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A DOUBLE BLIND TRIAL TO COMPARE THE EFFICACY OF VITAMIN E TO A PLACEBO IN THE TREATMENT OF FIBROADENOSIS OF BREAST.

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ABSTRACT:
One woman in four is referred to a breast clinic at some time in her life. A breast lump, which may be painful, and breast pain constitute over 80% of the breast problems that require hospital referral, and breast problems constitute up to a quarter of all women in the general surgical workload[1].
Fibroadenosis or FBD affects a large number of women during their Reproductive years[2]. It has been reported to occur in 25% to 50% of women during reproductive life.
Mastalgia the main symptom of Fibroadenosis is a common breast symptom that may affect up to 70% of women in their lifetime[3].And is the reason for 50% of all referrals to breast clinics.[4]
After a thorough history, examination and imaging, reassurance has been reported to have an 85% success rate as a first line treatment in mastalgia[5]
Many different drugs like Danazol, Tamoxifen, Bromocriptine, have been tried but have been abandoned due to their side effects.
All the clinical trials investigating the possible use of Vitamin E in the treatment of Fibroadenosis of Breast have shown conflicting results.
Thus use of Vitamin E in Fibrocystic Breast Disease is still a debated topic & needs further research to determine its effectiveness.
Therefore this study was undertaken to study the role of Vitamin E in the treatment of Fibroadenosis of Breast. The primary objective of this study was to compare the efficacy of Vitamin E to a placebo in the treatment of Fibroadenosis Breast. The safety and tolerability of Vitamin E are the secondary objectives.

KEY WORDS: Fibroadenosis, Vitamin E.

INTRODUCTION:

AIMS AND OBJECTIVES

1. To study the role of Vitamin E in Fibroadenosis of Breast.
2. To compare the efficacy of Vitamin E to a Placebo in the treatment of Fibroadenosis of Breast.

Material & methods

The following inclusion/exclusion criteria were used for recruitment of patients in the study.

Inclusion Criteria:

1. Female between 20 to 35 years of age.
2. Signs symptoms of Fibroadenosis.

Exclusion Criteria:

1. Sex - Male.
2. Age greater than 35 years.
3. Females with pregnancy or breastfeeding.
4. Palpable Lump in breast.
5. FNAC not suggestive of Fibroadenosis.
6. Nipple Discharge.

The study was conducted in the department of Surgery on 100 Outdoor patients with Fibroadenosis of Breast. During the period from 2011 to 2013.

All the Outdoor patients with Fibroadenosis of Breast were invited to participate in the study and written informed Consent was taken.This was a randomized double blind trial which involved 100 women with symptoms & signs of Fibroadenosis i.e. cyclical Mastodynia, Nodularity & tenderness.

The patients were randomly divided into two identical groups & both the group patients were given breast support and analgesics.

Group A 50 patients were also given Vitamin E

Group B 50 patients were also given a placebo.

The diagnosis of fibrocystic disease was based mainly on symptoms & clinical examination. Detailed history taking & clinical examination, Utrasonography of Breast & FNAC were used to aid the diagnosis.

The severity and duration of breast pain were measured according to the following methods:

- The Visual Analogue Scale
- Mandels score.
- Cardiff Breast Pain Chart & score.

The patients were regularly followed up in the Outpatient Department after One month, Three months & Six months intervals.

Symptoms & clinical findings were observed during follow-up.and, at that time, the severity, duration and side effects of intervention were evaluated.

The primary outcome measure was change in breast pain, measured by the Visual Analogue scale, Cardiff's Breast pain score & the Mansel's score at enrolment and at One, three & six months.

The Breast pain, breast tenderness and the duration of pain were assessed in all the patients using the following methods:

- Visual Analogue scale
- Mansel's Criteria for grading breast pain[11]
- Cardiff Breast Pain Chart and Nominal Days with Severe Pain (NDSP) Score[11,12].

Table No 01: Comparison of pain after 6 month of receiving the treatment regime

Visual Categorical Rating scale after 6 months		Treatment Regime		Total
		A	B	
No pain	No's	34	36	70
	%	68.0%	72.0%	70.0%
Mild Pain	No's	9	5	14
	%	18.0%	10.0%	14.0%
Moderate Pain	No's	5	4	9
	%	10.0%	8.0%	9.0%
Severe Pain	No's	2	5	7
	%	4.0%	10.0%	7.0%
Total	No's	50	50	100

	%	100.0%	100.0%	100.0%

Pearson Chi-Square Tests	χ^2 Value	df	p value	Not significant (p>0.05)
	2.597	3	0.458	

Table No 02: Comparison of Mansels score for breast pain at 0,1, 3 and 6 months in between the patients of A and B treatment regime.

