

A comparative trial of Evening Primrose Oil and Ayurveda Formulations in the Management of Fibrocystic Breast Disease

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ABSTRACT

Background: Fibrocystic breast disease (FBD) is the most frequently encountered benign breast condition among women of reproductive age group with mastalgia and engorgement or lumpiness of breasts as the main complaints. Though multiple treatment options are available ranging from hormonal drugs to vitamin supplements, there have been issues of some serious side effects or recurrence. Being derived from natural sources and having a good safety profile, evening primrose oil (EPO) is usually considered a first line of therapy but with not so satisfactory response in many cases. In Ayurveda, FBD may closely be correlated with stana-granthi of vataja or kaphaja type. Kanchnar guggulu (KG) and chandraprabha vati (CPV) are two of the Ayurveda formulations indicated for management of conditions like granthi (lumps) and painful conditions associated with menstrual cycle. Therefore, in search of a safe and effective treatment alternative for FBD, efficacy of KG and CPV was compared to EPO.

Material and Methods: 30 patients of FBD were selected and randomly divided into three groups of 10 patients each. Group A patients received 1000 mg of EPO once daily while group B patients received 500 mg of KG twice daily. Group C patients were treated with both KG and CPV in 500 mg twice daily dosage of each. Treatment in all groups was given for 3 months and assessment was done by comparing pre-therapy and post-therapy (at the end of 4th month) scores for mastalgia, tenderness and lump size.

Results: Reduction in mastalgia, tenderness and lump size was noticed in all cases but the results were more significant both statistically and subjectively in group B than group A and in group C than the other two groups. 40% patients were completely relieved of symptoms and 60% got improved in group C compared to 30% and 70% respectively for group B while in group A, 20% patients had no improvement in symptoms.

Conclusion: Combined effect of KG and CPV was found more efficacious than KG alone or the EPO in alleviating the symptoms of FBD, thus improving the quality life of the affected person.

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INTRODUCTION

Fibrocystic breast disease (FBD) is the most common of all benign breast conditions in females of mature reproductive period (25-40 years) which includes multiple irregularities in the consistency and contour of the breast (nodularity) along with mastalgia of cyclic nature.¹ Though the real incidence of disease is difficult to estimate, studies have reported an incidence of 50% in females of

reproductive age^{2,3} which is estimated to be 90% by some authors.⁴ Pathological changes include cystic dilatation of the terminal duct lobular units, apocrine metaplasia, periductal mastitis, fibrosis in the stromal tissue, epithelial hyperplasia, calcifications and chronic inflammation.⁵

No specific etiology has been identified for this condition, however a number of theories have been proposed. The most widely considered theory of

etiology suggests an imbalance between estrogen and progesterone levels. As a result, many hormonal drugs have been tried till date like danazol (a synthetic androgen), bromocriptine (a prolactin inhibitor), tamoxifen (a synthetic antiestrogen), medroxyprogesterone, oral contraceptive pills etc. Though most of these drugs often bring a relief in the symptoms, the side effects like menstrual irregularities, intermittent vaginal spotting, polycystic ovary, hirsutism, acne, edema, headache, dizziness, alopecia, nervousness, depression etc. are common and thus are not tolerated by all. Recurrence of symptoms after cessation of therapy is another associated disadvantage. Vitamin supplementation with Vitamin E and Vitamin B6 has also been reported to be beneficial in some cases. Abnormal levels of certain essential fatty acids have been found associated with mastalgia and a good response to supplementation of gamma-linoleic acid (GLA) with evening primrose oil (EPO) has been reported in some studies. However, other reports are not that much satisfactory and conclusive with significance.^{1,6} Still, because of being from natural source and relatively free of side-effects, EPO is used as a first line therapy in cases of FBD⁷ but recurrence after stopping the therapy is also common. Therefore, there is a need to search for a safe alternative treatment with minimal side effects, low recurrence rate and significant effectiveness and hence Ayurveda formulations may provide an option.

As mentioned above, the main pathological features of FBD like cystic dilatation of the terminal duct lobular units, periductal mastitis, stromal fibrosis etc. causes the development of firm areas of nodularity or palpable lumpiness (with fluctuation in size of cystic areas) in the breasts along with pain and tenderness; the changes being usually cyclical. Based on these features of lumps or cysts with pain, FBD may be correlated stana-granthi of vataja or kaphaja type according to Ayurveda.⁸ For the management of glandular and cystic swellings like granthi-roga, a compound formulation called kanchnar guggulu (KG) has been described in various classical texts of Ayurveda⁹. Another compound Ayurveda formulation called chandraprabha vati (CPV), which is a commonly used drug in urogenital disorders, has been indicated in the management of granthi (cystic lesions), stree-roga (gynaecological disorders) and aartavajanya ruja (pain related to menstrual cycles).¹⁰ Being a gynecological disorder presenting with cyst formations in the breast tissue with mastalgia related to menstrual cycles, FBD

forms a good indication for use of CPV. Considering all these facts, present study was undertaken to evaluate the clinical efficacy of Ayurveda formulations, KG and CPV in comparison to another naturally resourced treatment, EPO in the management of FBD.

