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OBM Integrative and Complementary Medicine

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Original Research

A Multi-Centric Single-Blind Randomized Placebo-Controlled Trial to Evaluate the Efficacy of the Individualized Homeopathic Intervention in Breast Fibroadenoma

Chetna Deep Lamba [1, *], Praveen Oberai [1], Bharti Wadhwa [2], Suraia Parveen [3], Arti Soren [4], Rajachandrasekar Bhuvaneswari [5], Prasanta Kumar Pradhan [4], Vaishali Shinde [6], Jaya Gupta [2]

1. Central Council for Research in Homoeopathy, New Delhi, India; E-Mails: chetnalamba77@ccrhindia.nic.in; oberai.praveen@gmail.com
2. Dr D. P. Rastogi Central Research Institute of Homoeopathy, Noida, India; E-Mails: bhartiwadhwa@gmail.com; jgupta21@gmail.com
3. Dr. Anjali Chatterji Research Institute of Homoeopathy, Kolkata, India; E-Mail: drsuraia@gmail.com
4. Regional Research Institute of Homoeopathy, Puri, India; E-Mails: arti_soren@rediffmail.com; drpkpradhan@ymail.com
5. National Homoeopathy Research Institute in Mental Health, Kottayam, Kerala, India; E-Mail: dr.bhuvaneswarir@gmail.com
6. Regional Research Institute of Homoeopathy, Mumbai, India; E-Mail: drvhsb@gmail.com

* **Correspondence:** Chetna Deep Lamba; E-Mail: chetnalamba77@ccrhindia.nic.in

Academic Editor: Bruno Galeazzi

Special Issue: Homeopathy

OBM Integrative and Complementary Medicine
2023, volume 8, issue 2
doi:10.21926/obm.icm.2302021

Received: October 17, 2022
Accepted: May 09, 2023
Published: May 16, 2023

Abstract

The primary objective of this study was to evaluate the efficacy of homeopathic medicines in the reduction or resolution of breast fibroadenoma (FA) through ultrasound (US) assessment in intervention and control groups. The secondary objective was to compare the efficacy of the homeopathic intervention in single and multiple fibroadenomas. A single-blind, randomized, placebo-controlled pilot study was conducted from January 2014 to June 2018

at 4 research centers with 6 months of follow-up. Females in the age group 18 to 35 years, with a confirmed diagnosis of breast fibroadenoma measuring between 1 cm and 5 cm, measured by the US, with only one fibroadenoma per quadrant were randomized to either homeopathic intervention (HI) or identical placebo (P) (n = 85) in each group. All the patients were enrolled in the study with due consent from them. The Ethical Committee, Central Council for Research in Homoeopathy (CCRH), New Delhi, India, approved the study. The trial was registered with the Clinical Trial Registry-India (CTRI) vide no. CTRI/2013/11/004144 [Registered on: 14/11/2013]. Out of the 85 cases enrolled in each group, the ITT analysis was done for n = 73 participants with a mean area of FA (3.11 ± 3.00) in HI and n = 77 participants with a mean area of FA (3.65 ± 3.29) in the P group at baseline. US assessment of 12 cases in the intervention group and 8 cases in the placebo group exceeded the study duration. Therefore, was analyzed as a sub-group and was not considered under ITT analysis. FA was the unit of analysis. At 6 months, complete resolution occurred in 2 participants in the intervention group and none in the placebo group. Although there is a significant difference between the intervention and the placebo groups at 3rd and 6th months, the within-group difference is insignificant. No significant difference is observed between and within the single and multiple FAs groups. Out of the 85 cases in the medicine group, 78 received a single remedy throughout the study in centesimal potencies. The frequently prescribed medicines were Pulsatilla, Silicea, Phosphorus, Sepia, and Calcarea Carbonica. IIndividualized homeopathy has significantly reduced FAs compared to the placebo group. However, the difference within the groups is not statistically significant. Future studies should be conducted based on adequate samples with long-term follow-up for resolution and recurrence if any.

