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The comparison of the therapeutic effects of piroxicam gel and oral vitamin E in cyclic mastalgia

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Abstract

Cyclic mastalgia is a common condition among women. There are different methods in reducing pain in such patients, but there is yet no consensus in this regard. This study aims to compare the therapeutic effects of topical piroxicam gel and oral vitamin E in patients with cyclic mastalgia. Seventy females with mild to moderate cyclic mastalgia were recruited from an outpatient clinic in this randomized, double-blind, placebo-controlled clinical trial. The patients received either topical 0.5% Piroxicam gel four times daily or vitamin E 400IU capsules once daily for two consecutive months. The visual analogue scale (VAS) was used to report pain one and two months later. Thirty-five patients completed the study in each group. Although both medications were effective and safe in reducing pain severity, topical piroxicam led to a significantly better pain control outcome. Almost half the patients required analgesics five months after the study stopped. In conclusion, comparing topical piroxicam gel and oral vitamin E in patients with cyclic mastalgia showed that the former is more efficient in pain control in mid-term. Both medications were safe and well-tolerated.

Keywords: mastalgia; NSAIDs, vitamin E, Visual Analogue Scale

1. Introduction

Mastalgia or breast pain is a very common annoying experience. Some estimates indicate that almost 65% of women experience varying degrees of mastalgia during their reproductive age (1).

It could be cyclic, noncyclic, or extramammary (2). The cyclic form is the most frequent subtype, comprising about two-thirds of the cases who seek medical comfort. (3, 4) Although the main ethology of cyclic mastalgia is yet to be defined, its relation to the menstrual cycle, pregnancy, lactation, and menopause suggests underlying hormonal causes or aggravators (5, 6).

Cyclic pain resolves spontaneously in 20-30% of patients. However, in 60% of patients, recurring episodes might be seen (7). It has been reported that in up to 40% of patients with cyclic mastalgia the pain interferes with the normal life. Sexual and physical activities, work, and social interactions could all be negatively impacted in patients with cyclic mastalgia (8).

Reassurance alone or following nonpharmacological methods such as stress-management, relaxation techniques and wearing well-fitted and supportive brassieres have been found effective in relieving pain in many patients with cyclic mastalgia (9). In some cases, however, the pain is still bothersome and resistant to conservative managements. Pharmacologic therapy with Danazol, Bromocriptine, and oral contraceptives is considered the standard method of treatment. Side-effects and complications, however, are sometimes associated with using these medications and limit their liberal use (9). Employment of alternative treatments such as using oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs) and vitamin E has been advocated by some physicians but the clinical trials in support or against their use in cyclic mastalgia are still insufficient (10, 11).

The objective of the present double-blind clinical trial is to examine and compare the efficacy of topical piroxicam gel and oral vitamin E in reducing pain in women with mild-to-moderate cyclic mastalgia.

2. Materials and Methods

2.1. Study design and population

A total of 70 women with mild to moderate cyclic mastalgia, who came to our clinic during a 14 -month period of time (starting February 2021) was enrolled in this prospective, double-blind, randomized clinical trial.

This clinical trial study is registered by the Australian New Zealand Clinical Trial Registry (ANZCTR) under this registration number: ACTRN12622000103763.

This study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000 (available at

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http://www.wma.net/e/policy/17-c_e.html). Written informed consent was obtained from the participants. This study was approved by the ethics committee of Zabol University, date March 2020, no KH\432-12.

Patients were premenopausal females aged 18-45 years at the time of enrolment with a pain score of ≥3 on the visual analogue scale (VAS), measured in their first visit. They had no history of treatment for their pain during the last three months before the study. Pregnant women, those with concomitant or previous other medical condition (s) including a positive history of cancer, women with irregular menses, patients with abnormal findings in breast physical examination or imaging studies suggesting a possible underlying cause of breast pain rather than cyclic mastalgia were not included. Participants were tested nonallergic to the used medications before recruitment.

2.2. Study protocol

The patients were alternatively assigned to two groups. A colleague pharmacologist who was not involved in conducting the study prepared and provided medications as follows: The first group received topical Piroxicam gel (0.5% gel, RAZAK pharmaceutical Co., Tehran, Iran) four times daily plus placebo capsules (identical to vitamin E capsules in appearance, filled with distilled water) once daily both for two consecutive months (group PG). The second group received vitamin E capsules (E-Zavit, 400IU, Zahravi, Tabriz, Iran) once daily plus topical placebo gel (identical to Piroxicam gel tubes in appearance, filled with paraffin) four times daily both for two consecutive months (group VitE).

