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To Evaluate Clinical Efficacy and Safety of "Flaxseed Oil" an Essential Fatty Acid (EFA) in Patient of Osteoarthritis (OA)–A Randomized, Placebo Controlled, Single Blinded Study

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Abstract **Original Research Article**

Introduction: Arthritis, a chronic progressive illness, has the potential to cause joint destruction and functional disability but may present as acute episodes. Early medical intervention has been shown to be important in improving outcomes, can improve function, stop damage to joints as seen on x-rays, and prevent work disability. As is known that most of the Indians are vegetarians do not like to eat fish or do not like to use medicine derived from animal source. ***Objectives:*** A present study was planned to evaluate therapeutic efficacy and safety of flaxseed oil derived Essential Fatty Acids (EFAs) in arthritis (Osteoarthritis arthritis). ***Material and methods:*** The study is randomized, Placebo controlled, single blinded study at Department of Orthopaedic, Tertiary care teaching hospital, a city in Gujarat, India. ***Results:*** The results of this study was statistically significant (p<0001) effect of essential fatty acid in improvement of cardinal symptoms of osteoarthritis patient. There observed better tolerability of EFAs in this patient. ***Conclusion:*** The results of this study demonstrate that EFA which are normal component of our diet, play many important physiological roles and EFAs can be adjuvant therapy in this disease.

Keywords: Essential fatty acids (EFAs), Efficacy, linseed oil, Osteoarthritis arthritis (OA), safety.

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INTRODUCTION

Osteoarthritis (OA) is one of the most prevalent and disabling chronic progressive diseases affecting the elderly and the incidences are increasing day by day around the globe including India [1]. Its most prominent feature is the progressive destruction of articular cartilage which results in impaired joint motion, severe pain, as, ultimately, functional disability. Its high prevalence and its moderate-to-severe impact on daily life pose a significant public health problem in the modern society [2]. Imbalance in the dietary consumption of n-6 to n-3 fatty acids is one of a root cause for many health problems i.e. in the genesis and progression of chronic diseases including the degenerative disease like osteoarthritis (OA) [3, 4]. Over consumption of saturated and trans fatty acids rich in n-6 fatty acids in diet, results in overproduction of pro-inflammatory eicosanoids, proliferative cytokine's and tumour necrotic factors (TnF α) increases the risk of development of degenerative changes in joints whereas monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids i. n-3 FAs (PUFAs) reduces the risk in the development of degenerative changes in joints, reduces the cardinal symptoms and retards the progression of disease by producing anti-inflammatory and anti-proliferative eicosanoids and cytokines as well as of tumour necrotic factors (Tn F-α) [5, 6]. Main aim of medical management is to get relief from cardinal troublesome symptoms of osteoarthritis either using NSAID's or other measures [7-9] n-3 fatty acids (n-3-FA) are polyunsaturated fatty acids (PUFA), obtained from marine (cold water fish) and vegetables (walnuts, soy, flaxseed etc.) sources. n-3 Fatty acids include Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA) and α-linoleanic acid (ALA). These provide anti-inflammatory and anti-proliferative eicosanoids and cytokines, which halt the progression of arthritis, irrespective of osteoarthritis and/or rheumatoid arthritis, moreover, it also lowers serum cholesterol, LDL, VLDL and TG and development of atherosclerosis [4, 10]. Several studies have demonstrate the role in arthritis as anti-inflammatory, ant-proliferative and also

cardio-protective effect of EPA and ALA [11-13]**.** Flaxseed oil is derived from the seeds of the plant *Linium usitatissimum*. It is a good source of α-linoleanic acid (ALA), a precursor of EPA and DHA. However, its therapeutic efficacy in arthritis patients has not been studied adequately in Indian population. The present study aimed to assess therapeutic efficacy for improvement of inflammatory cardinal symptoms of OA and tolerability of Flaxseed-oil (FO) in arthritis patients at a tertiary care hospital and private clinic in Gujarat, India.