MATERIAL AND METHODS

It was a prospective, interventional, open-labelled, randomized comparative clinical trial approved from the institutional ethical committee. Patients (n = 30) of age between 15 and 50 years with signs and symptoms of FBD (viz. feeling of lumps and heaviness in breasts, mastalgia etc.) were recruited from the Outdoor Patient Department (OPD) of Shalya Tantra, Sir Sunder Lal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi and were randomly divided into three groups (Group A, B and C) of 10 patients each using computer generated randomization chart. Written informed consent was taken from all the patients in the trial. Ultrasonography of both breasts was carried out in all cases to establish the diagnosis of FBD. In addition, complete blood counts, fasting and post-prandial blood sugar measurements, serum urea and creatinine estimations as well as viral markers (for HIV, hepatitis B and C) were obtained for all patients to rule out any co-morbidity that may affect the outcomes of the trial.

All patients in each group were advised to wear properly fitting brassieres to maintain the breast support. Patients in group A and B were treated with EPO (oil obtained from the seeds of *Oenothera biennis* Linn.) and KG respectively while in group C, both KG and CPV were prescribed. Treatment was given for 3 months according to the protocol mentioned in Table 1.

Assessment was done for mastalgia, degree of tenderness and lump size/nodularity before starting the treatment and at 1 month follow-up after stopping the treatment i.e. at the end of 4th month. Patients were given the new breast pain (mastalgia) chart¹¹ to fill the entries on daily basis and mastalgia was assessed in terms of days of pain (DoP) i.e. number of days the patient experienced pain in a month and the mean breast pain score (MBPS) i.e. the mean value of the scores of pain (on Wong-Baker's face pain scale system, from 0 to 10) experienced by the patient on each painful day of the month. Degree of tenderness and lump size were assessed by palpation for each breast separately according to the criteria mentioned in Table 2. As the lumps in cases of FBD are diffuse in nature and not well defined, the size of lump was measured in terms of the extent of breast quadrants involved by the lump.

Table 1: Treatment Protocol of the study

Group	Drug/Formulation Prescribed	Dose	Duration
Group A	Evening Primrose Oil (EPO)	1000 mg OD	3 months
Group B	Kanchnar Guggulu (KG)	500 mg bid	3 months
Group C	Kanchnar Guggulu (KG) + Chandraprabha Vati (CPV)	500 mg bid + 500 mg bid	3 months

Table 2: Assessment criteria for tenderness and lump size/nodularity

Score	Degree of Tenderness	Lump Size
0	No tenderness	No Lump
1	Tender on deep palpation only (Mild)	Lump involving one quadrant only
2	Tender on superficial palpation (Moderate)	Lump involving two quadrants only
3	Refuse to touch (Severe)	Lump involving three quadrants only
4	-	Lump involving all four quadrants

RESULTS

Total 30 patients were enrolled in the study; of which, 16 (53.33%) belonged to age between 21-30 years and 17 (56.67%) were unmarried. Among the married women, 2 were nulliparous, 3 had one child while 8 were multiparous. 13 (43.33%) cases each had vataja and kaphaja type of prakriti with 4 (13.33%) belonging to pittaja prakriti. 23 (76.67%) of 30 cases had bilateral breast involvement. Mastalgia was present in all cases, being cyclical in 25 (83.33%) and non-cyclical in rests while tenderness was present in 90% cases only. 28 of 30 patients presented with diffuse lumps, of which, 15 involved both breasts while 13 had only one breast involved; thus accounting for a total of 43 breasts involved with palpable lumps. Of these, lumps involving single quadrant were found in 23 breasts and the upper-outer quadrant was mostly affected (34.87%) followed by the lower-outer quadrant (11.63%). In 19 breasts, lumps were present in two quadrants, jointly affecting the upper-outer and lower-outer quadrants the most (30.23%), followed by the joint involvement of upper-outer and upper-inner quadrant (11.63%). In one case, extent of lump involved three quadrants of the breast, namely the upper-outer, lower-outer and lower-inner quadrants. Apart from these, nipple discharge was also present in 6 (20%)

cases, though it was milky in all cases.