The study started from the beginning of a new menstrual cycle in each patient after she received adequate information regarding proper medication use, accurate documentation and reporting of breast pain severity, wearing well-fitted and comfortable brassieres, and avoiding stressful events and other pharmacological or non-pharmacological pain-reduction methods during the study period.

The VAS, a continuous scale ranging from 0 (no pain) to 10 (worst pain ever), was used to report the pain severity.

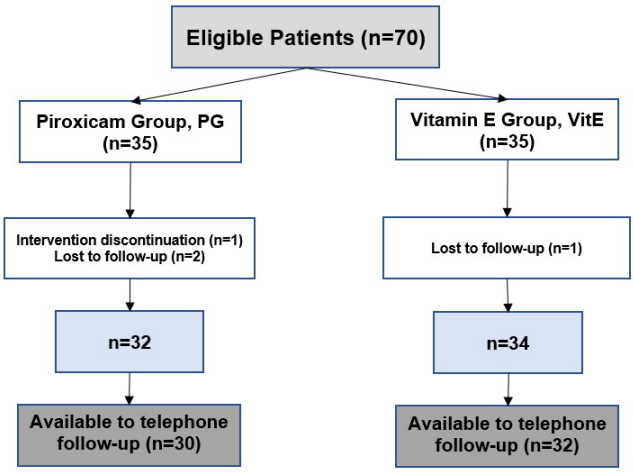

Fig. 1 Flowchart of the study groups

In-person follow-up visits were performed at the end of the first and second months after the interventions initiated. A telephone follow-up was performed five months after the interventions stopped (Fig. 1).

For blinding purposes, neither the patients nor the main investigators were aware of the grouping until after data analysis.

2.3. Statistics

The SPSS software version 25.0 (IBM Corporation, New York, USA) was used for statistical analysis. The normal distribution of numeric data was confirmed using the Kolmogorov-Smirnov analysis. The Contingency tables (Chi-square), independent samples t-test, and repeated measures analysis were used. A $P \leq 0.05$ was considered statistically significant.

3. Results

Patients' demographics and general information are summarized and compared between the two study groups in Table 1.

Table 1. Demographics and general information of the study groups

Variable	Piroxicam Group	Vitamin E group	P
Age (y)	31.7 (±8.4)	29.6 (±6.8)	0.28
Menarche (y)	12.8 (±1.8)	13.6 (±1.6)	0.08
Marital Status (Single)	12 (37.5%)	11 (32.4%)	0.66
Occupation (Housewife)	10 (31.3%)	11 (32.4%)	0.92
Regular Exercise	8 (25%)	9 (26.5%)	0.89

The PG and VitE groups were comparable in terms of age, age of menarche, marital status, occupation, and the history of regular exercise.

The mean duration of mastalgia was 4.6±2.0 years in the PD group and 5.1±1.5 years in the VitE group (P=0.23).

The mean pain severity at baseline did not differ significantly between the two groups (5.0±0.8 in PD group and 4.7±0.7 in VitE group; P=0.7). The pain severity decreased significantly in both groups at the end of the first and second months of intervention (P<0.001) (Fig. 2).

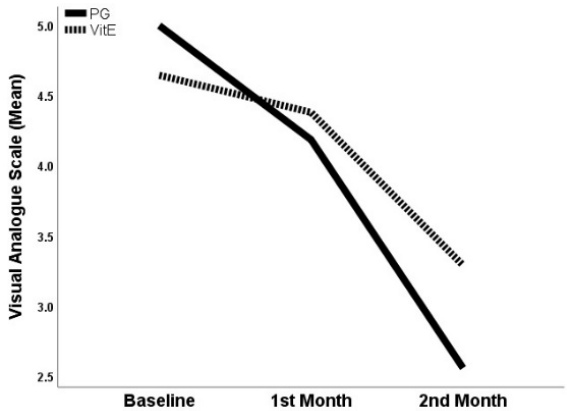

Fig. 2. Mean pain severity at baseline and one month and two months after starting interventions in two study groups

Percent decrease in pain severity was marginally more in the PG group than in the VitE group after one month, post-intervention (P=0.05). However, a difference was significant after two months, post-intervention (p<0.01) (Fig. 3).