Keywords
Homeopathy; fibroadenoma breast; individualization

1. Introduction

Fibroadenoma is the most common benign tumor of the breast [1]. It is estimated that 10% of the world's female population suffers from fibroadenoma once in a lifetime [2]. Usually 70%-90% of FAs are solitary and simple while 10%-25% are multicentric occurring in different quadrants of both breasts with sizes varying from 1 cm-10 cm but mostly measuring 2 cm-3 cm. These can range from asymptomatic masses to painful and rapidly growing tumors that can cause significant esthetic distortions of the breast [3]. Fibroadenomas shrink after menopause, and are less common in post-menopausal women [2]. Although previous studies show an elevated risk of breast carcinoma in FA patients compared to women of similar age in the general population, the malignant transformation from fibroadenoma to cancer is rare. Also, this risk rises in women above 35 or patients with complex fibroadenoma with a family history of breast cancer [4]. The US is used to detect fibroadenomas in women younger than 35 [2]. Cytology is essential to exclude malignancy if conservative treatment is in consideration [5]. Conservative management of fibroadenomas in patients under 35 is safe and acceptable to most women. However, a family history of malignancy and proliferative breast changes from previous biopsies must be considered [6]. The preferred

management of multiple FAs is complete excision, which can lead to undesirable scarring or to extensive ductal damage [7]. A minimally invasive treatment, ultrasound-guided, vacuum-assisted percutaneous excision facilitates the removal of benign breast lesions, including fibroadenomas. Despite successful percutaneous excision, fibroadenomas have been reported to recur [8].

Homeopathic treatment has shown positive results in cases of FA of breast [9-11] but the short duration of follow-up and lack of adequate sample size have been the major drawbacks in these studies. Per the treatment protocol in modern medicine, patients under 35 years with FA are to be followed up for 6 months without any intervention. In case, the FA doesn't regress or increase in size, intervention is required [7]. Therefore, a placebo-controlled randomized clinical trial with the primary objective to evaluate the efficacy of homeopathic medicines in the reduction or resolution of FA through US assessment and with the secondary objective to compare the efficacy of the homeopathic intervention (HI) in single and multiple fibroadenomas was undertaken.

2. Materials and Methods

2.1 Study Design

A randomized, placebo-controlled, single-blind study with 6-month intervention and follow-up was conducted at four centers' namely Dr. D. P. Rastogi Central Research Institute (H), Noida; Dr. Anjali Chatterjee Regional Research Institute(H), Kolkata; Regional Research Institute(H), Puri and National Homoeopathy Research Institute in Mental Health, Kottayam, from January 2014 to June 2018.

2.2 Participants

The inclusion criteria were as follows: (1) Female aged 18 to 35 years; (2) Diagnosis of breast fibroadenoma based on: clinical examination, US image, and confirmation by Fine Needle Aspiration Cytology; (3) Fibroadenoma size measuring between 1 cm and 5 cm at its largest dimension (measured by US); (4) The tumors may be single, multiple and/or bilateral; (5) Only one fibroadenoma per quadrant; (6) Written informed consent from the patient.

The exclusion criteria were as follows: (1) Patient pregnant or lactating; (2) Complex fibroadenomas and giant (juvenile) fibroadenoma of the breast; (3) Tumors that have hypercellularity suggestive of phyllodes, atypia, or equivocal pathology report (e.g., discordance between US and microscopic results); (4) Fibrocystic disease of the breast; (5) Tubular adenoma of the breast; (6) Hamartoma of the breast; (7) Family history of breast cancer or history of laser or radiation therapy to the target breast and (8) any other systemic diseases.

Four trained homeopaths, 1 at each center with professional experience of more than 10 years, were the investigators. They were given training for implementing the protocol before the initiation of the study to minimize bias. The patients were screened for eligibility and underwent US and Fine needle aspiration (FNA) to confirm diagnosis which was re-confirmed by two cytopathologists before enrollment. Routine investigations like complete blood count, urine and stool examination were also carried out during detailed screening to exclude pregnancy and major systemic diseases.

