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MASTALGIA;
COMPARISON OF TOPICAL NON STEROIDAL ANTI INFLAMMATORY DRUGS WITH EVENING PRIMROSE OIL

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ABSTRACT... Mastalgia is a common clinical symptom experienced by up to 70% of women at some stage of their life. A wide variety of therapeutic agents are available for the treatment of mastalgia. Both evening primrose oil and non steroidal anti-inflammatory drugs have been assessed in randomised controlled trials and demonstrated to be effective. The objective of this Quasi experimental study was to compare the efficacy and safety of topical nonsteroidal anti-inflammatory drugs with evening primrose oil in the treatment of mastalgia. We studied 90 female patients presenting with breast pain from 25 July 2006 to 25 July 2007 at the surgical outpatient department of CMH Kharian. The patients were divided into three groups. Group-1 was given capsule Effamol (evening primrose oil), group-2 topical brufen gel and group-3 topical Vaseline for two months. Patients were followed every two weeks for two months. Response was assessed using Cardiff breast pain score. Side effects of drugs were recorded at each follow up. Out of 30 patients of group-1, 14 (46.6%) had clinically significant response at the end of 8 weeks treatment as compared to 27 (90%) in group-2. 5 (16.6%) patients of group-1 showed mild side effects while none in group-2 had any side effect. p- value was < 0.0001 showing highly significant statistical difference between 2 groups. Topical nonsteroidal anti-inflammatory drugs are safe and effective as compared to evening primrose oil in the treatment of mastalgia.

Key words: Premenstrual syndrome, evening primrose oil, non- steroidal anti-inflammatory agents.

INTRODUCTION

The most frequent breast problem encountered in general practice is Mastalgia[1]. 47% of females visiting surgical outpatient departments for breast related problems have mastalgia as the underlying cause[2]. In a study of 1171 women attending a gynecology clinic in United States, 69% experienced regular premenstrual breast discomfort[3]. Most women with breast pain take medical consultation because of fear that they might be harbouring cancer[4,5,6]. In fact risk of cancer in women with Mastalgia as their only presenting symptom is only 7%[7].

Most women develop minor premenstrual breast pain associated with nodularity which resolves with menstruation. This is considered to be normal. But development of severe pain and nodularity that usually persists for most if not all of the cycle and interferes with

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the patient's sleep, routine activities and sexual relationship is considered to be abnormal[2,7].

Mastalgia may be cyclical, non cyclical or due to extra-mammary causes[8].Majority (85%) of patients with Mastalgia can be managed with exclusion of cancer, reassurance and some lifestyle modifications alone. However in 15% of patient pain may be so severe that it interferes with their routine activities. This group of patients become clinically significant and requires definite treatment[4,7]. It is associated with over utilization of mammography among young women, although it is a well documented symptom in premenstrual syndrome (PMS). Severe breast pain is not simply premenstrual syndrome and requires further investigation. In cyclical mastalgia pain may resolve spontaneously after menopause. In non cyclical mastalgia resolution may be spontaneous. Severe mastalgia at times run a chronic relapsing course often requiring repeated drug treatment.

Different modalities used for treatment of breast pain include physical measures like wearing of well fitted bra, a decrease in dietary fat intake, discontinuance of oral contraceptives or hormone replacement therapy, nutritional supplements, evening primrose oil, NSAIDs oral as well as topical and variety of hormonal agents like danazol, tamoxifen or bromocriptine etc. It is difficult to predict which treatment is most suitable for a particular woman as it bears no relation with reproductive history, personal or family history of any breast disease[2].

EPO has been widely used in West as first line therapeutic option[9-12] with danazol and bromocriptine as a second line therapy. In various studies danazol was found to be most effective drug with 70% efficacy[13] while bromocriptine and Evening Primrose Oil (EPO) having equal efficacy 45-47%[14].In another study tamoxifen was found to be most effective and least toxic hormonal agent for treatment of chronic refractory mastalgia[15]. Although hormonal agents are more effective in treating both cyclical and non cyclical mastalgia, they are associated with serious side effects making them unacceptable to most women[2].

Surprisingly, there has been little study done for the role of oral as well as topical non steroidal anti-inflammatory drugs (NSAID's) for treatment of breast pain[2]. A randomized study of topical NSAID's showed significant reduction (81%) in breast pain with no side effects[16].On the other hand another study demonstrated that topical NSAID's had no beneficial effect in managing Mastalgia[4]. Therefore the overall picture remains blurred.