Mansels Total score	Treatment Regime	N	Mean Rank	Sum of Ranks
0 months	A	50	53.71	2685.50
	B	50	47.29	2364.50
	Total	100		
1 month	A	44	41.03	1805.50
	B	44	47.97	2110.50
	Total	88		
3 months	A	33	31.45	1038.00
	B	35	37.37	1308.00
	Total	68		
6 months	A	16	16.06	257.00
	B	14	14.86	208.00
	Total	30		

Test	Mansels Total score 0 months	Mansels Total Score 1mth	Mansels Total Score 3 mth	Mansels Total Score 6 mth
Mann-Whitney U	1089.500	815.500	477.000	103.000
Wilcoxon W	2364.500	1805.500	1038.000	208.000
Z	-1.138	-1.287	-1.285	-.402
p value	0.255	0.198	0.199	0.687
	NS(p>0.05)	NS(p>0.05)	NS(p>0.05)	NS(p>0.05)

Statistically there was no significant (p>0.05)difference of Mansels score for breast pain at 0,1, 3 and 6 months in between the patients in A and B treatment regimes group .

Table No 03: Comparison of Cardiff Breast pain score at 6 months in between patients receiving A and B treatment regimes.

Cardiff Breast pain score 6 months		Treatment Regime		Total
		A	B	
I	No's	7	10	17
	%	43.8%	71.4%	56.7%
II	No's	8	3	11
	%	50.0%	21.4%	36.7%
III	No's	1	1	2
	%	6.3%	7.1%	6.7%
Total	No's	16	14	30
	%	100.0%	100.0%	100.0%

Pearson Chi-Square Tests	χ^2 Value	df	p value	Not Significant (p>0.05)

	2.681	2	0.262	

On comparison of the Cardiff breast pain score at 6 months between female patients taking A and B treatment regime it was found that there was statistically no significant ($p>0.05$) difference.
Thus it is concluded that Vitamin E has no positive therapeutic effects on Fibroadenosis & cyclic mastalgia as compared to a placebo.

DISCUSSION:

In our study of 100 patients evaluated during period of 2011 - 2013.
Patients were randomly divided into two identical groups:
Group A – 50 patients
Group B - 50 patients
50 patients of Group A were given Vitamin E.
50 patients of Group B were given a placebo.
Both group A & group B patients were given Breast support and analgesics.
In this study out of these 100 women diagnosed of fibroadenosis 71% had the pain in relation to menstruation ie they had cyclical mastalgia.
Out of this there were 66% (33) and 76% (38) females in A and B treatment regimes respectively having the complaint of pain in relation to the menstruation.
Thus There was statistically no significant difference($p>0.05$) in the presence of breast pain in relation to menstruation in between number of females of fibroadenosis taking A and B treatment regime.
It was further noted that 68% females had regular menstrual cycle while 32% had irregular menstruation.
In A regime 64% (32) while in B regime 72% (36) females had regular menstruation. And irregular menstruaton was noted in 36% (18) females of A treatment regime and 28% (14) females with B treatment regime.
There was statistically no significant difference ($p>0.05$) in menstruation history of the females in the A and B treatment regimes.
At the start of the study out of 100 females diagnosed with fibroadenosis 18% had mild pain, 13% complained of moderate pain and 60% had very severe pain.
In A treatment regime 78 %(39) female and B treatment regime 60%(30) females had severe breast pain.Moderate type of pain was complained by 8% (4) females in A treatment regime and 18%(9) females included in B treatment regime.
There was statistically no significant ($p>0.05$) difference of severity of breast pain rated according to visual categorical rating scale at the start of the study in between patients included in A and B treatment regimes.
The primary outcome measure was change in breast pain, measured by the Visual Analogue scale, Cardiffs Breast pain score & the Mansels score at enrollment and at One, three & six months.
After one month of the treatment 44 %(22) females in A regime & 54%(27) females in B regime , perceived severe pain , 30%(15) women in A regime & 18%(9) women in regIme B perceived moderate pain whereas 14%(7) of women in A group and 16%(8) in B group had mild pain. 12% (6) female in each A and B treatment regime group had no breast pain after 1 month treatment.
Thus there was statistically no significant ($p>0.05$) difference in the severity of pain in patients as per visual categorical rating scale after 1 month in between A and B treatment regime.
After three months of the treatment 8 %(4) females in A regime & 18%(9) females in B regime , perceived severe pain , 32%(16) women in A regime & 28%(14) women in regIme B perceived moderate pain whereas 26%(13) of women in A group and 24%(12) in B group had mild pain. Thus 34% (17) female in A treatment regime and 30%(15) in B treatment regime group had no breast pain after 3 month treatment. Hence there was statistically no significant ($p>0.05$) difference

in the severity of pain as per visual categorical rating scale after 3 month in between A and B treatment regime.