Effect of therapies was measured at the end of 4th month in terms of mastalgia, tenderness and lump size. Mean number of days a patient experienced pain in a month (DoP) and the mean breast pain score (MBPS) reduced in all groups but the improvement was more conspicuous in group B and group C where the compound Ayurvedic formulations were prescribed. Changes were significant in group A but highly significant in other two groups. Tenderness also reduced in all groups with results being more significant in group B and C. However, the combined treatment with CPV and KG worked better than KG alone in reducing mastalgia and tenderness.

In case of lump size also, reduction was noticed in all groups with slight better results in group B than group A but the degree of reduction was highly significant in group C compared to group A and B, thus implying that the combination therapy of CPV and KG was more effective than KG and EPO in reducing the symptoms of lumpiness in breasts.

Overall, on a subjective assessment, 4 patients got freed of all symptoms in group C and 6 had significant improvement while in group B, 7 had improvement and 3 got relieved of symptoms. But, in group A, only 8 patients showed improvement in symptoms while 2 remain unchanged in terms of their pre-therapy scores.

Table 3: Comparative effect of therapy

Assessment Parameter	Group	Mean \pm SD		Mean Difference	WSR test*
		BT	AT	BT-AT	p value
DoP	Group A	15.4 \pm 9.59	9.6 \pm 9.29	5.8	<0.05
	Group B	15.7 \pm 9.07	6.8 \pm 7.12	8.9	<0.01
	Group C	12.6 \pm 6.87	3.4 \pm 3.41	9.2	<0.01
MBPS	Group A	6.0 \pm 1.33	3.2 \pm 2.53	2.8	<0.05
	Group B	6.5 \pm 2.55	2.4 \pm 2.27	4.1	<0.01
	Group C	7.4 \pm 2.07	2.0 \pm 1.88	5.4	<0.01
Tenderness	Group A	1.4 \pm 0.89	0.7 \pm 0.64	0.7	<0.01
	Group B	1.5 \pm 0.83	0.7 \pm 0.47	0.9	<0.001
	Group C	1.5 \pm 0.99	0.4 \pm 0.50	1.1	<0.001
Lump Size	Group A	0.9 \pm 0.60	0.6 \pm 0.50	0.3	<0.01
	Group B	0.9 \pm 0.91	0.4 \pm 0.59	0.5	<0.01
	Group C	1.3 \pm 0.87	0.3 \pm 0.48	1.0	<0.001

*Wilcoxon signed rank test

DISCUSSION

Benign breast disorders are a heterogeneous group of lesions or abnormalities, the spectrum of which includes developmental abnormalities, inflammatory lesions and the epithelial and stromal proliferations. Among the large group of these benign conditions of breast, FBD is the most common condition with classical symptoms including mastalgia and tenderness of cyclical nature along with a sense of increased breast engorgement, nodularity or lumpiness of fluctuating sizes specially during the premenstrual phase.¹ The description of breast diseases available in Ayurveda under the heading of stana-roga refer more towards the inflammatory and suppurative breast pathologies. However, on deducing on the basis of clinical features, FBD may be correlated with vataja or kaphaja type of granthi occurring in stana pradesha i.e. breasts.⁸ The prakriti of most of the patients in our study was also of either vataja or kaphaja type (43.33% of each) which is in accordance of principle of Ayurveda that particular types of diseases are more prone to occur in subjects of a particular type of prakriti. Moreover, more than half (56.67%) of the patients in our study were unmarried and about two-third (63.33%) of them were nulliparous. This is in contradiction to Sushruta's view that the stana-roga do not occur in young nulliparous girls as the dhamanya in their stana (duct system) are not

vivritta (open/dilated/differentiated) as in mature multiparous women.¹² These findings again prove that the stana-roga described by Sushruta does not refer to the benign breast entities like FBD and implied more towards inflammatory and suppurative conditions of the breast like breast abscess.

According to ANDI framework, cyclical mastalgia and nodularity is an aberration which most commonly affects the women in mature reproductive age group i.e. 25-40 years.¹³ The degree of diffuse palpable nodularity may increase in the third and fourth decades of life.¹⁴ In a study on benign breast diseases in Indian population (HS Shukla et al. 1989), the peak age for benign diseases was found to be 21-30 years with 43% patients falling in that age group while 90% of patients were younger than 40 years of age.¹⁵ Khanna et al. (1998) also reported a peak incidence in 21-30 years with 40.06% patients.¹⁶ In our study also, maximum patients (53.33%) were found belonging to 21-30 years of age, 73.33% were in their third and fourth decade of life and more than 90% were below 40 years of age. A similar age incidence was also reported in a recent study from Indian population by A. Chilakala et al. (2019) where 83% cases belonged to 21-40 years of age group.¹⁷