Because of the long term side effects of hormonal therapy, the idea was conceived to compare efficacy and safety of topical NSAID's with a non hormonal agent like EPO. This study was conducted at CMH Kharian to compare efficacy and side effects of topical NSAID (Brufen gel) with a non hormonal agent EPO in the trearment of mastalgia.

MATERIAL AND METHOD

This prospective quasi experimental study was carried out on 90 female patient's presenting with moderate to severe breast pain at the surgical outpatient department of Combined Military Hospital (CMH) Kharian from 25th July 2006 to 25th July 2007. Female patients between 20 and 40 years of age were included in the study. The following patients were excluded from the study:

1. Patients taking phenothiazines, anti convulsants and lithium.
2. Breast carcinoma patients.
3. Breast abscess and mastitis patients.
4. Nipple discharge.
5. Lactating and pregnant patients.
6. Estrogen therapy, digoxin, spironolactone, anticoagulants and alcohol.
7. Breast trauma and after breast surgery.

During the first visit a detailed clinical history and physical examination was done. Sonomammography and FNAC were done only in patients having lumps, to rule out breast carcinoma.

After taking written informed consent, patients were divided into three groups. Convenience sampling method by using a simple random number chart was used to allocate patients to one of the three groups.

Group 1 was given capsule Effamol (evening primrose oil) 500 mg twice daily with meals for two months. Group 2 was given Brufen gel (topical NSAID)for topical application twice a day to the affected area of breast for two months. Group III was given Vaseline (placebo) supplied from hospital for topical application for two months. Patients of all the three groups were given tablet Diclofenac 50 mg twice daily for initial one week to alleviate severity of pain. Patients were instructed not to take any other analgesic during the study.

Data was collected on a pre designed proforma by a doctor. In addition a breast pain chart was provided and explained to each patient to be filled by the patient each day for two months to assess her severity of pain. The response to treatment was assessed by using Cardiff Breast Pain Score (CBS) to classify severity of pain at each follow-up, which is as follows:

CBS1- An excellent response with no residual pain.

CBS2- A substantial response but with some residual pain considered by the patient to be bearable and not effecting sleep and daily routine.

CBS3- A poor response with substantial residual pain and effecting sleep and daily routine.

CBS4- No beneficial response at all.

Follow-up of patients was scheduled at two, four, six and eight weeks. Common side effects of the two drugs were inquired and recorded from each patient on their follow-ups. Treatment was not changed or modified before two months of therapy irrespective of the response.

Patients who were lost to follow-up were not included in the study.

Age was presented by mean ± SD (standard deviation). Side effects were presented by frequencies and proportions. Pain scores were measured and ordinary regression was used to compare the three groups. All data was analyzed with the help of SAS version 9. A p-value of less than 0.05 was taken as significant.

RESULTS

The mean age was 31.46 with Standard Deviation (SD) 5.25. The youngest patient was 20 years old while the oldest was 40 years old. Sixty patients had bilateral mastalgia while thirty had unilateral breast pain.

Characterization of type of pain by evaluating the breast pain charts revealed that 63 patients had cyclical mastalgia while 27 had non cyclical mastalgia. The distribution of type of pain in different groups is shown in table I.

Out of thirty patients of group-1 who were given EPO none had clinically significant response (CBS 1+2) at 4 weeks while 14 (46.6%) had significant response (p value 0.0001) at 8 weeks. In group-2 twenty three (76.6%) and 27 (90%) patients had significant response (p value <0.0001) at 4 and 8 weeks respectively.

Only 5 out of 30 patients of group-1 showed mild side effects while no side effects were seen in group-2 and 3.

Table-I. Distribution of type of pain in patients in different groups

Type of Pain	Group I	Group II	Group III
Cyclical Mastalgia	24 (80%)	17 (56.6%)	22 (73.3%)
Non-Cyclical Mastalgia	6 (20%)	13 (43.4%)	8 (26.7%)

Table-II. Response of patients in different group at 4 & 8 weeks						
Grade (CBS)	Response at 4 wks			Response at 8 wks		
	Group I (n=30)	Group II (n=30)	Group III (n=30)	Group I (n=30)	Group II (n=30)	Group III (n=30)
CBS-1	0 (0%)	8(26.7%)	0 (0%)	3(10%)	15 (50%)	2 (6.6%)
CBS-	0 (0%)	15 (50%)	0 (0%)	16(36.7%)	12 (40%)	2 (6.6%)
CBS-3	16 (53.3%)	5(16.7%)	10(33.3%)	8 (26.7%)	2 (6.6%)	4 (13.3%)
CBS-4	14(46.7)	2(6.6%)	20(66.6%)	8 (26.7%)	1 (3.4%)	22 (73.3%)

The positive value (0.7742) for the parameter estimate for group 1 indicates a tendency towards the lower numbered categories of the grade (i.e. CBS1, CBS2) relative to the group third. It means the first group is better respond than the third group. Similarly (5.1567) indicates the second group is better respond than the third group. The relative magnitudes of these slope estimates imply the preference ordering: second, first, third. The difference in effects of group one with respect to third group is not statistically significant as p-value 0.1381. Although the difference in effects of group two with respect to third group is statistically significant (p-value <0.0001).