MATERIALS AND METHODS

The present study was interventional, prospective study conducted at the outpatient Orthopaedics department of a tertiary care teaching hospital and a private clinic in a city of Gujarat. Permission to conduct the study was obtained from Medical superintendent of the hospital. Patients of either gender in the age group of 18-70 years, who were diagnosed of primary osteoarthritis (**OA**) of knee according to the clinical and radiological finding criteria's of American College of Rheumatology were included in the study after obtaining written informed consent. Patients with known food allergies, if they had any other musculo-skeletal joint disease, who was suffering from any other concomitant chronic condition, which could worsen during the study period necessitating removal of patient from the study, any other abnormal laboratory parameters, pregnant and lactating females and those who, according to screening doctor, were unable to comply with the study protocol were excluded. All subjects were on 1st line-drug therapy i.e. NSAID's for the controlled of their clinically troublesome inflammatory symptoms. None of them was considered severe enough to warrant second line drug therapy.

Out of 96 patient of osteoarthritis examined, a total of 70 patients were enrolled in the study according to the selection criteria. Patients were randomized into two groups namely placebo group and test group. Each group consisted of 35 patients. On the first day of patient enrolment, the inflammatory parameters were examined and recorded. The following parameters were assessed to evaluate therapeutic efficacy & tolerability of placebo & EFAs as an anti-inflammatory agent in both the groups at 0 day i.e. base-line as described by Jayaram S *et al.*, [14].

- Pain at rest.
- Pain on movement.
- Swelling on affected joint (s).
- Tenderness of joint.
- Duration of morning stiffness.
- Time to walk 50 feet just after waking up from bed in morning.
- Ability to perform physical activities.

Assessments of pain, swelling, tenderness and ability for work performance were done on a '4 point' categorical scale. Duration of morning stiffness and time to walk was measured in minutes. Pain at rest as well as pain on movement was measured on a 4-point categorical scale, where, 0 = absent, 1 = no interference in daily activities, 2 = some interference with daily activities and 3 = incapacitation. Swelling was measured on a 4-point scale where 0 = none, 1 = palpable, 2 = palpable and visible, 3 = distortion of joint centers. Tenderness was measured on a 4-point categorical scale, Grade 0 = No pain on pressure, Grade 1 = Slight pain on pressure, Grade 2 =Pain and winching, Grade 3 = Patient did not allow palpitation. Ability to perform physical activities (daily routine work) was graded on a 4-point scale: where, Grade 0 = No discomfort, Grade 1 = some discomfort, Grade 2 = Discomfort and difficulty, Grade 3 = Not possible. For parameter 1, 2, 3, 4, and 7 score grading was decided on the basis of observed change in clinical symptom by the investigator's assessment and by the patient's own experience explanation to the investigator in response to symptoms. Furthermore, the dose and number of NSAID used increased, decreased or stopped were also observed and recorded.

Observer's opinion for degree of disease symptoms was recorded on the basis of pain score as given below Table-A [27].

Table-A:

Grade 0	**Remitted**
Grade 1	Slight or mild
Grade 2	Moderate
Grade 3	Severe

Therapeutic efficacy was rated on the basis of results and patient's experience at the end of the clinical study as given in below Table-B:

Table-B:

Score 0	Excellent
Score 1	Good
Score 2	Fair
Score 3	Poor

Following this, placebo group were prescribed liquid paraffin in soft gelatine capsule (1 ml/capsule); 2 capsules TDS for a period of 6 weeks. Similarly, test group received flaxseed oil in soft gelatine capsule (150-mg/capsule); 2 capsules TDS for a period of 6 weeks. Same parameters were examined and were recorded on 1st day of 7th week i.e the end of 6 week of placebo and test drug treatment.

STATISTICAL ANALYSIS

Demographic characteristics, height and body weight of patients of both groups were analysed for statistical significant difference using unpaired t- test.