2.2.1 Interventions

A detailed case-taking of patients fulfilling the eligibility criteria was done in the specially

designed Case Recording Proforma after enrollment and randomization as per a computer-generated randomization chart [12] to receive either HI or an identical placebo (P). Homeopathic treatment was advised per the guidelines Hahnemann laid down in the 5th edition of Organon of Medicine. Medicines were given in 6c, 30c, 200c, or 1M potency as per the prescribing totality based on a pragmatic approach and were repeated as needed in accordance with the principles of Homeopathy [13]. If characteristically individualized medicine was identified, it was given in higher potency with infrequent repetition. Without characteristic symptoms, if medicine was prescribed for common symptoms, lower potency was given with frequent repetition. A placebo immediately followed the reduction or resolution of FA. In case, there was no change in the FA and the same medicine was indicated, it was repeated in higher potency. If the patient did not respond to the indicated remedy even in higher potency or if the size increased or some other medicine was indicated, a change in remedy was considered.

The medicines were purchased from Good Manufacturing Practices (GMP) certified manufacturer, Sharda Boiron Laboratories, Pvt. Ltd., Shrestha Vihar, Delhi, India.

One dose consisted of 4 globules (size 30).

2.3 Criteria for Follow-Up Assessment

Patients were assessed at a monthly interval (or earlier as per the need) for 6 months. Symptomatic assessment and breast examination were done monthly, and ultrasound (US) was done at 3rd and 6th months.

2.4 Outcomes

The primary outcome was the reduction/resolution of breast fibroadenoma assessed through the US. The secondary outcome was to compare the efficacy of the homeopathic intervention in single and multiple fibroadenomas.

2.5 Sample Size

Initially, a sample size of 200 was calculated and the study was planned at the Regional Research Institute, Mumbai, as one of the centers. But due to the non-enrollment of patients there, it was shifted to Kottayam and the sample size was fixed arbitrarily subsequently as per the availability of cases.

2.6 Randomization

The participants were randomly assigned to receive homeopathic intervention or placebo based on a randomization sequence generated by an independent statistician. Assignments were stratified according to center, where 50 participants per center were allocated in a 1:1 allocation ratio in unequal block sizes of 4 and 6. All the centers shared their respective randomization sequence before the initiation of the study.

2.7 Allocation

The patients fulfilling the eligibility criteria were enrolled and randomized to receive either HI or

an identical placebo. Allocation concealment was not done.

Only the patients were blinded to the identity of the treatment group. Homeopathic and placebo medicines were identical. The taste and appearance of the medicines were kept identical to blind the patients' gustatory and visual senses.

2.7.1 Implementation

The participants were enrolled and assigned to the intervention by the study site investigators.

2.8 Data Collection

Each case in both groups was followed up for 6 months to assess the treatment outcome. The study data were collected at baseline, at every follow-up (monthly or early if required), and at the final/termination visit.

2.9 Statistical Methods

Data obtained during the study were entered in an electronic format designed in MS-excel with suitable validation checks. The baseline characteristics between the two groups were compared using an independent sample t-test for continuous variables and a chi-square test for categorical variables. The mean area of breast FA was compared within the group by using paired sample t-test and between groups, comparisons were made using an independent sample t-test. The categorical data has been presented as numbers and percentages, while continuous data has been presented as mean and SD. The analysis was done using SPSS version 15.0. A p-value of <0.05 has been considered significant.

Intention-to-treat (ITT) principle was applied. Missing data of lost to follow-up cases was imputed by following the Last Observation Carried Forward (LOCF) method.

2.10 Ethical Approval

The study protocol was by the latest revision of the Declaration of Helsinki on human experimentation [14] and Good Clinical Research Practice [15]. Necessary clearance of the Ethical Committee, CCRH, was obtained. All the patients were enrolled in the study after obtaining their consent. The trial was registered with the Clinical Trials Registry-India (CTRI) vide no. CTRI/2013/11/004144 [Registered on: 14/11/2013].