The log odds ratios and odds ratios in the table-IV and table-VI indicate the relative differences between the groups. The odds ratio of 2.168 in the "Exp(LogOR13)" row in table-IV indicates that the odds of group 1 being in lower grade categories is 2.8 times the odds of group 3 being in lower grade categories at 4th week. Similarly the odds ratio of 0.1324 in the “Exp(LogOR12)” row in Table-VI indicates that the odds of group2 being in lower grade categories is 7.55 times the odds of group1 being in lower grade categories (i.e. CBS1, CBS2) at 8th week. Results for the comparison of drug groups at 8th week are presented in Table-V and Table-VI.

Table-III. Comparison of efficacy of drub in different groups at 4th week							
Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-square	Pr > ChiSq
Intercept 1	1	-6.1929	0.9234	-8.0028	-4.3830	44.98	< .0001
Intercept 2	1	-4.0424	0.7934	-5.5974	-2.4875	25.96	< .0001
Intercept 3	1	-0.7191	0.3845	-1.4728	0.0345	3.50	0.0615
Group 1	1	0.7742	0.5222	-0.2492	1.7977	2.20	0.1381
Group 2	1	5.1567	0.8964	3.3998	6.9135	33.10	<.0001
Group 3	0	0.0000	0.0000	0.0000	0.0000		
Scale	0	1.0000	0.0000	1.0000	1.0000		

Table-IV. Pair wise comparison of groups at 4th week							
Label	**Estimate**	**Standard Error**	**Alpha**	**Confidence Limits**		**Chi-Square**	**Pr>Chisq**
Log OR 12 Exp(LogOR12)	-4.3824 0.0125	0.8586 0.0107	0.05 0.05	-6.0652 0.0023	-2.6997 0.0672	26.06	<.0001
Log OR 13 Exp(LogOR13)	0.7742 2.1689	0.5222 1.1325	0.05 0.05	-0.2492 0.7794	1.7977 6.0354	2.20	0.1381
Log OR 23 Exp(LogOR23)	5.1567 173.5878	0.8964 155.5978	0.05 0.05	3.3998 29.9594	6.9135 1005.785	33.10	<.0001

Table-V. Comparison of efficacy of drug in different groups at 8th week							
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Chi-Square**	**Pr> ChiSq**
Intercept 1	1	-4.0849	0.5821	-5.2257	-2.9441	49.25	<.0001
Intercept 2	1	-1.9625	0.4674	-2.8785	-1.0465	17.63	<.0001
Intercept 3	1	-0.9608	0.4122	-1.7688	-0.1529	5.43	0.0198
Group 1	1	2.0781	0.5354	1.0288	3.1275	15.07	0.0001
Group 2	1	4.1000	0.6472	2.8315	5.3685	40.13	<.0001
Group 3	0	0.0000	0.0000	0.0000	0.0000		
Scale	0	1.0000	0.0000	1.0000	1.0000		

Table-VI. Pair wise comparison of groups at 8th week							
Label	**Estimate**	**Standard Error**	**Alpha**	**Confidence Limits**		**Chi-Square**	**Pr>ChiSq**
LogOR12 exp(LogOR12)	-2.0219 0.1324	0.5206 0.689	0.05 0.05	-3.0422 0.0477	-1.0016 0.3673	15.0	 0.0001
LogOR13 exp(LogOR13)	2.0781 7.9894	0.5354 4.2775	0.05 0.05	1.0288 2.7976	3.1275 22.8161	15.07	 0.0001
LogOR23 exp(LogOR23)	4.1000 60.3394	0.6472 39.0514	0.05 0.05	2.8315 16.9710	5.3685 214.5337	40.13	<.0001

DISCUSSION

Mastalgia, or breast pain is a frequently encountered clinical problem in women of all age groups[1]. Reassurance, exclusion of cancer and some life style modifications are usually sufficient for majority of patients having mild pain. However, severe persistent mastalgia adversely affecting quality of life demands active therapy[4,7].