Therapeutic efficacy of placebo and flaxseed oil treatment on improvement of inflammatory cardinal symptoms of OA as well as its safety and tolerability were by estimating LFT, RFT, BT, CT, PT, Haemoglobin, total count and FBS were assessed and analysed for statistical significance using paired t test (intragroup comparison) and unpaired t test (intergroup comparison).

RESULTS

A total of 70 patients were enrolled in the study according to the selection criteria as mentioned previously. Of these 35 patients received placebo treatment (liquid paraffin in soft gelatine capsule) and 35 patients were prescribed flaxseed oil (test group) (soft gelatine capsule). All had completed study protocol successfully without any drop out. The following observations were made in this study, where common presenting complaints by all the diagnosed Osteoarthritis patients enrolled in the study were joint pain at rest and on movement, joint swelling, and morning stiffness were nearly similar at baseline level in both the groups as shown in Table-1.

Table-1: Common complains of patients enrolled in placebo group (n=35) and test group (n=35) at baseline

Patient Complains	Placebo-Group		Test Group	
	No. of patients	Percentage (%)	No. of patients	Percentage (%)
Joint-pain (at rest & on movement)	35	100	35	100
Joint-swelling	35	100	35	100
Morning-stiffness	35	100	35	100

A highly significant lowering of the mean score values and mean time durations of the evaluated parameters for the major complains, cardinal signs, clinical symptoms and physical activities were noted in the EFA (test drug) treated group compare to placebo treated group at the end of 6 week of study period compare to base line score values (Table-2A; 2B and Fig-1A; 1B).

Table-2A: Comparative difference of effect of placebo (n=35) and Test drug (n=35) treated group at the end of 6 week compare to base line scores on the common complain of OA patients

Clinical Symptoms (Parameter) →	Mean score for Pain at rest		Mean score for pain on movement		Mean score for joint swelling		Mean score for tenderness	
	Placebo	Test	Placebo	Test	Placebo	Test	Placebo	Test
Base-line (0-day)	1.63 ± 0.49	1.6 ± 0.5	1.6 ± 0.5	1.71 ± 0.46	1.4 ± 0.50	1.46 ± 0.50	1.57 ± 0.50	1.46 ±0.50
At the end of 6th week	1.70 ± 0.47	0.55 ± 0.51	1.8 ± 0.6	0.8 ± 0.57	1.47 ± 0.51	0.52 ± 0.57	1.63 ± 0.49	0.58 ± 0.50
Difference: base-line to end of 6th week	-0.1 ± 0.31 NS	1.03 ± 0.47 ***	-0.2 ± 0.41 NS	0.85 ± 0.57 ***	-0.1 ± 0.55 NS	0.94 ± 0.61 ***	-0.1 ± 0.31 NS	0.85 ± 0.36 ***

Values of score are expressed as mean ± SD; NS = Non significant , *** = Highly significant ($p< 0.001$)

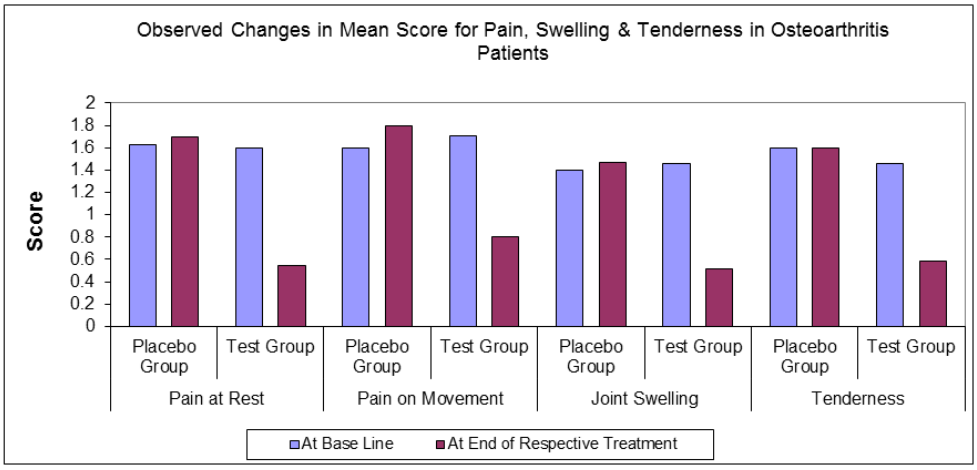

Fig-1A: Mean score of symptoms of Osteoarthritis

Table-2B: Effect of placebo (n=35) and Test drug (n=35) treatment respectively on the clinical symptoms of OA patients at base line and at the end of 6 week and the observed difference between both the groups