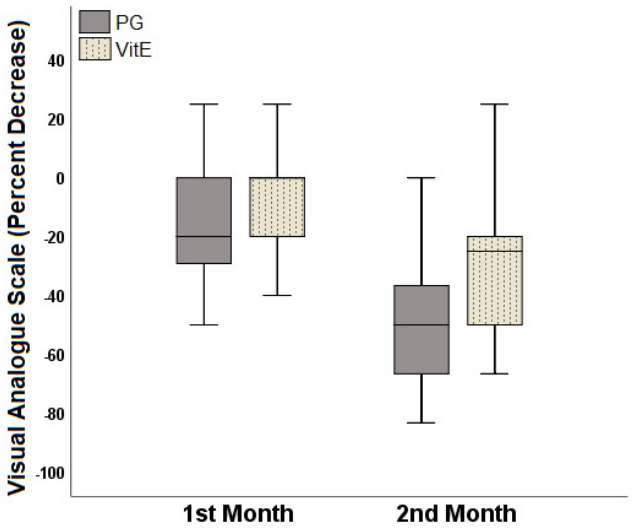

Fig. 3. Mean pain percent decrease one month and two months after starting interventions in two study groups

No significant complications or side-effects were reported by the patients in either group during or at the end of the study period.

Five months after the end of study 16 out of 30 reachable patients in the PG group (53.3%) had recurred mastalgia requiring treatment. This rate was 37.5% (12 out of 32 reachable patients). The difference, however, did not reach a statistically significant level (P=0.21).

4. Discussion

In this study, we showed that topical piroxicam gel was significantly superior to oral vitamin E in reducing cyclic breast pain after two months. The patients did not report any significant side-effects in either group.

There are a limited number of studies in the literature that have investigated the effect of topical non-steroidal anti-inflammatory drugs (NSAIDs) in treating mastalgia. In one of the first studies, the authors were successful in reducing pain in 11 out of 13 patients with cyclic breast pain (12) by using topical NSAIDs. Like in our study, the authors found the intervention safe and rapidly effective.

Colak et al. (13) administered topical NSAIDs or placebo three times daily for at least 6 months in 60 patients with cyclic mastalgia. They also found topical NSAIDs effective and safe in treating their patients.

In another study, Qureshi et al. (14) compared the oil of evening primrose and topical NSAIDs in the treatment of mastalgia in an open, non-randomized study. Fifty female patients with moderate to severe pain were recruited. A clinically significant response to topical NSAIDs was found in 92% of patients, with no significant side effects or complications.

In a study by Ahmadinejad et al (11), the authors compared the analgesic efficacy of piroxicam and diclofenac topical gels in patients with breast pain. Both topical medications were found successful in reducing pain after two months of application. However, the piroxicam gel was significantly along with better results. Only one patient was found to have side effects in the diclofenac group.

Regarding the use of vitamin E in mastalgia, however, the results of studies are more conflicting compared to the results of using NSAIDs. In some older studies, for example, the authors did not report clinically significant findings in this regard (15-17).

In contrast and in conformity with our findings, Pruthi et al (18) found that daily doses of 1200 IU vitamin E could effectively decrease the severity of cyclical mastalgia. Likewise, Shobeiri et al (19) showed that vitamin E supplementation, compared to the placebo, yielded significantly better results in pain control in patients with cyclic mastalgia.

The beneficial effect of vitamin E in the management of breast pain has been attributed to its antioxidant property. (9) To the best of the authors' knowledge, this is the first double-blind, randomized clinical trial that compares the pain-reduction efficacy of a topical NSAID and oral vitamin E in patients with mild-to-moderate mastalgia.

In a recent metanalysis, Groen et al (10) concluded that topical NSAIDs can reduce pain by almost 60% in patients with cyclic mastalgia. This is similar to the amount of pain reduction we saw by using topical piroxicam gel after two months of application (Fig. 3).

The rate of spontaneous remission up to 3 years has been found high in patients with cyclic mastalgia (20). However, about 60% of patients with cyclic mastalgia show a relapsing and remitting pattern of pain episodes, and in some patients, the pain recurs 2 years after therapy (7). In the present study, the rate of subjective remission, which needed pain killers was 53% in patients who received topical piroxicam and 38% in patients who were treated by oral vitamin E after 5 months of treatment discontinuation. Therefore, it seems that although both topical piroxicam and oral vitamin E are effective in ameliorating pain in cyclic mastalgia, they are required to be used regularly until the physician makes sure that the pain would not recur after the treatment stopped.

Further studies with larger sample size and comparing results with other convention al methods of treatment are suggested for future studies.

In conclusion, both topical piroxicam gel and oral vitamin E are safe and effective treatments in reducing pain in patients with mild-to-moderate cyclic mastalgia. The topical piroxicam is along with better results than the oral vitamin E, but discontinuation of the treatment may lead to pain recurrence severe enough to require analgesics in almost half

of the patients.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: R.B., T.E.B., Design: R.B., T.E.B., Data Collection or Processing: R.B., T.E.B., Analysis or Interpretation: R.B., T.E.B., Literature Search R.B., T.E.B., Writing: R.B., T.E.B.

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