As the etiology of mastalgia is poorly understood, different treatment modalities have been tried and recommended[2]. There is no ideal drug regimen for mastalgia. Ideal treatment is usually tailored according to disease severity, patient's preference of drugs, side effects of drugs, cost of therapy and doctor's personal experience.

Majority of our women are reluctant to take hormonal therapy due to their serious side effects, high cost, prolong duration of treatment and the fact that

contraception should be practiced during the treatment. This study was conducted with aim to propose and evaluate a non hormonal, effective, less toxic and rapidly acting therapeutic option for patients with severe mastalgia. In this study patients were mostly families of military personal.

The first drug used in this study for comparison was EPO which is rich in polyunsaturated fatty acids and is widely used in the West for treatment of cyclical mastalgia. It is thought to restore abnormal essential fatty acid profile in breast and is widely advocated as a first line therapeutic option[10-12,17-19]. EPO is considered useful for patients who require long term, non hormonal therapy and remain on oral contraceptives. EPO is available in form of capsule and in this study was prescribed in a dose of 500 mg capsule twice daily. The optimal dose and duration of treatment with EPO is controversial and in West usually ranges from 2 to 3 grams daily[20]. Dose of the drug varies with geographical region, races and dietary practices. Females in our country have smaller built and relatively less total body surface area as compared to Western countries, therefore the total requirement of the drug is reduced. In addition there is also a considerable difference in dietary trends in Pakistan and Western countries.

The second drug used in this study was topical Brufen (NSAID) in the form of gel. It was applied twice a day to the affected area of breast for two months. Topical NSAID's have a local effect due to their transdermal absorption. They have a swift onset of action. They are very effective and commonly used in relieving soft tissue and muscle pain[21]. A randomized study of topical NSAID's shows promising response with no side effects[21].

This study revealed overall efficacy of Brufen gel (topical NSAID) to be highly significant with a p-value <0.0001. Out of 30 patients of group-1 (EPO) 3 (10%) had CBS grade-1 response at the end of 8 weeks in contrast to 15 (50%) and 2 (6.6%) for group-2 (Brufen gel) and group-3 (placebo) respectively. Similarly 11 (36.6%), 12 (40%), 2 (6.6%) patients of group1, 2 and 3 respectively had CBS grade-2 response at the end of 8 weeks. This made overall effectiveness (CBS grade 1 + 2 at 8 wks) for group 1, 2 and 3 to be 46.6%, 90% and 13.3% respectively.

There is a variable response of EPO in relieving breast pain and results are conflicting in various studies. In one study the overall response rate with EPO was 58% in cyclical mastalgia and 38% for non cyclical breast pain[13]. A local study revealed that 64% patients showed CBS grade 1 response while 29% patients showed CBS grade 2 response and only 7% showed no response[1]. A recent double blind randomized trial of EPO showed no significant response when compared with placebo oil[22]. In this study among group-1 patients with clinically significant response (CBS-1 and 2 at 8 weeks) 11 patients (78.57%) had cyclical and 3 (21.43%) had non cyclical breast pain. Similarly in group-2 16 patients (59.26%) had cyclical pain and 11 (40.74%) had non cyclical breast pain.

As therapy with EPO is a form of dietary manipulation having slower onset of action, its optimal effects appear after 3 to 6 months[2,7]. Therapy with EPO should be continued for at least 4 months before accepting treatment failure[19]. In this study the EPO was given for only 2 months which was not sufficient duration for EPO to exert its optimal effects. This was the probable reason of low response rate in this study (46.6%) in contrast to 90% and 64% in other studies[1,7]. In order to assess maximal effects of EPO results should have been evaluated after completing 6 months of therapy with EPO[9].

Patients in group-2 who were given topical Brufen had rapid response as compared to group-1. 76.6% had clinically significant response (CBS-1+2 at the end of 4 weeks). None of the patients in group-1 had a clinically significant response at 4 weeks.

There is very little research done both nationally and internationally to compare these drugs. However, there are several studies done to compare EPO with other hormonal therapy in management of mastalgia. Sajida Qureshi and Naheed Sultan in their study showed an overall response of 64% with EPO and that of 92% with

topical NSAID (Piroxicam gel) after 3 months of use. 88% of patients who were given topical Piroxican gel showed a significant response at 4 weeks while none of patients at EPO showed response at 4 weeks. 4% of patients on EPO showed drug related adverse effects while no side effects were seen with topical NSAID[7]. Colak et al compared efficacy and side effects of topical Diclofenac gel with placebo in their study which showed that 47% patients with cyclical mastalgia and 50% patients with non cyclical mastalgia had a CBS grade 1 response after 6 months of therapy[21]. In another international study topical NSAID's revealed a satisfactory response in 81% of women with severe cyclical, non cyclical and surgical scar related breast pain[23]. These studies prove topical NSAID's are effective, safe and easily administered treatment for both severe cyclical and non cyclical mastalgia.