Clinical Symptoms (**Parameter**) →	Mean duration of morning stiffness **(in minutes)**		Mean time to walk 50 feet distance **(in minutes)**		Mean **score** for ability to perform physical activities	
	Placebo	**Test**	**Placebo**	**Test**	**Placebo**	**Test**
Base-line (0-day)	20.8 ± 3.87	18 ± 4.74	14.9 ± 3.23	14.2 ± 3.92	1.6 ± 0.66	1.57 ± 0.50
At the end of 6th week	21.1 ± 4.26	12.1 ± 3.84	14.8 ± 2.99	9.61 ± 3.17	1.57 ± 0.68	0.61 ± 0.50
Difference: base-line to end of 6th week	-0.2 **NS** ± 4.43	5.91*** ± 2.13	-0.1 **NS** ± 1.89	4.64 *** ± 1.29	0 **NS** ± 0.49	0.97 *** ± 0.39

Values of score are expressed as mean ± SD; NS = Non-Significant , *** = Highly significant (p< 0.001)

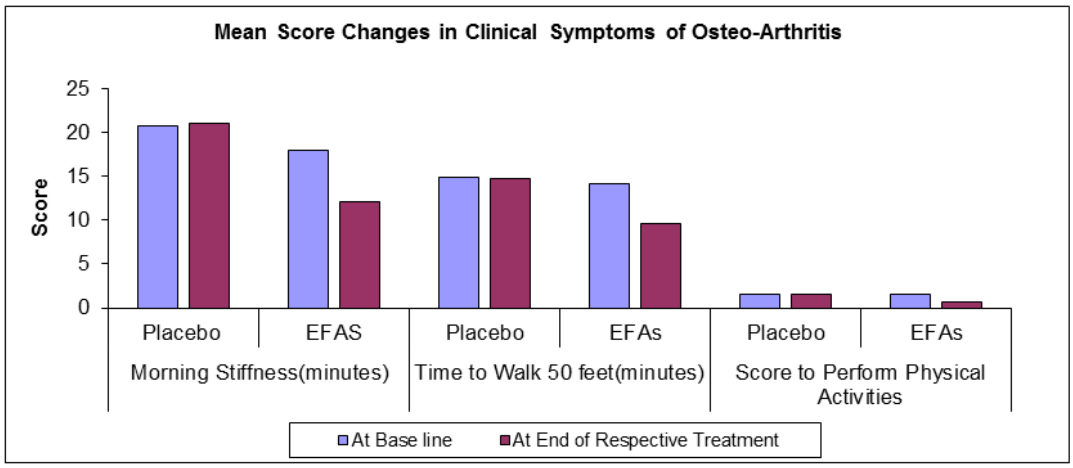

Fig-1B: Effect of placebo and the EFA treatment on mean duration of morning stiffness, mean time to walk 50 feet's and scores for ability to perform physical activities in osteoarthritis patients over the base line mean score

In order to ascertain the safety of flaxseed oil, no significant changes were observed in most parameters in both the group of patients as shown in the **table 3A and 3B**. Apart from biochemical tests a careful inquiry was made into EFA treatment emergent clinical adverse events seen in patients of Osteoarthritis and it has been observed that most of the adverse events were mild and self-limiting and did not lead to withdrawal of either placebo or test drug (EFA) therapy (Table-4).