After 6 months 4%(2) female in A regime & 10%(5) females in B regime had severe pain, 10%(5) n Group A & 8%(4) perceived moderate and in 18%(9) of Group A women & and 10%(5) of Group B women the pain was mild.

Thus 68% (34) female in A treatment regime and 72%(36) in B treatment regime group had no breast pain after 6 month treatment.

Hence there was statistically no significant ($p>0.05$) difference in the severity of pain as per visual categorical rating scale after 6 month in between A and B treatment regime.

Ernster VL, Goodson WH etal who conducted a double-blind, randomized trial on the effect of vitamin E to a placebo found no differences between the vitamin E and placebo groups in scores for changes in breast findings at the end of the study period and no differences in the proportion of women who reported feeling less premenstrual pain (40.0% and 41.4%, respectively)[8]

Similar findings were reported by Meyer E.C, Sommers D.K et al[7]

.Vera Rosolowich, et al after the review reported similar findings[9].

Further on comparing the Mansels score for breast pain at 0,1, 3 and 6 months in between the patients of A and B treatment regime. It was observed that statistically there was no significant ($p>0.05$) difference of Mansels score for breast pain at 0,1, 3 and 6 months in between the patients in A and B treatment regimes group.

This signifies that patents treated with Vitamin E showed no significant improvement in relief of breast Pain as compared to patents who received placebo.

Meyer et al.[7] attempted to evaluate the efficacy of Vitamin E in the treatment of benign breast disease (Fibroadenosis),105 women were randomly selected and entered into a double-blind, placebo-controlled crossover trial. All patients had mammographic evidence of benign breast disease. They received 600 mg of placebo and alpha-tocopherol acetate in 3-month treatment phases. Breast examinations and mammography were done, after each treatment, at approximately the same phase of the patient's menstrual cycle.

They observed No significant subjective or objective effects after treatment. Thus they concluded that alpha-tocopherol is not beneficial in the treatment of benign breast disease[7].

On the first day of examination out of 50 females having fibroadenosis in A treatment Regime group Cardiff breast pain score I and Score IV each was noted in 10%(5) females , 54%(27) females had score II and 26%(13) had cardiff breast pain score.

Out of 50 females included in B treatment regime group 12%(6) had cardiff breast pain score I, 70%(35) had Score II and 18%(9) had score III at first examination.

There was statistically no significant difference ($p>0.05$) of Cardiff breast pain score between females included for A and B treatment regimes.

At one months of treatment both A and B treatment regime group had 44 females with breast pain.

Of 44 females patient taking A treatment regime for 1 month Cardiff breast pain score I was found in 6.8% (3) patients, 68.2%(30) has Score II, 18.2%(8) had score III and 6.8%(3) had Score IV.

OF 44 females taking B treatment regimen 9.1%(4) females had score of I and Score IV, 45.5%(20) females had score II and 36.4%(16) females had score III. Thus there was statistically no significant ($p>0.05$) difference o f Cardiff breast pain scores in number of females having fibroadenosis taking A and B treatment regimes.

Comparison of Cardiff Breast pain score at 3 months in between patients receiving A and B treatment regimes showed that at 3 months treatment 33 female patients taking A regime and 35 females patients taking B treatment still had the complaint of pain of fibroadenosis.

In female taking A treatment regimen 60.6% (20) had Cardiff breast pain score I, 27.3%(9) had Score II and 12.1%(4) had score III.

In females taking B treatment regimen 31.4%(11) females had the cardiff breast pain score I, in 51.4%(18) females, score II was noted and score III was noted in 17.1%(6) females.