EPO is known to be associated with a number of side effects including nausea, vomiting, abdominal bloating, bad taste, headache, weight gain, depression, giddiness and rash[1,2,7]. A study reported side effects in 4% of patients, significant enough in 2% to stop the treatment[14]. As topical NSAID's bypass gastrointestinal tract so they have little or no gastric side effects. The transdermal absorption of the drug leads to local accumulation in target tissues by direct diffusion in greater concentration as compared to oral root[21]. Local delayed hypersensitivity type reaction may occur at the sight of application[7]. Topical NSAID's should be avoided in patients with known hypersensitivity to NSAID's. They should be cautiously used in patients having impaired renal function and acid peptic disease[7]. In this study side effects were mild so didn't required discontinuation of treatment. The probable reason for fewer and milder side effects was that the dose of EPO was lesser in this study as compared to other studies. In this study side effects with EPO were seen in 5 patients (16.7%) while no side effects were seen with Brufen gel. Mild to moderate headache was the most frequently occurring side effect seen in 3 patients.

Although EPO has low incidence of adverse effects but it has slow onset of action and peak effect often requires 6 months of therapy causing poor compliance by the patient. On the other hand topical NSAID's have significantly rapid onset of action and have comparable if not better efficacy in comparison to EPO. Considering these facts and that topical NSAID's are much more cost effective as compared to EPO they seem to have a clear edge over EPO[7].

CONCLUSION

The purpose of the study to compare the efficacy and safety of topical NSAID with evening primrose oil has revealed topical NSAID's to be an effective, rapidly acting and safe treatment option in moderate to severe mastalgia as compared to EPO.

Further studies are required to investigate this as a first line of treatment in cyclical and non cyclical mastalgia.

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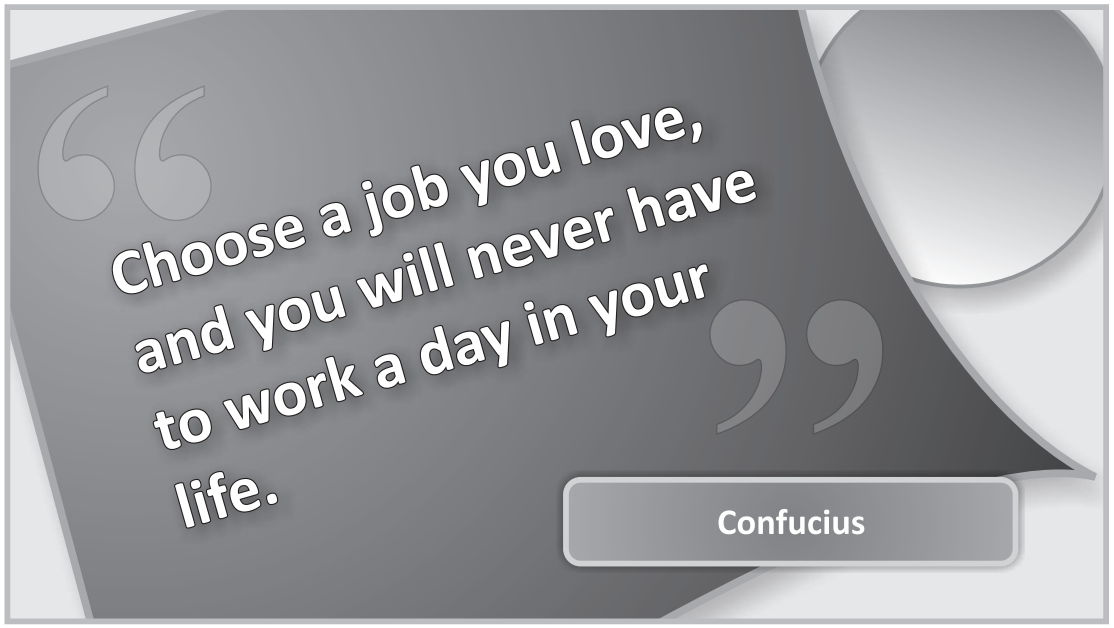

PREVIOUS RELATED STUDIES

- Muhammad Abid Bashir. Mastalgia. Professional Med J 2004; Vol: 11, No. 1, 3-10.