3. Results

Out of 593 cases of FA screened from the outpatient department of all the study sites, 170 were enrolled according to the inclusion criteria. US assessment of 20 cases (12 in the intervention group and 8 in the placebo group) exceeded the study duration and therefore, were not considered under ITT analysis. This sub-group was separately analyzed. A flow diagram of the progress through the phases of a parallel randomized trial of Homeopathy and placebo (i.e., enrollment, intervention allocation, follow-up, and data analysis) is depicted in [Figure 1]. Baseline characteristics were comparable in both groups and were not statistically significant despite some variation. There was a history of FA in two cases in homeopathy and three cases in the placebo arm [Table 1]. No adverse

events were observed or reported.

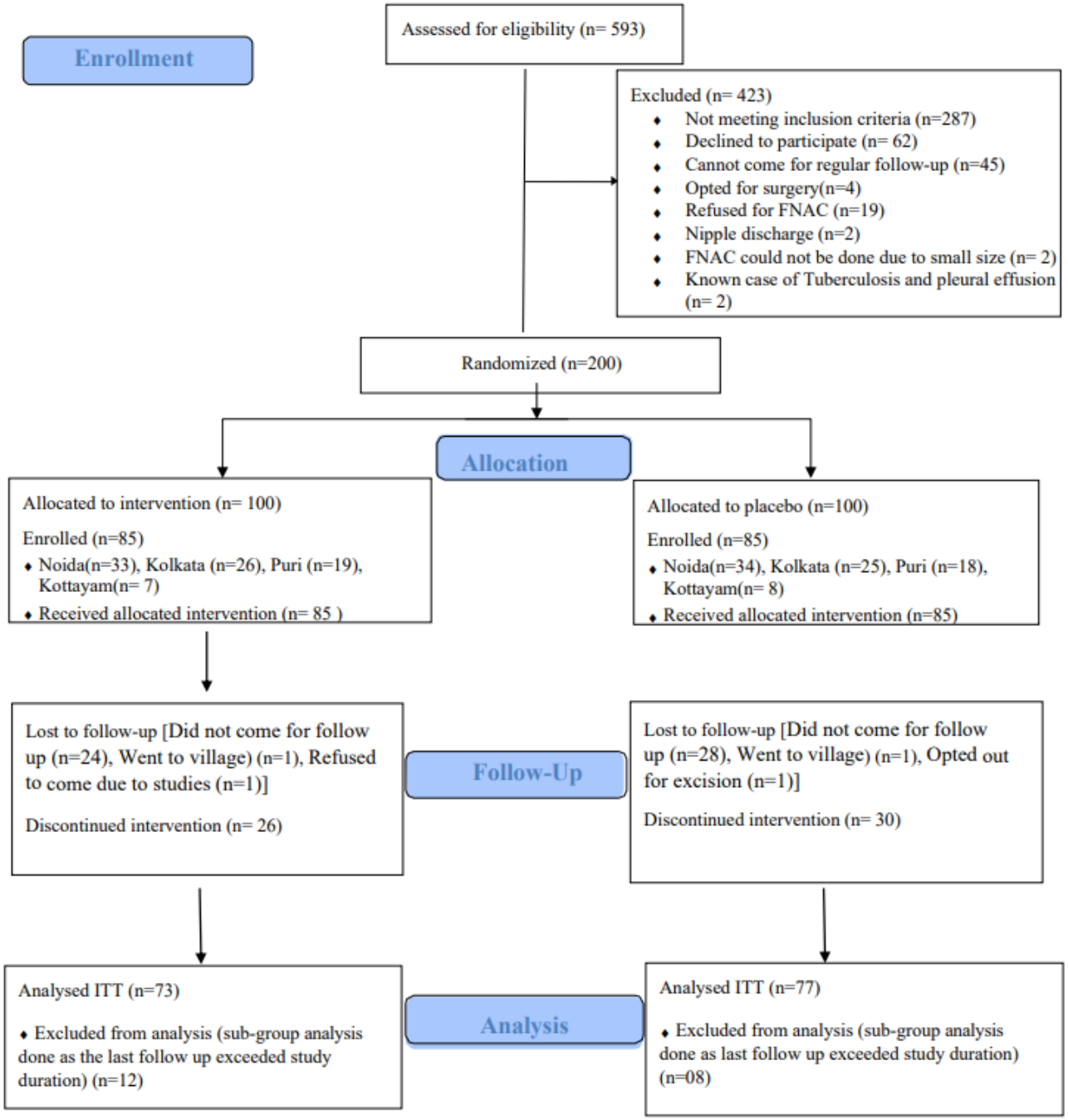

Figure 1 Study flow chart: CONSORT 2010 Flow.

Table 1 Baseline characteristics of the participants.

Variables	Homeopathy Group (n = 85)	Placebo Group (n = 85)	*p-value*
[#]Age (yrs): Mean ± SD	24.74 ± 6.317	24.99 ± 5.870	0.791
[#]Body Mass Index (Kg/m^2): Mean ± SD	21.15 ± 3.580	21.43 ± 3.668	0.617
[$]Family history of FA: n (%)	2(2.3%)	3(3.5%)	0.659
[$]Income Group: n (%) Middle	59(72.8%)	60(74.1%)	0.859

	Low	22(27.2%)	21(25.9%)	
$Parity: n (%)	**Nulli para**	54(63.5%)	58(68.2%)	0.483
	Multi para	31(36.5%)	27(31.8%)	

Compared using independent sample t-test.

$ Compared using chi-square test, data not available for remaining patients.

FA–Fibroadenoma.

Data pertaining to income group was missing for 4 participants each in Homeopathy and Placebo Group.