Table-3A: Values (Mean ± SD) of Bleeding time; clotting time; prothrombin time (controlled value for PT = 14 sec.), Hemoglobin (Hb%), WBC counts and Fasting blood sugar mg% in patients of placebo and treated group at base line and at the end of 6 week

	BT (in min.)		**CT (in min.)**		**PT (in sec.)**		**Haemoglobinmg%**		**Total Count**		**FBS mg%**	
	Placebo group	Test group	Placebo group	Test group	Placebo group	Test group	Placebo group	Test group	Placebo group	Test group	Placebo group	Test group
Base-line	1.36 ± 0.02	1.31 ± 0.08	3.39 ± 0.22	3.38 ± 0.13	15.45 ± 1.05	15.7 ± 1.03	11 ± 0.9	11± 1.2	7923 ± 697	7935 ± 681.2	91 ± 6.6	93.2 ± 5.91
At the end of 6-week	1.36 ± 0.18	1.31 ± 0.07	3.38 ± 0.17	3.42 ± 0.18	15.7 ± 0.95	15.85 ± 0.81	11 ± 0.7	11.3 ± 0.8	8048 ± 789.5	7979 ± 697.4	94.7 ± 5.7	95.4 ± 5.03
Difference between base-line and at the end of 6 week	-0.005 ± 0.01	-0.002 ± 0.01	0.02 ± 0.05	-0.47 ± 0.05	-0.25 ± 0..64	-0.20 ± 0.75	-0.1 ± 0.3	-0.3 ± 0.4	-125 ± -92.5	-44 ± -16.2	-3.7 ±0.88	-2.2 ± 0.88

Table-3B: values (Mean ± SD) of Liver function test and Renal-function test in patients at base line and at the end of 6 week of placebo and test drug treatment

	AST (SGOT) [U/L]		ALT (SGPT) [U/L]		S.Bilirubin (mg %)		Serum Urea (mg %)		Serum creatinine (mg %)	
	Placebo group	**Test group**	**Placebo group**	**Test group**	**Placebo group**	**Test group**	**Placebo group**	**Test group**	**Placebo group**	**Test group**
Base-line	37.26±4.07	40±5.57	22.9±1.69	26±3.89	0.43±0.09	0.53±0.12	28.5±4.22	30±2.86	0.90±0.14	0.9±0.09
At the end of 6-week	37.2±4.18	39.3±5.05	22.8±1..52	26.5±4.28	0.43±0.08	0.52±0.01	28.5±3.96	29.8±3.03	0.90±0.14	0.89±0.09
Difference between base-line and at the end of 6 week	0.06±4.07	0.66±0.52	0.03±0.16	-0.5±-0.4	0.0±0.01	0.01±0.01	0.0±0.26	0.16±-2.9	0.0±0.0	0.0±0.01

Table-4: Adverse events observed with placebo (n=35) and Flaxseed oil (n=35) treatment

Serial no.	Adverse event	Number of patients In placebo group	Number of patients In EFA treated group
1	Nausea	10	4
2	Loose stools	15	6
3	Epigastric pain	11	2
4	Constipation	5	2
5	Dryness of mouth	5	1
6	Edema	9	2
7	Giddiness	16	8
8	Dyspnea	12	2
9	Glossitis	10	1
10	Non productive cough	8	2
11	Chest pain	1	4
12	Infection	2	4
13	Headache	4	2
14	Blurring of vision	5	4

DISCUSSION

The present study was conducted at a tertiary care teaching hospital and a private clinic in Gujarat, India to study the efficacy and tolerability of flaxseed oil an EFA's treatment in osteoarthritis (OA) patients. The study was conducted over a period of 2 years. Purpose, protocol of study and the nature of drug were explained to all OA patients diagnosed by the orthopaedic surgeon. A total of 70 patients gave their willingness in the written informed consent to participate in the drug study. Patients were divided randomly into two group, placebo group and test group, each group consisting of 35 patients. Based on clinical history and their clinical presentation, approximate 77% patients were affected by Osteoarthritis (OA) in between 31 to 50 years of age. Of this, ratio of male and female in this study was 1:1.6 in placebo and 1:1.4 in test group patients; which correlates with the study of Adami S *et al*., [10]. The cardinal inflammatory parameters were recorded in both the groups at 0 day and labelled as base line values. Subsequently, patients received either placebo (liquid paraffin 1 ml soft gelatine capsule, 2 capsules BD) or EFA-flaxseed oil (150 mg soft gelatine capsule, 2 capsules BD) for a period of 6 week. During the study period they were allowed to continue their prescribed anti-inflammatory drugs if taking without any increment in the prescribed dose.