Thus on comparison between number of female patients having Cardiff breast pain score at 3 months taking A and B treatment regime it was found that there was statistically no significant ($p>0.05$) difference.On comparison of Cardiff Breast pain score at 6 months between patients receiving A and B treatment regimes it was observed that out of 16 females taking A treatment regime having complaint of pain due to fibroadenosis at 6 months of treatment Cardiff breast pain score in 43.8%(7) was Score I, 50% (8) had Score II and only one female had Score III.
Whereas of 14 females taking B treatment regimen the Cardiff breast pain score in 71.4% (10) was Score I, 21.4%(3) had score II and one female had Cardiff breast pin score III.
None of the females in both the group had Score IV.
While 14 females in A regime and 16 females of B treatment regime had no pain on evaluation at 6 months.
However on comparison of the Cardiff breast pain score at 6 months between female patients taking A and B treatment regime it was found that there was statistically no significant ($p>0.05$) difference.
Further Paired Comparison of Cardiff Breast pain score in patients receiving A and B treatment regimes using Wilcoxon Signed Ranks Test showed no significant statistical difference.
Thus on comparison of the Cardiff breast pain score in females taking A treatment regime, it was found that there was statistically significant ($p<0.05$) reduction of score at 1 months than that at the first evaluation, also statistically significant ($p<0.01$) reduction of score was noted at 3 months to that of 1 months score, and 6 months to that of 3 months score.
But in females taking B treatment regime, Cardiff breast pain score had no statistically significant ($p>0.05$) change at 1 months compared to that at the first evaluation but statistically significant ($p<0.01$) reduction of score was noted at 3 months compared to 1 months score , and 6 months compared to 3 months score.
Thus from these observations & results it shows that the administration of Vitamin E did not have any significant curative results as tested at One month, Three months & Six months intervals.
Pearson Chi-Square testing indicated that after One, Three & Six months of therapy, the efficacy demonstrated by the Vitamin E recipient case group was equivalent to that of the group that received a placebo.
Sousan Parsay et al conducted a double blind clinical trial; in which 150 women with cyclic mastalgia were taken and randomly divided into two distinct case and control groups; each containing 75 patients. . Simple, chewable tablets of either Vitamn E or a placebo were prescribed twice a day for 4 months for case and control participants, respectively The severity and duration of breast pain were measured according to both the Cardiff Breast Pain Chart and the Visual Analog Scale. They concluded that Vitamin E has positive therapeutic effects on cyclic mastalgia[14].
However contrary to the above study, our randomized double blind trial using Visual Analogue scale, Mansels score & Cardiff score ,the observations & results in our study shows that the administration of Vitamin E did not have any significant curative results as compared to a placebo.
Vera Rosolowich, et[13] al reviewed the Three Randomised Control Trials.
. In the first, patients were asked whether their breast pain was better, worse, or unchanged after 2 to 3 months of therapy. & In each group, 40% reported

Improvement[6] The second trial did not assess breast pain, but found no improvement in nodularity[8].
The third found no improvement in nodularity or mammographic density, and although a larger proportion of women in the vitamin E group reported improvement in breast tenderness, this was not statistically significant[7]Thus she recommended that Vitamin E should not be considered for the treatment of mastalgia[9]. In our study comparing Vitamin E to a placebo in the treatment of Fibroadenosis of Breast Vitamin E has not been found to be beneficial in the treatment of Fibroadenosis of Breast.
As mentioned above Vitamin E has not been successful in the treatment of Fibroadenosis of Breast.
Vitamin E has not been found to be beneficial n the treatment of Fibroadenosis of Breast[7,8]

RESULTS

Vitamin E has not been found to be beneficial n the treatment of Fibroadenosis of Breast[7,8]
From our study we recommend that Vitamin E should not be prescribed for the treatment of Fibroadenosis of Breast.Reassurance of the patient is the hall mark of treatment of Fibroadenosis of breast & should be an integral part of the treatment along with breast support and.analgesics.
The results of our study are comparable to parallel study carried out by Ernster VL, Goodson WH et al[8] & Meyer et al[7].

CONCLUSION

Out of Hundred patients fifty were on Vitamin E & Fifty were on Placebo, both groups of patients were also given Reassurance, Breast support & analgesics.
The patients were regularly followed up in the Outpatient Department after One month, Three months & Six months intervals. The response was observed.
It was observed that the patients who were treated with Vitamin E had no significant improvement in Breast pain as compared to patients who received the placebo.
This signifies that Vitamin E is not beneficial in the treatment of Fibroadenosis of breast.
The results of our study are comparable to parallel study carried out by Ernster VL, Goodson WH et al[8] & Meyer et al[7].
From our study we recommend that Vitamin E should not be prescribed for the treatment of Fibroadenosis of Breast.
Reassurance of the patient is the hall mark of treatment of Fibroadenosis of breast & should be an integral part of the treatment along with breast support and.analgesics.

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