In the homeopathy group 117 FAs were present, and 125 FAs were present at baseline in the placebo group. Both groups were comparable (p = 0.418). Maximum FAs (n = 46) were present in the right upper inner quadrant followed by (n = 40) in the right upper outer quadrant [Table 2].

Table 2 Quadrant wise distribution of Fibroadenoma.

Quadrant	Homeopathy Group	Placebo Group
Centre of right breast	1(0.9%)	0
Left mid outer quadrant	1(0.9%)	0
Left lower inner quadrant	9(7.7%)	11(8.8%)
Left lower outer quadrant	8(6.9%)	14(11.2%)
Left upper inner quadrant	14(12.0%)	12(9.6%)
Left upper outer quadrant	26(22.2%)	12(9.6%)
Right lower inner quadrant	7(6.0%)	14(11.2%)
Right lower outer quadrant	10(8.5%)	17(13.6%)
Right upper inner quadrant	24(20.5%)	22(17.6%)
Right upper outer quadrant	17(14.5%)	23(18.4%)

Values are presented as n (%) of Fibroadenoma in different quadrants.

Total number of Fibroadenoma in homeopathy group = 117.

Total number of Fibroadenoma in placebo group = 125.

Total participants in Homeopathy group = 85.

Total participants in Placebo group = 85.

1, 2 and 3 FAs at baseline were present in n = 48, n = 21, and n = 4 participants in the HI group and resolved in 3, 2 and 1 participants respectively at 6 months. However, the placebo group did not observe complete resolution of FAs [Table 3].

Table 3 Number of FAs at baseline, 3rd and 6th month.

Number of FA	Homeopathy Group						Placebo Group					
	Baseline		3rd month		6th month		Baseline		3rd month		6th month	
	Pa	FA	Pa	FA	Pa	FA	Pa	FA	Pa	FA	Pa	FA
0			1	0	2	0						
1	48	48	49	49	45	45	53	53	55	55	52	52
2	21	42	16	32	19	38	17	34	12	24	15	30
3	4	12	3	9	3	9	4	12	6	18	7	21

4					1	4	2	8	1	4	3	12
5			3	15	2	10	1	5	3	15		
6			1	6	1	6						
Total	73	102	73	111	73	112	77	112	77	116	77	115

Values are presented as number of patients and Fibroadenoma.