In our study, at the end of 6 week of treatment with soft gelatine capsules of flaxseed oil (EFA=n-3 FA) in the test-group, we have observed a significant improvement in the cardinal inflammatory signs and symptoms i.e. reduction in pain at rest, pain on movement, joint swelling and tenderness in osteoarthritis (OA) patients compare to the placebo group patients treated with soft gelatine capsules of liquid paraffin. Our study result supports the result observed in the study done by Van der TH *et al.*, [15]. As compared to placebo it has been observed that EFAs (n-3 FA) therapy lead to greater and statistically significant ($p < 0.001$) changes (decrease in scores) in all the parameters is suggestive for EFAs (n-3 FA) therapeutic efficacy in amelioration of inflammatory cardinal signs in OA [13].

There also observed statistically significant (p <0.001) decreased in mean duration of morning stiffness in joints, mean time to walk 50 feet and mean score for ability to perform physical activity in test group (flaxseed oil treated) as compared to Placebo controlled group (liquid paraffin treated) is suggestive for flaxseed-oil (n-3 FAs) therapeutic role as an adjuvant in therapeutic management of OA with NSAIDs. Our results show the changes observed with flaxseed-oil (n-3 FAs) therapy over a period of 6 weeks are supporting the studied observation by Robert B Zurier *et al*., [16]. Research regarding the use of n-3 fatty acid supplements for inflammatory joint conditions has focused almost entirely on rheumatoid arthritis [17, 18]. Based on laboratory studies, however, many researchers suggest that diets rich in n-3 fatty acids (and low in n-6 fatty acids) may benefit people with other inflammatory disorders, such as OA, Ulcerative colitis [19-23].

In fact, several laboratory studies of cartilage-containing cells have found that n-3 fatty acids decrease inflammation and reduce the activity of enzymes that break down cartilage. Fatty acid imbalances are commonly seen in patients with chronic inflammatory conditions such as arthritis (OA &/or RA) and many more diseases [23, 25]. Based on Examination of patients with cartilage degradation in OA has linked increased severity of lesions with a higher proportion of arachidonic acid, an omega-6 fatty acid that shifts production toward more inflammatory prostaglandins, leukotrienes, and thromboxanes [3, 13, 24, 26].

Safety assessment in the present study was conducted using assessment of adverse events and effect if flaxseed oil and placebo treatment on laboratory parameters. AEs observed in both treatment groups were found to be non-serious and self-limiting. GIAEs were more frequent in both groups followed by CNS AEs and respiratory AEs (Table-4), however, stoppage of drug therapy was not required during study period in treatment groups indicating good tolerability of drugs used. Moreover, treatment with placebo or flaxseed oil for a period of six weeks did not result in any significant alteration of LFT, RFT, FBS, BT, CT, Hb and total count (table 3AB). However, a longer duration multicentre study is recommended to evaluate these parameters in view of chronic therapy and to establish the safety profile of flaxseed oil.

CONCLUSION

Treatment of flaxseed oil reduces the prominent cardinal signs and symptoms of inflammatory joint pain in OA patients. Moreover, there observed an improvement in the physical activity performance in the test group - flaxseed oil treated patients, compare to those patients treated with placebo – liquid paraffin without any adverse effect on blood parameters, liver and renal function during 6 week study. Further long term studies are recommended to evaluate the anti-inflammatory, anti-proliferative effects and safety of flaxseed oil treatment in a larger number of arthritis patients.

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