More than three-fourths of the cases in our study had bilateral breast involvement which is in concordance with the observations recorded in earlier studies also that the fibrocystic breast

changes usually involve both breasts at the same time.^{13,18} In the study by A Chilakala et al. also, most of the patients of cystic nodularity with mastalgia suffered bilateral breast involvement.¹⁷ Further, the upper-outer quadrants of breast were found to be involved more frequently in our study, followed by the lower-outer quadrant. The same has been depicted in various textbooks of gynecology^{13,18} as well as in other studies also; the reason being the presence of more breast tissue in upper-outer quadrant. Marchant DJ (1998)¹⁹ and Rissanen T et al. (2001)²⁰ have also reported the maximum affliction of upper-outer quadrant in cases of benign breast disease.

All patients in our study reported with complaint of mastalgia and in most of them (83.33%), it was cyclical in nature. The others, in whom the mastalgia was non-cyclical or continuous, also reported an increase in severity of the pain during the premenstrual phase with reduction in degree of pain after menstruation. Thus, they also displayed a cyclic variation in the degree of pain. This is in concordance with the characteristic nature of the fibrocystic breast disease that the mastalgia is usually of cyclical nature.^{1,13,18,21} Moreover, Blommers J et al. (2002), in their randomized trial comparing EPO and fish oil in chronic mastalgia, also reported 21.67% cases with non-cyclical mastalgia and 78.33% cases of cyclical mastalgia.²² These findings are similar to the incidence found in our study also. Apart from pain, tenderness and lump, nipple discharge was also reported in this study by 6 (20%) cases which was however milky in all cases. Similar findings were also reported by N Kaur et al. (2012) who in their study on 262 patients, found 5.7% cases to be presenting with complaints of nipple discharge which was milky in most (>70%) of the cases.²³

In this study, the therapeutic efficacy of two compound formulations of Ayurveda, kanchnar guggulu (KG) and chandraprabha vati (CPV) was compared with that of evening primrose oil (EPO), a frequently prescribed therapeutic agent in cases of FBD. EPO contains essential fatty acids, linoleic acid and gamma-linolenic acid (GLA) which are poly-unsaturated-omega-6-fatty acids. Body forms DGLA (dihomo-gamma-linolenic acid) from GLA and this DGLA is a precursor of anti-inflammatory prostaglandins (1-Series PGs like PG-E1 etc.)

and prevent the formation of pro-inflammatory prostaglandins (2-Series PGs like PG-E2, PG-F2, PG-D2 etc.) and leukotrienes (4-series LTs like LT-B4, LT-E4 etc.). It is believed that the fatty acid metabolism is altered in patients of fibrocystic changes and they are not able to synthesize GLA due to blockage of enzyme delta-6-saturase, eventually leading to the hypersensitivity of the estrogen and progesterone receptors present at the cell membranes of the breast tissue to the circulating hormones.²⁴⁻²⁷ Gateley et al. (1992) published their 17 year experience report at the Cardiff Breast Clinic and concluded that the therapeutic efficacy of EPO was almost equal to danazol in the treatment of mastalgia and owing to it being from natural resources and free from adverse side-effects, it should be the first line of treatment for the patients presenting with mastalgia.²⁸ Studies by S Pruthi et al. (2010)²⁹ and F Jahdi et al. (2018)³⁰ also showed a significant effect of EPO in reducing the complaints of mastalgia. The ultimate role of EPO administration is therefore the anti-inflammatory activity by providing GLA, owing to which it has shown good results primarily in the treatment of cyclical mastalgia.

KG is a compound formulation containing twelve herbs of which kanchnar and guggulu constitute the largest proportions. The pharmacodynamic properties of most of the contents are laghu, ruksha, tikta, kashaya, katu and are predominantly vata-kapha-shamaka. The whole compound formulation is said to possess properties like shophaghna, medohara, lekhana, srotoshodhana, vedana-nashana etc.; owing to which, kanchnar guggulu has been described to have a prominent role in the treatment of cystic and glandular swellings like granthi etc.⁹ According to Ayurveda, kapha is the main dosha responsible for the formation of granthi. The kanchnar guggulu, by virtue of its prabhava, laghu-ruksha guna, katu-tikta rasa and the ushna veerya, is able to counteract the vitiation and progressive concentration of kapha. The lekhana, srotoshodhana properties of guggulu further reduces the concentration of kapha and thus decreases the development of granthi. Owing to the shophaghna, vednanashana and vatahara properties of guggulu, the pain and inflammation subsides.