No. of FAs at baseline, 3rd month and 6th month has been calculated by adding no. of FAs per patient.

Pa – Participants.

FA – Fibroadenoma.

No. of FAs at baseline, 3rd month, and 6th month has been calculated by adding no. of FAs per patient.

Although no significant reduction is observed within the groups, the between-group analysis suggested a significant difference at 3rd and 6th months [Table 4].

Table 4 Within and between group analysis of area (centimeters^2) of Fibroadenoma.

	Intention-to-treat analysis		
	Homeopathy Group (n = 73)	**Placebo Group (n = 77)**	***$p-value***
Enrollment	3.11 ± 3.00	3.65 ± 3.29	
3rd month	2.85 ± 2.62	3.77 ± 3.44	0.047 (*)
6th month	2.78 ± 3.49	3.94 ± 3.55	0.036 (*)
#p-value	0.275	0.247	

Within group p-value computed using Repeated Measure ANOVA.

$Between group p-value was compared using ANCOVA to adjust the baseline differences.

(*) denotes p-value is significant at 5% level of significance.

The ITT analysis of the area for single and multiple FAs did not indicate any significant difference between and within groups [Table 5].

Table 5 ITT analysis of area (cm^2) of single and multiple Fibroadenoma.

	Homeopathy Group	**Placebo Group**	***$p-value***
Single FA			
Enrollment	3.93 ± 3.399	3.97 ± 3.209	
3rd month	3.40 ± 3.000	3.96 ± 3.387	0.087
6th month	3.37 ± 4.075	4.22 ± 3.521	0.050
#p-value	0.155	0.373	
Multiple FA			
Enrollment	1.55 ± 1.886	2.36 ± 3.317	
3rd month	1.76 ± 2.224	2.72 ± 3.415	0.332
6th month	1.57 ± 2.325	2.77 ± 3.890	0.160
#p-value	0.587	0.255	

Within group p-value computed using Repeated Measure ANOVA.

$ Between groups p-value compared using ANCOVA to adjust for baseline differences.

Single FA: Homeopathy (n = 48), Placebo (n = 53).
Multiple FA: Homeopathy (n = 25), Placebo (n = 24).

Sub-group analysis of the cases which exceeded the USG assessment timeline indicated $p < 0.05$ at 1st and 2nd follow-up USG assessment in the homeopathy group.

Out of 85 cases in the medicine group (including 12 cases of the HI arm of the sub-group), 78 received a single remedy throughout the study based on the totality of symptoms. These medicines were *Pulsatilla* (n = 29/7), *Silicea*(n = 13/5), *Phosphorus* (n = 7/3), *Sepia* (n = 7/1), *Calcarea carbonica*(n = 7/4), *Conium maculatum*(n = 5/2), *Sulphur*(n = 4/2), *Natrum muriaticum*(n = 3/0), *Belladonna* (n = 1/0), *Lycopodium* (n = 1/0) and *Thuja occidentalis*(n = 1/0) where the first no. indicates the no. of cases prescribed and the second gives the no. of cases improved.

In the 7 remaining participants the medicines were changed. The participant who received *Belladonna and Phosphorus* and another who received *Phosphorus, Calcarea fluorica, and Silicea had* shown improvement. However, 5 participants where *Phosphorus, Sepia; Phosphorus, Pulsatilla; Pulsatilla, Calc flour; Pulsatilla, Silicea* and *Sulphur, Phosphorus* was prescribed did not show improvement.

4. Discussion

Fibroadenomas are the most commonly occurring breast lumps in young females. Nearly 65% of the participants were nulliparous in the study population, corroborating Ajao OG's findings [16]. These are generally painless and may spontaneously resolve but are the most excised in adolescents which can cause disfiguring of the breast and may re-appear after excision. Homeopathic treatment has shown positive results in cases of breast fibroadenoma [9-11]. These most commonly occur in the breast's upper outer quadrant, which has been corroborated in this study (n = 78) [17]. Fibroadenomas are usually single lumps. About 10%-15% of women have several lumps that may affect both breasts. In the present study, around 70% of the participants had a single breast FA. 73% of the participants were from the middle-income group and 66% were nulliparous. 97% did not have a family history of FAs. The mean age of the study population was 25 years, and the mean BMI was 21. There was no significant association of BMI with the size and number of FAs in this study which aligned with the findings of Mehreen et al. [18].

