated using chi-square test. Results are shown in **table 3.**

Table 2: Evaluation of response to treatment (both groups compared)

	NSAI gel group N=35		**EPO group N=35**	
At the end of 1 month	**N=x**	**%**	**N=x**	**%**
CBS 1	2	5.7	0	0
CBS 2	6	17.2	1	2.9
CBS 3	19	54.2	12	34.3
CBS 4	8	22.9	22	63.8
χ^2 =13.69, d.f.3, P- value= 0.00336				
At the end of 2 months				
CBS 1	16	45.7	7	20
CBS 2	12	34.3	9	25.7
CBS 3	5	14.3	11	31.5
CBS 4	2	5.7	8	22.8
χ^2 =9.8, d.f.3, P- value= 0.0203				
At the end of 3 months				
CBS 1	30	85.8	7	20
CBS 2	2	5.7	9	25.7
CBS 3	1	2.8	12	34.3
CBS 4	2	5.7	7	20
χ^2 =30.4, d.f.3, P- value= 0.000001				

P- Value less than or equal to 0.05 is significant

Table 3: Comparison of the two drugs according to effectiveness, rapidity of response, side effects & acceptability of the cost

	NSAI gel		**EPO**			**Test used**
	N=x	**%**	**N=x**	**%**	**P-Value**	**χ2**
Overall effectiveness (CBS 1 + CBS 2 at 3 months)	32	96.5	16	45.7	0.00029	13.09 Yate corrected
Rapidity of response (CBS 1 + CBS 2 at one month)	8	22.9	1	2.9	0.032	χ^2 =4.59
Side effects	0	0	2	5.7		
Acceptability of cost	29	82.8	30	85.7	>0.05	χ^2 =1.0

Cost of 3 month treatment is 65 U.S $ for NSAI gel versus 47 U.S $ for EPO
P-Value equal or less than 0.05 is significant

Discussion:

Regarding overall effectiveness of the two drugs, NSAI gel was found more effective compared to EPO (P-Value= 0.00029), so for the rapidity of response (P-Value=0.032). Cost wise, there was no statistically significant difference between the two groups (P-Value more than 0.05).

Although mastalgia with or without nodularity can be a distressing symptom, many patients responds to reassurance after exclusion of an underlying carcinoma. However, severe persistent symptoms require further management especially when it had significantly affected the quality of the life of the patient [8].

Currently; multiple options are available for the treatment of moderate to severe mastalgia including hormonal and non-hormonal agents, and since most of the patients have no desire to take hormonal therapy, consultation with the patient is preferable before any treatment is initiated [8,9].

The present study conducted a clinical trial to evaluate a non-hormonal first-line treatment for moderate to severe mastalgia among a cohort of Iraqi female patients regarding effectiveness and patient compliance. The two agents used are EPO and a topical NSAID. EPO is a natural product. rather than a drug, very familiar in UK as a first line treatment for mastalgia [10]. It is rich in poly-saturated Omega-6 essential fatty acids and believed to restore the abnormal fatty acid profile in the breast [10]. Reviewing the literature; doses of EPO have varied from 2 to 3 gms daily for 2-6 months but the optimal dose and exact duration of treatment is a point of controversy [10,11] The total requirements of the drug are directly related to the body surface area and it also differs according to dietary habits of the patient [11].

The other drug used was a topical application of NSAIDs; a Diclofenac Sodium gel twice daily on the painful parts of the breast for 3 months. The early 80s of the past century witnessed the introduction of topical agents to treat mastalgia and in spite of controversies; it had been suggested to be feasible, effective and ideal form of treatment [12]. It had been established as having a local effect through trans-cutaneous absorption and can rapidly relieve soft tissue and muscular pain [13].

Evaluation of the overall effectiveness of the two agents revealed that topical NSAI gel was more effective (P-Value= 0.00029) with a quicker patient response than in case of EPO (P-Value=0.032). In the present analysis, the overall response rate for EPO was 45.7% which is in consistence with various studies [11,14,15]. The overall response rate for topical NSAI gel in this study was a little higher than the rate reported in other studies [16,17].

Nowadays; the old controversy that had surrounded the introduction of trans-dermal NSAIDs is not any more supported. The success of trans-dermal absorption lies in the enhanced topical delivery and local accumulation in target tissue by direct diffusion and the concentration of the drug in the subcutaneous tissue and muscles is substantially higher than in plasma after dermal application [18].local hypersensitivity reactions to topical NSAIDs, although reported, are rare [19]. Generally; these agents are contraindicated in subjects with known hypersensitivity to NSAIDs, it should be avoided on non-intact skin or unhealthy skin and in patients with compromised renal function [20].

No patient in this study had any side effects after topical Diclofenac Sodium gel application. Two patients in the EPO group complained of nausea and altered taste not severe enough to stop the treatment. In the literature, the reported side effects of EPO included bloating, nausea, weight gain, headache, depression, giddiness, rash and bad taste. The reported rate was in the range of 6-20% and it was dose related (10).

Conclusions:

Topical NSAI Diclofenac Sodium gel is safe, relatively quick in action with reliable patient compliance and compares favourably with an established recommended first-line treatment for mastalgia; namely EPO.

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Department of surgery/Al Mustansiriya College of Medicine/ Baghdad/Iraq