Various scientific studies on important constituent drugs of kanchnar guggulu have also been conducted. For example, guggulu has been proved to have anti-inflammatory and analgesic _

properties. Guggulosomes prepared using guggulu with ibuprofen were studied for anti-inflammatory activity. It was clearly shown that guggulosomes had more efficacy than ibuprofen and both guggulu and ibuprofen had synergistic effect.³¹ Kanchnar has also shown anti-inflammatory properties. In a study by Koteswara et al. (2008), phytochemical analysis of non woody aerial parts of *Bauhinia variegata* yielded six flavonoids with one triterpene caffeine. These seven compounds showed anti-inflammatory activity; they inhibited the lipopolysaccharides and interferon γ induced nitric oxide (NO) and cytokines.³² It has also shown anti-oxidant³³ and anti-goiter activity in different studies.³⁴ Crataeva nurvala (varun), another important ingredient of kanchnar guggulu, also exhibited significant analgesic³⁵ and anti-inflammatory³⁶⁻³⁷ activities in different studies owing to presence of lupeol. Moreover, in a study by P. Tomar et al. (2018), kanchnar guggulu has been shown to have antimitotic and anti-proliferative activities due to the presence of flavonoids and phenolics.³⁸ All these studies demonstrate the anti-inflammatory, analgesic and anti-tumor activities of the kanchnar guggulu and thus prove the findings in our study wherein treatment with kanchnar guggulu brought a significant reduction in the pain, tenderness and also the size of lumps and has shown beneficial effect on the FBD.

CPV, used in treatment in group C of this study, is a compound herbomineral formulation indicated in a variety of clinical conditions and is said to possess properties like rasayana, vrishya, shophaghna and tridoshaghna, especially kapha-vata shamana.¹⁰ Shilajeet and guggulu are the main constituents of CPV. Shilajeet, which is a natural mineral substance used abundantly in various preparations in Ayurveda, has been proved to possess anti-inflammatory, antioxidant and immunomodulatory activities in many studies like by Goel et al. (1990)³⁹, Ghoshal et al. (1995)⁴⁰, Bhattacharya et al. (1993)⁴¹ and Bhaumik et al. (1993)⁴². Moreover, the studies on CPV itself have also shown anti-inflammatory, analgesic and anti-fibrotic activities in therapeutic doses. In a study on experimentally induced benign prostatic hyperplasia and carrageenan induced paw inflammation in rats, RK Dumbre et al. (2012) noticed a significant reduction in gland

proliferation, epithelial and cellular hyperplasia and stromal proliferation along with inhibition of paw inflammation⁴³; thus proving its effect on diseases wherein the pathological features involve glandular and stromal proliferations, epithelial hyperplasia and inflammation like in FBD. MS Bagul et al. (2005) demonstrated the free-radical scavenging properties of CPV experimentally owing to the presence of phenolic compounds, thus demonstrating its anti-inflammatory activity.⁴⁴ To demonstrate these activities further, P. Rajagopala et al. (2020) performed microarray analysis of genes in experimental animals after treatment with CPV and found that the treatment with CPV showed upregulation of certain genes that are responsible for anti-inflammatory, anti-fibrotic and anti-tumorigenic activities.⁴⁵ These effects also work to break the pathogenesis of fibrocystic breast disease and hence justify its therapeutic effect in FBD.

Thus, we can see that both KG and CPV exerted anti-inflammatory, analgesic, anti-tumor effects. Hence, the results in Group C, where the combination of both these drugs was used, were better (in terms of reduction of mean score for sign and symptoms) than Group B where only KG was used for treatment and more patients were cured in Group C compared to Group B. However, patients in Group A, where they were treated with EPO only, showed less improvement in symptoms and in overall results, two patients even remained unchanged compared to their pre-therapy symptom profile as they did not report any appreciable improvement. Therefore, we can say that EPO reported a lesser efficacy than KG and its combination with CPV in our study. However, the small sample size and a small follow-up period of only one month have served as the limitations of our study.

CONCLUSION

From the observations and results of this study, it can be concluded that the Ayurveda formulations like kanchnar guggulu and chandraprabha vati are more effective in alleviating the symptoms of FBD than evening primrose oil. The combined use of both these drugs worked in a synergistic manner to produce better results than the lone use of kanchnar guggulu. These drugs hence can offer a safe alternative to the available treatment options for the management of fibrocystic breast disease and improve the quality of life of the affected person.

AUTHOR'S CONTRIBUTION

All authors contributed to the literature review, design, data collection and analysis, drafting the manuscript, read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

FINANCIAL DISCLOSURE

Nil.

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