Although there is a significant difference between the intervention and the placebo groups at 3rd and 6th months, the within-group difference is insignificant. Since this was a first-of-its-kind study where Individualized Homoeopathy was given and considering the practical difficulties of blinding many medicines in various potencies and their controls, the study was designed as a single-blind study which was a flaw of the study. However, fibroadenoma can be evaluated through a physical or ultrasonological examination, which minimizes bias. The authors were unaware of allocation concealment when the study was planned and, therefore, a limitation. Keeping in view the poor enrolment at the Kottayam center and availability of cases in the Noida center, additional target of 25 participants (from serial number 26 to 50 of randomization sequence generated for Kottayam) was assigned to Noida and 1 more patient was enrolled at Kolkata center beyond the randomization sequence. Therefore, a small amount of selection bias cannot be denied. High dropout is a limitation of the study which could have been mainly due to the painless nature of FAs. A detailed baseline assessment could have reassured the patients regarding this being a benign condition. Only one patient in the placebo group went for surgical excision. Also, this age group being actively productive

may not find time for hospital visits. Subgroup analysis of the cases that exceeded the follow-up USG assessment timeline indicated a significant difference in the reduction of FAs in the homeopathy group compared to the placebo group. This further substantiates that a longer duration of follow-up is required for reduction/resolution of FA and that homeopathic medicines have the forward carry effect as some of the cases could not visit for timely US assessment after finishing their medicines.

Further limitations include a short duration of follow-up for the assessment of complete resolution and recurrence of FAs if any.

5. Conclusion

Although Individualized homeopathy has shown a significant reduction in the area of FAs compared to the placebo group due to the limitations mentioned above, it is impossible to draw precise conclusions. The difference within the groups is not statistically significant. No significant difference is observed between and within the single and multiple FAs groups. Future studies should be conducted, overcoming the limitations mentioned above, based on an adequate sample with long-term follow-up for resolution and recurrence if any.

Acknowledgments

The authors are grateful to Dr. Subhash Kaushik, Director General, CCRH; Dr. Anil Khurana, Former DG, CCRH and Dr. Raj. K. Manchanda, Former DG, CCRH for administrative support. We are thankful to Dr. Richa Singhal, Senior Statistical Assistant, Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, GOI, for statistical analysis. Dr. Himadri Bhoumick is acknowledged for screening the cases at DACRRI, Kolkata.

Author Contributions

Chetna Deep Lamba: Protocol development; Coordination for implementation of study; Compilation and consolidation of data, Data verification; Analysis and interpretation of data; Drafting the article; Final approval of the version to be submitted. **Oberai Praveen**: Coordination for implementation of study; Revising the article critically for important intellectual content; Final approval of the version to be submitted. **Wadhwa Bharti**: Acquisition of data; Compilation and consolidation of data, Data verification; Final approval of the version to be submitted. **Parveen Suraia**: Acquisition of data; Final approval of the version to be submitted. **Soren Arti**: Acquisition of data; revising the article critically for important intellectual content; Final approval of the version to be submitted. **Bhuvaneswari Rajachandrasekar**: Acquisition of data; revising the article critically for important intellectual content; Final approval of the version to be submitted. **Pradhan P. K**: Acquisition of data; revising the article critically for important intellectual content; Final approval of the version to be submitted. **Shinde Vaishali**: Protocol development; Final approval of the version to be submitted. **Gupta Jaya**: Protocol development; revising the article critically for important intellectual content; Final approval of the version to be submitted.

Funding

The study was funded by the Central Council for Research in Homoeopathy, under the Ministry of AYUSH, Government of India.

Competing Interests

None declared.

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